Selectivity engineering of exothermic multistep reactions using flow reactors

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Date : 31/01/2021
Place: Pune

Dedicated to my mother

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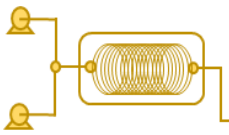


Introduction

"A good scientist is a person with original ideas. A good engineer is a person who makes a design that works with as few ideas as possible. There are no prima donnas in engineering."

- Freeman Dyson

A surge in the economic power of today's world and information explosion over a decade has significantly increased the demand for energy, raw material, products, and new technologies with a new and improved way of production, process intensification, zero-emission, and energy intensity enhancement, all leading to sustainability[1]. Scientific and technological innovations for efficient water purification systems intensified manufacturing units with lower environmental footprints, new ways of farming to meet the demand are driven towards sustainability for fighting the challenges of food, water, energy, and space in the world.

Though being a developing economy for more than a century, the Indian chemical and petrochemical market size has been at ~ 165bn, which is predicted to reach ~300bn in the next 5 years. Indian chemical industry is very diversified with around 80,000 products in its portfolio, whilst employing more than 2 million people[2]. India contributes nearly 3% to the global chemical industry, whereas the chemical industry accounts for 7% of Indian gross domestic production. It is expected to grow at a compound annual growth rate (CAGR) of 9.7% for the next 5 years. The growth of Indian chemical industries can be attributed to factors like structural advantages, increasing domestic consumption, diversification, and promising export potential. Recognition of the chemical industry as a key growth element of the Indian economy has paved the way for the government to reform foreign direct investment (FDI) rules and ease the investment policies[3]. The focus of chemical manufacturers is shifting towards sustainable development, where water, environmental safety, raw material, balanced life cycle, and energy use are some of the challenging issues[3]. This also involves the use of new technologies to optimize the processing and adherence to the local regulations of environment protection[4]. A greater demand coupled with limited resources, and increasing investment potential have led to the discovery of new ways of synthesis and processing towards sustainability in the chemical industry.

Some of the key innovations of the modern chemical world, which have taken shape over a decade are Nano pesticides, Enantioselective organocatalysis, Metal-organic frameworks, Porous materials for water harvesting, Directed evolution of selective enzymes, Water splitting, Energy storage devices, and Flow chemistry, etc.[5]. Among these innovations, the one which overcomes the challenges faced by the modern world in the form of a new product, process, and technology is Flow chemistry, which plays a significant role as a process intensification tool by increasing the efficiency of chemical syntheses whilst providing reliable access to a wider range of reaction conditions in a safe manner[6]. This ultimately results in

enhanced safety, reduced load on utility, smaller plant footprints, improved yield, selectivity, and clean processes.

1.1 Flow micro-reaction technology (Flow chemistry)

The petrochemical industry is operating in a continuous mode for decades. However, fine and specialty chemicals, and the pharmaceutical industry has relied mainly on general-purpose batch operation for the synthesis of molecules and active pharmaceutical ingredients (API's). Conventional batch reactors have performed well over the years where the same batch reactor can be used for multiple operations but with the limited resources and with stringent environmental regulation, operational issues and underperformance have become a major challenge. Though batch reactors are suitable for chemical processing with a varied product portfolio in the case of the pharmaceutical and specialty chemicals industry, they underperform in a variety of aspects namely, heat and mass transfer efficiency, reaction time, utility requirement, and maintaining reproducibility for different batch cycles. Most importantly, rapid chemical reactions, chemical reactions happening at extreme conditions, and highly exothermic reactions are very difficult to handle in batch reactors. Also, atom economic, selective, cost-effective, and valuable reagents cannot be employed most of the time due to the highly reactive nature of some of these reagents. At the same time, special synthesis approaches viz. electrochemistry, photochemistry, etc., which are very selective, but require specific conditions, are not easily extended for implementation in large scale batch environment. In general, new chemistries and processing conditions are developed keeping in mind the limitations of batch reactors, where the reaction rate, exothermicity, etc. are controlled by either performing the reactions at very low temperatures or by using a large amount of solvents which lead to longer reaction times, substantial waste generation, lower selectivity, and purity.

Implementation of flow chemistry for the chemical synthesis could eliminate many of the batch limitations, but the crucial benefits of continuous flow were realized over the past 15 years when miniaturization was introduced in field [7]. Miniaturization for flow synthesis provides many advantages compared to batch counterpart because of the possibility of reactions to be carried out in unexplored parameter space (conditions favorable for performing reactions at inherent kinetics), which wasn't possible easily before. The principal advantages of flow micro-reaction technology are obtained from very small volumes due to very small channel dimensions and the continuous nature of the processing. The continuous operation ensures no downtime for charging or discharging, whereas small dimensions provide excellent heat and mass transport. Furthermore, the small volume of the reactors limits the amount of energy release in case of unforeseen accidents, thus enhancing the safety aspect of any hazardous chemistry that needs to be performed. Continuous processing in small volumes, with enhanced transport properties in a relatively safer environment, has resulted in many new processes involving gaseous reagents, high energy reagents, toxic and hazardous reagents, reagents that need immediate consumption and reactions requiring strict control on reaction times, which usually not possible to control in a batch environment.

Continuous flow micro-reaction technology enabled ease of access to obtain constant reaction parameters such as residence time, temperature, and mixing, thus resulting in significant improvements in product quality and reproducibility. High heat and mass transfer coefficient, improved safety, easy scale-up and scale-out, fast process characterization, improved yield, and selectivity are some of the key benefits of the flow synthesis utilizing micro reaction technology[8]. Performing chemical synthesis in continuous flow (flow chemistry) of channel dimensions in micro/millimeter range (Micro and milli reactors) has resulted in the development of many green and sustainable processes[9]. There is abundant literature on the use of microreactors for carrying out a variety of single-phase and two-phase

single-step reactions (viz. sulfoxidation[10], halogenations[11], ozonolysis[12], nitration[13,14], catalytic hydrogenation[15], Grignard exchange reaction[16], synthesis of caprolactam[17], production of high-performance polymers[18], etc.). Also, the implementation of flow micro reaction technology enables the use of energy-intensive techniques e.g. ultrasound[19], microwave[20,21,] etc. productively and systematically, which were not easily applicable for the large-scale batch operations.

An unconventional way of utilizing catalysis[22-24] in flow has resulted in many green processes avoiding intermediate separation stages[25]. The reports involving inline analysis[26-30] connected to the flow micro reaction technology is an example of the future where intelligent reaction platforms can be envisaged, where machines can interpret the analysis of data and device the experiments on their own for deterministic studies or for synthesizing specific molecule, thereby reducing the involvement of a synthetic chemist or chemical engineer in repetitive tasks. Furthermore, integrating multiple steps in flow with inline analysis and separation[31,32] have paved a way towards the development of autonomous synthesis platforms[33,34], which can be set-up or delivered at the point of production.

The inherent benefits of flow chemistry and available reports on the conversion of a large number of batch chemistries in continuous flow suggests the tremendous scope for implementation of flow technology in chemical manufacturing especially in the case of specialty chemicals and the pharmaceutical industry either in the discovery phase or large-scale manufacturing in a safe manner. The kind of reaction space covered and transformations demonstrated in literature is huge and is still increasing day by day. As attention is shifted from batch to continuous transformation, incorporation of inline analysis and separation, integration of multiple steps, development of automated reaction platforms, and very recently utilization of machine learning coupled with artificial intelligence, flow chemistry has covered a long journey. Though flow chemistry has witnessed a radical change in academia and industry in

the way chemical synthesis is performed (moving out from flask), some of the associated challenges remain. The development of efficient micromixer, handling of solids in flow, fully automated on-demand synthesis platforms, development of smart algorithms for determination of kinetics using self-optimization systems, and reaction specific scale-up approach are some of the challenges which are still in the exploration stage and need significant attention and incorporation of new designs or methodologies.

This chapter discusses the developments in some of the core areas of the flow micro-reaction technology (**Figure 1.1**) which have evolved over time and associated challenges. These areas have contributed significantly to the development of chemical synthesis using flow chemistry either by developing efficient micromixers, coupling reaction and separation stages in flow, incorporation of inline analysis, developing ready to use devices for the fast reaction screening and developing molecule libraries, and also devising scale-up methodologies for some of the critical reactions and showing the working plants at pilot scale. Development of self-optimization platform and machine learning assisted synthesis are new developments happening in this field which are not discussed here however, *chapters 9* and *10* provide greater insight and way forward. The coming section sheds light on core areas of flow chemistry with significant milestones and challenges involved which will formulate the basis for the work presented in the subsequent chapters. Though discussed in the brief and in isolation, these areas have contributed collectively to the development and implementation of the flow synthesis for chemical manufacturing in academia and industry. However, some of the challenges still need focused attention and collaborative effort.

Ready to use commercial flow synthesis and separation devices

This area is dedicated for providing ready to use devices, either for synthesis or separation in order to reduce the time and labor involvement in performing routine synthesis, for screening parameter scope or determining kinetics.

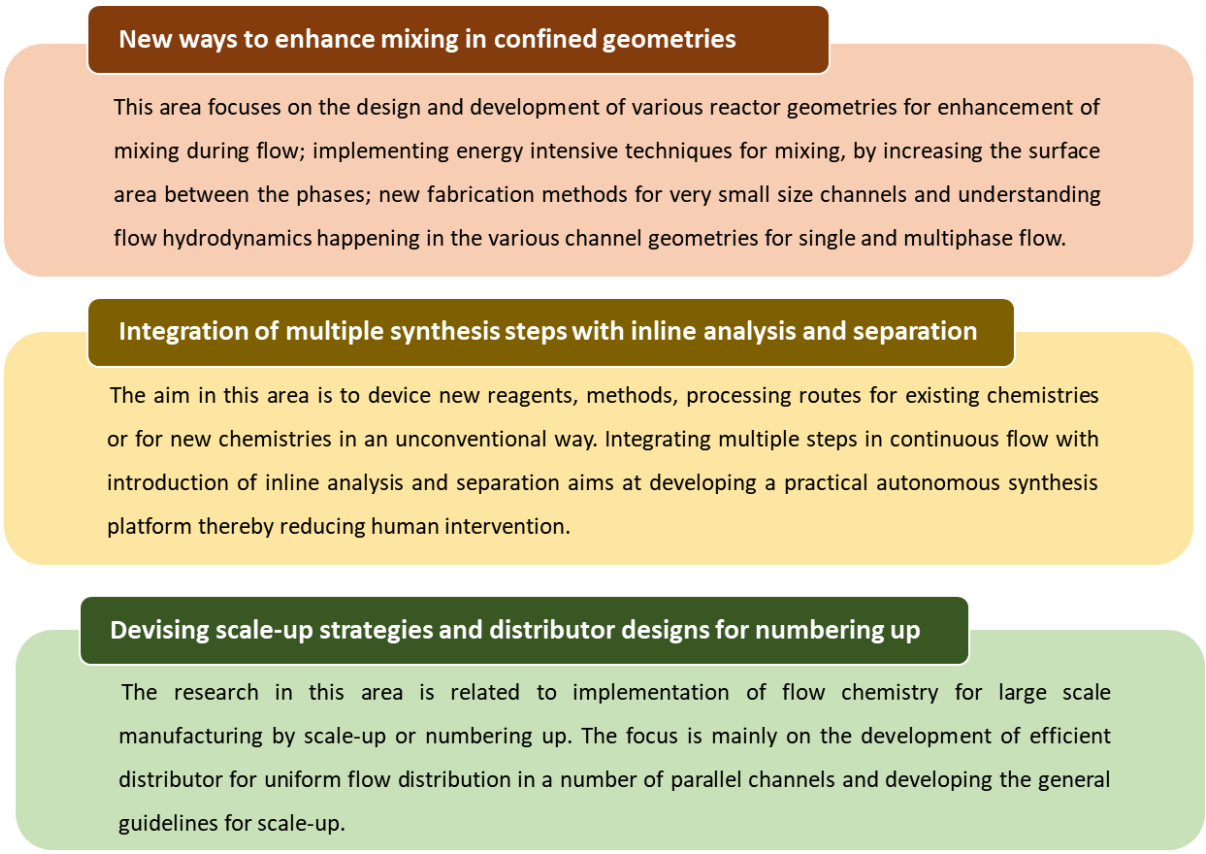


Figure 1.1 Core areas of flow chemistry

1.2 Core areas of Flow chemistry

1.2.1 Ready to use devices

A typical flow synthesis set-up utilizes pumps (for pumping the reagents), a mixing element (typically a micromixer for rapid mixing of reactants), a residence time tube (tube maintained at a constant temperature for providing residence time for the reaction to happen), and a thermostat (to maintain the reaction temperature) (**Figure 1.2)**. Other peripheral components are incorporated in the setups as per the specific reaction demand. Though enormous reports are mentioning continuous flow synthesis of various molecules, the time and efforts involved in assembling a flow setup that involves different components are rarely paid attention to. **Table 1.1** gives a brief list of components that can be used during the assembly of the continuous flow synthesis setup in the laboratory as per the need of the reaction and

separation steps. However, the material of construction, dimensions, and utility of components can vary based on their requirement in specific cases (Setups become more complex when handling corrosive gases such as chlorine).

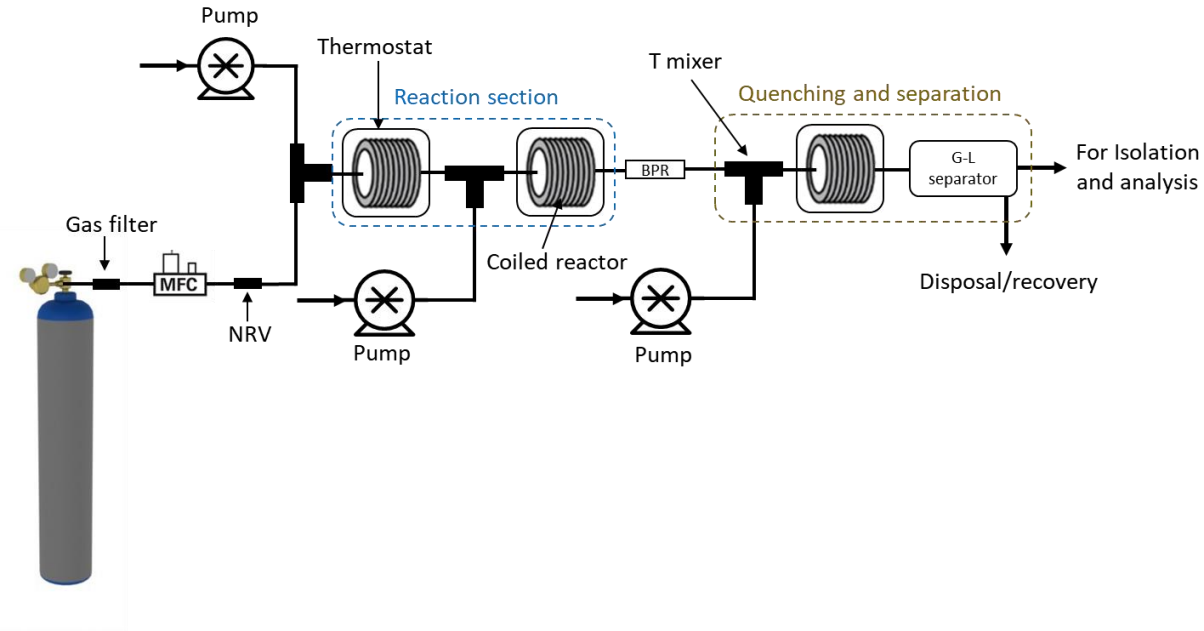


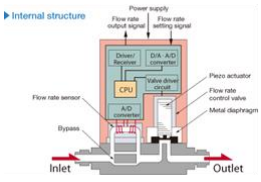
Figure 1.2 Typical experimental set up for flow synthesis

Performing reactions in enhanced parameter space in continuous flow increases the rate and reduces the reaction time significantly (to a few seconds or a few minutes), which gives an ability to screen many reaction conditions for either optimization or kinetics. However, the time scale of isolation and analysis becomes a bottleneck when calculated the overall time for the data generation. In the laboratory environment, separation and analysis are performed mostly offline also time involved in assembling the set-ups reduces the advantages of flow chemistry in terms of overall time involved in any particular synthesis. To reduce the time involved in the assembling setups and performing a large number of iterations led to the development of ready to use set-ups for performing repeated (with varying reaction conditions) experiments in one go. Many companies (Vapourtec[35], Syrris[36], Thalesnano[37], Future

Chemistry[38], Uniqsis[39,] etc.) have emerged during the initial development of flow synthesis for providing the solution to save time and labor to perform a large number of synthesis steps in flow. These machines could also be integrated with inline separators and auto-samplers, where a particular set of conditions can be fed to the computer, and the instrument can perform experiments independently at a given set of conditions. Once the set of parameters fed to the computer these instruments can perform synthesis round the clock.

Table 1.1. Components for flow synthesis

Pump	For pumping the fluid (heart of flow synthesis)	
Micromixers	Provides mixing before reaction	
Residence time tube	For providing enough residence time for reaction to happen at desired temperature	
Union expander reducer	For connecting different parts of flow synthesis set-up	
Sampling valves	For intermittent sampling during reaction	

Tools for connection	For tightening the connections or joints in the set-up	
Constant temperature bath or circulators	Provides the required reaction temperature	
Pressure sensors	To measure the pressure inside the flow synthesis setup during reaction	
Back pressure regulators	To maintain the specific pressure requirement in the flow set-up	
Temperature sensors	To measure and regulate the desired reaction temperature	
Gas cylinder	For reaction involving gaseous reagents or maintaining the inert atmosphere	
Gas filters	Necessary component in case of moisture sensitive reaction to remove traces of moisture from gases	
Mass flow controllers	To provide regulated flow of gases as per the stoichiometry	 

Non return valve	To avoid the back flow of reagents in case of pressure difference	

Though these machines can reduce the job of chemist or engineer during initial screening, the requirement of different components for a varied range of chemistries adds extra cost for procurement of those components. Also, troubleshooting has remained one of the main bottlenecks to date, mainly in the region where equipment is imported and expert personals are not readily available.

1.2.2 New ways to enhance mixing in confined geometries

Fabrication point of view, a microreactor is a device that incorporates at least one dimension less than 1 mm, usually in several micrometer ranges, while from a reaction engineering point of view, a microreactor is a device that eliminates or minimizes the resistance in mixing, heat transfer and mass transfer. **Figure 1.3** gives a brief idea about the dimensions of microfluidics devices and volumes associated with them[40]. A microreactor can be classified into three categories based on contacting principles[41] i.e. micromixer, microchannel, and falling film microchannel.

Micromixer: Reactor where mixing happens only due to internal structure at high flow rates

Microchannel: Reactor where mixing occurs due to convection and diffusion

Falling film microchannel

Small volumes require a small quantity of reagents during reaction or analysis, which enhances safety in difficult scenarios with a very high surface to volume ratio. When compared to the laboratory flasks, microreactors provide ~500 times increased specific surface areas (**Table 1.2**).

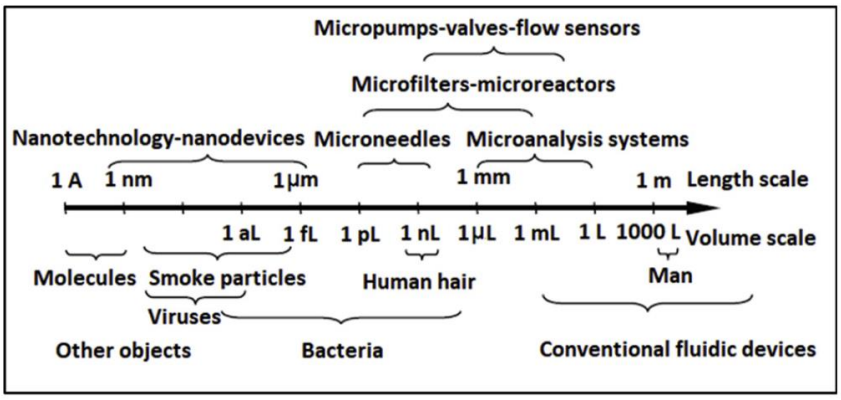


Figure 1.3 Length scale of microfluidics devices[40]

Though this enhancement leads to significant increases in heat and mass transfer rates, the flow inside the microreactors remains in the laminar regime due to small channel dimensions and small channel velocities (primarily necessary to avoid extremely high-pressure drop). For example, in a water-based (a fluid density of 1000 kg/m3 and a viscosity of 0.001 N·s/m2) microfluidic system with a channel width of 100 µm and a flow rate of 1 µL/s, the Reynolds number is 0.1 and it takes 1 s for the fluids to diffuse 1 µm and 1000 s for 1 mm. At the same time, the channel length of 10 cm offers a 40.81 mbar pressure drop. An increase in the velocity or viscosity by 2 times will increase the pressure drop by 2 times but can affect the residence time as well by 2 times, thereby either needing a longer reactor length that facilitates the necessary residence time or mixing length.

Table 1.2 Surface to volume ratio comparison of reactors

Reactor type	Specific area (m^2m^{-3})
Microreactor	10000
Microreactor (gas – liquid)	5000
250 ml round bottom flask	80
Round bottom flask with head space	20

Moreover, a high mixing index can be achieved by modifying the geometry of the micromixer (passive mixing techniques) or by supplementing the micromixer with energy intensifying techniques (active mixing techniques) like pressure, acoustics, magnetic, electromagnetic radiation, etc. Active mixing techniques utilize separate instruments for additional energy input for mixing to increase the contact area between fluids, which adds to the cost of the process and also imparts design and maintenance challenges at a large scale. In the case of Passive mixing strategies, the modification in the geometry is the only change done to impart turbulence during the flow. This is done by changing the flow direction or velocity variation during flow through variation in the dimension of the cross-section. A large number of reviews have been written summarizing the active and passive mixing techniques in detail. **Table 1.3** provides brief information about the principal mixing strategy involved in the various mixing intensification techniques applied to the microreactors.

Also, when it comes to the fabrication of complex geometries, techniques such as laminates, polymer molding, three-dimensional printing, and nanofabrication are employed. **Table 1.4** lists the important methods of fabrication for complex microchannel geometries. However, these fabrication techniques are very specific, useful for small scale fabrication, need complex steps, skillful hands, and are expensive to be used on large scale.

Table 1.3 Active and passive mixing techniques in micro-mixers

Passive mixing strategies
Lamination based geometries
- Artificial segmentation of flow to induce mixing through inertial effects through wedge shape inlets, T shape inlets or Y shape inlets.
Introduction of chaotic advection
- Enhancement of mixing in micromixer through splitting, recombining, rearranging the component flows via intersecting channels, introduction of barriers during flow, by using converging diverging channels, twisted channels, tesla structure etc.

Using high velocity jets
- Mixing by creating high velocity jets by reducing the nozzle diameter
Active mixing strategies
Pressure field driven
- Involves alternate perturbation using pulsatile flow micro-pump or using two micro-pumps to alternatively inject the liquid or using oscillatory perturbation
Electric field driven
- Introduction of electrodynamic instability using electrically charged fluids under the influence of alternating or direct current to disturb the fluid interface
Sound field driven
- Use of acoustic resonant disturbance
Magnetic field driven
- Application of magneto hydrodynamics and magnetic stirring on magneto fluid which can induce secondary flows for stirring and mixing
Thermal field driven
- Use of thermal bubble for mixing

Table 1.4 Micromixer fabrication techniques

Laminates
- Bonding of two or more layers to create pattern micro-channels
Polymer moulding
- Soft lithography, injection moulding and hot embossing
Three-dimensional printing
- Three-dimensional printing using 3D printer
Nano fabrication
- Using electron beam lithography and extreme ultraviolet lithography

In all, the designs of developed micro-mixers are complex and involve various strategies for efficient mixing however, involved fabrication techniques are very specific and not economically viable when required at a large scale. Also, some of these micro-reactors do not have the advantages of scale-up by dimension enlarging due to diminishing mixing indexes

with an increase in dimension and a large number of units are required when going for throughput enhancement.

1.2.3 Integration of multiple synthesis steps in flow including inline separation

A vast body of literature is available on a single step and two-step flow synthesis.[42-46] However, implementation of continuous work-up or separation is essential to extend the approach to a truly multi-step flow synthesis. Preparation of medicinal drugs involves several synthesis steps and between two reaction steps, the workup involves many unit operations *viz.* phase separation, evaporation, extraction, crystallization and purification, etc.[47-49]

Integration of multiple steps in sequence involves optimization of each step separately and then matching the time scale of separation steps in between to produce the synthesis route where end to end synthesis can be achieved. The main objective here is to either convert a one-pot synthesis method to a continuous flow synthesis method where a lesser number of reagents are employed during synthesis (thus yielding fewer in between separation steps) or use of catalysts, extreme process conditions, or selective reagents to yield target molecules with few byproducts that require further purification.

Recently, a multi-step flow synthesis approach has been implemented to access moderately complex molecules with diverse architectures such as natural products and APIs[50-53]. Notably, Jamison's quinolone antibiotic ciprofloxacin[54], a single dedicated platform for the multiple drug molecules[55] independently developed by Kobayashi[56] and Hessel[57], solid-supported synthesis of Imatinib[58] by Steven Ley, and end-to-end process for Aliskiren hemifumarate[49] stand out as significant milestones in the area of multistep-flow synthesis.

The integration of inline analysis has made real-time monitoring possible and provided precise control over the process and product quality. Also, the recent advancements in the development of intelligent synthesis platforms by inline analysis and development of smart

algorithms for instant data interpretations have resulted in the synthesis machines or synthesis platforms with minimal human intervention. Additionally, the introduction of camera-assisted synthesis has reduced the need for continuous monitoring by its ability to control the parameters from a remote area and thus enabling uninterrupted synthesis. This is particularly beneficial in the case of toxic and hazardous chemicals. Fitzpatrick and Ley have reported a successful integration of the batch and flow experiments on a single platform with an automated system for the synthesis of 5-methyl-4-propylthiophene-2-carboxylic acid[59]. They also incorporated automated downstream processing and solvent switching steps, thus freeing more time for chemists from routine laboratory tasks. A sophisticated approach that involves reaction automation, inline analysis, and feedback systems to drive the reaction systems to continuously generate new insights about the reaction has also been reported[60]. A continuous sequence for the synthesis of benzoxazole building blocks involving flow synthesis set-up, getting the heat profile of the reactors, and then finally combining the batch reactor, semi-batch reactors, and flow reactors to get the desired product is reported in a systematic manner[61]. Continuous manufacturing of drug prexasertib monolactate monohydrate on 24 kg scale involving 8-unit operations has also been reported[62]. Furthermore, the effect of recycling in the reactor and the crystallizer on the enhancement of yield and selectivity using dynamic simulations and optimization in an end-to-end continuous pharma manufacturing have also been studied[63].

Although these developments towards machine learning and artificial intelligence-driven synthesis look very promising, they come with very specific challenges. The need to match the time scale of separation and synthesis while modifying the synthesis steps at enhanced processing conditions can be particularly difficult since it may not result in a specific molecule or activity. More discussion about the challenges associated with the implementation and integration of multiple steps can be found in *chapter 9*. Also, implementing inline analysis

to every reaction environment is not easy and it applies only to a small number of molecules with very specific techniques. Further, the development of smart algorithms for reaction optimization and data analysis is very time-consuming (available only for a specific class of chemistries) and requires specific skills. Though literature reports the early implementation of data-driven independent platforms based on inline analysis and algorithms for self-optimizations, the incorporation of an experienced chemist or a chemical engineer in decision making process is quite challenging (*chapter 9*).

1.2.4 Development of chemistries at pilot scale

Processes are designed and developed for the manufacturing products at large scale through continuous flow micro-reaction technology. Though it is advantageous owing to its smaller dimensions, much of its benefits gets hampered due to changes in pressure drop, throughput and capital expenses when moved to a larger scale. However, it's the job of the chemist and chemical engineer to reproduce the advantages obtained in laboratory when translating any process from laboratory to plant environment without hampering the yield and selectivity.

The number of reports on commercial scale flow synthesis constitutes of less than 1% of the total number of publications on flow synthesis. In reality, the situation is changing, as in recent times a large number of industries have begun practicing flow synthesis at pilot and commercial scale. It becomes evident from the total number of large-scale flow reactors that are sold by various manufacturers (viz. Corning Inc.[64], Chemtrix LLC.[65], Kobelco Ltd.[66], Ehrfeld Mikrotechnik BTS.[67], Amar Equipments[68], Himile Microrectors[69], AM Technologies[70], etc.), otherwise which would not have sustained based solely on the laboratory scale flow synthesis devices.

Continuous process developed at the laboratory scale can be scaled up in number of ways:

Operating the laboratory setup for longer duration

Numbering up (scale out): Operating number of similar setups in parallel to multiply the throughput

Scale up: Increasing the channel dimension to acceptable limit without compromising on the critical properties

Operating the laboratory setup for longer duration is not feasible except in few cases where desired volumes are sufficiently low in required time frame depending on the reactor size, residence time and throughput. In case of numbering up, all the advantages of laboratory developed flow processes remain intact, but multiplying the complete setup to achieve some acceptable volumes of production will require many pumps and reactors which will increase the cost exponentially. Also, there are issues associated with the equal distribution of flow in all the parallel channels.

Among the very early reports of using a microreactor for commercial scale production, Mehrabi and co-workers have shown a reconfigurable system for adopting the varying manufacturing demands[71]. However, the reactor used is a horizontal flow reactor with capillaries at different levels. This approach would not work for reaction mass of lower viscosity due to the influence of gravity on distribution. May et al. have reported a continuous process for the 1H-4-substituted imidazole intermediate in two different approaches that use optimization and scale-up rapidly in plug flow reactor (PFR) and automated sampling, process analytical technology and inline separation for screening the best possible route for synthesis and scale-up, respectively[72]. Fitzpatrick et al. developed a software called Leylab for remote reaction monitoring and have demonstrated it for reaction optimization[73]. Laue et al.[26]

performed the lithiation reaction of fluoro-aromatics in the microreactor under non-isothermal conditions while achieving a controlled precipitation.

Scale-up through numbering-up works exceptionally well for ultrafast reactions[74]. However, throughput limitations and complexities of flow distribution are major challenges that need case-by-case scrutiny before design. For example, Iwasaki et. al. have demonstrated scale-up via numbering-up method for radical polymerization using micro-flow system for producing methyl methacrylate up to 2.5 kg of the product per week[75]. In another case, five parallel monolithic microreactors are used for synthesis of an intermediate of valsartan, a therapeutic agent for hypertension and diabetes[76]. Similar approach has been used for numbering-up of gas-liquid photocatalytic reactions[77]. As another example, it was shown that the productivity can be increased by parallelizing up to 32 visible light-mediated organic photocatalytic reactions in microfluidic reactors based on luminescent solar concentrators[78]. Very recently, Jang et. al. demonstrated ~4 g/hr of drug production. Their system comprises of a total of 10 photoreaction capillary reactors connected by 3D distribution modules needing a total residence time of 2.2 minutes from synthesis to product separation[79]. A similar approach has been demonstrated using an integrating flow distributor and a copper catalytic module for high productivity of 'Rufinamide'[80].

All these reports in the published literature are some of the many examples which are actually implemented in the industry. However, this brings out a very important question on deciding the viability of a "process for commercial scale" based on the "laboratory scale optimization" of multistep flow synthesis. In general, these two aspects are important yet unconnected, hence it is necessary to understand the reasons on how the former can help the latter, which is the ultimate reason for all the efforts put in for process development. In all, the reported scale-up approaches which involve integration of multiple steps and integration of separation and inline analysis involve thorough investigation of various parameters of the

process. Once each step or sequence of operation is optimized and integrated, they can run continuously as there is no scope for any significant change to be incorporated at the large scale. Usually, scale-up approach is very specific to the chemistry under consideration. General scale-up procedure depends on the available know-how, physicochemical properties of the chemicals/materials involved, specific chemistry and the experience of individuals involved in the exercise. Using artificial intelligence (AI) in incorporating automation in developing methodology and devising the algorithms with decision making ability will help to predict the scalability. There is a possibility of variations that can happen beyond the laboratory scale experiments when one uses them directly for scale-up. Efforts in development of self-optimization platforms will reduce the time and efforts which are necessary, but they also need to be coupled with reliable and predictive scalability.

1.3 Motivation

Over the years Continuous flow chemistry (Flow synthesis, Flow technology) has seen surge in implementation in the academia and industry for synthesis and process research (**Figure 1.5**). The growth potential for flow chemistry in India is more than 5% compared to the world for reactors and application (**Figure 1.4**). This presents the opportunities in terms of increase in the market share if more accessible and easy solutions are available in terms of research in process chemistries, flow reactors and other associated devices.

CAGR% by Reactor

	World	India
CSTR	7.3	11.3
Plug flow	8.6	13.2
Microreactor	21.0	25.2
Microwave systems	13.3	17.3
others	11.0	14.6

CAGR% by Application

	World	India
Pharmaceuticals	10.8	16.6
Chemicals	10.4	14.8
Academia & Research	8.8	9.6
Petrochemicals	9.9	12.7
Others	7.5	7.9

Figure 1.4 % CAGR comparison India and world

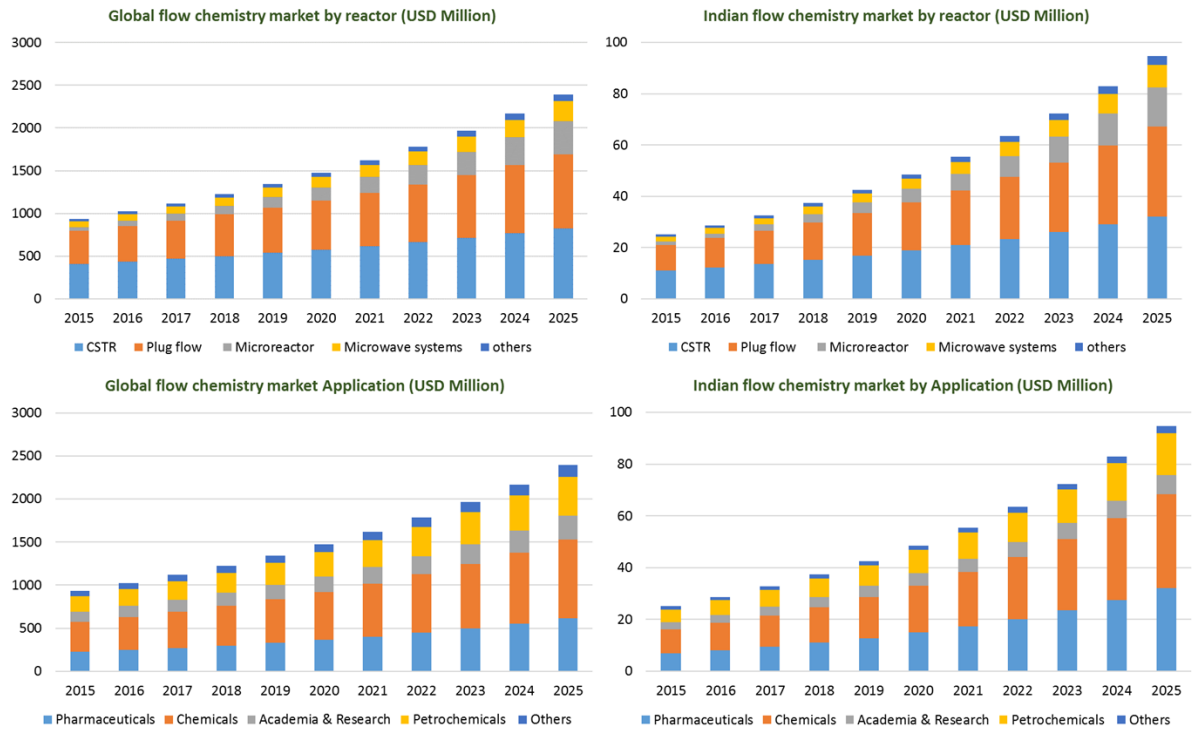


Figure 1.5 Market segmentation of continuous flow technology by reactor and application

The main focus of the research happening in the field of flow micro-reaction technology is towards development of sustainable manufacturing either by enhancing the transport properties (design and development of efficient micro-mixers and mixing strategies), reducing the labor required during synthesis, screening, isolation, analysis (process integration with inline analysis and separation and development automated synthesis platform) and reducing the limitations of scale in safe manner (scale-up by dimension enlarging or numbering up).

Researches happening in parallel in core areas has resulted in a variety of micromixer designs, many new synthesis methodologies using flow reactor with new processing conditions and with new reagents, automated machinery for doing reactions in flow at lab scale and development of pilot plant for the product at larger scale. Although it is envisaged that flow micro reaction technology is the future of chemical synthesis and processing, anything and everything should not be converted in flow[81]. Though there is huge literature on the various

types of microreactors/flow reactors/ *(chapter 2, 3*), micro-mixers, /continuous flow devices and micro separation devices the fabrication techniques are still complex, expensive and not suitable for conventional scale-up. To design the simple yet efficient flow reactor with simple fabrication technique pinched tube flow reactor is presented in *chapter 2*. Through the design of pinched tube reactor it is shown that a simple modification in the normal tube is sufficient to get enhanced mixing via continuous velocity variation over the length of the reactor.

Challenges associated with solid handling is yet to be solved completely (*chapter 3*) as over 65% of the exothermic liquid-phase reactions have solids as products or byproducts., though some very specific solutions are presented in the literature methods employed generally utilize mechanical stirring in a flow environment. The mechanical stirring is not viable for the large-scale production since the mechanical parts wear and tear at prolong use. Along these lines we propose a novel reactor concept for handling solid suspensions in flow, which can be categorized as passive process intensification equipment. The proposed reactor does not contain any moving parts and uses kinetic energy and the geometry to make solids remain suspended during flow. The novel cavity design can be easily extended to large scele for high throughput operations.

Most of the developed flow synthesis procedures are just the transformation of batch chemistries to continuous flow, which lacks the relevant discussion on the scale-up/numbering-up related challenges in flow. Developed devices working efficiently at the laboratory environment are not feasible to enhance the throughput by multiplying the number of such units due to cost associated with them (*chapter 5*). Also, when going for numbering up, the efficient distributor which can distribute flow evenly is still missing. In order to utilize in house designed pinched tube reactor, scale-up of di-nitration reaction of done in pinched tube reactor and approach is presented for safe scale-up through smart dimensioning and parametric similarity approach. It is well understood that numbering up is a viable option up to certain

scale and critical economic analysis is also presented for different scenarios for the utilization of numbering up approach using a nitration reaction.

For known molecules the use of continuous flow process integration with chemical synthesis steps using harsh reagents or novel process windows can reduce number of steps involved significantly thereby reducing the economics of the overall process completely. This could be beneficial for the expensive pharmaceutical drugs where costs are high. Also, distributed manufacturing using continuous flow can provide the solution to the shortage of supply by making the small plant which can be supplied to the point of need. The enclosed and continuous nature makes synthesis and handling of molecules safe and in controlled manner. Though, benefits are more matching the timescale of the multiple steps involve various parameters to be controlled (residence time, temperature, time for heating cooling, reactor volume etc.). To harness the benefits of flow process integration two important drugs Edaravone and Ivacaftor was synthesized and presented (*Chapter 6,7*). Also, the implementation of advanced algorithms for determination of kinetics and reaction screening are at the primary development stage where though development of algorithms are still a challenge and time consuming (*chapter 8*). When it comes to scale up, strategies followed are still reaction specific.

1.4 Objectives

In the view of the above-mentioned challenges the main objectives of present work are as follows:

- Design novel and scalable reactors with easy fabrication techniques for exothermic liquid phase reactions
- Design new flow reactors for handling solids in flow which does not contain any moving parts

- Scale up of exothermic aromatic nitration reaction using flow reactors at the scale of 50 kg/day
- Development of an end-to-end multistep continuous flow procedures for synthesis of various drug molecules
- Understanding the challenges associated with development of self-optimization techniques and design of unified flow synthesis platform in the direction of Synthesis 4.0.

1.5 Organization of the thesis

The present thesis is divided in 4 parts covering the area of reactor design, scale-up, integrated multistep flow synthesis and understanding the challenges involved in designing the unified platform for flow synthesis in alignment with the aforesaid objectives.

Novel pinched tube reactor was designed, which can be fabricated easily and made into any shape and inserted into jacket for performing exothermic reactions in flow. ***Chapter 2*** provides the details about the hydrodynamics and performance analysis of the pinched tube reactor.

Chapter 3 gives the ides about another reactor for handling solid suspension in flow. The reactor used in this work does not contain any moving part and flow is gravity-aided. The uniquely designed cavities help in the mixing and does not allow solids to settle in the geometry. Details about the geometry optimization with hydrodynamics study and reactor suitability for various solids are presented in this chapter.

Performing nitration reaction at large scale is very challenging which required very tight process control. Though being regularly done in industry in batch reactor, handling nitration mixture at tonnes scale is very hazardous and possesses many safety challenges. However, the benefits of continuous flow chemistry seem to be very promising to be applied

to nitration and can be scaled up to large scale in a safe manner. One such nitration reaction to synthesize selective herbicide pendimethalin is presented in the ***Chapter 4.*** This chapter gives the details of reaction optimization, kinetic analysis, plant design and operation for the production capacity of 50kg/day.

In ***chapter 5*** we have shown the sustainability analysis of implementation of numbering up strategy for development of nitration reaction.

Synthesis of the drug Edaravone is presented in chapter 7 along the same lines as of ***chapter 6*** where microwave is utilized for flow synthesis.

Chapter 7 focuses on the development of multistep flow synthesis benchtop setup for the drug ivacaftor used in the treatment of cystic fibrosis. The reaction protocol involving quadrupole reaction and inline analysis was developed. The developed benchtop setup was able to produce enough drug amount to treat 50 patients/day.

Chapter 8 and 9 present the challenges associated in developing the unified platform for flow synthesis and the implementation of self-optimization related to the scope of scale-up

Chapter 10 gives the overall summary of the presented research work

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Novel flow reactor designs

National Chemical Laboratory (Pune) - INDIA

Chapter 2

Novel Pinched tube reactor for flow synthesis

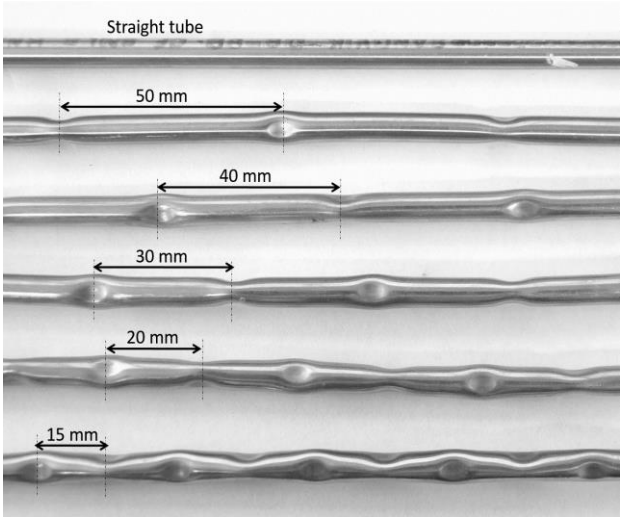
This chapter is based on:

Sharma, M. K., Potdar, S. B. and Kulkarni, A. A.,

Pinched tube flow reactor: Hydrodynamics and suitability for exothermic multiphase reactions,

AIChE journal, (2017), 63, 358-365.

https://doi.org/10.1002/aic.15498



A novel tubular flow reactor where a straight tube is modified by pinching it periodically at a fixed pitch and at different angles is presented in this chapter. Pinched tubes of 3 mm and 4.5 mm diameter with pinching at a pitch of 2.2 to 11 and at an angle of 90° between successive pinching are studied. This work reports a detailed hydrodynamic study involving single- and two-phase flow for pinched tube in the form of straight tube as well as helical coils of different sizes. The performance is compared with a normal straight tube of identical length.

2.1 Introduction

Development of compact continuous flow reactors is an important component of process intensification.[1,2] Having compact reactors helps to achieve decentralized/spot synthesis, smaller chemical foot print, enhanced safety and distributed production. Such reactors need to be efficient in terms of mixing, lower axial dispersion, better heat transfer and enhanced interfacial mass transfer. The nature of operation of these reactors depend upon the mode of energy supply, i.e. kinetic energy (spinning disk reactor, Holl tube in tube rotating reactor, Higee reactor, rotating packed bed contactor etc.), pressure energy and new forms of energy supply (viz. ultrasound[3], microwave, plasma, etc.). This chapter focuses on the second category of pressure energy driven systems, which includes excellent examples, oldest being the static mixers. One of the primary ways to achieve rapid mixing in such flow reactors is by using smaller dimensions and/or spatial variations in the cross-sectional area and/or spatial splitting and recombining the flow and/or imposing tortuous path to enhance chaotic advection or shear. Depending upon the system under consideration and the objective behind design, it is necessary to design a flow reactor that has one or many of the above features.

For example, the Corning's Advanced Flow Reactor[4] is an excellent example of a sequence of two-dimensional converging zones with an internal flow splitting and recombining mechanism and high heat transfer area that allows rapid mixing as well as generation of very fine fluid-fluid dispersion. On the other hand 3D flow reactor[5] comprises of a sequence of three dimensional converging units with or without flow splitting that further allows enhancement in the capacity with a marginal loss of heat transfer area and also a relatively lower pressure-drop due to pressure recovery mechanism. In an early example, Wilhite et al.[6] have demonstrated the use of a microfabricated supersonic converging nozzle for intensification of mixing for continuous generation of singlet oxygen. Their sequence of microscopic converging units included a pressure recovery system helped avoid generation of shock waves and choking

of nozzles. The orifice microreactor for a two-phase exothermic reaction showed that having orifices allows enhancing the throughput without a linear enhancement in pressure drop.[7] Su et al.[8] have demonstrated the use of a packed microchannel reactor for conducting a mixing limited exothermic reaction. The use of inert packing helps to create a tortuous path while handling very low liquid quantities, which helps to retain the heat generation rates in the desirable limits.

As mentioned earlier in *chapter 1* most of these reactors need specific fabrication methods viz. micromachining, lithography, glass embossing, etc. and it makes the accessibility limited to some extent. On the other hand, static mixers although can be inserted in straight tubes/pipes, that limits the overall geometrical configuration of the reactor.

In view of this, in this chapter we propose pinched tube reactor as an option that uses pinching of straight tubes in various ways and then the straight tubes/pipes can be given any form to fit in any space without getting limited by the change in the cross-sectional area at various locations. This reactor can also be used as high throughput flow reactor for process intensification to carry out fast and exothermic reaction, which will be presented in subsequent chapters. However, use of pinched tubes is not new in refrigeration or oil cooling in radiators where pinched tubes are inserted in straight tubes[9,10]. Thus, in variety of cases the flow takes place through the periodically changing cross-section of an annulus or in the partly-pinched capillary tubes.

2.2 Making a pinched tube

A normal straight tube of small diameters (viz. inner diameter, d = 1 to 5 mm) usually gives a parabolic velocity profile under laminar flow condition and the extent of dispersion increases with increasing tube length. This extent of dispersion can be reduced by breaking the nature of flow and making it undergo continuous spatial mixing. In order to achieve the same,

the tube was pinched periodically at a fixed pitch (P) in terms of the tube diameter **(equation 2.1)**. In the present study with d = 4.5 mm, the pitch (P) was varied between 2.2 to 11. The pinching was done using a motorized system that allowed to maintain specific pitch between two successive pinches. The angle of pinch was changed by changing the axis of pinching. To determine the optimal angle between successive pinching (θ) pinched tubes were made in glass with θ of 30°, 45° and 90°, respectively and flow visualization studies were done. Once a straight tube is pinched, it can be then oriented in any form to achieve a helical coil or a serpentine shape to reduce the overall space occupancy. In the present work, 15 different pinched tubes were made having 5 different P values (**table 2.1)** and with three geometries (helical coils of diameter 50, 100 mm and straight tube). Typical geometries of the pinched tube and pinched coil are shown in **figure 2.1.**

$$Pitch(P) = \frac{distance\ between\ successive\ pinches\ (mm)}{inner\ diameter\ of\ the\ tube\ (mm)} \quad \textbf{(2.1)}$$

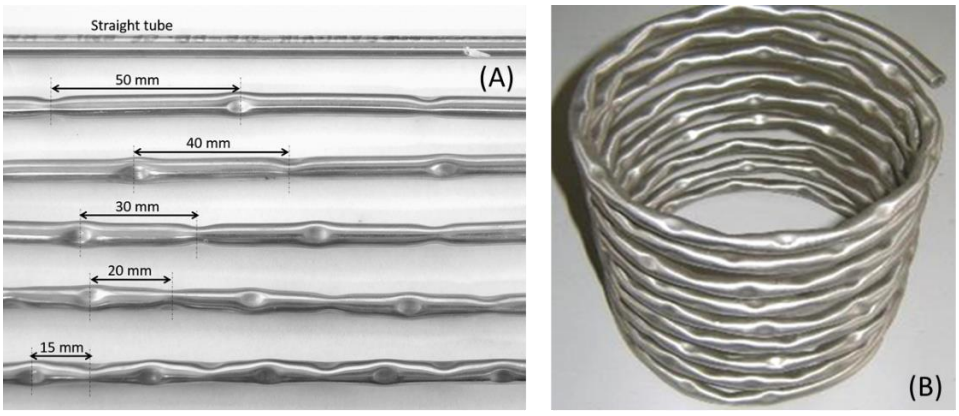


Figure 2.1 (A) Straight pinched tubes with varied pinching distance; (B) coil made from pinched tube

Table 2.1 Pinched tube parameters used in this study

	Unit	P = 2.2	P = 4.4	P = 6.6	P = 8.9	P = 11
Outer diameter (o.d.)	mm	6	6	6	6	6
Inner diameter (i.d.)	mm	4.5	4.5	4.5	4.5	4.5
Wall thickness	mm	1	1	1	1	1
No of pinch (*P*)	--	62	42	30	23	19
Length	m	1	1	1	1	1
Inlet Reynolds no	--	10-1060	10-1060	10-1060	10-1060	10-1060
Residence time	s	450-4.5	450-4.5	450-4.5	450-4.5	450-4.5

2.3 Result and Discussion (Experimental)

2.3.1 Experimental set-up

Pinched tube reactors were made using ¼" o.d. (*i.d.* = 4.5 mm) SS316 tubes of 1 m length each. The experiments were carried out by placing the straight tubes as well as the coil axis horizontally. Normal tap water was used for the single-phase experiments whereas for two phase experiments two immiscible liquid system water (ρ = 998.2 kg/m^3, μ = 0.001 Pa s) and kerosene (ρ = 786 kg/m^3, μ = 0.00162 Pa s) was used. The interfacial tension (σ) for this system is 0.05 kg/s^2. All the fluid properties are at 25°C. A Schematic of the experimental setup is shown in **figure 2.2**. During the experiments for measuring the hydrodynamic properties, liquids were pumped in the reactor through two peristaltic pumps at equal flow rates. Flow rates of both the fluids were varied over a range from 1 ml/min to 100 ml/min. For each experimental condition and for each parameter, the data was recorded at least 3 times and the average value was used for further calculations.

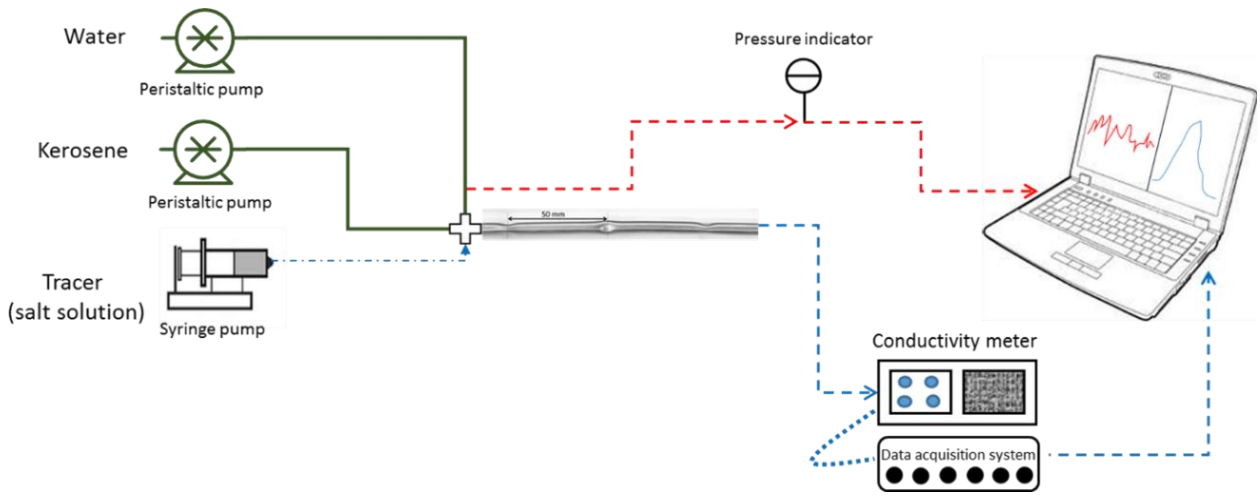


Figure 2.2 Experimental setup for hydrodynamic study

2.3.2 Mixing study

Mixing experiments were performed using a pinched tube flow reactor made in glass (*i.d.* = 3 mm) for determination of optimal angle of pinching before fabrication in SS316. Three different glass tubes with different angle of pinching (30°, 45°, and 90°) were used for the mixing characterization. Commercially available water soluble red and blue inks were used as colors for monitoring mixing. All the experiments were performed using aqueous solution of inks (10 ml ink dissolved in 400 ml water). Solutions were pumped with the help of a syringe pump at equal flow rates over a range of 10 ml/min to 60 ml/min. Images were recorded at pinched sections 1, 4 and 5 starting from the inlet with the help of a DSLR camera (Sony Corp.) and then analyzed to monitor the uniformity in color over the tube diameter (**figure 2.3A – 2.3D**).

Periodically varying cross-sectional area and also the flow direction at the pinch point result in a spatially periodically varying shear field along the tube length. This kind of a flow will also help in achieving rapid mixing of miscible fluids. In general, with increase in the inlet velocity by two times, for a fixed cross-sectional area at pinch point there is an enhancement in the axial velocity by 2.29 times. This observation was consistent over a wide range of flow rates. At the

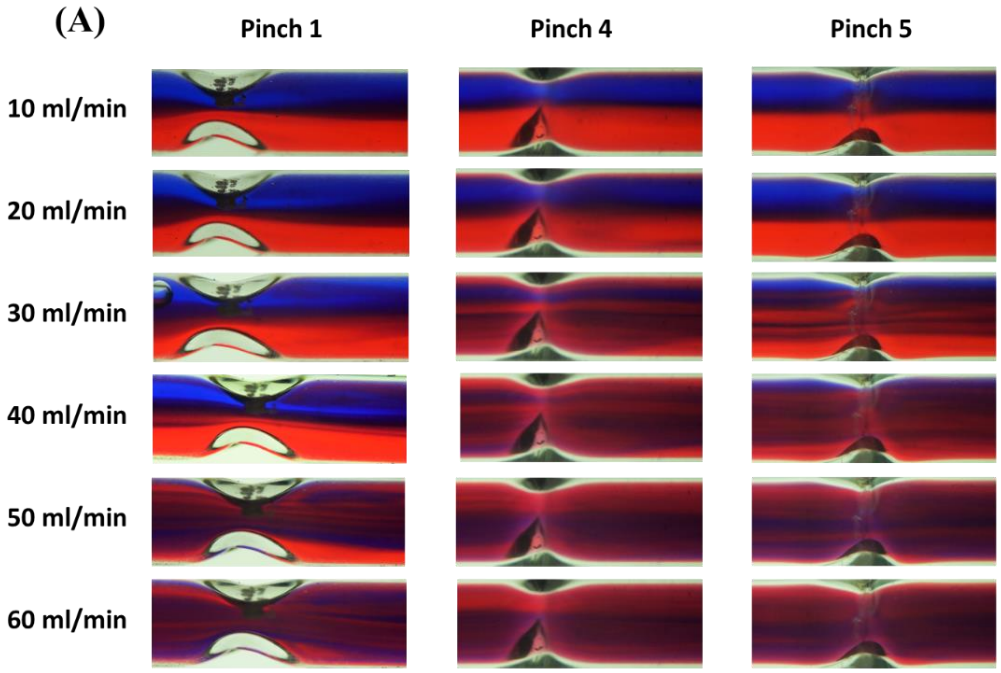


Figure 2.3A Variation in the nature of mixing along the length in a pinched tube flow reactor with 30° angles between successive pinches for a range of flow rates.

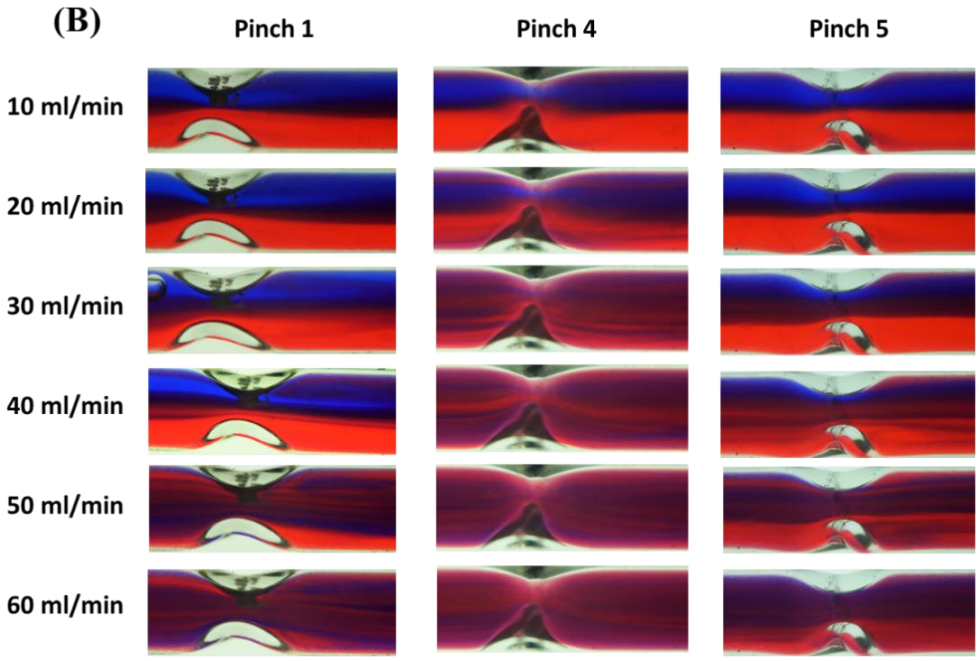


Figure 2.3B Variation in the nature of mixing along the length in a pinched tube flow reactor with 45° angle between successive pinches for a range of flow rates

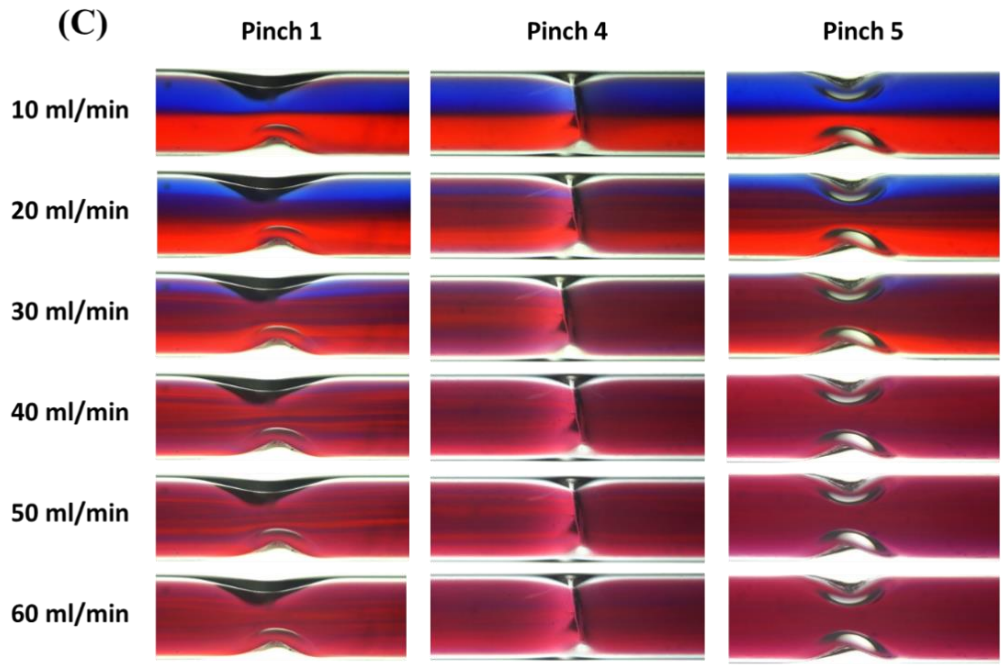


Figure 2.3C Variation in the nature of mixing along the length in a pinched tube flow reactor with 90° angle between successive pinches for a range of flow rates

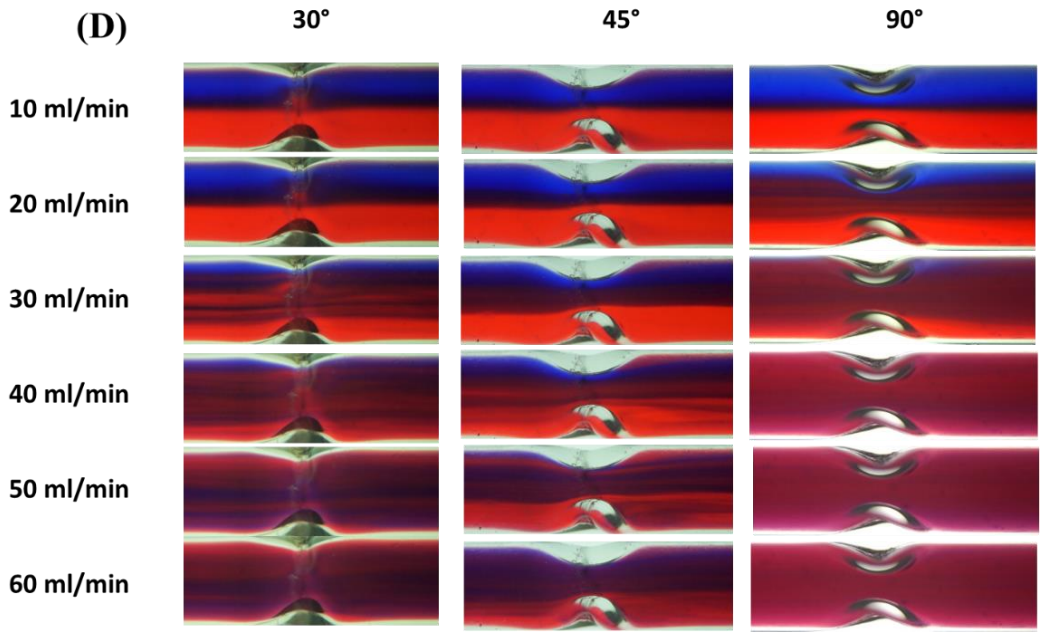


Figure 2.3D Effect of angle between successive pinches on mixing in a pinched tube flow reactor for a range of flow rates. Images are taken at the 5th pinch point from the inlet

pinch points the contribution of pressure energy would decrease and that of kinetic energy would increase. Thus, a sequence of pinched sections with alternate pinching in directions perpendicular to each other is expected to enhance mixing in the reactor much significantly than a normal tube. The effect of pinching angles on the extent of mixing was monitored and the observations are shown in **Figure 2.3A – 2.3D**.

The images indicate that although increasing the flow rates helps to achieve better mixing, an angle of 90° between successive pinching gives much shorter mixing length than angles of 30° and 45°. While the extent of shear at every pinch point is almost identical, the alternate perpendicular pinching forces the fluid streams to break away from relatively lesser variations in the change of direction and hence intensifies mixing when $\theta = 90°$. Mixing was monitored at different pinch points i.e. 1^{st}, 3^{rd} and 5^{th} pinch point from the inlet. For $\theta = 90°$, at lower flow rates (Q < 20 ml/min) the fluids flow almost in parallel for some length. With increasing flow rates, the striations of individual color were observed to get thinner, which with change of pinching plane almost diminished. These observations showed that it was possible to achieve very good mixing over a length less than 16 times the tube diameter without using any static mixers. The mixing length can be further decreased by at higher flow rates or for higher flow rates tubes of larger size can be used with similar pinching profile ($P < 3d$). Thus, short pinched tubes can be used for mixing of reactants or reagents before the reaction mixture enters in sections of reactor where only longer residence time is needed for a reaction to get completed. If the range of flow rates is below 20 ml/min, it is better to use pinched tubes of smaller diameter (*i.d.*< 3 mm). In view of the excellent mixing performance with $\theta = 90°$, for the rest of the study all experiments were performed using pinched tubes having successive pinches perpendicular to each other.

2.3.3 Pressure drop study

Pressure drop over the reactor length was measured for single-phase and two-phase flow using a digital manometer (HTC instruments, China) for the flow rate range of 2-200 ml/min. The data was recorded online and then subjected to statistical analysis.

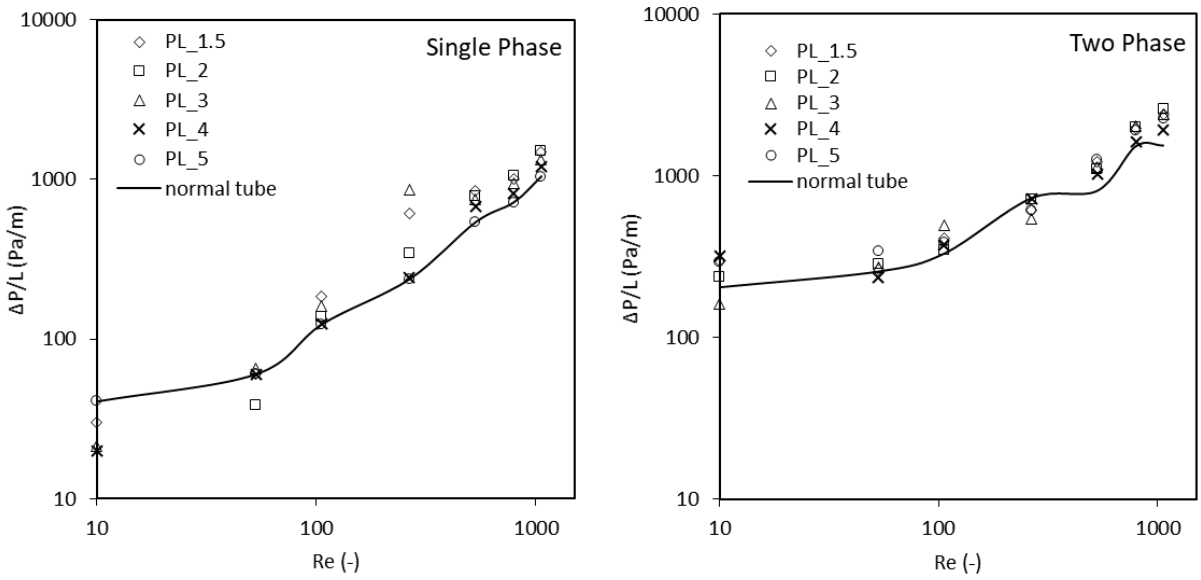


Figure 2.4 Single-phase and two-phase (open symbols) pressure drop for pinched tube (1/4" o.d.) in the coil form (coil diameter = 5 cm). Lines are for coil made from a normal tube.

The observations are shown in **Figure 2.4**. In general, there was a standard deviation of ±3.4% over the entire flow rate range. The values of ΔP for the pinched tube reactors of different pitch showed trends similar to the normal straight tube. For *Re* < 100, the normal tube showed higher ΔP as compared to pinched tubes and depending upon the pitch or number of pinches per unit length pressure drop increased. However, for *Re* > 100, despite having as number of pinch sections over a range from 20 to 66, the extent of rise in the pressure drop varied at the most by 1.4 to 3 times. As discussed in the previous section, each pinched section is comprised of a sequence of straight portion, a reducing section, an expanding section and again a straight section. The length of straight section changes depending upon the pitch while

the geometry of reducing and expanding sections was maintained identical in all the cases. This implies that every pinch section would behave similar to a venturi and there would be a finite pressure recovery after the pinched section. The estimated values of pressure recovery over a range of flow rates for different *P* values show that at higher flow rates loss coefficient reaches to that of normal venturi. The pressure drop data indicates that around *Re* ~ 100 there could be change of flow regime.

The pressure drop for two phase flow was significantly higher than the case of single-phase experiments and the pressure drop in coils was higher than in the straight tubes. Literature on the analysis of two-phase pressure drop in converging and diverging sections indicates that both, converging as well as diverging sections act differently in enhancing the pressure drop. The continuous shearing effects with change of pinch direction by 90° are expected to break the dispersed phase droplets continuously thereby generating fine dispersion. Generation of smaller droplets from inlet to outlet will lead to enhancement in the interfacial area and hence the frictional resistance between the two phases. This would enhance the pressure drop by as much as 2 times when compared to single phase flow. Upon estimating the pressure drop for two-phase flow using the Lokhart-Martinelli method, it was observed that the Chisholm parameter does not follow the values for standard straight tubes and in order to take care of the pressure recovery in pinched tubes, the values of *C* need to be given as a function of the two-phase *Re* as $C = 118.2\ Re^{(-0.66)}$. This observation was consistent even for small diameter pinched tube. Incidentally, the range of two-phase pressure drop for pinched tube varied over a narrow range even for various pitch values and hence the above value of *C* can be used independent of pitch.

2.3.4 Residence time distribution (RTD) study

Pulse input method was used for the measurement of residence time distribution for every pinched tube over the entire flow rate range. Tracer solution was prepared by dissolving 14 g common salt in 100 ml water and a pulse of 100 µl was given in 0.1 s using a syringe pump. The conductivity of the fluid at the outlet was recorded with the help of pre calibrated conductivity meter. The concentration vs. time data was subjected to further analysis to obtain an E-curve and then to quantify the dispersion.

The extent of dispersion in pinched tube reactor was estimated using the concentration in the form of conductivity data measured at the reactor outlet. Open-open boundary condition was used for analyzing the data and axial dispersion model was used for estimation of the dispersion coefficient. E curves for the pinched tube reactor with 50 mm and 15 mm pitch between successive pinch points are shown in **Figure 2.5A-B**. It can be observed that with a greater number of pinch sections the extent of dispersion decreases and the system behaves closer to a plug flow. The data is not strictly Gaussian and it show features of CSTRs in series with some dead volumes resulting in a longer tail. In order to quantify the extent of dispersion, vessel dispersion number was estimated for all the configurations over a range of flow rates (2 – 200 ml/min) and the observations are shown in **Figure 2.5C-D**.

The estimated values of D/uL were greater than 0.01, indicating large deviation from plug flow and a significant dispersion compared to the straight tube and coil of same diameter without pinch. These findings indicate that pinching the straight tube improves the mixing performance but also enhances the dispersion to some extent. Thus, these types of reactors are suitable for reactions that need rapid mixing or mass transfer but which do not have any sequential reactions.

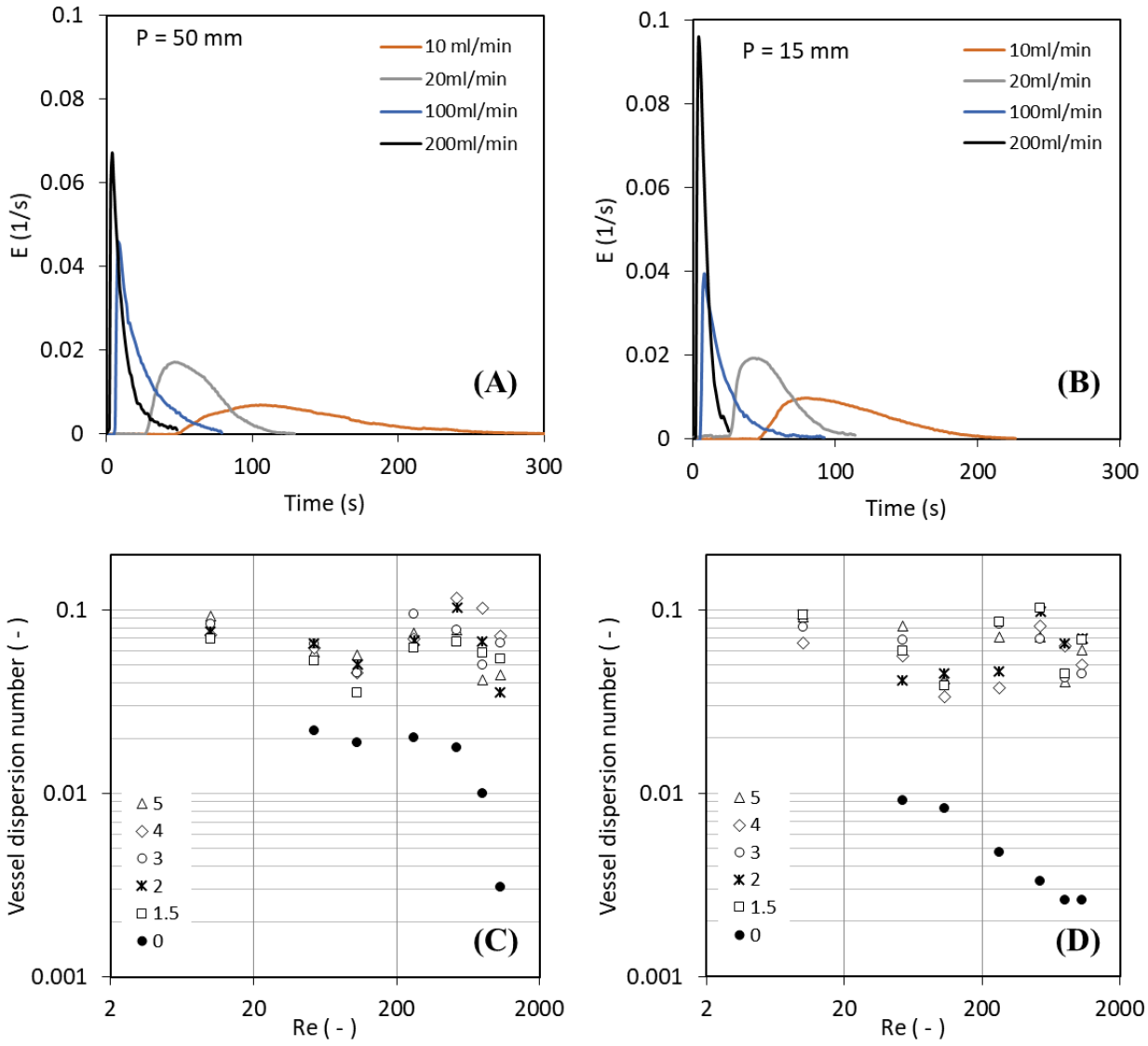


Figure 2.5 RTD analysis of pinched tubes (A-B) E-curves for pinched tube with 50 mm and 15 mm pitch between two successive pinch sections, (C-D) vessel dispersion number vs. Re for 1 m long straight tube and helical coil with and without pinch. Legends show the distance between pinching in pinched section

2.3.5 Mass transfer coefficient study

Kerosene-water-propionic acid system was chosen for the determination of overall mass transfer coefficient. Transfer of propionic acid from kerosene to water was monitored to determine the overall mass transfer coefficient ($K_L a$). Stock solution was prepared by dissolving 12 ml propionic acid in 1000 ml kerosene and this stock solution was used for every experiment. Both the liquids were pumped to the pinched tube using two peristaltic pumps at

equal flow rates (1-100 ml/min). At the outlet the solutions were allowed to get immediately separated in a separating funnel and conductivity of the aqueous phase was measured. For the determination of concentration in aqueous phase calibration chart was prepared by measuring the conductivity of water at different know concentrations of propionic acid in a separate experiment. Mass transfer coefficient was estimated as,

$$K_L a = (\frac{1}{t}) ln \frac{(C_{in} - C^*)}{(C_o - C^*)} \quad \textbf{(2.2)}$$

Where,

C_{in} , C_{out} and C^* are the concentration of propionic acid in water at the inlet, outlet and the equilibrium concentration respectively and t is the mean residence time. For determining equilibrium concentration, the equal amount of stock solution and water was kept for stirring for more than 8 hours for getting equilibrium transfer of propionic acid from kerosene to water. The determined value was used for each calculation.

The interfacial liquid-liquid mass transfer is an essential hydrodynamic parameter that is often chosen to identify the right design and operating condition for a two-phase flow synthesis. The $K_L\underline{a}$ values for different configurations of pinched tubes (pitch values, straight tube, coils of different coil diameters, etc.) when compared with that of the normal tube or helical coil it was observed that pinching has always helped in getting higher mass transfer rates (**figure 2.6**). In general, $K_L\underline{a}$ for helical coil with smaller radius of curvature was higher. At identical power consumption per unit volume (P_w), the values of $K_L\underline{a}$ due to pinching were higher by 8-9 times that of straight tube without pinching and can increase further at higher flow rates (**figure 2.7**). Enhancement in $k_L\underline{a}$ can be attributed to sequential reduction and enhancement in the cross-sectional area, which accelerates and decelerates the flow thereby improving mixing and contacting between the phases.

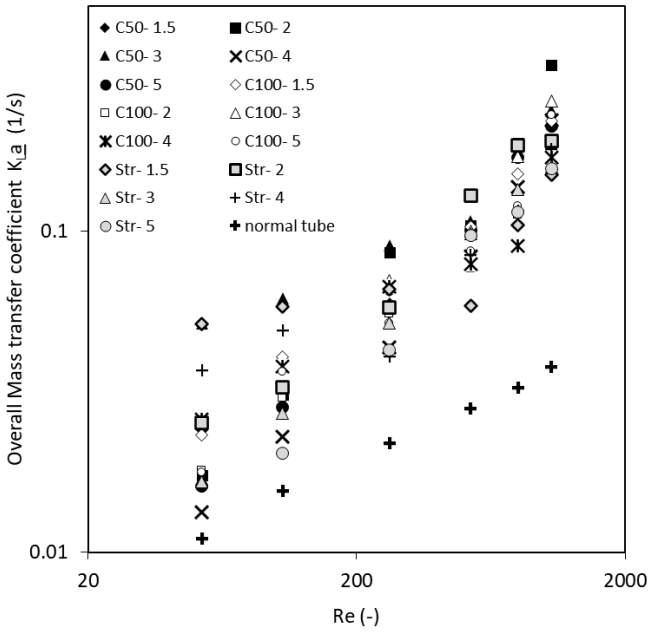


Figure 2.6 Overall mass transfer coefficient measured for straight pinched tube, pinched coil of 50 mm and 100 mm coil diameter and normal straight tube of 4.5 mm i.d.

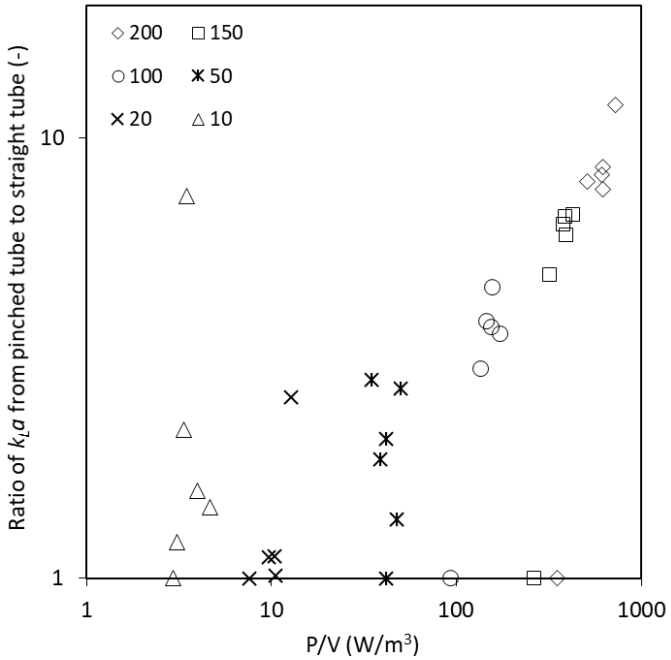


Figure 2.7 Ratio of mass transfer coefficient for pinch tube reactor of coil diameter 50 mm to non-pinched coil at different inlet flow rates

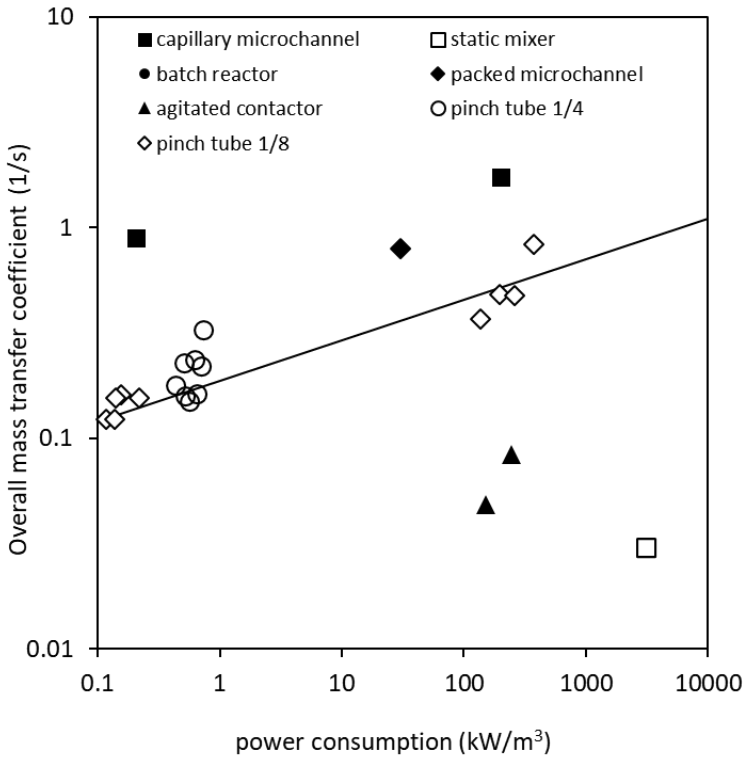


Figure 2.8 Comparison of overall mass transfer coefficient values for pinched tube and different flow reactors.

The secondary flow generated due to the coil shape also has a positive effect. The mass transfer coefficient obtained in the pinch tube reactor is comparable to the different microreactor devices available in the literature **(figure 2.8)**. It was observed from the analysis of pinched tube reactors of 2.5 mm and 4.5 mm diameters that the values of $K_L\underline{a}$ follow a power law behavior with P_w and can be given as $\text{Log}(K_L\underline{a}) = 0.186\ [(\log (P_w)]^{0.192}$ with an error of less than ±7.2%. Thus, a simple geometry made out of commonly available tubes yield an excellent flow reactor with simpler fabrication.

2.3.6 Case study for performance evaluation of pinched tube reactor

On the basis of hydrodynamic study and the RTD studies, which recommends the use of pinched tubes for reactions that need rapid mixing or mass transfer but which do not have very fast sequential reactions, here we have chosen a single phase and a two-phase aromatic

nitration reaction, where the activation energy for secondary nitration is higher than the mono-nitration. Highly exothermic homogeneous nitration of Bromobenzene (ΔH = -86.94 kJ/mol) with mixed acid and nitration of benzaldehyde (ΔH = - 172 kJ/mol) with fuming nitric acid was chosen for performance evaluation of pinched tube reactor and compared with normal tube of same volume and diameter.

2.3.6.1 Bromobenzene nitration

Usually nitration of Bromobenzene in batch mode is done by adding Bromobenzene in solution of pre cooled mixed acid over a period of 2 hour. Once addition is complete temperature is raised to 60-80°C with precise temperature control to avoid di-nitration reaction. After the reaction is complete whole content of batch is dumped into ice to recover the solid product which is mixture of *p*- and *o*-nitrobromobenzene. Previous knowledge for the same reaction done in our lab helped in deciding the operation condition for continuous flow nitration. Solution of Bromobenzene in acetic acid (1:5 v/v) was prepared by adding Bromobenzene to acetic acid with stirring in ice bath. Mixed acid solution (40:60 v/v nitric acid to sulfuric acid) was prepared using concentrated nitric acid (69%) and sulfuric acid (98%). After the solution preparation was done, solutions were loaded in two different syringes and were pumped into the reactor from a tee mixer connected at the inlet section of the helical coil reactor made from normal tubing as well as pinched tube. The volume of tee mixer was less than 0.2% of the reactor volume. Reactions were done at 80°C and for residence time of 600 s. Product at the outlet was quenched in 50gm of ice and extracted with 30 ml toluene in three parts (15 ml, 10 ml, 5 ml). Extracted produce was washed two times with water and bicarbonate solution to remove traces of acid and later dried over sodium sulfate. The samples were analyzed using gas chromatograph (GC). The conversions at the outlet of helical coil

made out of normal tube and pinched tube (P = 4.4) were 76% and 92.7%, respectively. The isomer ratio of mono-nitro derivatives was identical.

2.3.6.2 Benzaldehyde nitration

Nitration of benzaldehyde with fuming nitric acid was chosen to evaluate the performance of pinched tube reactor. Two syringe pumps were used to pump benzaldehyde and fuming nitric acid through Tee mixer connected at the inlet of the reactor. Helical coil was immersed in a circulating water bath maintained at 40°C. Reactions were carried out at three different residence times i.e. 450, 90 and 45 s. At each residence time value, experiments were carried out at two different values of the mole ratio of nitric acid to benzaldehyde, i.e. 1.24:1 and 7:1, respectively. At lower concentration of nitric acid, the reaction will be limited by the kinetics while for the second condition it is expected to remain limited by interfacial mass transfer. The experiments were repeated for helical coils of 50 mm diameter made out of pinched tube and normal tubes, both having inner diameter of 4.5 mm. The samples of fixed volume were collected at the reactor outlet and sample preparation process as explained earlier was followed. Samples were analyzed on GC to measure the conversion and selectivity. The results are shown in **figure 2.9**. At identical set of conditions pinched coil always showed higher conversion compared to that of normal coil without pinching. In all the cases, the isomer mole ratio (i.e. *m*-Nitrobenzaldehdye to *o*-Nitrobenzaldehdye) was almost same (2.9:1 to 3.1:1). Both of these stoichiometric conditions would bring different volumetric flow rates and hence different flow regimes. Using pinched tube always helps to achieve a better liquid-liquid dispersion as compared to a segmented flow that is expected in a normal tube. This specific feature helps to achieve better conversion and hence higher yield of the desired isomer when using a pinched tube.

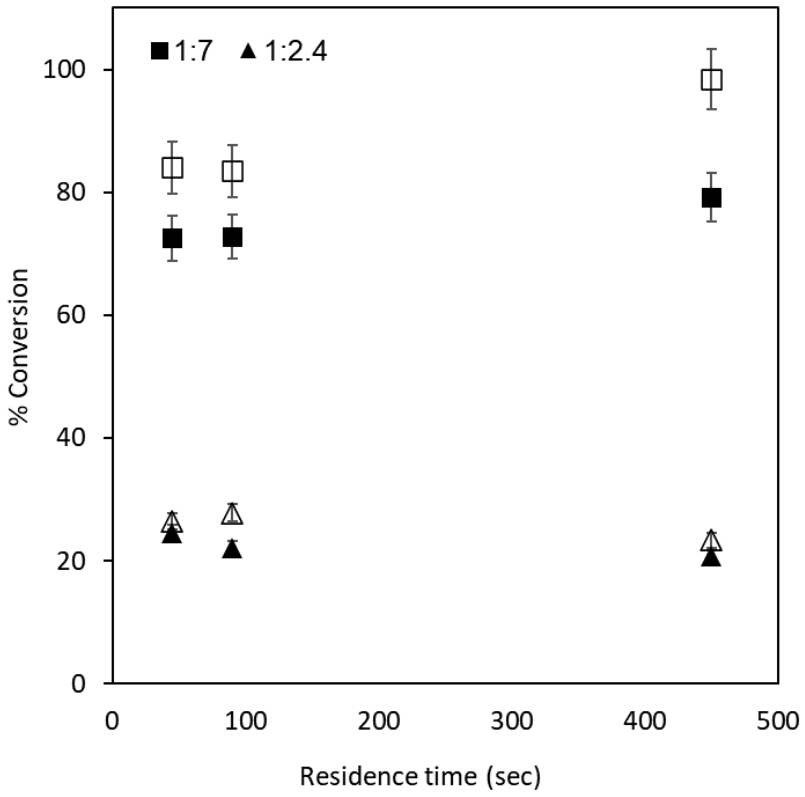


Figure 2.9 Comparison of performance of helical coil reactors made out pinched tube (□) and normal tube without pinching (■) at different residence times and concentrations of nitric acid

2.3.7 Liquid-Liquid extraction

As the pinched tube flow reactor shows relatively higher mass transfer coefficient values, it can also be used for liquid-liquid extraction, which is one of the most common separation steps in flow synthesis. In order to verify the usefulness of pinched tube for L-L extraction, a model system comprising of toluene, n-butanol and water was chosen for the liquid extraction experiments.[11] 18% (w/w) stock solution of n-butanol in toluene was prepared and used for the liquid extraction experiments. Distilled water was used for extraction of n-butanol from toluene. Experiments were done at 4 different flow rates (10, 50, 100 and 200 ml/min) where stock solution and water were pumped at equal flow rate. A pinched tube flow reactor made from SS316 tube (6.32 mm outer diameter and 4.5 mm inner diameter) with pitch of 50 mm between successive pinches for pinching and $\theta = 90°$ was used for the experiments.

Experiments were conducted at different flow rates. The flow rates of phases were maintained identical. Samples were collected at the outlet of the reactor and the toluene phase was analyzed after layer separation for quantifying the amount of n-butanol remaining in toluene. The balance would get extracted in water. Analysis of organic phase was done using gas chromatography (GC) with bromobenzene as internal standard. Equilibrium concentration of n-butanol in toluene was determined by stirring the equal volume of stock solution and water for 2 hours. The observations are shown in **figure 2.10**.

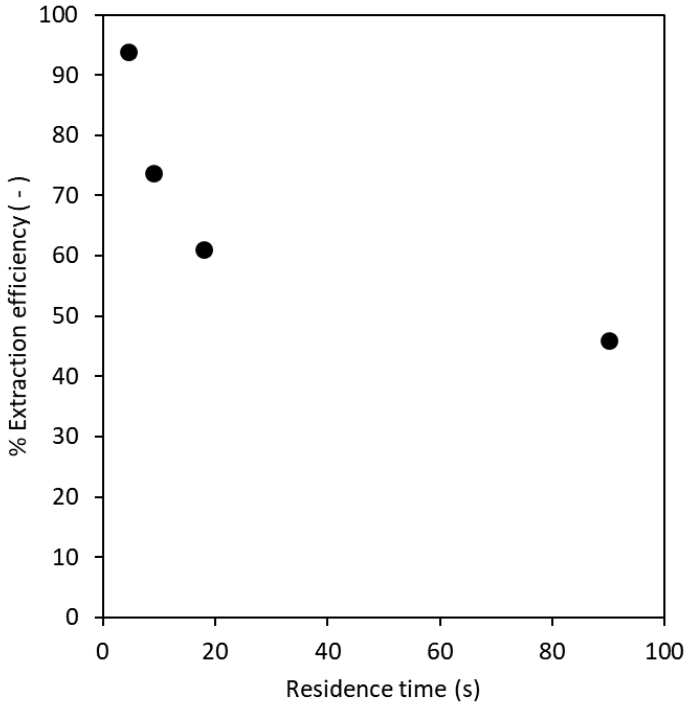


Figure 2.10 Variation in the extraction efficiency of a pinched tube flow reactor (length = 1 m, volume = 12 ml) as a function of residence time.

Increasing the flow rate increase the extraction of n-Butanol from toluene to water. This can be attributed to the high shear rate at pinch points, which would result in very high interfacial area for mass transfer. Importantly, the extraction efficiency continued to increase when the residence time was less than 5 s. This implies that the interfacial area generated in the dispersion as well as the enhancement in true mass transfer coefficient due to high shear

was sufficient to overcome the limitation of small residence time. Result indicates that pinched tube flow reactor can be successfully utilized for liquid-liquid extraction.

Pinched tube reactor is a novel way of using a tubular reactor with better mixing. The concept has been developed and implemented in a few large-scale manufacturing processes for production to the tune of few hundred kg/day. Details of these processes and designs cannot be revealed due to confidentiality.

2.4 Result and discussion (Numerical study of Pinched helical coil tube)

Also, in the present work, the two helical coils i.e. one with pinching (Pinched helical coil tube) and one with no pinching (Helical coil tube), are studied numerically for the Dean flow at different values of the *De*. The geometries used for simulating the helical coil, pinched tube helical coil and a photograph of the pinched tube helical coil are shown in **Figure 2.11**. The results obtained were compared to show the presence of dominant Dean Vortices at high *De* for the same flow parameters in the pinched helical tube. While at lower *De*, due to high dissipation, there is no such difference is observed between pinched helical coil tube and helical coil tube.

Figure 2.11 Geometry used in the model (A) simple helical coil geometry, (B) pinched tube helical coil geometry and (C) photograph of pinched helical coil tube

2.4.1 CFD methodology

The effect of pinching of helical coil is studied by Computational Fluid Dynamics using ANSYS [version 17] and using Fluent to solve the governing equations. Hence the methodology implemented here is dictated by the software itself. The physics involved in the study is relatively simple and hence single-phase steady state approach is used for the analysis. The analysis is done only for fluid flow and hence the equations that are being solved are continuity equation and Navier-Stokes momentum equation. Simulations were carried out for six different flow rates spanning over laminar as well as turbulent flow regime. Appropriate model is used in the respective simulation which solves its corresponding equations. Equations of motion and continuity for single phase flow are not mentioned here for the sake of brevity. For simulations, water (density = 1000 kg/m^3 and dynamic viscosity = 0.001 Pa.s) is used as a working fluid. For the laminar regime, laminar viscosity model that solves Navier-Stokes equation using molecular viscosity. For the turbulent regime, standard k-ε model is used. The selection of the turbulent regimes is governed by the computational power requirement and the physics involved, as the standard k-ε model solves Reynolds Averaged Navier-Stokes equation that comprises of turbulent viscosity using only two additional equations and hence it is very economical and suitable for the simplicity of the problem poised as a simply the flow through pipe. To aid this turbulent model for near-wall effect, the mesh near the wall is made fine by adding the inflation layers and also supported by using Standard wall function available in Fluent which resolves the boundary layer flow to take into account the wall-effect. The other parameters regarding the selection of solver algorithm and discretisation methods that has been used in the present work are detailed in subsequent sections where they are more appropriate.

2.4.2 Model geometry and Meshing

The tube diameter is 4 mm and the radius of the curvature of the helical coil is 38.1mm. In order to have the sharp curvature to have the dominant effect, the pitch of the helix is kept low which is 7mm and the height is 8mm which is enough to have the one complete rotation of the helical coil. As mentioned earlier, the pitch and angle of rotation for the pinches is chosen based on the experimental study. Workbench platform provided by ANSYS Inc. is used for geometry creation and meshing. The mesh of the pinched helical coil has 2786130 tetrahedral elements while mesh for the helical coil geometry has 5533374 hexahedral elements. As mentioned earlier, to resolve mesh in the near wall regions, inflation layers (six in numbers) with first layer thickness of 0.05 mm and growth rate of 1.05 are provided to the pinched helical coil tube.

2.4.3 Solution method

The simulations were carried out using Fluent (ANSY Inc.) for six different flow rates. The values of flow rates and corresponding Reynolds number (*Re*) and Dean Number(*De*) are tabulated in **Table 2.2**.To ensure the given amount of the fluid enters the domain, Velocity-inlet is used as inlet boundary condition ensuring the fluid entering perpendicular to the inlet, Pressure-outlet is used as the outlet boundary condition, which ensures the uniform pressure over entire cross-section of the outlet boundary. The value at this boundary is specified by giving the value of gauge pressure (i.e. 0 Pa) relative to the operating condition (~ 1 bar). Hence the value of pressure drop across the domain is obtained by measuring the pressure over the inlet boundary. The boundary condition for the wall used is a Stationary wall with no-slip condition, which is more realistic to represent the actual tube wall.

Table 2.2 Flow rates used for simulations

Q (ml/min)	V (m/s)	*Re* (-)	*De* (-)
10	0.01327	57	13
20	0.02654	115	26
50	0.06635	288	66
100	0.1327	577	132
200	0.2654	1154	264
500	0.6635	2886	661

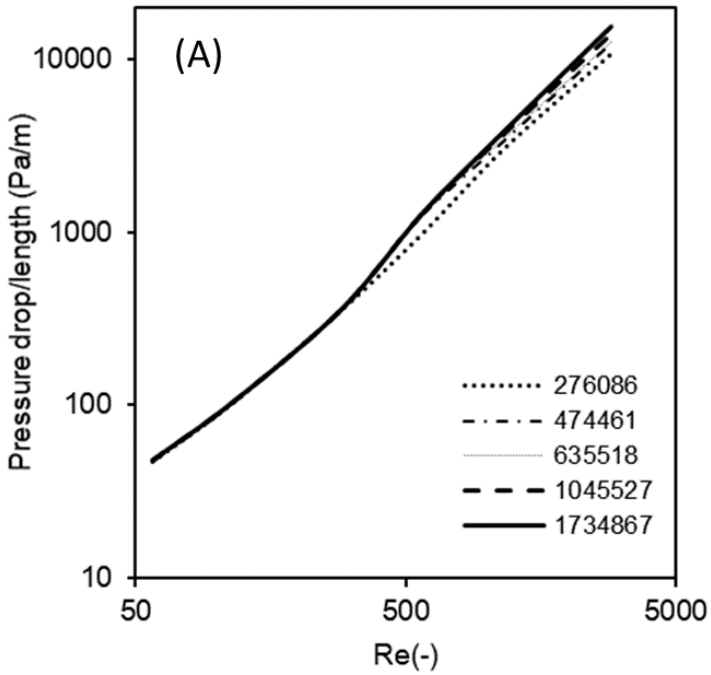
As mentioned earlier, laminar viscosity model is used where values of *Re* below the critical value. Though the curvature of the tube increases the critical *Re*, the flow in the entry of the tube is still developing and hence to account for this turbulence, standard k-ε model with standard wall function is used for coiled tube where flow rate is high. Pressure based segregated solver is used along with SIMPLE algorithm to couple the pressure and velocity term due to simplicity of the numerical problem and cost-effectiveness of the solver for computational resources. Solution is performed in steady-state mode using cell-based formulation for gradients and the Discretisation schemes used are second order for pressure and second order upwind for momentum equation which are higher order methods which provide reliable results. The turbulent quantities are discretised using first order upwind method which provide reasonable accuracy.

2.4.4 Model validation

In order to validate the model, first the grid independence study is performed on the pinched tube with five different cell counts and then the values of pressure drop per unit length of the tube obtained experimentally for the pinched tube by Sharma et al. are compared with the simulation results. The mesh refinement was done for 5 different cases and the number of

elements in each case are given as follows: 276086, 474461, 635518, 1045527 and 1734867. The results in terms of pressure drop per unit length are shown in **Figure 2.12A**. The variation in the values beyond 635518 mesh elements is very less even for higher flow rates and hence for all further simulations mesh with size with 635518 elements was used. For validation of the model approach, experimental results obtained for water as fluid using identical coil dimensions (4.5mm and pitch of 15 mm) were compared with the numerical simulations over a range of flow rates mentioned in **Table 2.1**. The values of pressure drop are obtained and the comparison is shown in **Figure 2.12B**. There is some deviation in the low Re range, however beyond Re > 100, the predictions match reasonably well with the experimental data. Slight overprediction was also observed at higher flow rates, however this does not mean that the velocity flow field would be significantly different. Based on these comparisons, the above model was used for all further simulations.

The effect of Dean Number variation on the formation of Dean Vortices is analysed by plotting the vector and contour plots on the planes along the length of the tube at angular positions at every 90^0 intervals starting from inlet to the outlet (**Figure 2.13**).



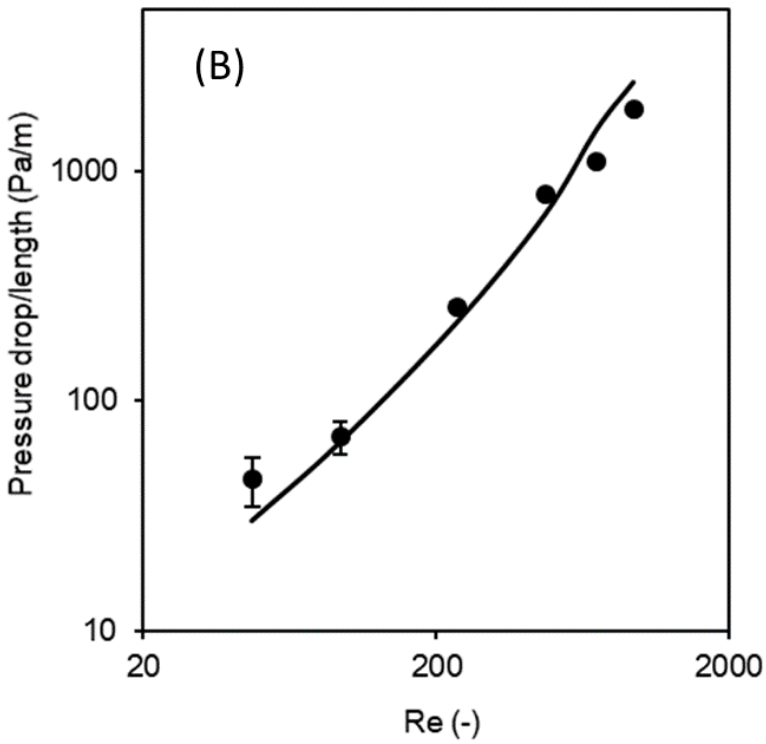


Figure 2.12 (A) Variation in the pressure drop over the coil length for a different grid sizes and (B) Comparison of simulated pressure drop per unit length with the experimental data.

The normalised non-dimensional velocity profile and local average velocity is also plotted along the diameter of those planes for the pinched helical coil and helical coil to understand the effect of pinching.

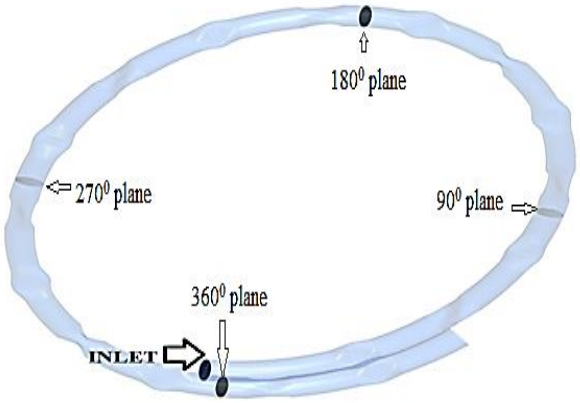


Figure 2.13 Location of planes for monitoring the flow pattern along the tube length

2.4.5 Effect of variation of Dean Number

2.4.5.1 Change in the inlet velocity

Increasing the flow rate facilitated increasing *De*, which helps in increasing the magnitude of centrifugal force. This would result in an imbalance between the forces thereby making the fluid elements tend to move swiftly in the core section while movement is slow along the wall. It is known that inducing a tangential flow results in generation of re-circulating vortices over the cross-section of the pinched tube helical coil. When compared with the normal helical coil tube, the vortices are stronger in case of pinched helical coil tube because of increased velocity. The velocity vector plots and contour plots at different flow rates are shown in **Figure 2.14**, which clearly indicates presence of Dean Vortices for the flow rate of 500 ml/min for helical coil tube and pinched helical coil tube at plane located at 90° from inlet. The maximum velocity for pinched helical coil tube is 1.036 m/s (**Figure 2.14**) while for the normal helical coil tube, the value is 0.925 m/s (**Figure 2.15**) and hence the value of centrifugal force is more in case of pinched helical coil tube. At low flow rate i.e. at 10 ml/min, the magnitude of centrifugal force is very less and hence the formation of re-circulation vortices is not observed which is shown in the **Figure 2.14A**.

Velocity contours plots for these different geometries show that the pinched helical tube gives a slight bimodal velocity profile over the cross-section. **Figure 2.16** depicts the variation of normalised non-dimensional velocity profile plotted along the diameter of the tube with respect to flow rate on the plane drawn at 90° from the inlet. Also, similar profiles were obtained in all the planes for respective flow rates. Here the normalisation of the local velocity magnitude is done by the dividing it by the average inlet velocity. At high flow rates, the velocity profile is skewed towards the outer wall of the tube due to unidirectional swirl exerted by torsion is superimposed on two-vortex flow.

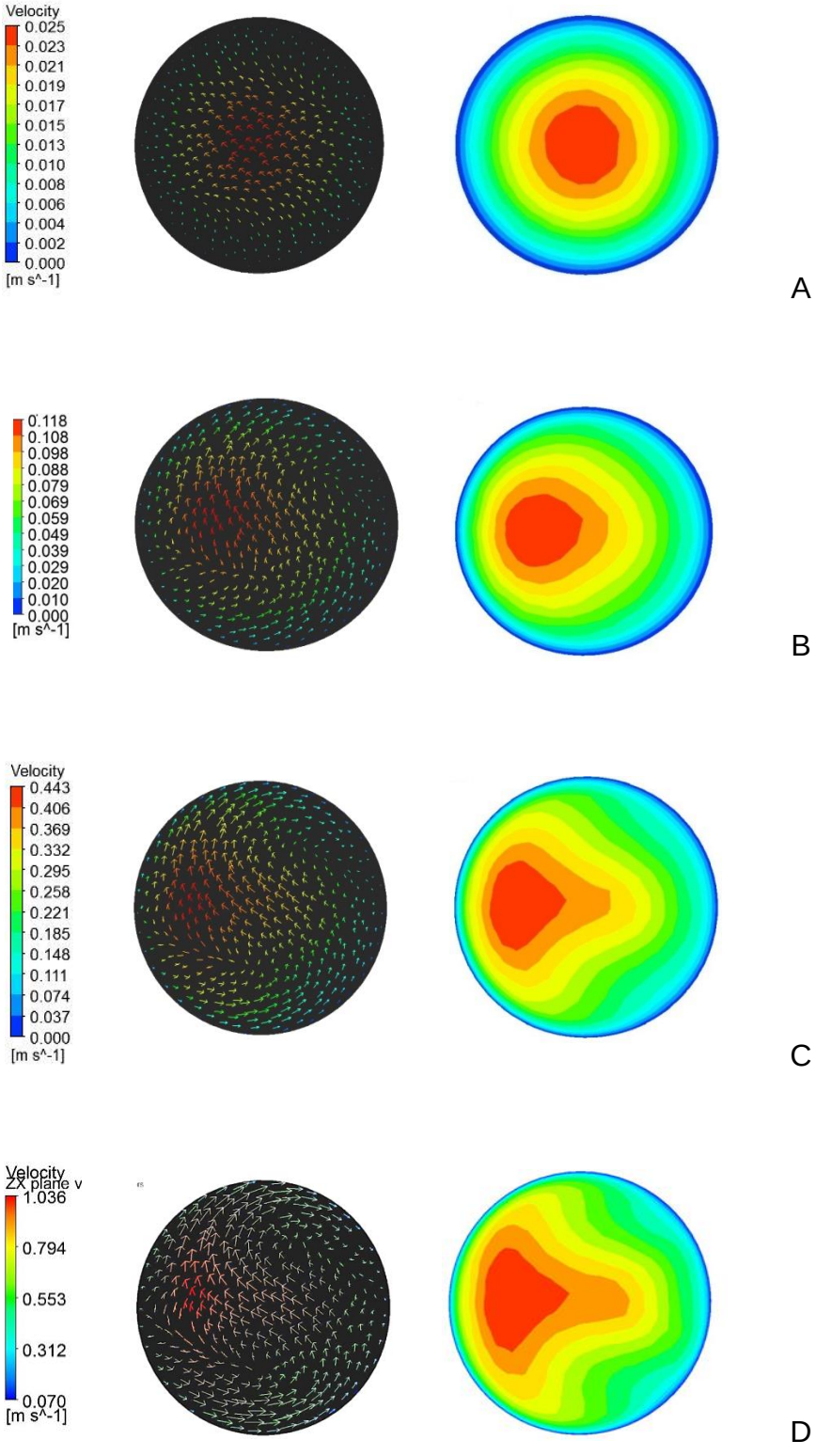


Figure 2.14 Vector and contour plots for pinched helical coil tube at different inlet flow rates (A) 10 ml/min, (B) 50 ml/min, (C) 200 ml/min, and (D) 500 ml/min

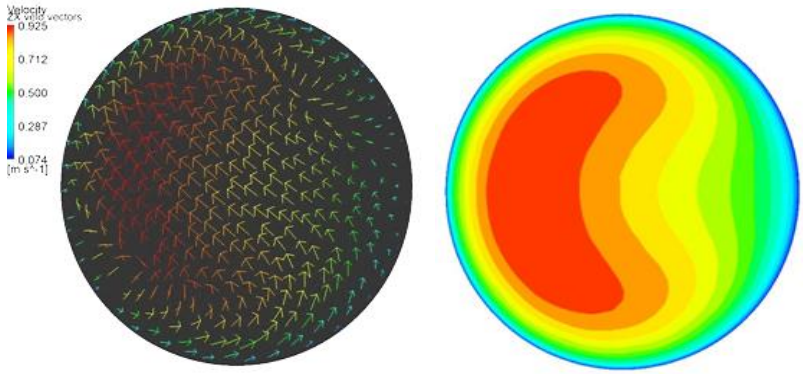


Figure 2.15 Velocity vector plot and velocity contour plots at 500 ml/min in a helical coil tube

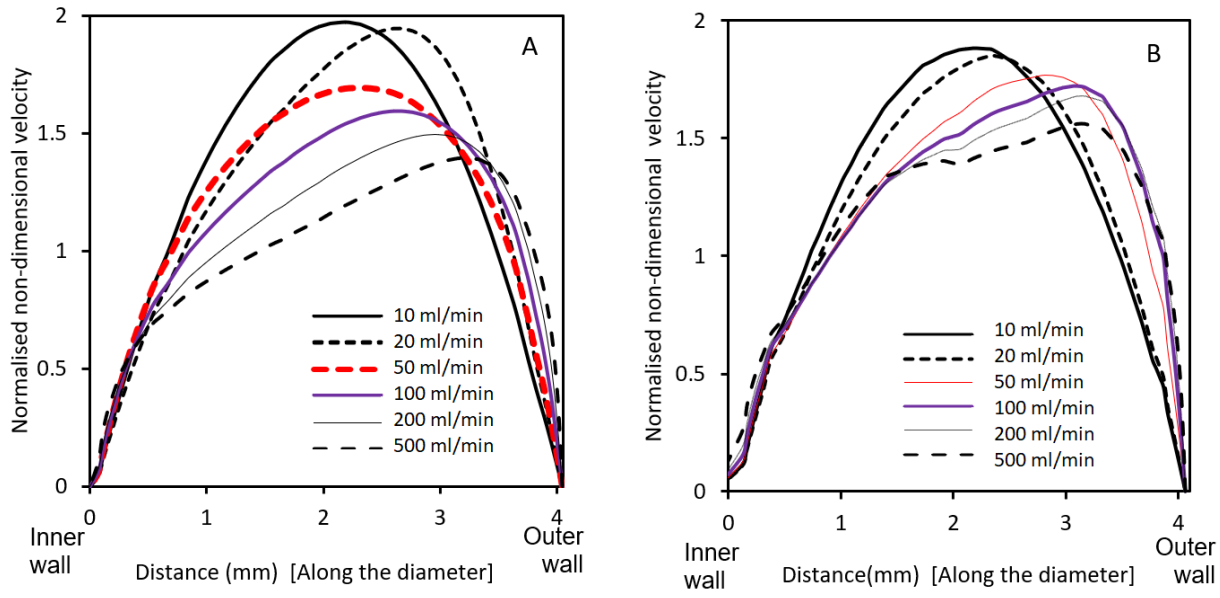


Figure 2.16 Effect of flow rate on velocity profile for (A) helical coil, (B) pinched helical coil

With decreasing flow rates, the skewness of the velocity profile reduces and at the 10 ml/min flow rate, the velocity profile is exactly parabolic in shape. These observations indicate that the on-set of Dean Vortices, which is characterised by requirement of minimum values of Dean number (De > 70) is similar for normal helical coil as well as for the pinched helical coil.

This also implies that synergistic effects of pinching of tubes and curvature resulted in higher values of velocity magnitude can be seen only at higher flow rates. This observation is important in terms of deciding the inlet flow rates while using pinched helical coils. **Figure 2.17** shows the difference in velocity profiles for inlet flow rates of 500 ml/min and for 10 ml/min. Effects of curvature of tubes becomes evident beyond 20 ml/min inlet flow rate, where for both the cases, profiles get skewed. For normal helical tube, due to normalizing, the effect got amplified compared to pinched helical tube.

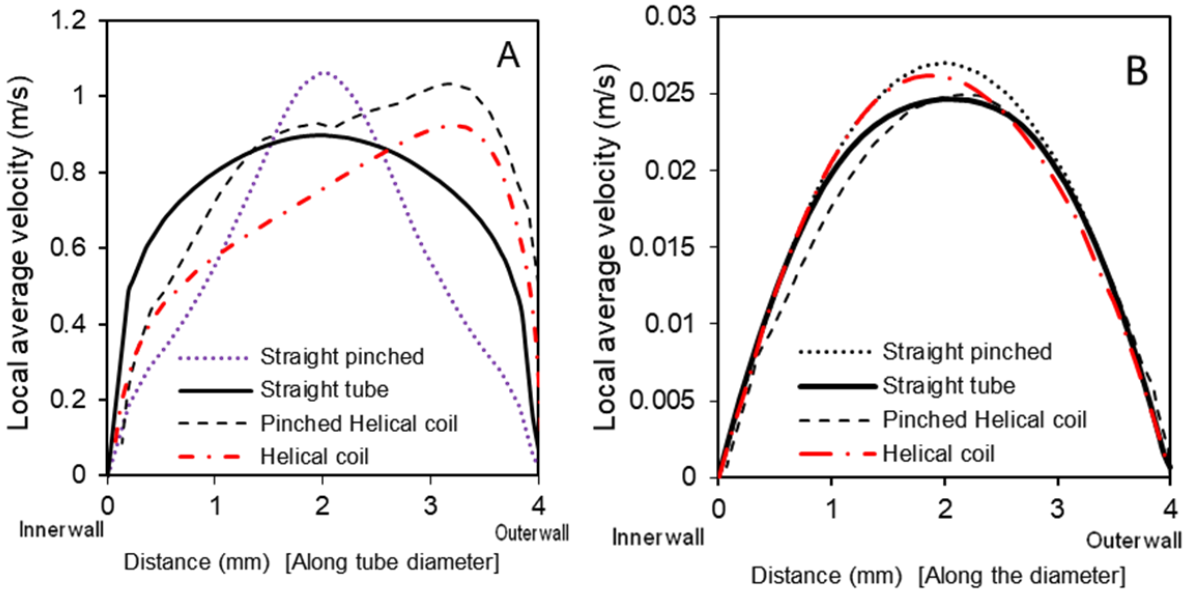


Figure 2.17 Velocity profile at different flow rates (A) 500 ml/min and (B) 10 ml/min

2.4.5.2 Change in the coil diameter

The nature of secondary flow in a coil can also get altered by changing the radius of curvature. At a given *Re*, the change in the value of R_C has an inverse square root effect on *De*. This implies that since usually, the $R_C > D_h$, increase in the radius of curvature will always reduce the De and thus would reduce the extent of secondary flow and thus the tube diameter becomes the limiting value for the radius of curvature. The simulations of pinched tube coils of different radius of curvature (Figure 8, RC = 76.2 mm, 50.8 mm and 25.4 mm) showed a

few very strong centrifugal motions for smaller radii of curvature which also lead to formation of two counter-rotating vortices. The corresponding values of Dean number for these three different radii of curvature are 661.26 to 809.87 and 1145.3 respectively. The location of the maximum velocity was also seen to change significantly with change in the radius of curvature. Smaller radii also offer very strong velocity gradients over the tube cross-section, which would help achieve better mixing. These observations in **Figure 2.18** are different than the normal helical coils where only two counter rotating vortices are seen with decreasing radius of curvature.

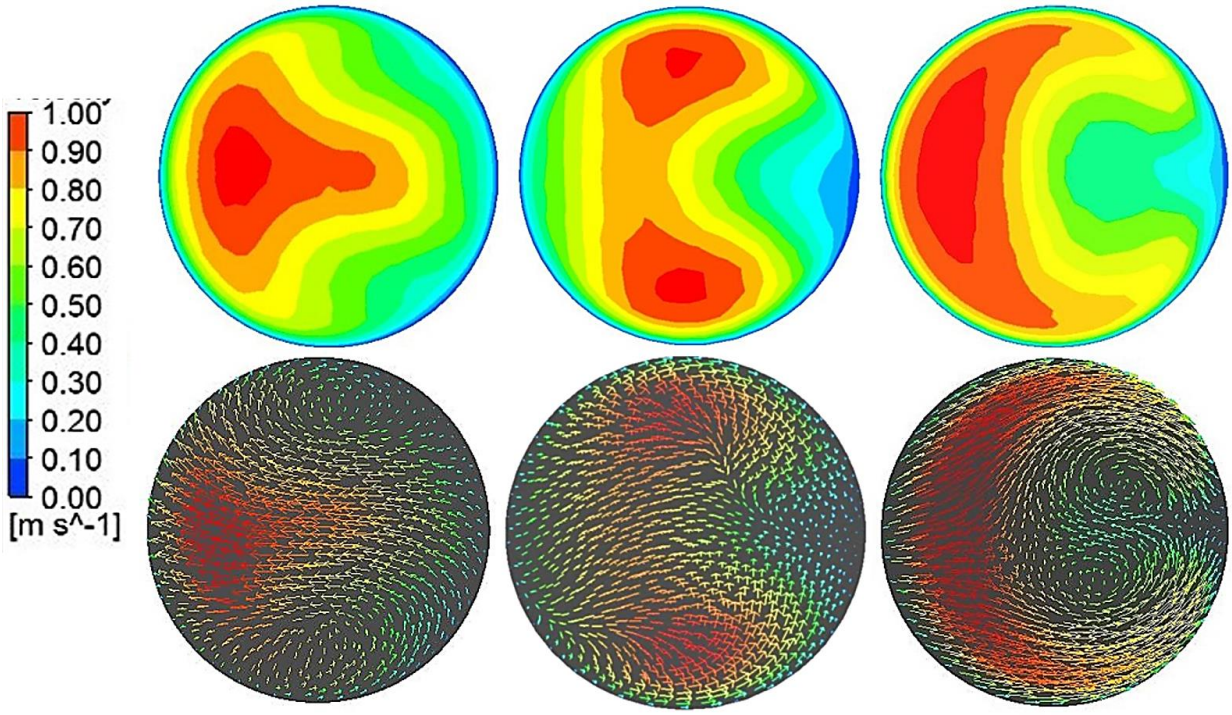


Figure 2.18 Effect of radius of curvature on the flow pattern in pinched tube helical coils for a flow rate of 500 ml/min. Top row: Velocity contour plots, Bottom row: Velocity vector plots, (Left) R_C = 76.2 mm, (Middle) R_C = 50.8 mm, (Right) R_C = 25.4 mm. Tube diameter = 4 mm.

2.4.6 Comparison of the local velocity profile

To study the effect of the pinching on the helical coil, the velocity profile of local average velocity along the diameter is plotted for two different flow rates. As it was observed in **Figure 2.16**, at higher flow rates, the velocity magnitude is high for pinched helical coil as

compared to normal helical coil, while at low flow rates the helical coil shows slightly higher maximum velocity than other forms of coils and straight tubes. The maximum velocity along the diameter of plane for pinched helical coil tube was 1.036 m/s while for normal helical coil tube, it was 0.926 m/s, an overall enhancement of 11.87%. This increase of velocity magnitude is due to variation in cross-section of the tube in the pinched part. A slight dip or presence of double-peak in the velocity profile of the pinched helical coil is due to vortex formation caused by centrifugal force with an effect of pinching. While in case of pinched helical coil tube, because of pinching in alternating directions, the flow changes its direction as it passes through pinched sections get disturbed continuously and hence crescent-like shape is obtained in velocity profiles even after 45° from inlet.

2.4.7 Effect of the location of the plane on velocity magnitude

The plot of local average magnitude along the diameter for different planes along the length of tube is also obtained to get an idea about the variation present along the tube length. It is clearly evident that the velocity profile exactly matches along the diameter of the coil in both the cases. The same results are obtained for all the flow rates in both tube and also the Dean vortices show the similar behaviour with respect to location of plane. Thus, for a fully developed flow, the location along the coil length has no effect on the velocity profile and ultimately on the vortices.

2.4.8 Shear rate variation

The shear rate profile which is the gradient of axial velocity component along the diameter is plotted to get more insight into the difference in the flow due to pinching under helical form of coil. **Figure 2.19** shows the shear rate variation obtained for pinched helical

coil tube, helical coil tube and normal tube obtained for 500 ml/min inlet flow rate (zoomed) to capture the variation in the region slightly away from the wall.

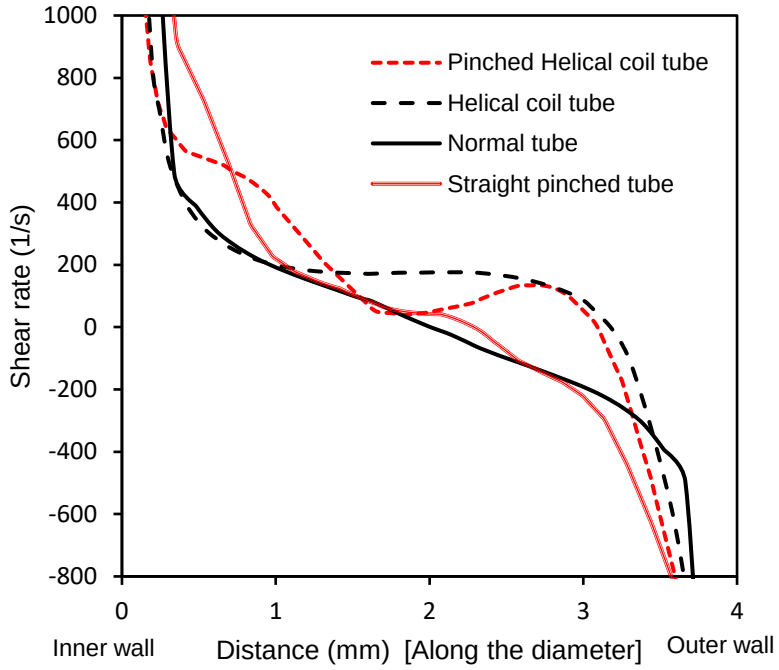


Figure 2.19 Variation of shear rate

The profile for the straight tube is symmetric about the centre with gradual variation in both of its sides indicating smooth transition from zero velocity at the wall to maximum at the centre while in case of helical coil tube, the profile is asymmetric and there is large gradient present near the outer wall region indicating the shift of maximum velocity towards that wall. The shear rate profile for the pinched helical coil tube also shows the crescent-like shape similar to that of velocity profile. Also, the value of shear rate over the tube diameter for pinched helical coil is more than the helical coil in the region close to inner wall while near the outer wall. The nature of shear rate profile also suggests the presence of two vortices in the region, which would intensify mixing.

2.4.9 Pressure drop analysis

While the variation in the flow field and in shear rates would give finer aspects of velocity in the coils, pressure-drop per unit length will help get a quantitative comparison of the volumetric energy dissipation in the tubes. The simulations showed that on an average pressure drop is higher in case of pinched tube due to increased resistance to the flow due to continuous change in the cross-section of the tube, which requires more pumping power for a given flow rate. Although after the pinch section, there is a pressure recovery to some extent. Immediate entry in another pinch section in a different plane (at 90°) does not allow pressure to be recovered completely, which actually, facilitates mixing. The quantitative comparison shows that the pinched helical coil shows 95% and 166% higher pressure drop than the helical coil for 10 ml/min and 500 ml/min, flow rates, respectively. The data is given in the Supporting Information. This further implies that at higher flow rates pressure drop would increase almost exponentially. Analysis of data showed that the pressure drop in a pinch tube can be predicted as a correction to the pressure drop for a helical coil. The presence of dominating vortices that arise out of pinching in addition to the asymmetry in the flow induced by helicity of the coil result in higher pressure drop. Correlation for pinched tube helical tube is obtained by plotting the ratio of simulated pressure drop per unit length of pinched helical coil tube (ΔP_P) to that of the pressure drop per unit length helical coil tube (ΔP_H) with *Re*. The correction factor [$\alpha = (\Delta P_P)/(\Delta P_H)$] can be then used for multiplying with the pressure drop values obtained using the correlation by White et al. as:

$$\Delta P_P = \alpha * \Delta P_H \tag{2.3}$$

where, $\alpha = \left(0.24[\ln(Re)] + 1.022\right) * [Re]^{0.188}$ and (2.4)

$$\Delta P_H = \frac{4}{\left\{1-\left[1-\left[\frac{11.6}{De}\right]^{0.45}\right]^{2.22}\right\}}\left(\frac{2}{Re}\right).\left(\frac{lv^2}{gd}\right) \tag{2.5}$$

where, h is the pressure drop in helical coils, μ is the dynamic viscosity, ρ is fluid density, v is the average velocity, d is the inner diameter of the pipe, l is the length of the pipe, g is the acceleration due to gravity and Re is the Reynolds number. The correlation has been tested for a range of different diameter pinched tubes for variety of liquids and also for two-phase flow and a parity plot over a range of Re is shown in **Figure 2.20**. While the correlation predicts the pressure drop very well, small deviations are due to slight difference in the number of pinch points over the length. A detailed investigation of the experimental analysis of pinched tube coils of various sizes (3 mm to 30 mm inner diameter) for single phase flow as well as for multiphase flow is in progress and will be reported separately.

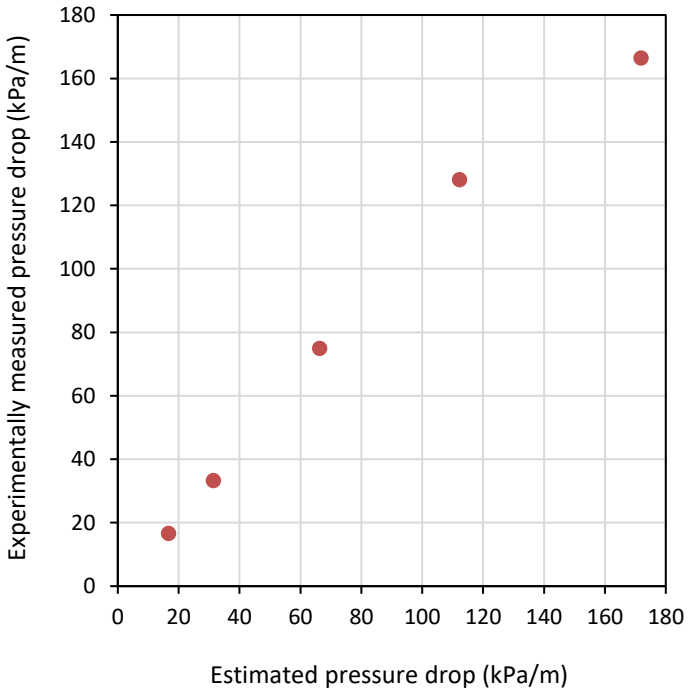


Figure 2.20 Comparison of predicted and experimentally measured pressure drop in pinch tubes of ½" o.d. (1 mm wall thickness) for a range of Re (6000 – 30000). The correlation is valid when ratio of pitch between two successive pinch points to the outer diameter of the tube is between 1.5 and 2.5.

2.5 Conclusions

A novel concept of pinched flow tubular reactor is proposed in this chapter and analyzed in terms of hydrodynamics and performance for a reaction. Large number of experiments were carried out for pinched tubes of different tube diameter, pitch between pinch sections, coils diameters and flow rates.

In general, at a given Re, the increase in number of pinch sections per unit length does not have a proportional increase in the pressure drop. The estimated values of pressure recovery over a range of flow rates for different P values show that the pressure loss coefficient reaches to that of venturi at higher flow rates. The pressure drop data indicates that around $Re \sim 100$ there could be change of flow regime.

The pressure drop for two phase flow was significantly higher than the case of single phase. The analysis using Lokhart-Martinelli method, showed that the Chisholm parameter does not follow the values for standard straight tubes and needs correction to take into account the pressure recovery in pinched tubes.

The analysis of RTD data showed that with a greater number of pinch sections the extent of dispersion decreases and the system behaves closer to a plug flow. The number of tanks in series correlates positively with the number of pinch sections. The vessel dispersion number-based analysis showed large deviation from plug flow and significant local dispersion for pinched tubes when compared to the straight tube and coil of same diameter without pinch. Pinching the straight tube improves the mixing performance but also enhances the dispersion to some extent. Thus, these types of reactors are suitable for reactions that need rapid mixing or mass transfer but which do not have very fast sequential reactions.

In general, $K_L\underline{a}$ for helical coil with smaller radius of curvature was higher. At identical power consumption per unit volume (P_w), the values of $K_L\underline{a}$ due to pinching were higher by 8-9 times that of straight tube without pinching and can increase further at higher flow rates. The

values of $K_L\underline{a}$ follow a power law behavior with P_w. Thus, a simple geometry made out of commonly available tubes yield an excellent flow reactor with simpler fabrication.

Highly exothermic nitration of bromobenzene and benzaldehyde (with mixed acid and fuming nitric acid, respectively) were chosen for performance evaluation of pinched tube reactor and compared with normal tube of same volume and diameter. Pinched tube always helps to achieve a better liquid-liquid dispersion as compared to a segmented flow that is expected in a normal tube. This specific feature helps to achieve better conversion and hence higher yield of the desired isomer when using a pinched tube.

The flow pattern in pinched helical coil tube is studied using computational fluid dynamics to investigate the role of Dean flow on the overall flow field. Two prominent Dean Vortices are observed in case of pinched helical coil tube at high flow rates as compared to the helical coil tube and for the same flow rates. The effect of pinching on overall flow pattern was negligible at lower inlet velocities (< 0.015 m/s). It was interesting to observe that despite pinching, the tube curvature (i.e. *De*) has an effect on the nature of flow pattern and it becomes significant with enhancement in *Re*.

Effects of curvature of tubes becomes evident beyond 20 ml/min inlet flow rate, where for both the cases, profiles get skewed. For a fully developed flow, the location along the coil length has no effect on the velocity profile and ultimately on the vortices. Also, the value of shear rate over the tube diameter for pinched helical coil is more than the helical coil in the region close to inner wall while near the outer wall. The nature of shear rate profile also suggests the presence of two vortices in the region, which would intensify mixing.

At a given inlet flow rate and tube diameter, the pressure drop for pinched tube coil is always higher than normal helical coil and the ratio of the specific values of pressure drop increase with Re. A simple empirical correlation could be used as a correction factor for obtaining pressure drop in pinched tube coil by multiplying with the pressure drop of a helical

coil. The observations of relatively higher pressure drop in pinched tube coils when compared to normal helical coil indicate that the pinched helical coil tube offers a significantly intensified mixing over a short length because of periodic pinching in different direction and the secondary flow generated due to Dean flow.

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Chapter 3

Reactor for handling solid suspension in flow

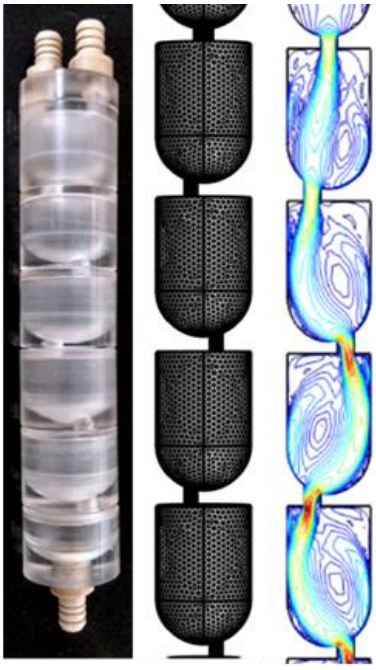
This chapter is based on:

Sharma, M. K.; Suru, A.; Joshi, A.; and Kulkarni A. A.,

A Novel Flow Reactor for Handling Suspensions: Hydrodynamics and Performance Evaluation, Ind. Eng. Chem. Res. 2020, 59, 37, 16462-16474.

https://doi.org/10.1021/acs.iecr.9b06864

A novel reactor concept that can handle solid particles without any moving components in the reactor is proposed and demonstrated in this chapter. The proposed reactor is designed by arranging the unique shape cavities in a sequence where inlet and outlets are positioned off-center to each other at specific angles and distance. The reactor also offers high mass transfer coefficients and is useful for liquid-liquid reactions and extraction. Reactor is suitable for handling a variety of solid suspensions (glass particles, activated carbon, starch particles, magnesium hydroxide) at wide range of flow rates. The proposed reactor can handle up to 22% (w/v) solid concentration without any clogging for a longer duration of the operation.



3.1 Introduction

Process intensification (PI) is well known term in chemical industry and academia today. In general, PI aims at reducing the size of the plant without compromising on the production capacity while achieving a noticeable enhancement in the efficiency in terms of cost, space, time, energy, raw material consumption and environmental discharge limits etc.[1] PI also helps in terms of reducing the capital investment and operating cost improving the profitability and also reducing the emission of greenhouse gases.[2] The PI strategies can also be applied at different scale[3] (molecular scale, macroscale and plant scale) depending upon the bottle-neck in the reaction/phenomena/process and largely it happens through enhancement in the limiting process parameters[4]. The whole PI exercise can be divided in two areas: i) process intensifying equipment – Use of equipment which intensify the mixing, heat transfer and mass transfer and ii) Process intensifying methods i.e. utilization of hybrid methods or integration of different unit operation in one process (viz. reactive distillation, reactive filtration, reactive extraction, reactive crystallization, etc.)[5]. A vast body of literature on process intensification can be referred to understand different methods and approaches. A large number of process intensifying equipment are available in literature such as spinning disc reactors[6-8], monolith reactors[9-12], static mixer reactors[13-16], rotating packed bed reactors[17-20], etc. Among these, microreactors or continuous flow reactors without any moving components occupy a very special space in the entire process intensification approach[5]. The smaller dimension of these reactors enhances the transport process significantly when compared to conventional equipment[21]. While many of these types of equipment are used at commercial scale production, in recent times there has been a surge in application of microreactors at various capacities for chemical synthesis/production.

Utilization of microreactor/flow reactor technology has resulted in significant improvement in many processes in the specialty chemicals and pharmaceuticals industry[22].

Although the potential of implementing flow reactors in selectivity sensitive and/or exothermic reactions is huge, the application of microreactors remains limited in many cases, primarily because of the possibility of generation of solid particles during the reaction. It is interesting to realize that, while a very large heat transfer area per unit volume offered by the microreactors is useful for efficient heat transfer, the same surface area is also available for adhesion and deposition of solids generated during the reaction. This limits the applicability of microreactor or flow reactor for exothermic reactions involving solids. Handling of liquid-solid suspension in confined geometries is complex, as solids can exhibit different behavior depending upon the density difference between phases. Solids with higher density than that of liquid would undergo settling depending upon additional factors like viscosity and surface tension (for nano-particles). At low flow rates, particle settling velocity can be higher than superficial fluid velocity and particles tend to settle along the reactor length. Particles that are lighter than fluid would follow a very different behavior. Usually, they form aggregates that float on the upper half of the channel. For the neutrally buoyant particles, which is a very less likely situation, the flow of particles will continue along with the liquid and only effects such as thermocapillary or lift force will change the particle flow.

Many methods have been proposed in the literature for the handling of solids in flow reactor e.g. addition of inert phase in the reaction medium[23], use of external energy to keep particles suspended during flow[24-26] (ultrasound[23], vibrations, etc.), using large volumes of the solvent to dissolve the generated solids in the reaction, use of high temperature to melt the solid, etc. However, every reaction that generates solids has a different set of physicochemical properties associated with it and hence such methods are only useful for some special cases[27]. A variety of reactors have been developed for handling solids in flow or for the processes which involve solids as one phase e.g. Coflore agitated cell reactor[25], coflore agitated tube reactor[28], a cascade of CSTRs in series[26], taylor couette flow reactor[29], continuous oscillatory baffled

reactor[24] etc[30]. **Table 3.1** gives the information about the typical operational flow rates for some of these reactors.

Table 3.1 Range of operational flow rates for some of the mentioned devices

Device	Typical operational flow rates (min^{-1})
Spinning disk reactor	~ 60 ml
Static mixer	1 ml – 1 L
Agitated cell reactor	~ 3 – 6 ml
Agitated tube reactor	~ 5 – 10 ml
Cascade of CSTR	~ 400ul – 1 ml
Taylor couette flow reactor	~ 400 ml
Oscillatory baffled reactor	~ 20 – 120 g
Rotating packed bed reactor	~ 6 – 20 L

Recently, Ley group has shown the use of a Coflore agitated cell reactor for synthesis of N-iodomorpholinium hydroiodide salt[25] where the reactor uses the transverse motion for mixing and suspending the solids during the reaction. Jensen et. al. has demonstrated a cascade of miniaturized CSTRs for a reaction involving solids [26]. Though these reactors possess advantages in terms of handling solids to some extent, handling capacities are usually low and mixing happens mainly with the application of external energy. Moreover, these methods also have issues related to scalability and one needs to do thorough on-site optimization for continuous operation.

In this chapter, we propose a novel reactor concept for handling solid suspensions in flow, which can be categorized as passive PI equipment. The proposed reactor does not contain any moving parts and uses kinetic energy and the geometry to make solids remain suspended during flow.

3.2 Reactor Conceptualization and design approach

Conventionally, the microreactors and compact flow reactors that are designed and reported in the literature have smaller dimensions for the wetting parts that provide higher heat transfer area per unit volume of the reactor. Smaller diffusion lengths help to achieve rapid mixing, while longer flow paths (or aspect ratio) provide the necessary residence time. Depending upon the orientation of these reactors, geometry (i.e. channel shape and shapes of any obstacles), dimensions and the system under consideration (viz. gas-liquid, liquid-liquid, gas-liquid-liquid, etc.), the flow direction can be horizontal, vertical or mixed[31] as in static mixers. The orientation of the reactor is usually not given any attention due to the smaller flow dimensions of microreactors. While this aspect can be insignificant for homogeneous reaction mass, it has severe implications on the hydrodynamics for multiphase systems. **Table 3.2** provides a list of important reactor parameters and their role in the design study.

For the systems involving solid particles gravity plays a significant role and keeping particles suspended throughout the reactor poses an important challenge. A vast body of literature exists on the clogging of channels due to particles[32-39]. Clogging has been attributed to particle size, the density difference between particles and the fluid, the relative values of superficial fluid velocity and the settling velocity of particles. The role of inertial effects, drag offered by particles lift force acting on particles that push particles towards wall depending upon the relative values of lateral forces acting on particles, particle shape, surface structure (including adhesive effects, if any), ratio of particle size to channel diameter and the *Re* are among a few parameters that lead to microscopic effects having different time scales relevant to flow of particles. A greater understanding of the flow fields in the vicinity of particles in small channels is essential to develop new designs that help understand the limiting conditions that prevent clogging.

Table 3.2 Role of reactor parameters on the design study

Reactor	Parameter	Role in design study
Microreactor & compact flow reactors	Geometry	For easy fabrication and maintenance
	Diffusion length	Decide the nature of mixing in the reactor (fast/slow)
	Flow path	To provide necessary residence time for reaction/process
	Orientation	Critical parameter for reaction involving solids, or biphasic reactions having significant density difference in contacting phases
	Pressure drop	Direct implication in energy input
	Residence time distribution	For getting the desired product quality and nature of flow inside the reactor (plug flow/mixed flow)
	Mass transfer coefficient	Important for biphasic system (liquid-liquid, gas-liquid, liquid-solid etc.)
	Heat transfer area	For efficient heat removal for extremely exothermic reactions (process involving efficient and fast heating/cooling)

One of the ways usually followed in large scale operations involving solids is to generate a very strong flow field (viz. in cyclone separator) that helps not only to avoid settling of particles but also use centrifugal force to classify the particles. Generating such a large centrifugal force with liquids in confined space is not easy, however, it is possible to induce flow field that does not allow particles to settle. In view of this, here we propose a novel flow reactor concept involving no moving parts yet uses the fluid dynamics and appropriately located exit ports to avoid any particle settling.

3.3 Design options and their evaluation

With the previously stated expectations, a reactor has been designed with continuous change in the flow direction to have prolonged residence time with no stagnant zones. It

becomes necessary to have: (i) a gross downward flow, (ii) continuous change in the flow direction to avoid any dead zones, (iii) multiple mixing units having (iv) no moving parts, (v) a large difference between the inlet/exit diameter and cavity size to develop low pressure and high pressure zones that would improve the residence time by holding the fluid in each cavity and (vi) impingement of fluid from the cavity above into the cavity below to induce mixing. Also, the individual mixing section or cavity should not have any sharp edges anywhere in the reactor and on the surface to eliminate the possibility of solid traps inside the units which may eventually result in agglomeration of particles.

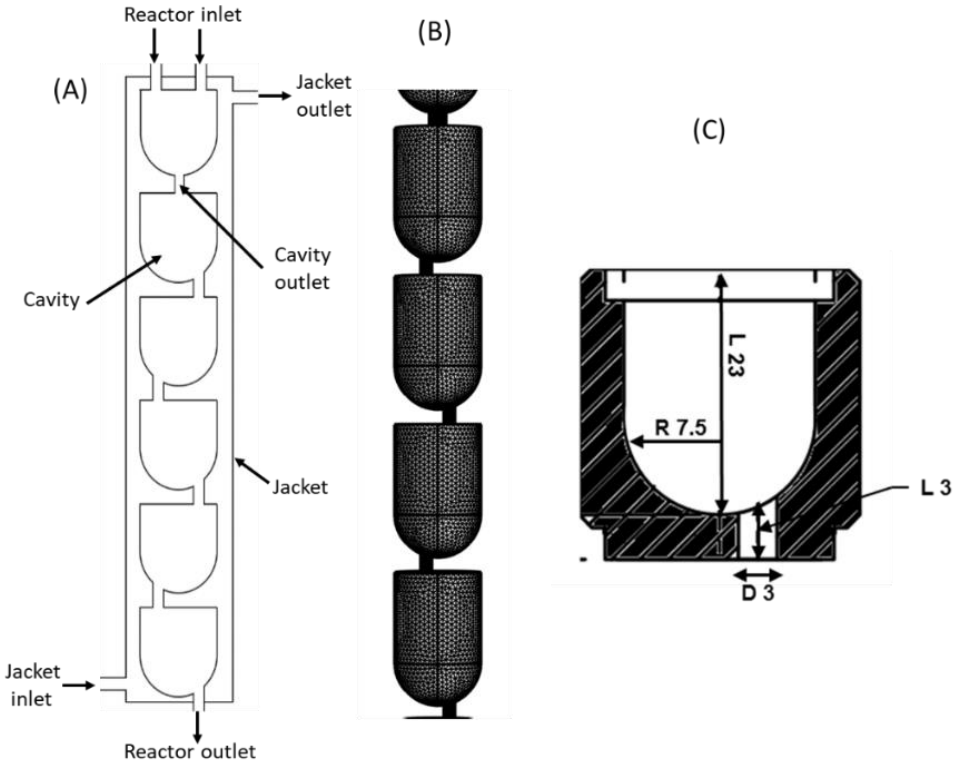


Figure 3.1 **(A)** General reactor geometry for the handling of solids **(B)** typical simulation grid **(C)** Optimized dimension of the cavity [dimension in mm.]

With the above conditions that are expected to generate the desired flow pattern in every cavity that would help particles remain suspended, a flow reactor was designed by arranging multiple cylindrical cavities in sequence with the top cavity having 2 or 3 inlets (depending

upon the need of reaction) and one outlet positioned off-centre, which opens in the second cavity. The sequence of subsequent cavities would continue such that the outlet ports in each cavity would be off-center and yet positioned at 90° or 120° angle with respect to the line joining the inlet from the previous cavity with the center of the cavity. Thus, all subsequent cavities need to be designed and arranged such that the outlets are at a fixed angle with respect to the inlet ports (**Figure 3.1A**).

Before fabrication, extensive flow simulations were carried out (using COMSOL Multiphysics®) to study the flow pattern inside the cavities for a range of flow rates and locations of inlet-outlet ports. **Table 3.3** provides the information about all the parameters studied for optimization of reactor geometry. The simulated flow field was used for identifying the low pressure zones that need to be avoided in the reactor. The laminar flow model for incompressible fluids was used in the COMSOL multi-physics 5.3 for generating the velocity profile in all the simulations. Grid independence study showed that as the number of elements increased the change in velocity becomes negligible beyond the normal mesh size (**figure 3.2**).

Table 3.3. Range of parameters variation for simulation studies

Parameter	Range	unit
Distance of outlet from centre	0 – 3 – 5 – 7	mm
Cavity height	9 – 15 – 30 – 45	mm
Change in outlet angle of successive cavities	45 – 90 – 180	°C
Inlet velocity	0.10 – 0.12 – 0.14 – 0.19 – 0.25	m/s
Reynolds number	400 – 2000	
Flow rate	40 – 75 – 90 – 114 – 150	ml/min

Hence in all the simulations, the normal mesh size with 518690 elements was selected.(**figure 3.1B**). Water was used as the fluid for all simulations with density and viscosity 1000 kg/m^3 and 8.9 x 10^{-4} Pa.s respectively. The total reactor volume with 6 optimized cavities (**figure 3.1C**) is 21.86 ml.

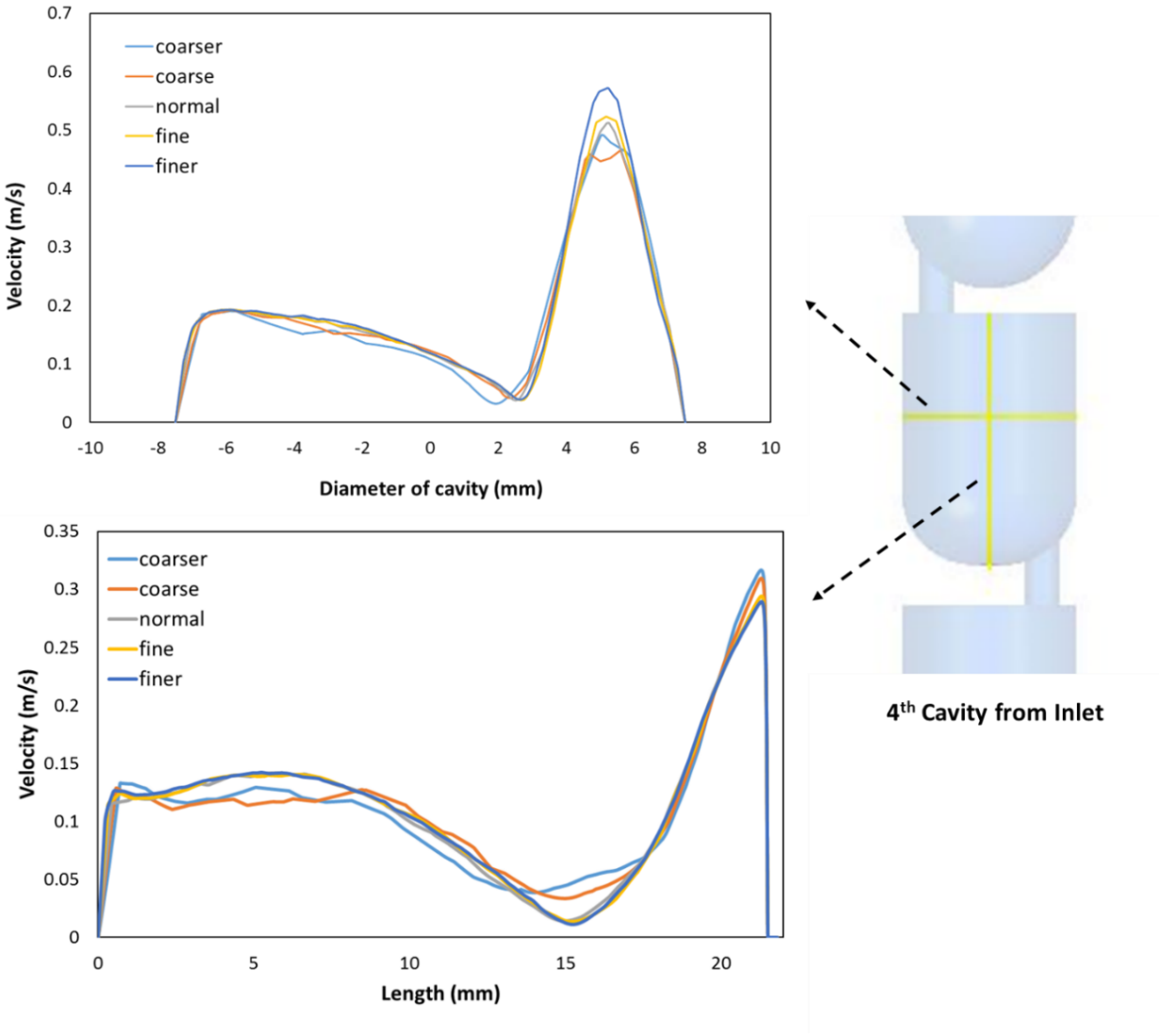


Figure 3.2 Effect mesh elements on velocity

3.3.1 Model assumptions

- Reactor is isothermal and operating at steady state

- Water is used as the fluid in all the simulations with constant properties (density, viscosity, etc.)
- The flow is assumed to be laminar where Reynolds number is in the range of 400-2000 based on experimental flow rates which are in the range of 40 to 150 ml/min (for determination of Reynolds number inlet diameter (3 mm) of the cavity was used with fluid property of water)

3.3.2 Boundary conditions

- Continuity at all internal boundaries
- No-slip at the reactor wall
- No backflow at the reactor outlet
- The pressure at reactor outlet is atmospheric

3.3.3 Location of outlet

Since the proposed device aims at setting strong flow in the cavity with almost no dead zones, it was necessary to identify the location of the inlet/outlet ports. Geometries were drawn with 4 different outlet configurations. In the first cavity, the outlet was always at the centre of the cavity while for subsequent cavities the location of outlet ports was varied along the diameter of the bottom of each cavity. The simulated velocity contour plots for various configurations at inlet superficial velocity of 0.25 m/sec. are shown in **figure 3.3**. For the sequence of cavities having inlets and outlets both along the centre, as expected it created a toroidal vortex but also a large portion of fluid short-circuiting through the cavity, which would result in a bimodal residence time distribution. Upon moving the outlet gradually away from the centre, strong 2D flows were seen with a single strong vortex getting formed in each mixing cavity. The strength of the cavity was seen to go through a maximum. For the cases where the

outlet ports were away from the centre, the formation of strong vorticial flow is seen to reduce the regions with zero velocity (i.e. dead zones) near the outlet ports and thus would help to handle a suspension of particles by not allowing them to settle in the flow cavities. A comparison of the velocity profiles in each design given in **figure 3.3** in the third cavity from the inlet is shown in **figure 3.4**. It is clear that irrespective of the location of the inlet port the extent of variation in the velocity over the cross-section was almost identical. However, shifting the inlet port away from the center created strong circulation zones that can be seen with the change in radial velocity. In the middle of the cavity, the velocity gradients were observed to be almost identical over a larger cross-section, which would generate an asymmetric vortex. Towards the outlet port of the same cavity, the flow would have a strong tangential motion as the outlet would be on a different plane. Such a flow is expected to help particles remain suspended in the cavity and do not get accumulated anywhere.

However, for the outlet close to the wall, a low-velocity region was detected on the diagonally opposite side of the outlet port indicating that low velocities in certain sections would make the particles settle easily in the section close to the cavity bottom. Hence it was desired to have an outlet port having diameter and distance from the center of each cavity at 0.2 times and 0.3 times the cavity diameter, respectively at 90° or 180° angle.

3.3.4 Effect of cavity height

Further simulations were carried out to study the flow pattern in geometries having cavities of different heights. The selection of the right aspect ratio was essential to decide the volume of each cavity without compromising on the criteria discussed earlier. In view of these cavities of different aspect ratios 0.6 - 3 (H/D) having the outlet ports located at 5 mm distance from the center of each cavity of 15 mm diameter were simulated. In each case, strong vortex flows were seen after the 3rd cavity in sequence.

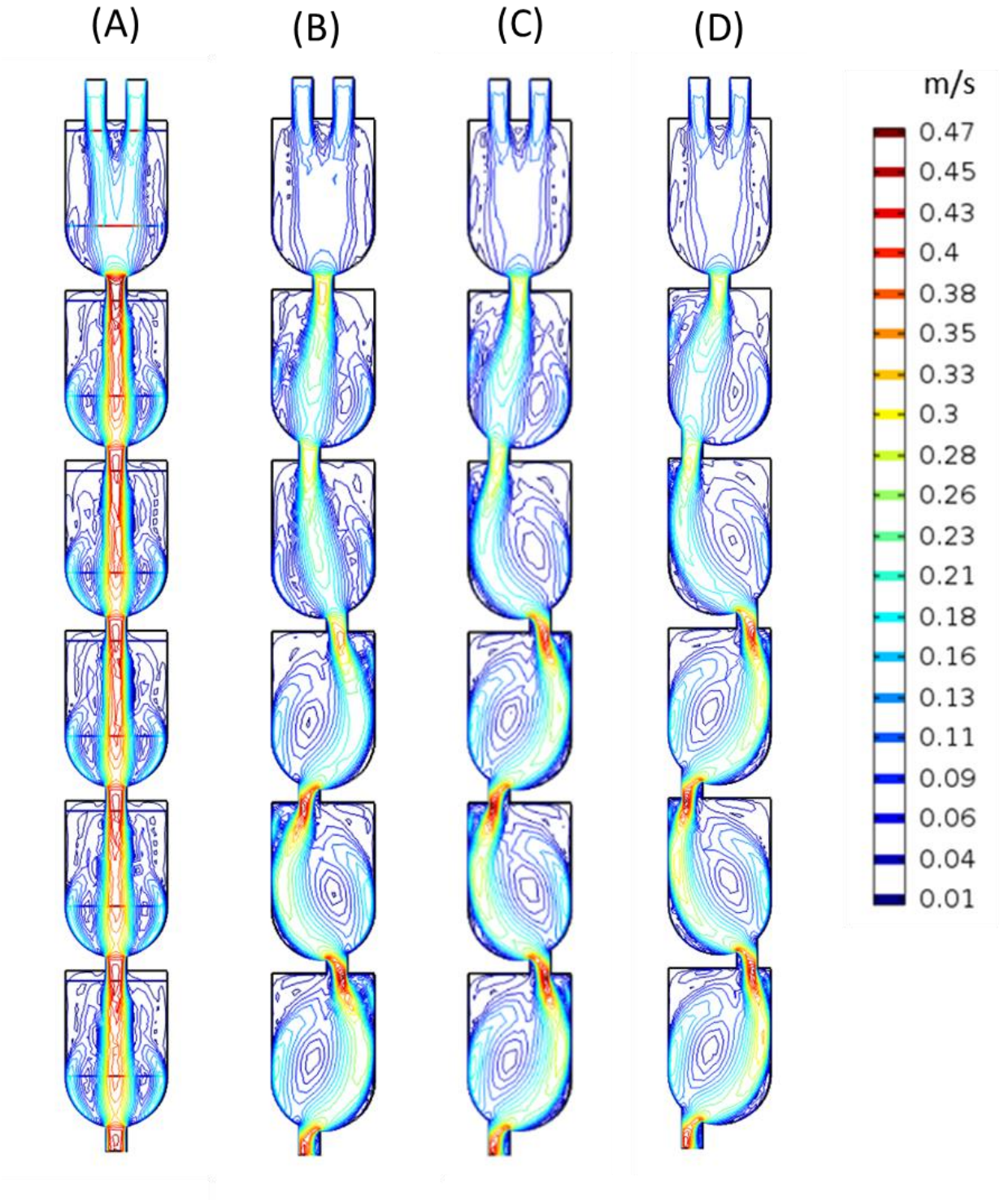


Figure 3.3 Velocity contour plots for the different configurations of the reactor having outlet ports at different distances from the center: **(A)** 0 mm, **(B)** 3 mm, **(C)** 5 mm and **(D)** 7 mm

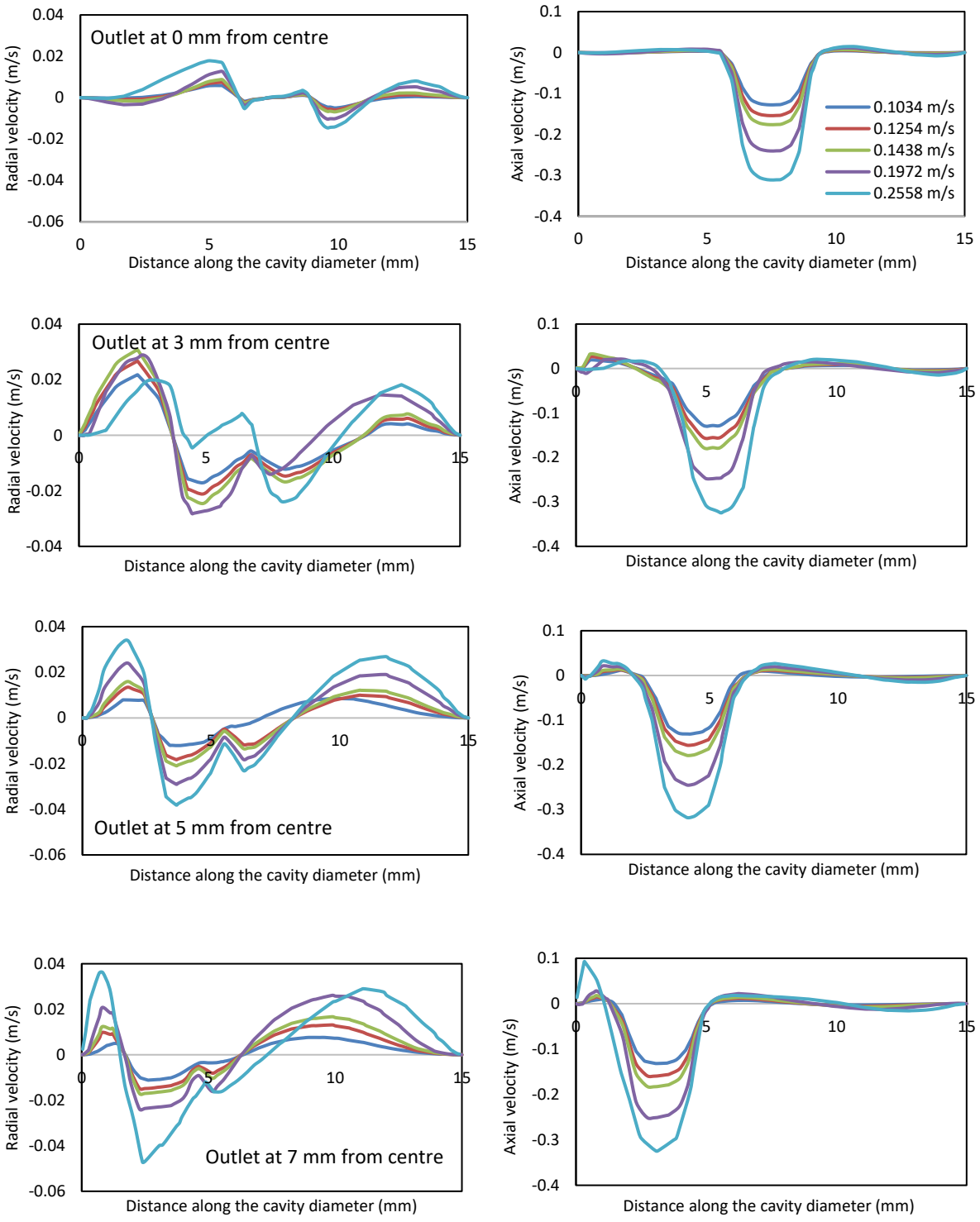


Figure 3.4 Velocity profiles over the diameter close to the inlets of the 3rd cavity in each sequence shown in the configurations shown in Figure 2. Profiles in each row correspond to the specific location of the outlet in that cavity. left column: radial velocity component; right column: axial velocity component.

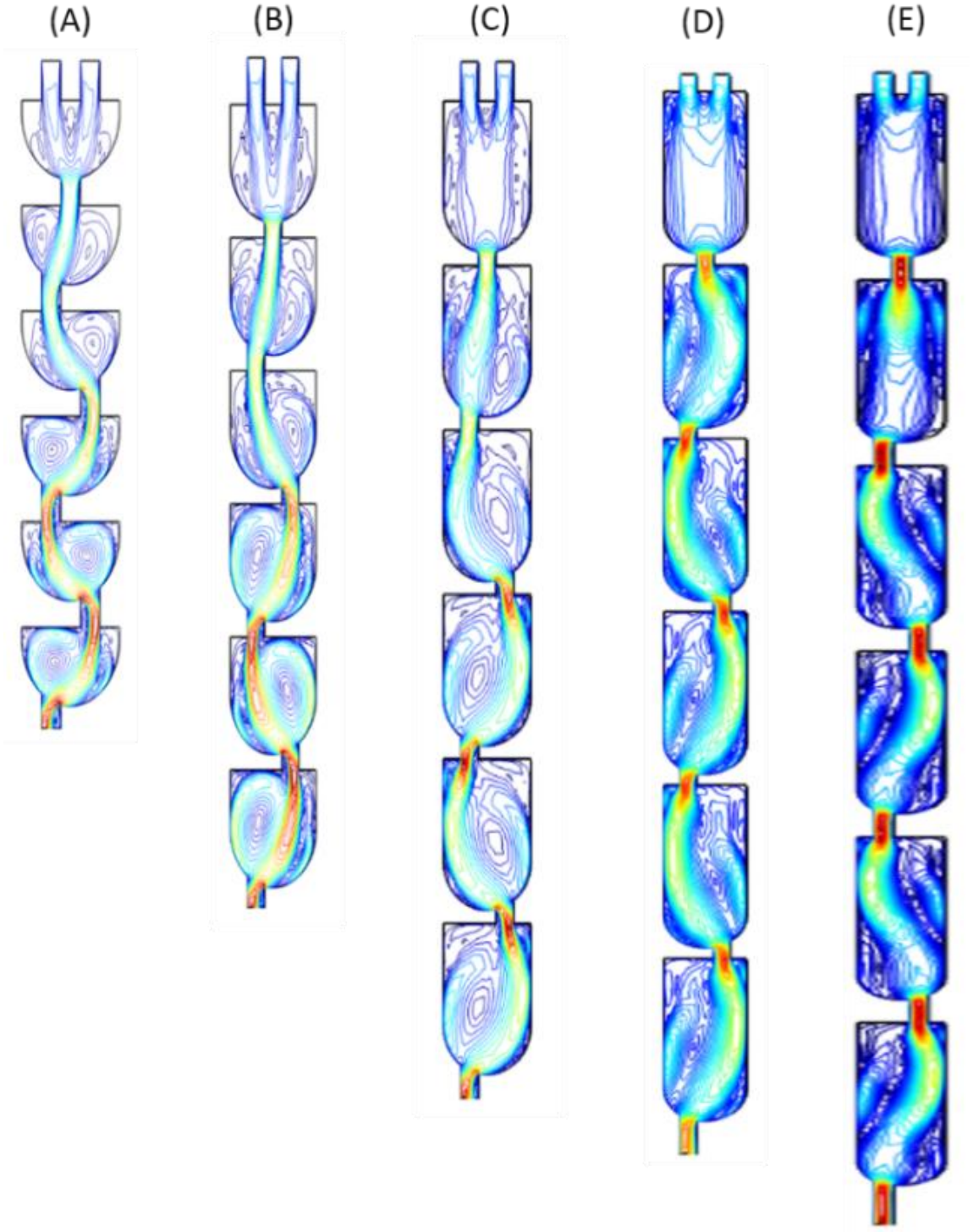


Figure 3.5 Velocity (0.2558 m/s) contour plots for the flow through different configurations of the reactor having different aspect ratios: (A) 0.6, (B) 1, (C) 1.53, (D) 2, and (E) 3.
*(Diameter 15 mm in all the simulations).

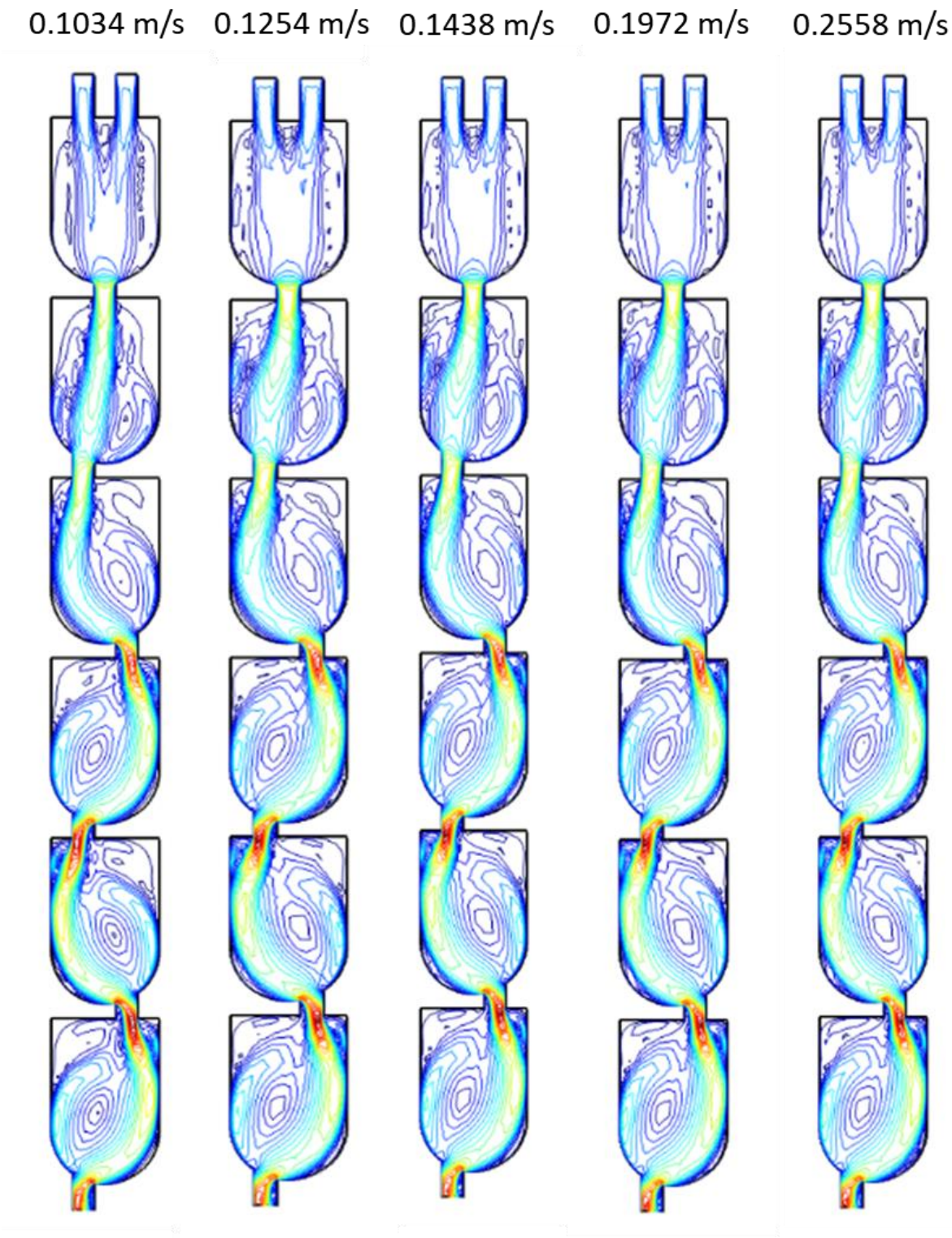


Figure 3.6 Streamline plot of outlets at a distance of 5 mm from the center

The strength of vortex was seen to decrease with an increasing aspect ratio (**figure 3.5**). However, for the aspect ratio of 1.53, almost no dead zones were observed when compared to two other geometries. Hence for all further simulations and for experiments, a device was fabricated having 6 cavities with an aspect ratio of 1.53 and the outlet ports as discussed in the previous sub-section. The streamline plots for the final configuration at different inlet flow rates given in the **figure 3.6** indicate that after the third cell a single vortex remains in every cavity and continuous change in the direction of outlet/inlet ports helps to change the flow field making it thoroughly mixed locally. This further implies that a long sequence of these cavities would yield a plug flow reactor and might be suitable even to carry out homogeneous (single phase) or two-phase (liquid-liquid) reactions in flow.

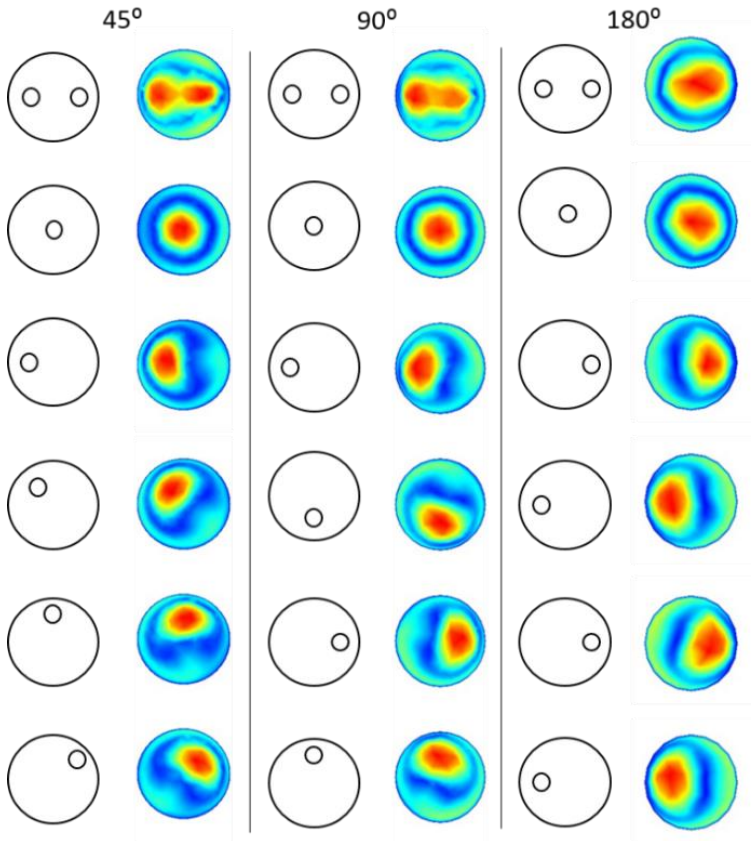


Figure 3.7 Effect of position of the outlet along the perimeter of 0.3D on the flow patterns in individual cavities. White circles: Schematic of the outlet ports along subsequent cavities for 45°, 90° and 180°, colored circles: Velocity contour plots for cavities having outlet ports at 45°, 90° and 180° in subsequent cavities. The first cavity always had two inlet ports and one outlet port at the center.

3.3.5 Effect of change in outlet angles of successive cavities

Change in direction of flow successively along the flow path generates the secondary flow and helps in enhancing mixing, which is the basic principle of many static mixing devices. To enhance the mixing effect over the flow path we studied the change in position of the outlets in each cavity in succession. The angle of outlets was changed successively to 45°, 90° and 180° in three different simulations. The velocity contours near the inlet and outlet of the third inlet are shown in **figure 3.7**.

It is visible from the contours that an increase in the angle distributes the velocity in the complete cavity. Cavities with outlets set at 45°, a region of low velocity zones are prominent compared to 180° where direction alternate in the successive cavity flow. Having a low velocity region may cause the settling of the particles if the settling velocity of the particle becomes higher than the velocity in that region. The low velocity region can also contribute to the particle agglomeration due to the increase in the residence time in that region which can lead to solid build up during the long run. The yellow high velocity region near the wall will sweep any particle sedimentation over the wall reducing significantly the chances of particle build up, which is the case where the outlet is positioned at 180°. With the simulation and velocity profiles, it becomes clear that after the first cavity with one or more inlets, for each subsequent cavity the aspect ratio can be 1.53 with outlet diameter of 0.2D, outlet positioned at 0.3D from the center of the cavity and at 180° from the previous outlet is better from mixing and possibly for handling suspensions.

A device was fabricated with above dimensional aspects and used for experimental studies for characterization of pressure drop, mass transfer, heat transfer, residence time distribution studies and finally for a reaction that generates solids. Experiments were also carried out to test the flow of model suspensions.

3.4 Experimental set-up

As shown in **figure 3.8** the experimental set up consisted of 2 peristaltic pumps (BT300-2J, Longer Pumps, China) for pumping the fluids. A digital manometer is connected to the inlet of the reactor for recording the pressure drop at different flow rates during the experiments. Conductivity meter (Deluxe conductivity mater, model-601E) was used for measuring the conductivity of a salt solution (tracer) at the outlet of the reactor, which was used for estimating the residence time distribution. For the measurement of heat transfer coefficient, thermocouples connected to the data acquisition system were inserted at the inlet and outlet of the reactor and also at the inlet and outlet of the jacket for recording the temperature variation during the experiments. For exploring the usefulness of this reactor for carrying out liquid-liquid two-phase reactions, the mass transfer coefficient was measured using kerosene – water – propionic

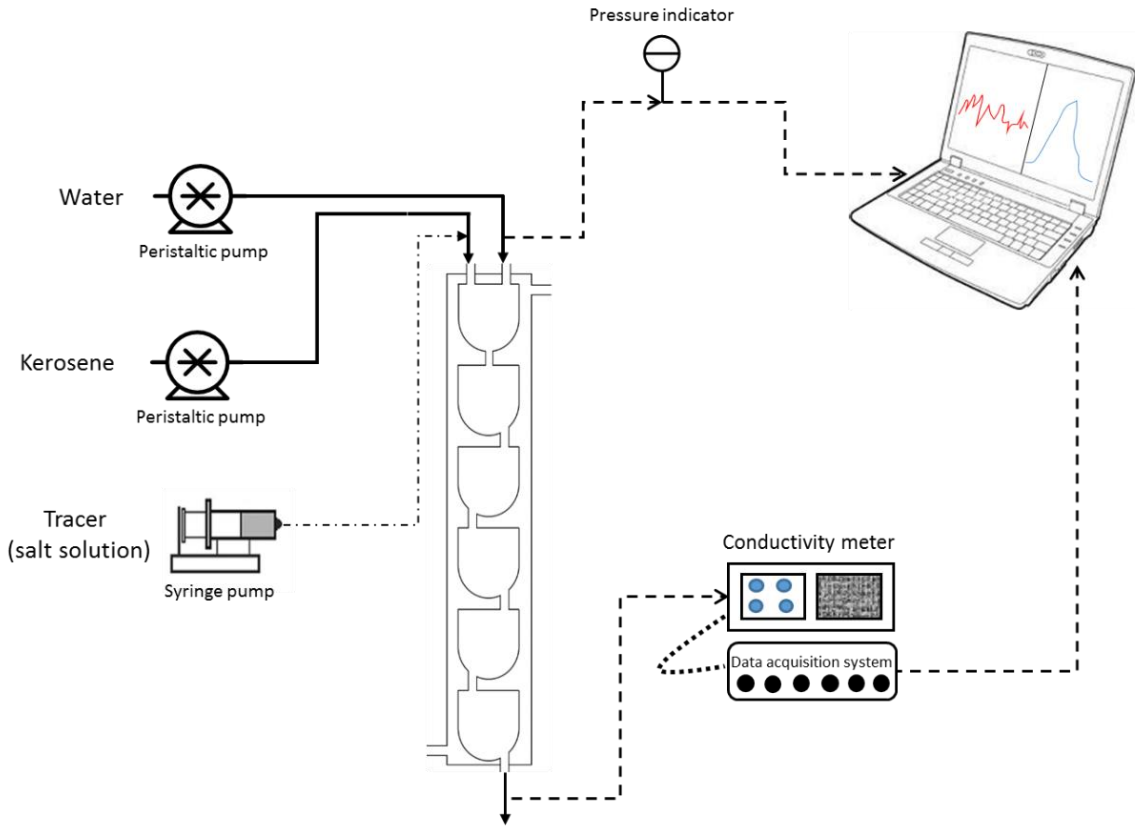


Figure 3.8. Experimental setup for hydrodynamics experiments

acid system. The conductivity of propionic acid in water was recorded using a conductivity meter. During all measurements, the superficial velocity of the single phase and two-phase experiments were varied in the range of 0.1034 – 0.2558 m/s. Every experiment was repeated twice to check the reproducibility of the data. All experiments were performed in the reactor made from SS316 material having a jacket for heat transfer.

3.5 Results and discussion

3.5.1 Pressure Drop

Pressure drop was measured at the inlet of the reactor using a digital manometer (HTC instruments – PM 6205). Tap water was used for single phase experiments and the water-kerosene system was used for measurement of two-phase pressure drop. The phase ratio of the water and kerosene was varied in the range of 40:60 to 10:90 (v/v) respectively. Water and kerosene were pumped from two inlets provided at the top of the reactor.

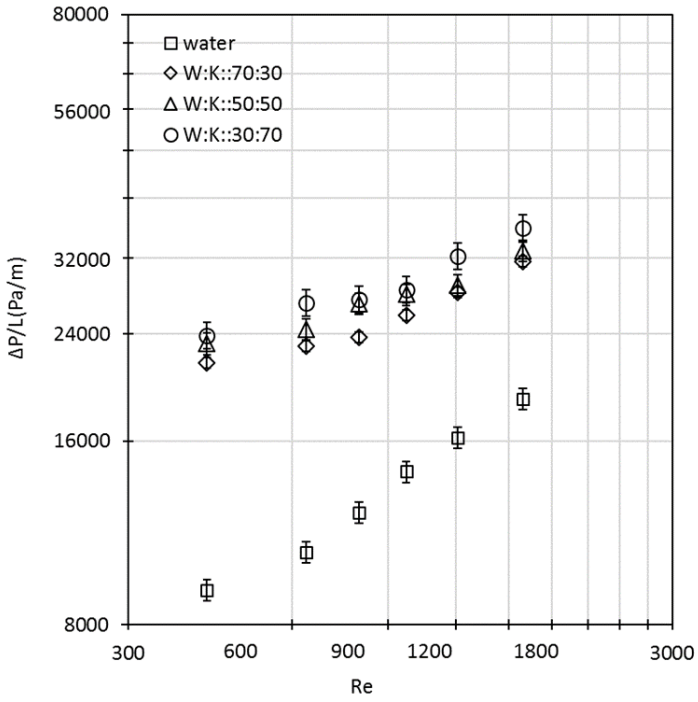


Figure 3.9 Single-phase and two-phase pressure drop in water kerosene system

Single phase and two-phase pressure drop measured for the reactor was analysed. As shown in **figure 3.9**, it is clear that the two-phase pressure drop was always higher compared to the single phase which increases with increasing the flow rate. No significant difference was observed in the case of changing the phase ratio of the two phases over the experimental Reynolds number (*Re*). In general, the standard deviation of ±7% was observed over the entire flow rate range.

3.5.2 Residence time distribution

Pulse input method was used for determining the residence time distribution. The salt solution of fixed concentration (0.34 mol/L) was used as a tracer. Conductivity probes were attached at the outlet of a reactor for the measurement of the tracer concentration in terms of conductivity through pre-calibrated conductivity meter. The conductivity meter was connected to the online data acquisition system for the data recording. Phase ratio of kerosene and water for two phase experiments were varied from 40:60 (v/v) and 60:40 (v/v) respectively.

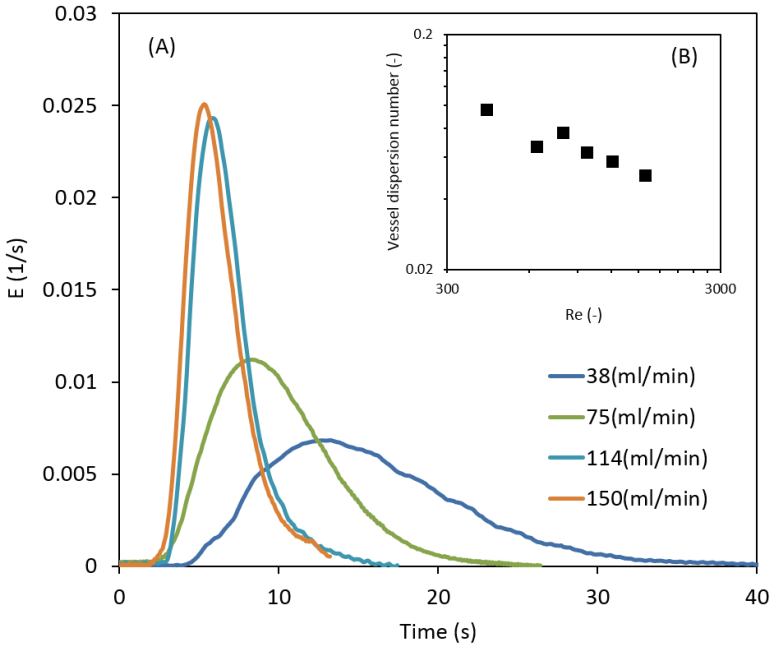


Figure 3.10 **(A)** E-curves for single-phase flow, **(B)** vessel dispersion number in the continuous flow reactor.

The extant of dispersion in the reactor was estimated from concentration in the form of conductivity at the outlet of the reactor. Open-open boundary condition was used for analysing the data and the axial dispersion model was used for determining the vessel dispersion number for the different flow rates. Typical E-curves for single phase flow for four different flow rates are shown in **figure 3.10A**. Dispersion numbers were calculated for all the experimental flow rates and over the entire range of *Re*, the vessel dispersion number was found to be greater than 0.01 (**figure 3.10B**), which verifies the mixed flow behaviour for the entire system and every cavity behaves as a perfect CSTR. For single phase flow, dispersion number decreased with an increase in flow rate which shows reactor approached plug flow behaviour at higher *Re*, whereas for two-phase the flow dispersion number was seen to increase with an increase in flow rate implying better mixing desired for multiphase reactions (**figure 3.11**).

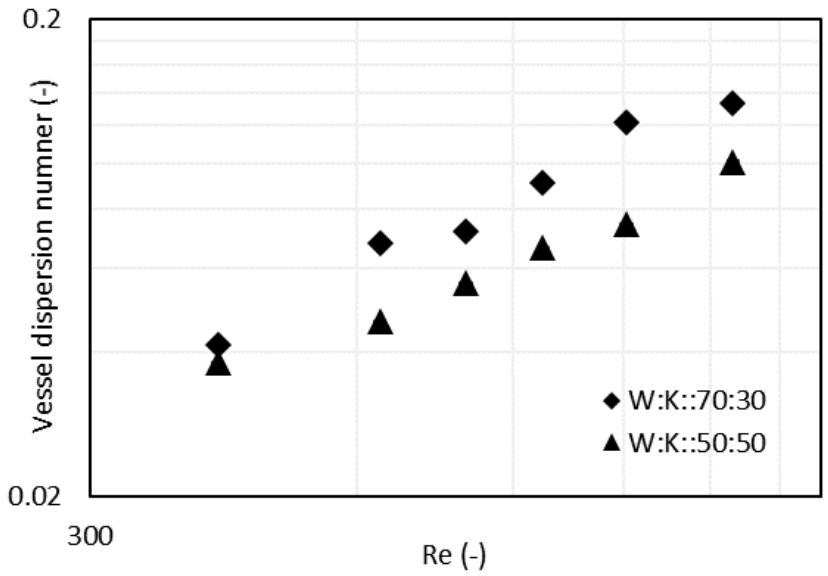


Figure 3.11 Vessel dispersion number for the two-phase flow

3.5.3 Mass transfer coefficient

Water – Kerosene – Propionic acid system was used for the determination of mass transfer experiments. Transfer of propionic acid form kerosene to water was measured for the

determination of the mass transfer coefficient. A stock solution of 1-liter propionic acid in 4-liter kerosene was used for all the experiments. The calibration chart was prepared for the conductivity of different propionic acid concentrations in water. For each experiment, equal phase ratio of kerosene and water was pumped through the reactor and at steady state 20 ml samples were collected at the outlet and with immediate separation, conductivity of the aqueous phase was measured. Measured conductivity was then converted into the propionic acid concentration with the help of the calibration curve. Each experiment was repeated thrice to get the concentration which was used for determination of mass transfer coefficient according to the formula given below[40,41].

$$K_{la} = \left(\frac{1}{t}\right) ln \left[\frac{C_{in} - C^*}{C_{out} - C^*}\right] \quad \textbf{(3.1)}$$

Where, C_{in} is the inlet concentration of propionic acid in water, C^* is the equilibrium concentration of propionic acid in water for water – propionic – kerosene system, C_{out} is the concentration of propionic acid measured in the separated aqueous phase at the outlet and t is the residence time and K_{la} is the mass transfer coefficient. For determination of the equilibrium concentration, a known quantity of water and stock solution of kerosene was allowed to mix for a long time (> 10 hr.) to attain the equilibrium. The concentration of propionic acid which gets transferred from kerosene to water was determined and used as equilibrium concentration.

The mass transfer coefficient for the experimental flow rates was calculated as described in the experimental section. The observed mass transfer coefficient was found to vary from 0.03 to 0.06 1/s. Power consumption per unit volume for achieving the same mass transfer coefficient is an important criterion for checking the efficiency of any device. To evaluate the proposed reactor, we compared the mass transfer coefficient with other standard reactors in the literature (e.g. corning advanced flow reactor, static mixer, capillary microchannel, etc.)[42] along with the previously published in-house reactors (e.g. 3D flow reactor, pinched tube

reactor) which are shown in **figure 3.12**. The mass transfer coefficient achieved in our device is comparable to the agitated contactor and impinging jet reactor. Greater mass transfer coefficient obtained in comparison with static mixer can be attributed to the unique shape cavities positioned at a specific angle for specific aspect ratio which helps in better mixing resulting in better mass transfer.

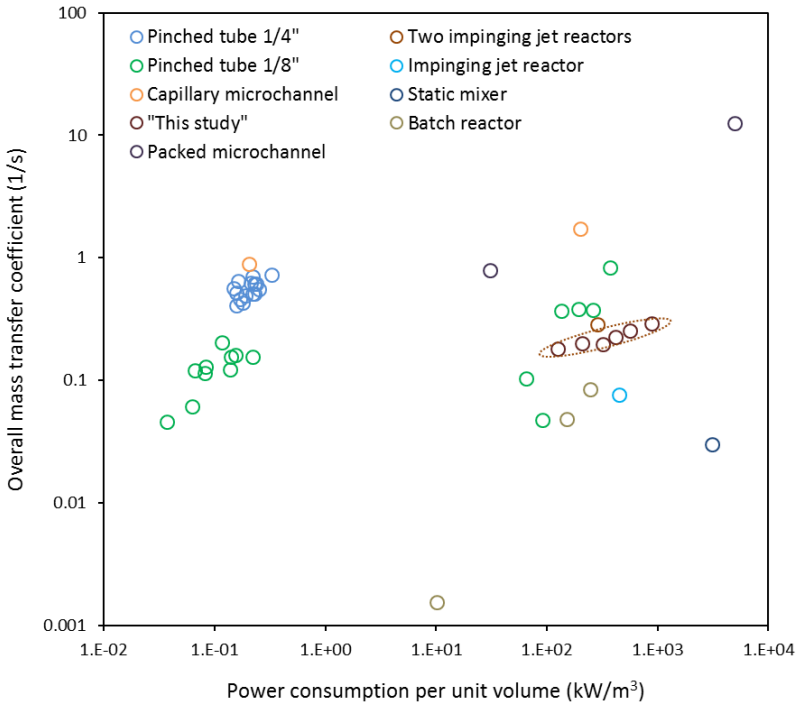


Figure 3.12 Comparison of the mass transfer coefficient from this study with the various reactors.

3.5.4 Heat Transfer coefficient

Heat transfer experiments were done using water as process fluid as well as jacket side fluid. The reactor jacket was maintained at two different temperatures 70°C and 80°C with a fixed flow rate (38 – 93 ml/min) for all the experiments. Process side water was pumped at room temperature and velocity was varied in the range of 0.1034 – 0.2558 m/s similar to the other experiments. Three thermocouples at the reactor outlet and the inlet and outlet of the jacket were connected to the data acquisition system to monitor and record temperatures on a

computer. Temperature values at steady state were recorded and used for calculation of heat transfer coefficient using the below formula:

$$\Delta T_{LMTD} = \frac{\Delta T_{in} - \Delta T_{out}}{\ln(\Delta T_{in}) - \ln(\Delta T_{out})} \quad (3.2)$$

$$Q = U \times Area \times \Delta T_{LMTD} \quad (3.3)$$

$$\Delta T_{in} = T_{jacket,in} - T_{reactor,in} \quad (3.4)$$

$$\Delta T_{out} = T_{jacket,out} - T_{reactor,out} \quad (3.5)$$

The heat transfer coefficient was obtained for two different temperatures of the jacket fluid (water) for all the experiments (**Figure 3.13A-3.13B**). The heat transfer coefficient was seen to vary in the range of 200 – 1000 (W/m^{2}K) for the jacket flow rate range of 40 – 160 ml/min.

3.5.5 Verification of the reactor performance for handling suspensions

We studied the utilization scope of the fabricated reactor for various solid types with various solid concentrations for sufficiently high flow rates and also using a neutralization reaction where a dissolved solute precipitate. Different solids types were chosen and a range of solid concentration solutions (mass % basis) were pumped in the reactor and analysed for solid settling/clogging in the reactor. A variety of solid suspensions (glass particles, activated carbon, starch particles, magnesium hydroxide) were tested over a range of flow rates for checking the solid handling capability of the reactor. To study the model systems reactor made from acrylic was used to have the visualization of solid flow inside the reactor. Solid

suspensions were pumped in the reactor using a peristaltic pump (BT300-2J, longer pumps, china).

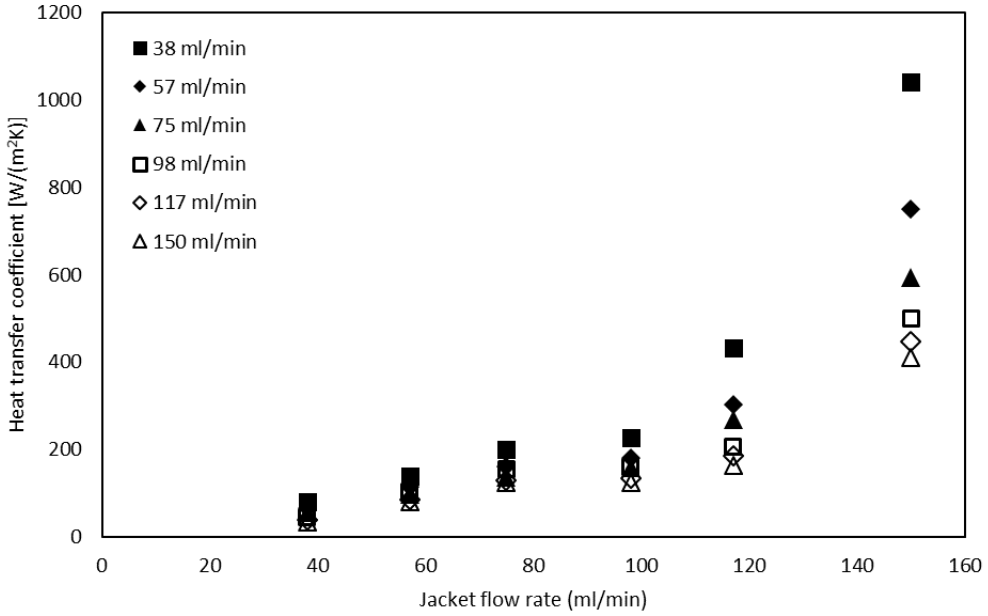


Figure 3.13A Heat transfer coefficient for jacket temperature of 70°C

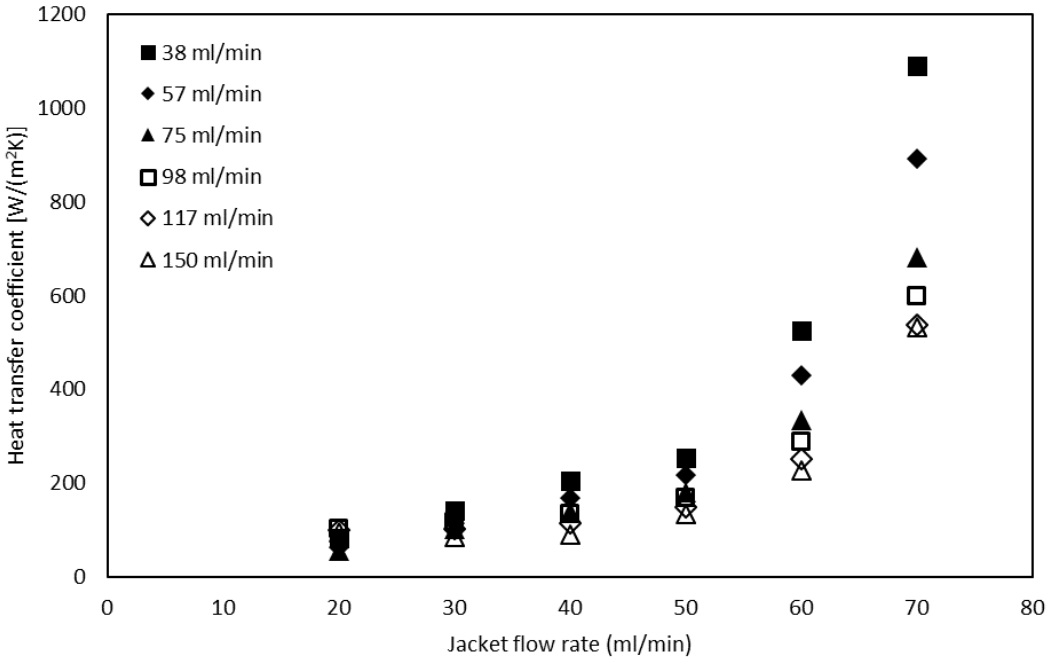
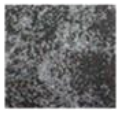


Figure 3.13B Heat transfer coefficient for jacket temperature of 80°C

Details of the observations are given in **table 3.4**. It was evident that the reactor can handle up to 25% solid concentration for sufficiently higher flow rates but for very sticky solids like starch particles they tend to stick inside the reactor ultimately blocking the flow. Based on the observations from the model systems it was clear that the proposed reactor was suitable for handling solids for certain concentrations and it should be possible to carry out reactions that generate solid as product or by-product or even for crystallization or precipitation purpose. In order to verify this possibility, in the next sub-section, we have discussed the observations from a precipitation reaction.

Table 3.4 Performance for different model system and a photograph of a clogged transparent reactor

Type of particles	Image	Density (gm/cc)	Mass % of solid	Particle Size (mm)	Flow Rate (mL/min)	Clogging ??
Glass particles (0.25mm)		2.50	25	0.25	125	No clogging
Magnesium hydroxide		2.34	25	0.15	75	No clogging
Activated carbon		2-2.10	15	Fine powder	75	No clogging
Starch particles		0.82	8	1.10	75	No clogging
Crushed starch particles		0.82	10	0.55	75	Clogging in the tube from pump

3.5.6 Precipitation by neutralization

The performance analysis of the reactor for precipitation of α-naphthol from NaOH solution by neutralization of NaOH for different throughput was carried out. α-naphthol was

precipitated from aqueous NaOH solution[43,44]. α-naphthol solution in NaOH was prepared by dissolving the 20.4 g in 525 ml water and by adding 50 ml of 30% NaOH solution (w/v) into it. This prepared solution was used for all experiments. 65 ml of 35% HCl was dissolved in 500 ml water and this solution was used for neutralization of above prepared α-naphthol solution. The prepared solutions were pumped from two inlets of the reactor fabricated in SS316 and the reaction mixture from the outlet was directly collected on the Buchner funnel to isolate solids precipitated during the reaction (to prevent the effect of further precipitation in the solution). Wet cake (which was sucked to dryness) collected on the Buchner funnel was weighed to check the quantity of the precipitated solid. Three different experiments were performed at different flow rate details of which are reported in **table 3.5**. The samples were collected after achieving the steady-state inside the reactor i.e. each reaction was run for 5 to 8 min. and then samples were collected for the time mentioned in **table 3.5**.

The details in **table 3.5** indicate that increasing the flow rate translated to a rise in the quantity of solids generated during the reaction. It also corresponds to the increased level of mixing with an increase in flow rate and solid handling capabilities of the reactor. As solids collected on the Buchner funnel can be directly correlated to the solid generated inside the reactor, the proposed reactor for solid handling was able to handle solid concentrations of 22-24 % (w/v) very easily without any clogging for this case for longer duration (120 to 350 times the mean residence time). It is interpreted here that as acid-base neutralization reactions are very fast and for the reaction where the product is solid, the reactor can work better without the implementation of any energy-intensive techniques to make solids remain suspended in the solution.

Table 3.5 Experiments carried out for increasing solid concentration

Solution concentration	α-Naphthol solution (ml/min)	HCl solution (ml/min)	R.T (Sec.)	Sample collection time (Sec.)	Weight of wet cake collected (g)	Volume of solution collected (ml.)	% solids generated in the reaction (± 1%)
α-Naphthol 20g/500ml	23	26	28	180	7	147	4.7
	50	53	13	60	5.7	100	5.7
	85	88	8	30	5	70	7.1
α-Naphthol 20g/250ml	23	26	28	150	15	120	12.5
	50	53	13	60	12	96	12.5
	85	88	8	30	10.8	86	12.5
α-Naphthol 20g/150ml	85	88	8	30	10	83	12.0
	127	132	5	20	11	80	13.7
β-Naphthol 40g/200ml	85	88	8	30	17	69	24.6
	127	132	5	15	12	54	22.2

3.6 Conclusions

A novel flow reactor having unique shape cavities for handling solids in flow with no moving parts is studied. The proposed reactor uses only pressure energy for flow and mixing, the flow of suspension happens purely due to the flow and the unique shape of the geometry. Simulations were done for finalizing the optimum geometry and it was found that cavities having aspect ratio 1.53 with outlet diameter of 0.2D (D – diameter of the cavity), outlet positioned at 0.3D from the center and at 180º from the previous outlet are better for mixing and handling suspensions. The reactor was fabricated with optimum geometrical configuration and detailed hydrodynamics studied were done for pressure drop, residence time distribution,

heat transfer, and mass transfer. The fabricated reactor shows a mixed flow behavior where vessel dispersion number increases with an increase in the flow rate. High mass transfer coefficient values (0.03 to 0.06 1/s) when compared to stirred reactors indicate its utility even for liquid-liquid reactions. The proposed reactor can easily handle a variety of suspensions at a sufficiently high concentration which also makes it useful for solid processing application and crystallization, except for cases where processes solids are heavy and sticky in nature. The demonstrated precipitation reaction clearly indicates the suitability of the reactor for reasonable (~ 22% w/v) solid handling capabilities for the reaction where solids are getting generated in the reaction. The good mixing ability at sufficiently low residence times makes the reactor useful for the very fast reactions generating solids in large quantities.

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Scale-up using flow reactors

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Chapter 4

Exothermic di-nitration reaction in continuous flow using pinched tube and scale-up

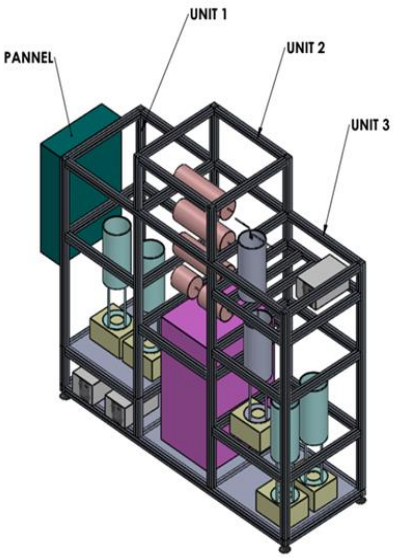
This chapter is based on:

Sharma, M. K., Sharma, M. K., Acharya, R. B. and Kulkarni A. A.,
Exploring the steady state operation of a continuous pilot plant for the di-nitration reaction, Chem. Eng. Technol. 2019, 42, 2241-225.

https://doi.org/10.1002/ceat.201900140

This chapter describe the Continuous flow synthesis of selective herbicide pendimethalin in 20 ml laboratory scale reactor and 450 ml pilot scale reactor using only concentrated nitric acid as nitrating agent. The di-nitration reaction follows second order kinetics where reaction is first order with respect to both reactant and nitric acid. Formulated reaction engineering model showed that only 450 ml reactor volume is necessary at pilot scale for the 2kg/hour production. Pinched tube reactor is chosen for pilot scale reactor fabrication. Di-Nitration in continuous flow, inline quenching, extraction and phase separation are some of the salient features of developed pilot plant. The importance of the start-up time for achieving steady state in the flow system at large scale which usually is not encountered at laboratory environment is highlighted. It is found that the initial time for steady state is the 5 times that of residence time at large scale compared to 2 times at laboratory environment.

Pendimethalin



4.1 Introduction

Continuous manufacturing using miniaturized flow reactors is now a well establish process intensification tool for the modern chemical production procedures. Short lead time, reduction in labor, reduction in plant and environmental footprint are some of the distinct advantages which led continuous manufacturing become popular in today's world [1-7]. For the cases where hazardous chemistry and harsh process conditions are involved with the rigid control over process parameters the continuous procedures are always preferred since these processes are continuously maintained in state of control. Among many, the advantages obtained in the continuous manufacturing include easy access and control over the parameters with the accessible tenability of the parameters in the case of slight disturbances which is very difficult to achieve in case of conventional batch procedures. Due to aforesaid benefits continuous manufacturing has attracted huge interest of industry and academia resulting in large number of process conversions from batch to continuous [6,8-15]. Though the laboratory scale procedure looks very attractive, transforming existing batch process to continuous or commercialization of new molecule via continuous process depends on many parameters (viz. process chemistry, critical parameters to be controlled, scale up strategy, stability criteria for the plant etc.). For the process at large scale (production > 500 kg/day of fine and specialty chemicals and intermediates), the suitability of the operating conditions to produce the desired output in a safer and controlled manner becomes very important and which is the function of steady state obtained in the process.

It is well understood that to obtain maximum safety and conversion from reactor it is very important to choose right steady state among the possible multiple steady states in a reactor. Incidentally, while CSTRs show multiple steady states and PFR's may not, continuous flow reactors that do not strictly follow either of these two ideal reactors, would show a complex behavior. The multiplicity arises due to the simultaneous interaction of reaction,

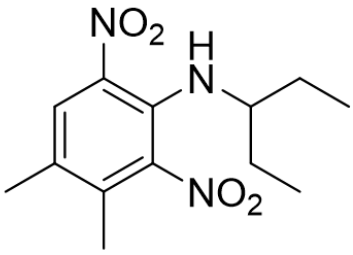
process parameters and transport process inside the reactor. Extensive literature is available in terms of nature of steady state in a reactor including the understanding of their bifurcation analysis at various conditions [16-18]. Though it is assumed that a general purpose plug flow reactor operates under steady state it is possible to have a runway condition due to spatiotemporal imbalance in the energy (heat generation rate vs. heat removal rate) due to operational failures, disturbance in the system parameter (viz. varying pumping rates of reactants or utility) or start-up/shut down protocol which are dynamic/unsteady in nature[19]. The thermal safety limit is another important parameter which needs to be characterize before scale up of any process[12]. Various models have been developed for understanding the various steady states in a reactor but time to achieve those steady state after start up or after any disturbance is rarely studied. The time to achieve a steady state is actually, the time required for a continuous system to undergo several different steady states. In the present chapter we have studied exothermic nitration at the pilot scale for the production of an herbicide. A fully operational pilot scale reactor was built and operated to check the time to achieve the steady performance.

4.2 Process description

N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitroaniline (Pendimethalin) is a widely used selective herbicide for the reduction and control of the grassy weed and broad leaf weed, which was introduced in the market in the year 1974. It is classified as di-nitro aniline-based herbicide and is available in many formulations in the retail market. It is also used in combination of another herbicide e.g. pendimethalin + Imazethapyr (**figure 4.1**). The most popular and practiced manufacturing approach for Pendimethalin is by di-nitration of N-(1-ehtyl propyl) -3,4 –dimethyl aniline (EPDMA) (**scheme 4.1**) where di-nitration can be done in single step or in two steps with mixed acid or with only nitric acid as nitrating agent. Conventional batch

synthesis procedure involves in-situ mono-nitration followed by di-nitration using mixed acid with large quantity of solvent (40 – 60%) in single reactor. Temperature is kept low usually less than 40°C. Reaction also generates the byproduct N-nitroso-N-(1-ethylpropyl)-3, 4-dimethly-2, 6-dinitroaniline (Nitroso) which can be further converted into pendimethalin via separate procedure, which is not the scope of this work. Increase in temperature, high mole ratio of nitric acid and long reaction time have positive impact on amount of nitroso formed in the reaction[20].

Year of introduction	1974
Classification	di-nitroaniline
Combinations	Pendimethalin + imazethapyr Pendimethalin + imazamox + imazethapyr
Registered formulations	30% EC, 5% Gr, 38.7% CS
Combination product	Pendimethalin 30%+Imazethapyr 2% EC

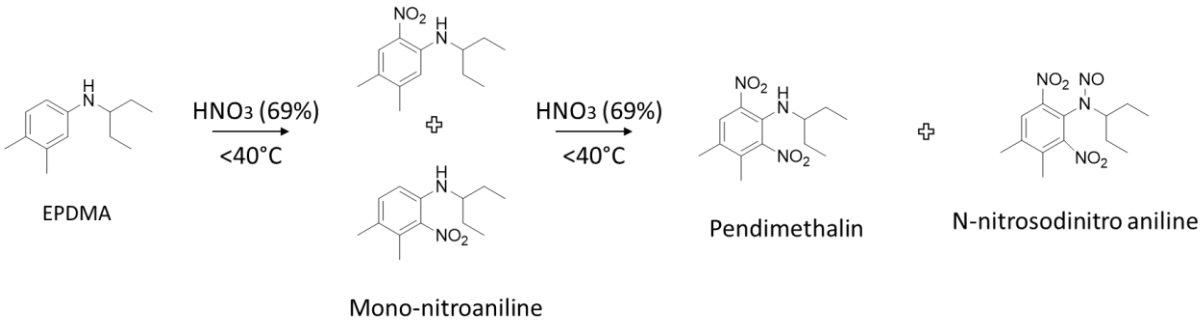


Pendimethalin

Broad leaf weed

Grass weed

Figure 4.1 Pendimethalin uses and combinations



Scheme 4.1 Reaction scheme for synthesis of pendimethalin starting from Dimethyl aniline using only concentrated nitric acid

In the conventional batch synthesis approach, large quantity of solvent leads to dilution with subsequent reduction in reaction rates and operation of low temperature ultimately results in long reaction time, which is necessary for the safe operation for large scale manufacturing. The estimated heat of reaction for both the reaction steps are 98 kJ/mol and & -198 kJ/mol. For large scale manufacturing, say for 1 ton per batch (i.e. 1000 kg/batch) the overall heat generation will be 355800 kJ/batch. Considering one batch every 16 hours (excluding batch reactor preparation, washing, discharge, etc.) and considering the fact that this is a two-phase reaction that is usually limited by mass transfer, the design and operation is always focused around the efficient heat removal and completion of di-nitration reaction. Efficient heat removal can include multiple strategies including (i) slow addition of one of the reactants, (ii) using large excess of sulfuric acid that helps rapid absorption of the water released in generation of nitronium ion and also provides high heat capacity, (iii) using cooled reactants and (iv) external heat removal using the plant utility. However, in general the reaction is carried out such that the reactor temperature never exceeds above 40°C. Selectivity is another issue in the di-nitration case owing to the dilute reaction conditions and long reaction time which may lead to the oxidation of the product. Approximately 16 – 20 hours are required for one successful batch operation for pendimethalin synthesis starting from reagents charging and final product discharge after achieving the desired product quality. Low heat and mass transfer capabilities of conventional batch reactor thereby enforces purposeful reduction in the inherent reaction rates by slow heat generation for better control over the process and having a safer operation. Other major issue is the disposal of aqueous waste which arises due to presence of sulfuric acid in the effluent, which when neutralized generates solid waste. Moreover, the organic layer after layer separation is given water wash to remove residual traces of dissolved acidic moieties. Solvent used in the process needs to be recovered, recycled for reuse, which involve efficient

solvent removal facility in consequence adding extra machinery, increasing plant footprint and proportional release of volatile matter.

Literature suggests that this di-nitration can be done utilizing only nitric acid of different concentration in two separate stages of batch operation[21]. In the first step mono nitration is done using low concentration nitric acid (~ 50%) followed by di-nitration using high concentration nitric acid (69%) in the second step. After the second step the remaining aqueous phase which is mostly nitric acid of concentration ~ 50% can be utilized for the mono nitration in the step one with slight adjustment, utilizing almost complete aqueous phase. Though this process seems lucrative, it poses the same challenges of conventional batch operation, except the issue of disposal of sulfuric acid. One way to surpass the challenges associated with the existing conventional process is to use the continuous flow synthesis technology [20]. Microreactor system utilized is only of 0.2 ml volume and variety of conditions were evaluated for range of aniline derivatives. Authors have used 16 channel microreactor system for the scale up of process and suggest that throughput can be enhanced to the multiple of 100 in same manner. Since, scale up by numbering up possesses its own challenges in terms of equal distribution of immiscible reagents in all the channels, and developing method to quantify the effect of variation in phase distribution on the yield, it was preferred to find relook at the approach [22]. Here, we aim to go for scale up by increasing the channel diameter for the production capacity of 2 kg/hr. and understand the complexities in operation of such a plant with an objective to obtain complete conversion of the reactant, less than 1% mono-nitro derivative and rest of the desired product (although it would contain some nitroso compounds which after de-nitrosation leads to formation of the desired product).

4.3 Pendimethalin synthesis using laboratory jacketed batch reactor

As a standard practice, although it is known that certain types of reactions are amenable in flow synthesis, it is necessary to carry out them first in batch mode (except for the reactions that fit in the category of flash synthesis). This allows one to identify the challenges involved e.g. flow of reagents, generation of solid, change in density, viscosity etc. In view of this di-nitration reaction was performed in batch mode before going for flow synthesis using only nitric acid. Initially, concentrated nitric acid (69%) was taken in jacked glass reactor (100 ml) and heated to 60°C. It is not advised to add the neat reactants in one go in a batch mode (even for as less as 2 gm scale). *(caution: whole reaction mixture starts to boil in just few second and explode out of the flask due to extreme exothermicity of the reaction which required proper control of temperature during the reaction in batch mode hence required the large quantity of solvent, slow addition and low temperature.)* In a typical batch experiment, the starting material EPDMA diluted with EDC (60% wt./wt.) was added drop wise maintaining the temperature below 60°C. The mole ratio of nitric acid to EPDMA was 2.75: 1. After completion of addition, the reaction mixture was allowed to react for 2 hours. Reaction progress was monitored by of taking samples periodically (every 10 min) and the progress is shown in **Figure 4.2**. In the batch synthesis, no solid generation was observed and during sampling change in the density of the product was observed which was higher than the starting material.

It was observed that initially within 10 minutes **(Figure 4.2)** pendimethalin forms in 80% yield with significant amount of nitroso by product (9-12 %). The large amount of nitroso by-product can be attributed to the large quantity of nitric acid present initially[20]. Although the literature mentions that reaction can be stopped at the mono nitration stage with use of lower concentration of nitric acid (45 – 55 %) however, all attempts of getting only mono-nitro product with low concentration of nitric failed and all the products (mono-nitro, pendimethalin and nitroso) were obtained in every set of experiments. Since both the mono-nitro products

resulted in the pendimethalin and nitroso, yields of mono-nitroaniline are combined and reported in this work.

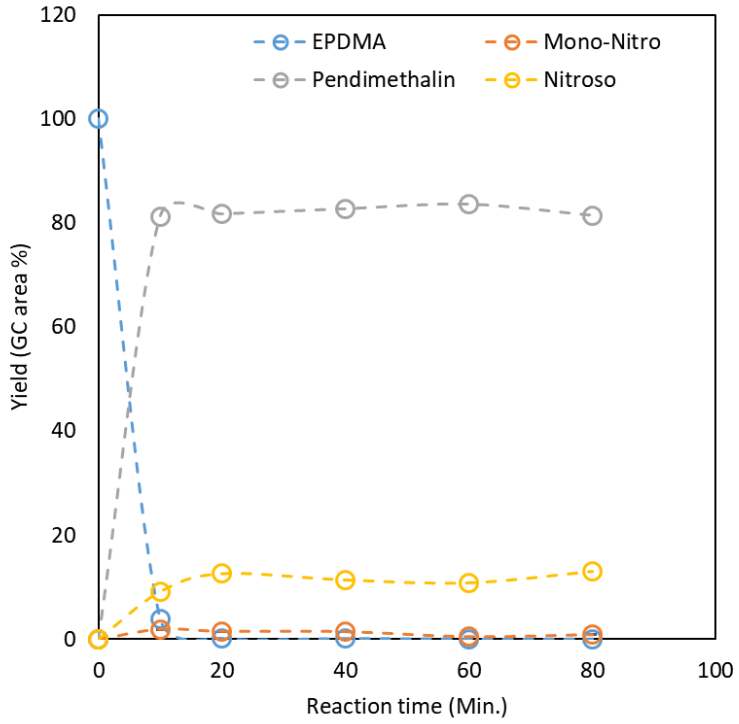


Figure 4.2 Synthesis of pendimethalin in jacketed batch reactor using only nitric acid at 60°C with 60% EPDMA and mole ratio of nitric acid to EPDMA 2.75:1

4.4 Pendimethalin synthesis using continuous flow reactor

In accordance with the previous reports[20] initial flow experiment was planned at 60°C. A tubular helical coil reactor (1/8-inch o.d., in SS316) was made having five sampling ports after every 4 ml volume (**Figure 4.3**). Reagents EPDMA (60% wt./wt.) and concentrated nitric acid (69%) were pumped with the help of a syringe pump into SS316 Amar 1 micromixer (Amar Equipments Pvt. Ltd., India) attached at the start of the coiled tube reactor. Flow rate was maintained to keep the mole ratio of reactant to nitric acid of 1:2.75. The entire assembly was dipped into the thermostat for maintaining the temperature of 60°C. Initially experiments were performed at different temperatures keeping 10 minutes residence time (as observed from batch experiments) and reaction mixture was collected only at the final outlet of the reactor.

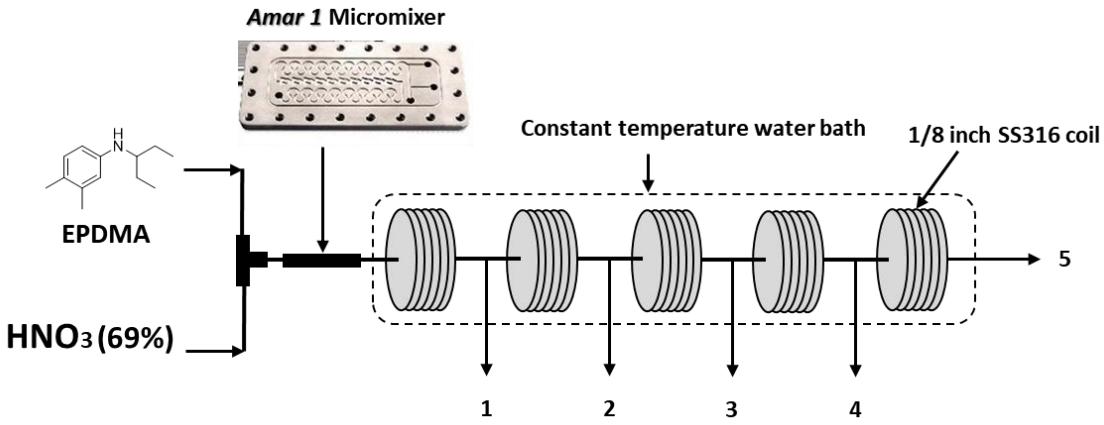


Figure 4.3 Flow reactor set-up for the di-nitration reaction

It was observed that reactions done using tubular reactor resulted in better yield compared to the batch experiments in 10 minutes residence time yielding more pendimethalin with lower nitroso byproduct (**Figure 4.4**). However, increasing the temperature to 70°C the yield of pendimethalin as well as of the nitroso byproduct was found to increase.

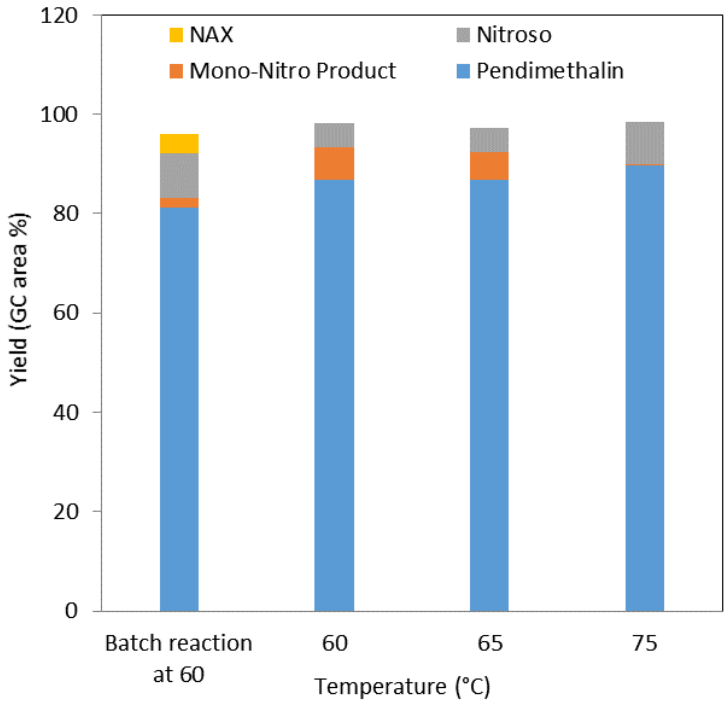


Figure 4.4 Synthesis of pendimethalin 1/8-inch continuous tubular reactor made of SS316

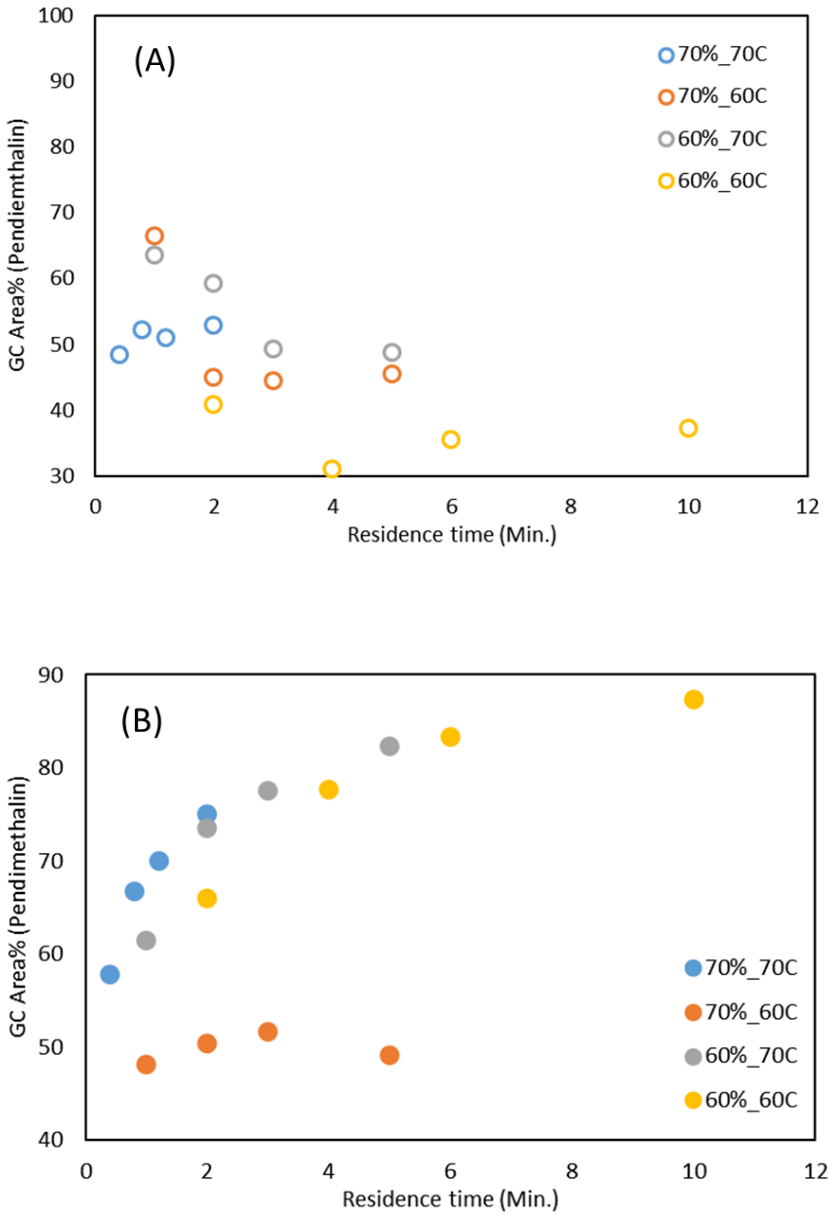


Figure 4.5 Synthesis of pendimethalin 1/8-inch continuous tubular reactor made of SS316 at various concentration of EPDMA diluted with EDC and temperature using (A) Amar 1 Micromixer with piston pumps. (B) Amar 3 Micromixer with piston pump

As mentioned earlier initial experiments were performed using syringe pumps and with the help of Amar 1 micromixer (internal volume 1 ml). However, when going for continuous synthesis at large scale pumps with higher pumping capacities are required (e.g. piston pump, gear pump, peristaltic pump etc.). Also, nitration reaction using only nitric acid in molar

proportions is usually bi-phasic in nature and mass transfer limited. In order to check the possible role of micromixer, experiments were carried out using Amar1 and AmAR3 (internal volume 0.3 ml) micromixers followed by a tubular reactor and reactants were pumped using piston pumps for different combination of temperature and dilution of EPDMA and for different residence times. Flow rates were determined for keeping the predefined residence time at the mole ratio of nitric acid to EPDMA of 2.75:1.

Though initial experiments with syringe pump (longer, china) and Amar 1 micromixer resulted in better yield and selectivity of pendimethalin, yields were significantly decreased when piston pumps (SSI instruments, USA) were used (**Figure 4.5A**). This effect can be attributed to the pulsating pumping of the HPLC pumps where reactant and nitric acid stream was injected in the micromixer without any synchronization that could have resulted in poor mixing and mass transfer. However, when AmAR3 (Amar Equipments Pvt. Ltd., India) micromixer was used the yield were increased significantly which provided good mixing due to sequential conical designs with internal velocity variation (**Figure 4.5B**) which eliminated the pulsating effects. This confirmed the requirement of good mixing and mass transfer to get the desired conversion and yield at the lab scale as well as at the enhanced throughput.

4.5 Experimental set-up

In the present work, we have used only concentrated nitric acid (69%) for the single step di-nitration of EPDMA to yield pendimethalin. Reactions were done in 1/8-inch coiled SS316 tubular reactors in the laboratory environment for the initial feasibility and optimization to attain product quality similar to the industry standard. Two syringe pumps are used to inject the EPDMA and concentrated Nitric acid in the tube reactor. 3D flow reactor (as a static mixer) is connected at the inlet of the tube reactor to provide good mixing (**figure 4.6**). 3D flow reactor is used for all lab scale experiments and the whole setup is immersed in the constant

temperature water bath to achieve and maintain desired reaction temperature. Though, overall reaction is exothermic, it progresses in two steps where mono-nitration step is endothermic and di-nitration is exothermic, some initial temperature is needed to kick off the reaction which was found to be >40°C. Consequently, all experiments are planned to be done above 40°C. Methodical parametric analysis for mole ratio, temperature, solvent concentration and residence time are done and kinetics is determined. The determined kinetics is further used for the reactor selection, design and scale up.

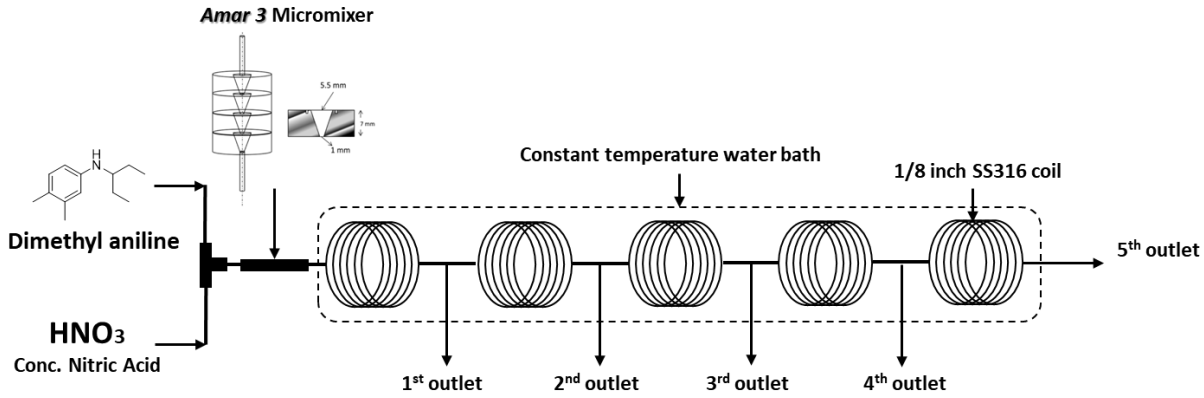


Figure 4.6 Reactor set up for the di-nitration reaction with the tube divided in 5 sections to collect the samples at different residence time

4.6 Reactor design and scale up

4.6.1 Reaction kinetics

To deduce reaction kinetics 1/8-inch SS316 tube reactor which was used in the laboratory for initial screening and process optimization is divided in five sections (**figure 4.6**) with a sampling valve between two sections. The samples are quenched in ice cold water followed by the extraction of the organic phase in ethylene dichloride (EDC). In a few experiments the organic reactant was dissolved in EDC. Gas chromatography (GC) was used for determination of the conversion and yield of the product. Since by-product nitroso is not

detectable on the selected GC column separate analysis method i.e. high-performance liquid chromatography (HPLC) technique is used for capturing the amount of nitroso formed.

In order to obtain the information about the reaction kinetics, experiments were performed for the combination of three different EPDMA concentrations diluted with EDC and at three different temperatures (**table 4.1**). As reactor is divided in five parts every set of experiment resulted in five data points over the length of the reactor. Increase in temperature enhances the rate of reaction whereas increase in solvent reduces the rate. Increase in residence time always has the positive impact on conversion of EPDMA and yield of pendimethalin but is also results in increase in the quantity of by-product nitroso. In general, the reaction followed a second order kinetics where reaction is first order with respect to both, reactant EPDMA and nitric acid[24].

Table 4.1 Experimental conditions for Kinetics experiments

Reactant % (wt. /wt.) diluted in EDC	Temperature (°C)	Residence time (s)
40 50 60	40 50 60	50 80 140 225 285

Rate constants were determined based on the curve fitting for the second order rate expression. K_1, K_2 and K_3 (**table 4.2**) represents the rate constants for the formation of mono-nitro product, pendimethalin and by-product nitroso respectively. After several efforts it is found that two isomers formed for mono nitro product are not separable and both after di-nitration generate pendimethalin irrespective of the isomers, hence K_1 is determined as combined rate constant for the mono-nitro product formation step one. The rate constants reported in **table 4.2** are lumped values which include the effect of mass transfer and

dispersion, if any. The role of mass transfer and dispersion on reaction kinetics and performance are elaborated later. Rate constants are determined assuming reaction is completely isothermal since complete setup was immersed in constant temperature water bath. The data was subsequently used in the model equations and validation of the laboratory experiments data.

Table 4.2 Experimentally obtained kinetic parameters

Temperature (°C)	K1 (L/mol.s)	K2 (L/mol.s)	K3 (L/mol.s)
40	1.7E-06	7.7E-07	1.7E-08
50	2.4E-06	1.6E-06	3.9E-08
60	4.8E-06	2.7E-06	1.7E-07

4.6.2 Model equations and model validation

$$dCa/dt = -K1 * Ca * Cb \quad (4.1)$$

$$dCb/dt = -K1 * Ca * Cb - K2 * Cc * Cb - K3 * Cc * Cb \quad (4.2)$$

$$dCc/dt = K1 * Ca * Cb - K2 * Cc * Cb - K3 * Cc * Cb \quad (4.3)$$

$$dCd/dt = K1 * Ca * Cb + K2 * Cc * Cb + K3 * Cc * Cb \quad (4.4)$$

$$dCe/dt = K2 * Cc * Cb \quad (4.5)$$

$$dCf/dt = K3 * Cc * Cb \quad (4.6)$$

Equation 4.1. Rate equations for EPDMA (*a*), Nitric acid (*b*), mono-nitro product (*c*), water (*d*) generated, pendimethalin (*e*) and nitroso (*f*) product formed respectively

Typically, in the di-nitration reaction, in the first step one mole of nitric acid reacts with the reactant and second mole of nitric acid reacts with the mono-nitro product formed in first

step to yield pendimethalin and nitroso by-product simultaneously. Model equations (**equation 4.1**) were formulated as in essence that the complete reaction involves formation of mono-nitro and pendimethalin in series and formation of pendimethalin and nitroso compound in parallel.

With the formulated model equations and obtained kinetic data, a MATLAB code was written to solve the model equations simultaneously to predict the reactions outcome which subsequently validated with the acquired experimental data. The predicted value and experimental results were comparable (**figure 4.7**) demonstrating the reliability of the obtained reaction kinetics and formulated model equations which was further used for predicting reaction performance at large scale. However, at this point we did not consider energy balance since the reactions were conducted isothermally. During scale up consideration energy balance equations (**equation 4.2**) were also formulated to predict temperature variations along the length of the reactor during reaction.

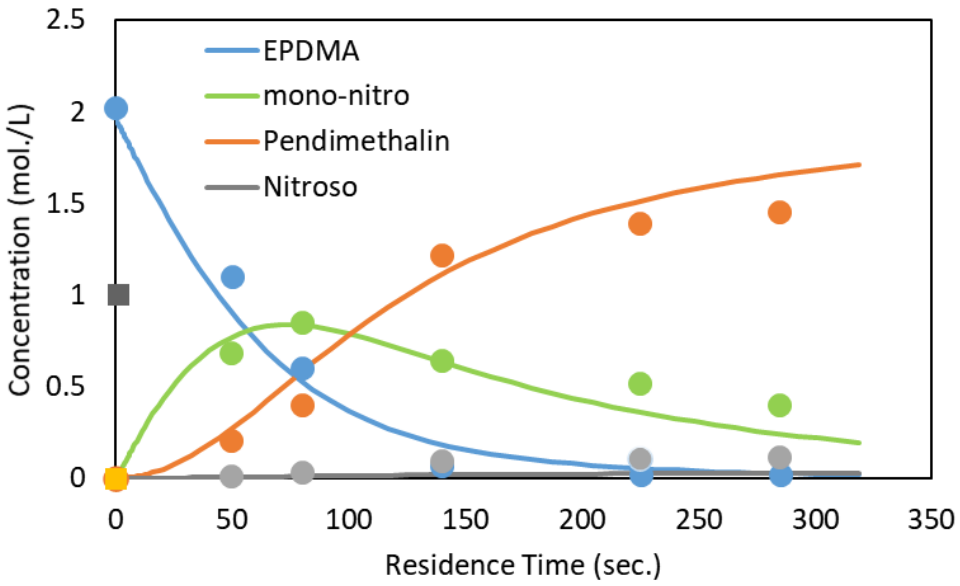


Figure 4.7 Comparison of model prediction and experimental results for 60% EPDMA concentration

4.6.3 Reactor design for the scale up

$$\frac{dTr}{dt} = \frac{(K1 * Ca * Cb - K2 * Cc * Cb - K3 * Cc * Cb) * (-Hr) - U * A * (Tr - Ta)}{(Ca * Cpa + Cb * Cpb + Cc * Cpc + Cd * Cpd + Ce * Cpe + Cf * Cpf + Csol * Csol) * Q} \quad (4.7)$$

$$dTj/dt = (U * A * (Tr - Tj))/(Q * Cpwater) \quad (4.8)$$

Equation 4.2 Energy balance equation for reactor and jacket

Reactor sizing and selection of tube diameter for the flow reactor is very important when going for the scale up. Throughput requirement with the optimum residence time sets the volume required for the reactor (*mass balance*). The excellent heat and mass transfer obtain in laboratory reactor is not easily achievable in the reactors of larges dimensions. Selecting the optimum diameter for the flow reactor is very crucial since it is going to dictate the heat transfer (*energy balance*) and pressure drop (*directly related to pumping cost*) inside the large-scale reactor. For getting the same performance at the large-scale reactor some parameters like residence time distribution and mass transfer coefficient has to remain similar with reactor in lab environment. Mass balance with reaction kinetics at optimum conditions infer the reactor volume to be 380 ml for the proposed pilot plant capacity of 2 kg/hr. production of pendimethalin. Since the same capacity can be build using different diameter tube, selecting the optimum tube diameter for getting optimum performance in terms of heat and mass transfer is of principal concern. To deduce the diameter of the pilot scale reactor, based on the formulated model equations and obtained kinetic information mass balance (**equation 4.1**) and energy balance equations (**equation 4.2**) were solved simultaneously to get the heat profile and

concentration profile along the reactor length. Simulation were done for the 3 tube diameters and the results were compared. It can be easily calculated that with increase in tube diameter the tube length required to occupy the same volume goes on decreasing significantly. This have some good implications in terms of pressure drop since with increase in tube diameter the pressure drop decreases significantly for fixed optimum flow rate across the reactor. The critical parameter which contributes most in the selection of tube diameter is the heat transfer and conversion across reactor for the different tube diameter.

To determine the optimum tube diameter, we simulated temperature profile and concentration profile inside the reactor for 3 different tube diameter of sizes ¼ inch, 3/8 inch, and ½ inch tube since this size tubes are commercially available. The model equations for concentration and temperature were solved simultaneously for above stated tube diameters with the same initial conditions and the results were compared.

For the same jacket temperature of 60°C it can be seen (**figure 4.8c**) that tube of diameter 10 mm does not reach to the desired temperature whereas tube of diameter 4 mm required lesser volume for achieving the required temperature inside reactor at steady state. This difference in the temperature profile will control the conversion inside the reactor since temperature can influence the reaction kinetics. Achieving the desired temperature inside the reactor at much smaller tube length with the required residence time is very necessary for the desired conversion. For the case of the tube of diameter 10 mm extra volume needs to be provided to achieve the desired conversion. Increase in volume will result in the increased capital cost. When concentration profile was plotted it was clearly visible that the conversion achieved in the 10 mm diameter tube is 10 % less than the tube of diameter 4 mm (**Fig.4.8a, b**).

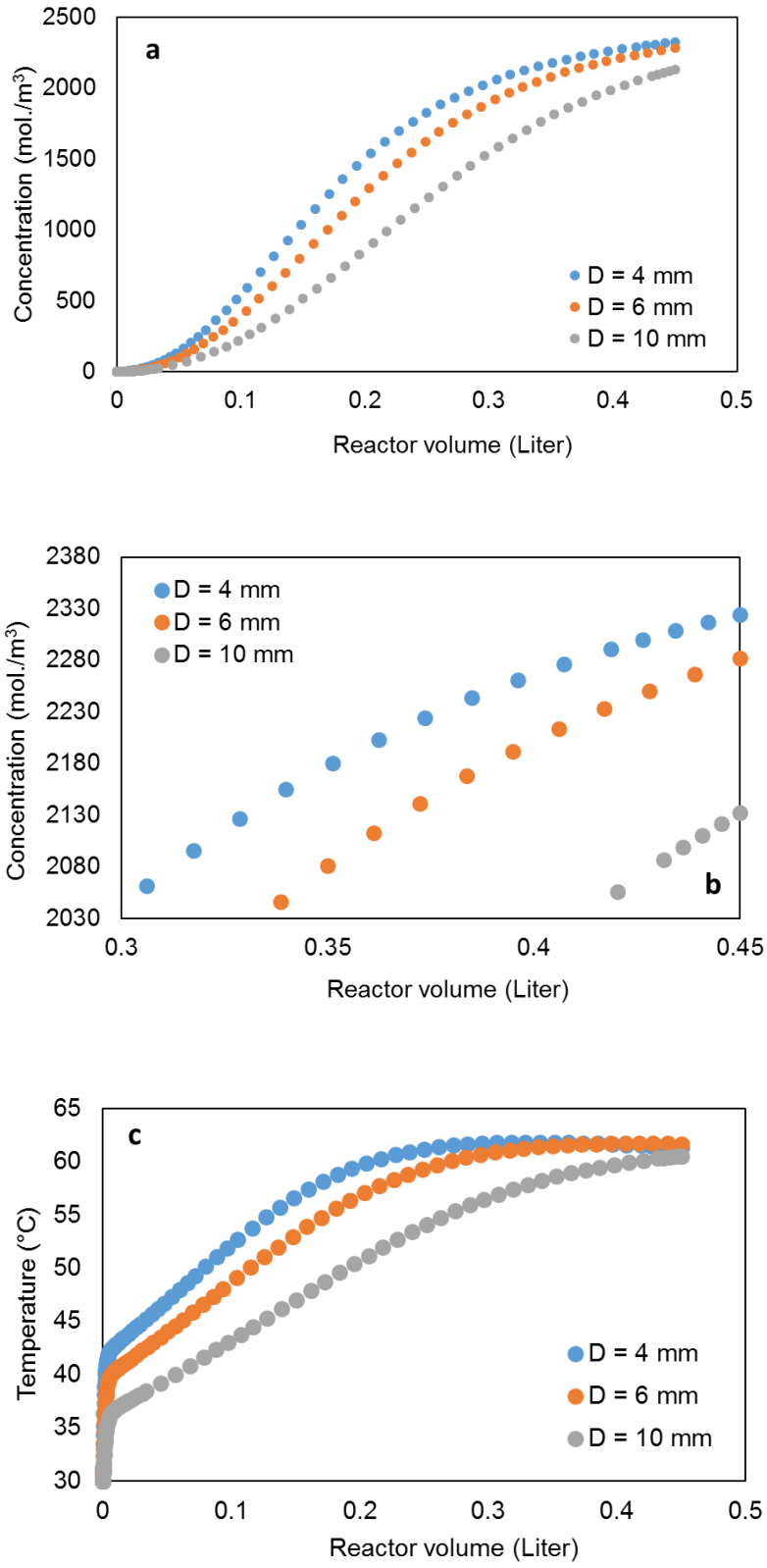


Figure 4.8 Predicted concentration and temperature profile along the reactor for 3 different tube diameters (a) concentration profile for 450 ml reactor volume (b) difference in product concentrations at the reactor outlet (c) temperature profile along the reactor for 450 ml with initial temperature of 30°C

Results showed that 4 mm is optimum diameter for the pilot scale reactor. Since we did not consider the effect of dispersion (in lumped kinetics) 15% extra volume was included in the plant scale reactor to account for any effect of axial dispersion. The simulations were done for the higher reactor volume to constitute for the axial dispersion effect at the higher scale and also reactor was fabricated for the same volume to compensate for the extra residence time if at all needed.

4.7 Hydrodynamics study

Two peristaltic pumps were used for studying the hydrodynamic parameters e.g. residence time distribution and mass transfer (**figure 4.9**). Residence time distribution and mass transfer experiments were carried out at the experimental flow rates at which reactions were performed and optimized for the proposed throughput.

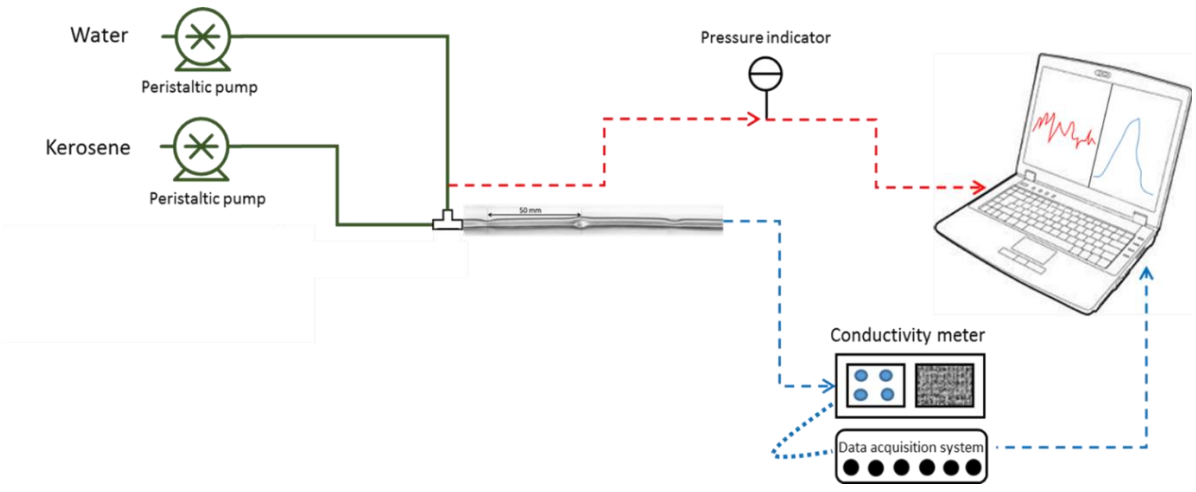


Figure 4.9 Experimental set-up for hydrodynamic characterization of 1/8'' inch coiled tube laboratory reactor and ¼ inch pinched tube reactor

4.7.1 Residence time distribution

Water and salt solution were used for single phase residence time distribution study. Salt solution (14 g salt/ 100 ml water) in deionized water was used as tracer and step input

method was used for all experiments. Two peristaltic pumps pumped the solution in the reactor where conductivity of the tracer solution was obtained using conductivity probes connected at the outlet of the reactor. Open-open boundary condition was assumed during data analysis and dispersion number was calculated for the desired parameter range.

Different fluid elements that enter the reactor, can take different paths during their flow, which results in different length of time to pass through vessel. This distribution of time, also known as residence time distribution (RTD) at different scales when matches very well, clearly indicates the similarity in the flow inside the reactors. Tracer experiments were done to characterize these distributions. In the present study, step input method was used for determining the RTD. Same procedure was used for the lab scale and pilot scale studies. The reactors at both scales were characterized for the flow rates required for the desired throughput and also at the flow rates at which reactions were performed for lab scale and pilot scale. RTD experiments for laboratory 1/8-inch tubular reactor was performed at 5, 4, 2 ml/min for the reactor volume of 20 ml and for pilot scale reactor the calculated flow rates was 39, 28 and 19 ml/min for reactor volume of 500 ml pinched tube reactor. However, we want to highlight here that residence time laboratory tubular reactor and pilot scale pinched tube reactor do not match due to the provided extra volume in addition to the prediction of the model equation for handling the other similar reactions with different residence time. The variation in the measured conductivity with time was considered as the concentration (C) curve and the data was subjected analysis to obtain vessel dispersion number for all the experiments (**Table 4.3**). The RTD was determined at each outlet, where obtained F curves were the characteristic of the total reactor volume with the entire reactor before that outlet. The characteristic F curves for different flow rate is shown in **figure 4.10**.

F curve is the normalized concentration of tracer **(Figure 4.10)** relative to the new steady state concentration after the step input, and t/τ is the normalized time, where $t/\tau = 1$

represents one mean volume turnover. During the di-nitration reaction most of the experiments were performed at flow rates of 2 ml/min at lab scale and 39 ml/min at the pilot scale. The corresponding axial dispersion number at these two flow rates were D/μL = 0.000015 and D/μL = 0.00091 respectively (**Table 4.3**).

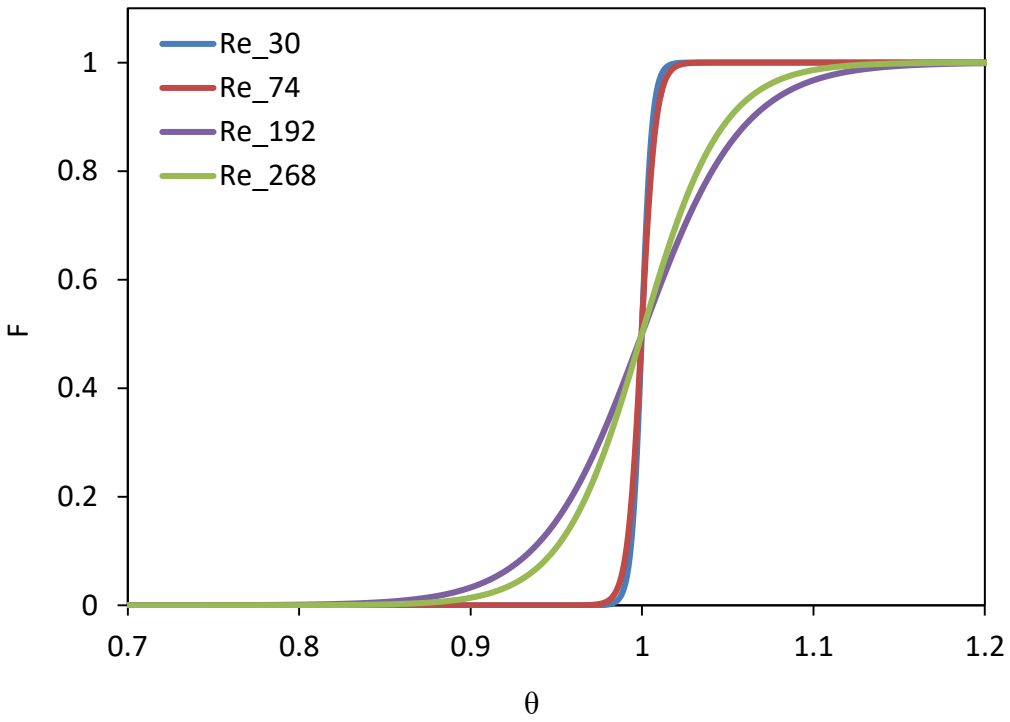


Figure 4.10 F curve for the lab scale reactor and pinched tube pilot scale reactor at different Reynolds number

These small values of the dispersion number indicate that the reactor behaved as ideal plug flow reactor. It can be seen that for lab scale, axial dispersion number was less for the slow flow rate (2 ml/min). However, at the pilot scale the opposite was true, where the axial dispersion number was less for the high flow rate (39 ml/min). This was expected because in lab scale reactors the axial dispersion was mainly guided by diffusion but in pilot plant scale it was guided by radial mixing. However, while comparing from lab scale, in pilot plant D/μL

was more, which can be attributed to the used pinched tube reactor. The fact that obtained axial dispersion number for both the scales were very low, the pinched tube reactor was found to be suitable for pilot plant scale operation and beyond.

Table 4.3 Estimated dispersion numbers at various flow rates

No.	Reactor volume (ml)	τ (min)	Re	D/μL
1	20	10	30	0.000015
2	20	4	74	0.000027
3	500	26.32	130	0.00592
4	500	17.86	192	0.00144
5	500	12.82	268	0.00091

4.7.2 Mass transfer coefficient

Water – propionic acid – ethylene dichloride (EDC) system was used for determining mass transfer coefficient for laboratory flow reactor and pilot scale flow reactor. Stock solution of propionic acid in water was made where propionic acid was transferred from water to EDC. Flow rates were calculated for keeping the total residence time of 5 min and 10 min in laboratory reactor and 7, 8, 9 and 10 min for the pilot scale reactor. These residence times were decided based on the throughput which was fixed according to the plant production capacity. Two different phase ratios were chosen according to the ratio of organic phase and acid phase during the experiment at 2 extremes. For each case phase ratio did differ slightly from 1:1. The transfer of propionic acid from water to EDC was monitored with the help of pre-calibrated conductivity meter. The data was recorded and mass transfer coefficient was determined for residence times mentioned above. It is worth to highlight that for the laboratory experiments the Reynold number obtained were significantly low (22, 44) compared to the Reynold number

obtained at the pilot scale (267 – 281) for the specified throughput. Mass transfer obtained in all the pilot scale experimental throughputs were same as that of laboratory scale (**figure 4.11a, 4.11b**).

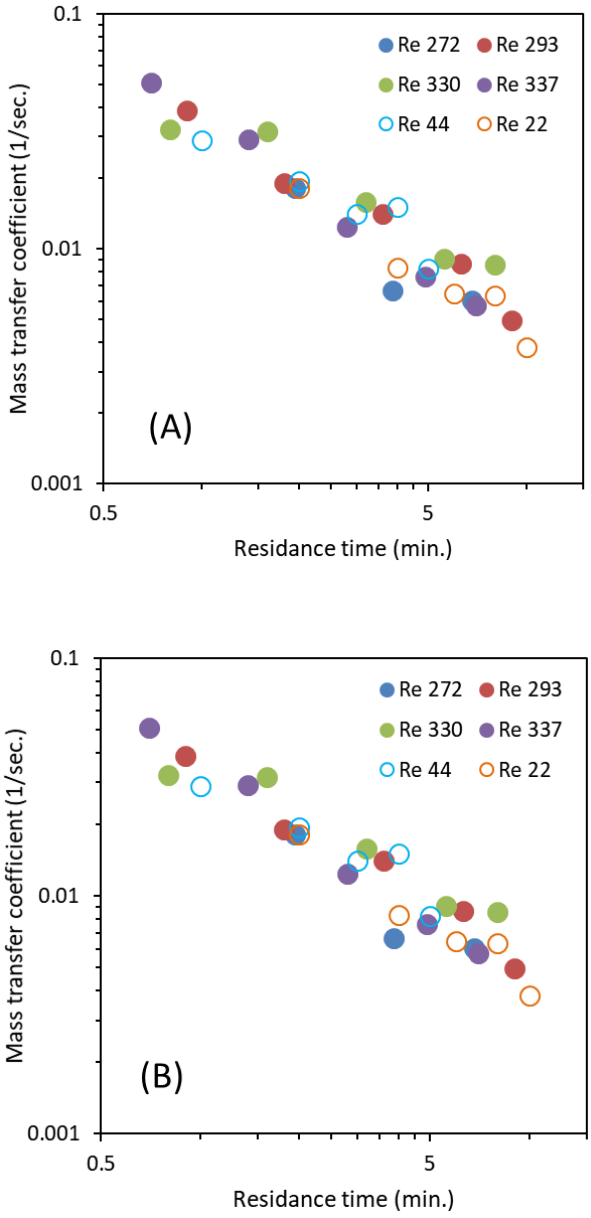


Figure 4.11 Mass transfer coefficient comparison for lab reactor and pilot scale reactor for 2 different phase ratios (a) for mole ratio of 1:2.75 (b) for mole ratio of 1:3.5

This clearly indicate that the pilot scale reactor was performing at the same level as that of laboratory reactor. The increase in scale does not have any effect on the mass transfer obtained and the fabricated reactor is on par with the lab scale tube reactor. Decreasing trend

of mass transfer coefficient was observed with increase in the residence time this signifies that almost all mass transfer is happening at the start of the reactor and at later stage reactor is utilized for maintaining the residence time with slight decrease in the mass transfer coefficient.

Though lab reactor had smaller tube dimension and external micromixer for mixing and mass transfer the pilot scale reactor was equally efficient when compared to lab reactor without having any external mixer with the chosen reactor dimensions. Changing the phase ratio according to mole ratio of 3.5 resulted in the almost 100% increment in mass transfer coefficient (**figure 4.11b**) that can be attributed to the increase in the volume available for the transfer.

4.7.3 Heat transfer coefficient

As the total reactor volume was divided into five parts of different volumes (50+50+100+150+150 = 500 ml). The reactors were jacketed to maintain the temperature where water was used as jacket circulating fluid and the temperature of which was maintained by thermostat. Initially, thermostat was set for desired reaction temperature and after attaining the temperature, water was pumped into the reactor. Once the system reached steady state, the temperature of the fluid coming from outlets was recorded.

Heat transfer coefficient was determined for all the reactors individually as well as when connect in series. Initially heat transfer coefficient was calculated for individual reactors to check the possible variation in the heat transfer coefficients with the flow rates. The set of experiments done on each reactor are tabulated in **Table 4.4**. All the reactors when arranged in the series give a total volume of the reactor to 500 ml and overall heat transfer coefficient was calculated. The heat transfer coefficient was estimated for the 500 ml reactor volume at four different flow rates and at four different temperatures. Increasing flow rate resulted in higher heat transfer coefficients (**Figure 4.12**) indicating that retaining the geometric features as in a

pinched tube while using longer reactor lengths would help. So, having a high heat transfer coefficient during the reaction in pilot plant will allow maximum heat removal.

Table 4.4 Experimental conditions for heat transfer experiments

For individual reactors of 50, 100- and 150-ml volume		For connected reactors of 500ml volume	
Flow rates on tube/reactor side (ml/min)	Shell side temperature (°C)	Set of flow rates (ml/min)	Shell side temperature (°C)
37.5	40, 50, 60 & 70	20	70
75		40	
112.5		60	
150		80	

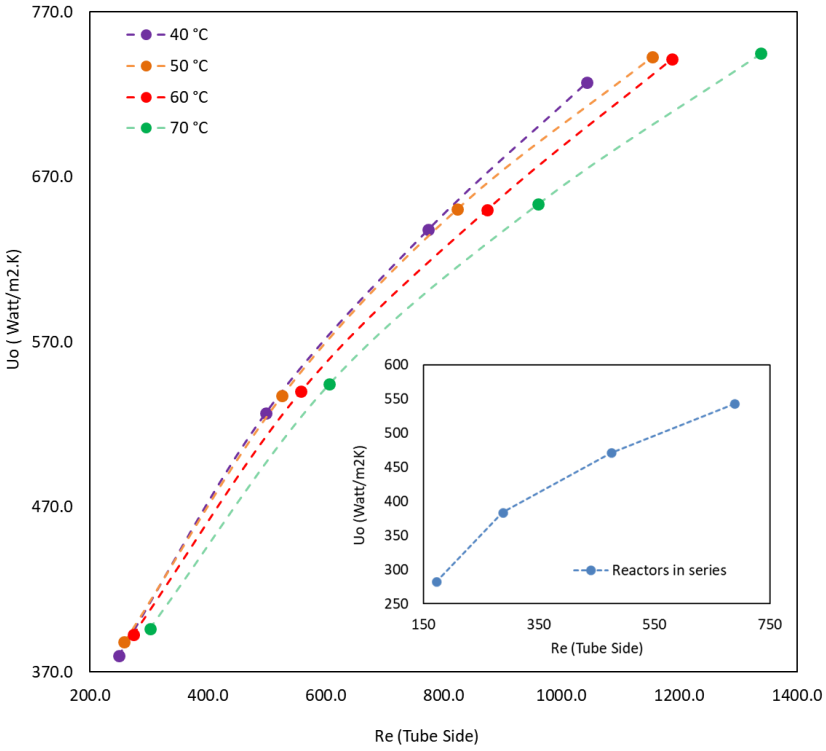


Figure 4.12 Determined heat transfer coefficient at different flow rates and at different temperatures.

The range of HTC obtained for these conditions (~500 W/m^{2}K) is sufficiently high to avoid exotherm or unmanageable hot spots in the reactors. The overall HTC of the entire 500 ml reactor in the pilot plant was anologous to the individuals reactors indicating that losses are negligible.

4.8 Reactor Scale-up

4.8.1 Pinched tube reactor

It is well known that with increase in tube size the benefits in terms of transport process gets reduced. To get the similar performance with the higher tube diameters some modification has to be incorporated to influence the transport process. So, to enhance the transport process at large scale in comparison to normal tube, pinched tube of same diameter was chosen for fabrication of reactor at pilot scale[25]. Pinched tube reactor is made by pinching the tube at different locations along the tube length at various angles (**chapter 2**). This pinching provides reduction in cross section area which help in improving mixing due to increase and decrease in velocity at each pinch. Having change in angle in successive pinching changes the direction of flow and enhances the mixing. This pinched tube reactor has been shown to perform better compared to the straight tube of same dimension. The dispersion is higher in this reactor leading to stirred tank behavior and also the mass transfer coefficient is comparable to static mixers. The detailed hydrodynamics and performance evaluation is studied in the chapter 2 of this thesis[25].

For the pilot scale reactor pinched tube chosen was of 36 meter length of ¼ inch diameter (volume 450ml) and distance between successive pinching of 5 cm. Total tube length was divided in 5 sections of length 3, 3, 6, 12, 12 meter respectively and individual reactors were constructed making the tube in helical shape and jacketing each tube for heating through

constant temperature water circulation unit. The reactor made from above tube were connected in series (**figure 4.13A**). At each intermediate connection point between the reactors a provision for sampling was made and also temperature indicator was added for temperature monitoring along the reactor length (**figure 4.13B**).

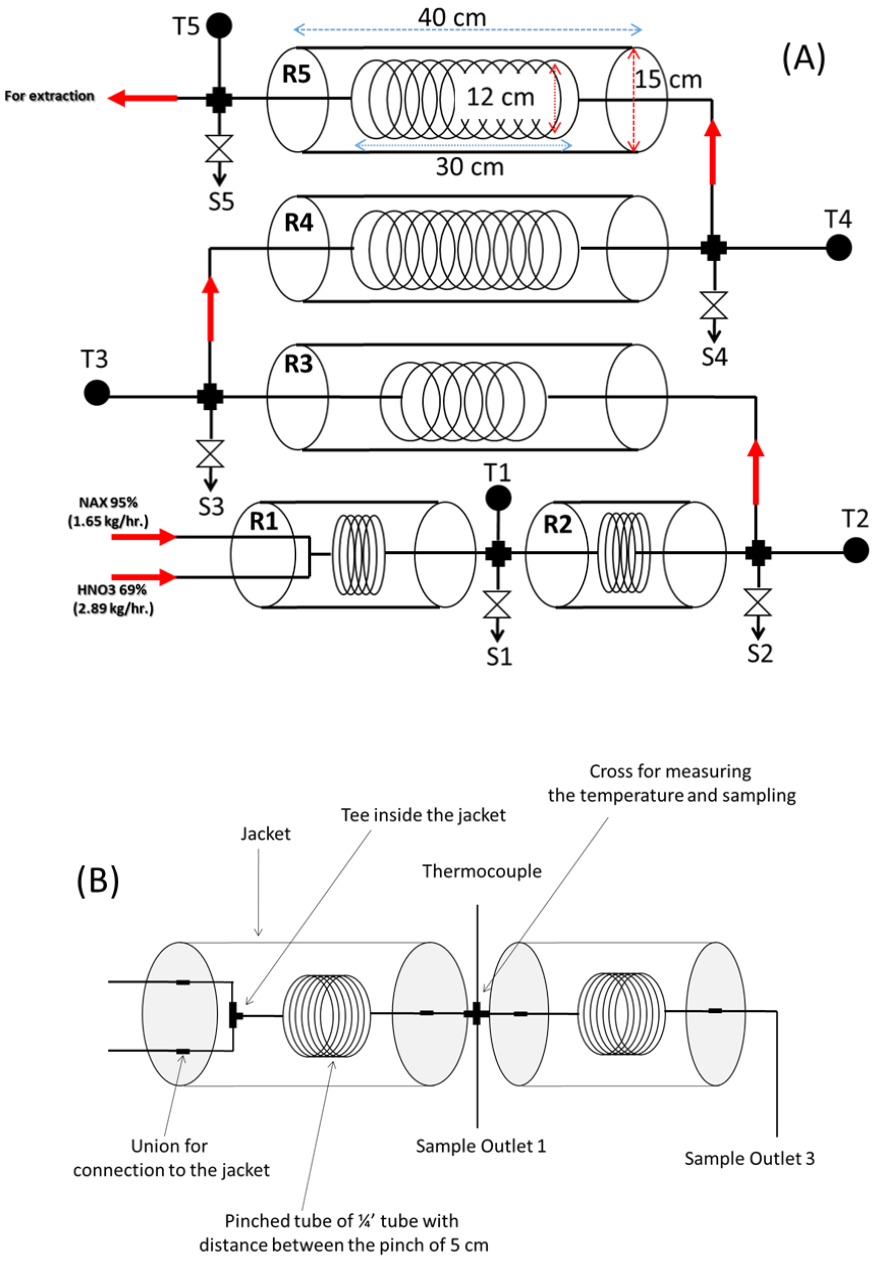
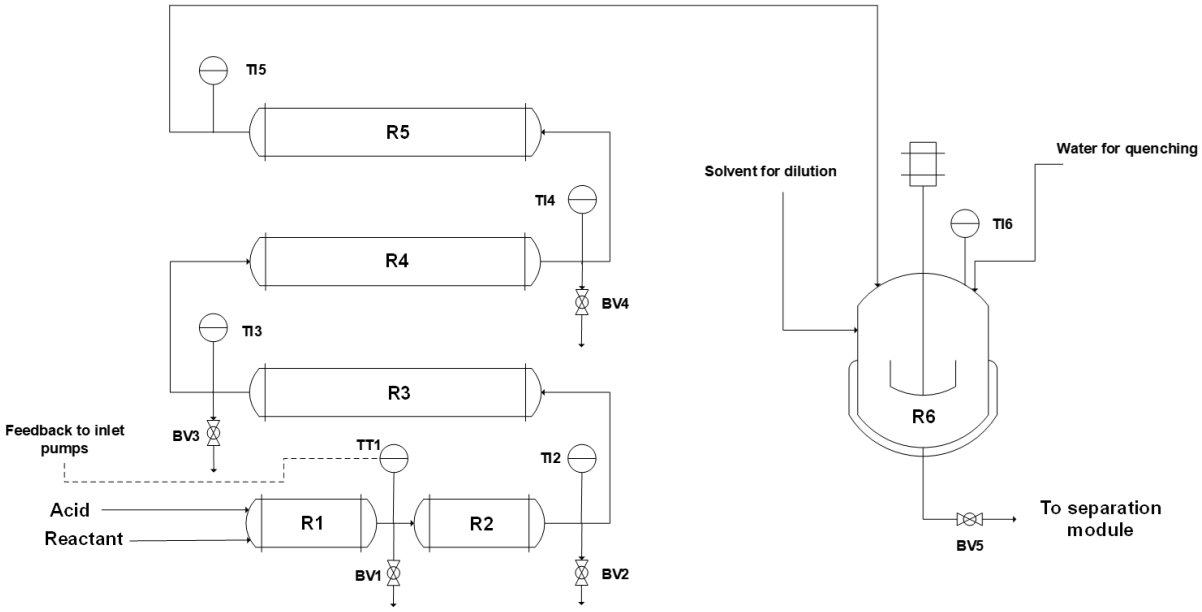


Figure 4.13 (A) Pinched tube reactor connected in series for 2kg/hour production;(B) Internal configuration of reactor



R1-R5	Pinched tube reactor in series
R6	CSTR for quenching and dilution
BV	Ball valve for intermediate sampling
TT	Temperature transmitter
TI	Temperature indicator

Figure 4.14 Process flow chart for pendimethalin manufacturing using pinched tube reactor in series for synthesis and CSTR for quenching

The inlet was provided at the first reactor where reactant and nitric acid is to be added with the help of piston pump. Reaction happened in the reactor from 1 to 5 and the reaction mixture was collected in the CSTR where water and solvent were added continuously to quench and extract the product from reaction mixture (**figure 4.14**). After quenching and extraction, the solution was subjected to continuous gravity separation where bottom layer (*organic phase*) was collected to the product tank and upper layer (*aqueous phase*) was collected in the tank for waste disposal. The procedure for quenching, extraction, separation was applied only at the fifth outlet however, samples collected at intermediate reactor were analyzed in terms of conversion with the same procedure of quenching, extraction and separation done offline. Based on the process flow diagram above and pinched tube reactor in series a pilot plant was fabricated incorporating various component all made in SS316. In the pilot plant all the storage

tanks were kept on weighing balance to continuously monitor the reduction in weight to check the flow rate. **Figure 4.15** shows the final fabricated pilot plant for the production of pendimethalin using pinched tube reactor connected in series.

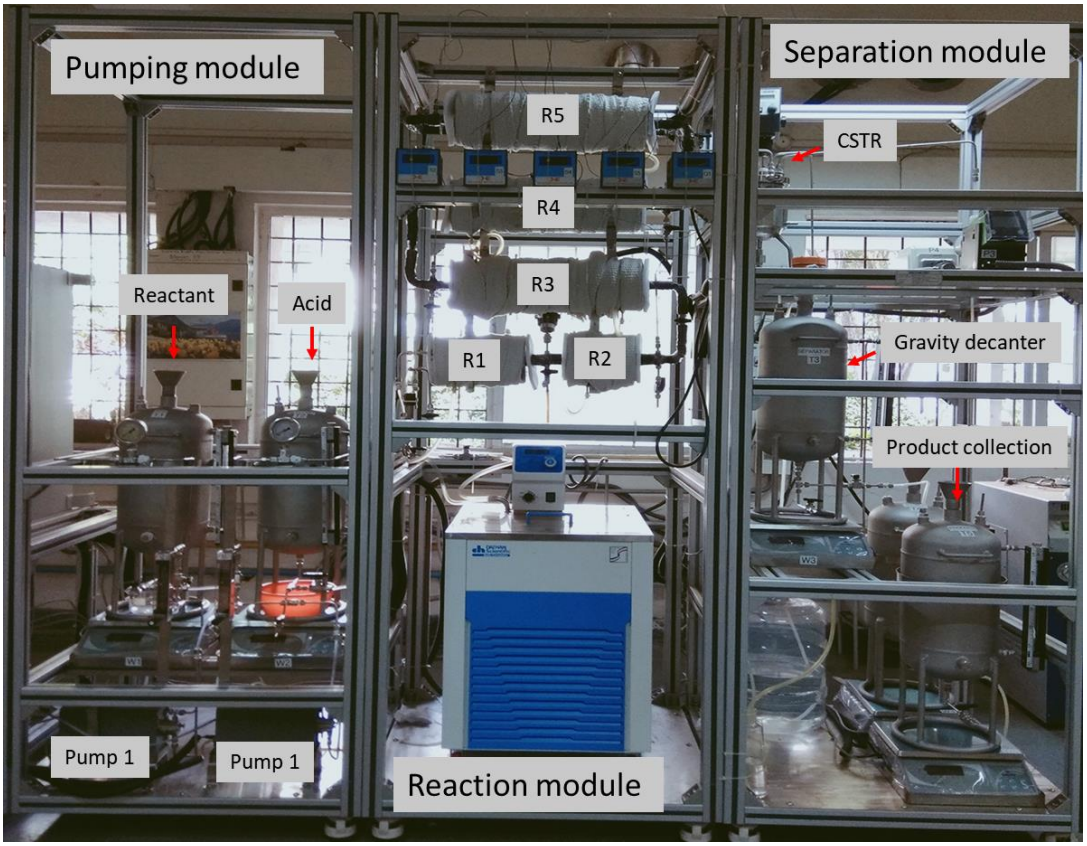


Figure 4.15 fabricated pilot plant for pendimethalin production

4.9 Evaluating the role of process equipment on steady operation

Large number of experiments were performed before running the pilot plant for optimized conditions obtained from the simulation. Different combinations of residence time (20 – 7 min), temperature (50 – 80°C), mole ratio (2.5 – 3.8) and the reactant composition (60 – 90%) were checked at the pilot scale. Each reactor was operated separately in combination with the previous one till it reached the steady state. The primary aim was to check the functionality of the instrumentations involved and also to identify any challenges associated (e.g. pulsation in pumps, reactor clogging, pressure monitoring, efficiency of separation etc.) before full capacity operation. For operation at scale up reactor developed lab protocol was

followed where the reactor was initially filled with nitric acid and the temperature was allowed to reach at the desired reaction condition. Once temperature was obtained the reactants were pumped in the reactor and the reactor system was allowed for achieving the steady state in terms of temperature. When temperatures were stabilized (shown by temperature indicators installed between the reactors) the samples were taken and analyzed according to the procedure mentioned previously. Experiments done at initial performance evaluation conditions showed that (**figure 4.16**) for any combination of parameters the product yield obtained was above 80% with by-product and other impurities below 20% which can be further converted into the product via separate procedure.

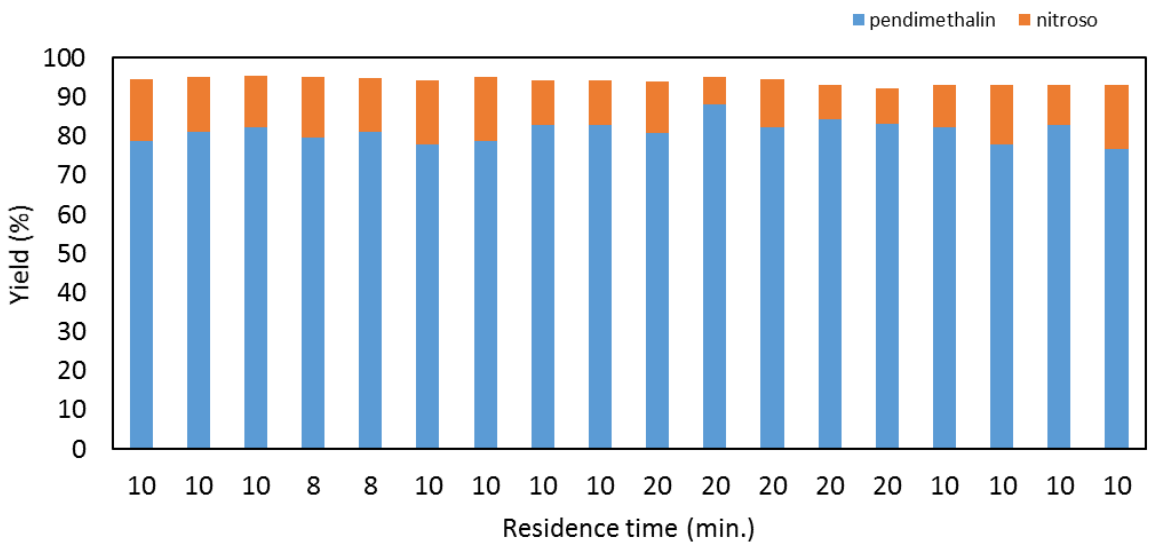


Figure 4.16 Reactions done at the pilot scale facility for the mole ratio of 1:3.65 (EPDMA: Nitric acid) for temperature range of 70°C to 90°C

4.11Steady state operation of the pilot plant

Conventionally, a batch reactor operates under the transient/dynamic conditions where concentration inside reactor changes continuously over time. Whereas CSTR and flow reactors operate under the steady state condition where concentration remains constant at the outlet of

the reactor and conditions at which reactor is to be operated is decided by the steady state conversion. In general, for any continuous reactor, the operations like start time, run time and shut-down time are unavoidable. The run time of a reactor is what is usually monitored carefully as that aims at achieving a reproducible and consistent performance in terms of production rate. However, the start time is equally important as it helps overcome all the limitations before the system reaches a steady state. For any reactor or process to reach a steady state, the slowest phenomena govern the specific time that ensures smooth operation of a pilot plant and that time decides the end of the start-up protocol. The time taken to achieve the steady state can be different and may vary for same reactor or process even at different conditions. Usually material produced before achieving steady state may or may not be useful as while it does not comply with the quality parameters, sometimes it can be recycled. So, the time required to achieve steady state will also correspond to the loss of production before getting the consistence output from the reactor. In general, it is assumed that for a CSTR the time required to achieve the steady state is more than three times the residence time, for a plug flow reactor and its variants the time is two times the residence time. These assumptions/thumb rules of steady state time are acceptable at the laboratory scale operation where the loss of material is not significant. Moreover, at laboratory conditions time for achieving steady state is considered, usually neglecting the time to achieve the steady state of temperature since at smaller dimension it is assumed that reactor is completely isothermal. At very small scale, the transport processes happening are usually better compared to systems at larger scale. As the characteristic length scales (viz. reactor volume, tube diameter, etc.) increase the diffusion path for mass, momentum and heat also increase significantly. This further implies that the relevant phenomena become less efficient and they add to the time needed to reach steady state. Usually temperature steady state is ignored, however sometime, being the slowest, it has greater implications on concentration steady state. In general, reactors are designed assuming certain

steady state performance (sometimes even considering a temperature profile) along the reactor length. Since temperature has a positive effect on the kinetics, need of longer time for reaching the required temperature results in loss of material quality for that duration. While these phenomena are inevitable, it is necessary to understand the role of different phenomena that lead to a steady condition of a reactor.

For bulk materials where cost is low and where reactor is going to be operated for several years after start up this time required for steady state does not matter much but still adds to the waste generated if time for steady state is considerable since operational flow rates are usually high. For the cases where output is low and reactor is to be operated as and when demand arises, every start-up time and shut down time play the critical role in deciding the effective profit from that operation. This issue can be very important in case of pharmaceuticals and nanomaterials where production capacities are low and material costs are very high [15,26-31].

In a pilot plant and at large scale commercial scale continuous production plant, complexity of the system and various interactions cycles between different instruments/streams/phenomena happening in the system cause the delay in reaching steady state. Key characteristic time scales relevant for mixing, mass transfer and reactions in a reactor include residence time (τ), reaction time (τ_R) dispersion time (τ_D) mixing time (τ_{mix}) , time scale of mass transfer (τ_m) time scale of heat transfer (τ_h). Effective rates of reactions and therefore effective conversion occurring in the reactor $X = f(\tau, [\tau_D, \tau_R, \tau_{mix}, \tau_m],\ C_{A0},\ T)$ may therefore depend on these characteristic time scales and is largely controlled by the longest scale or the slowest phenomena. In order to be able to realize full benefits of intrinsic reaction rates, it is essential that time scales of mixing, heat transfer and mass transfer are smaller than characteristic time scale for reaction (which is in turn smaller than the residence time). Interfacial mass transfer is particularly important for the case of multiphase reactions as in the present case. In addition to these time scales there are different instrument related time scales

and their interactions. Together it forms a complex situation that may not follow the thumb rules. For example, assumption that pumps operate under steady state is not always true. Pumps are the back bone of any flow plant, any fluctuation in the flow and the mechanism of operation also results into the disturbance in the system which directly affects the performance thereby sometime even deviating from the steady state even during operation. The other instruments which are located in the flow path of reaction mixture also interact very differently (viz. valves). As any disturbance in the flow path results in very different flow profiles it affects the performance to some extent. All of these effects together can delay the time to reach to the desired steady state of a plant.

It is very necessary to study this effect in separation since this phenomenon is very important to be quantified at larger scale. Once way to approach the problem is to do the complete system simulation but that may be quite complicated and will required large amount of data handling and will be very time consuming. Also, as plant requirements do vary depending upon the process, no general solution is possible for each case. We tried to simulate the reactor performance including only the effect of mass transfer and dispersion as these parameters significantly affect the system at large scale. Mass transfer is very important phenomena for the case of two-phase reaction and as the scale increase dispersion effects also become important. The reduction in mass transfer coefficient will result in reduction in rate of reaction since for the fast reactions the transport of one species form one phase to other will govern the kinetics. Maintaining the similar residence time distribution at every scale of operation is very crucial to have the same residence time for the conversion desired at every scale. This means that obtained axial dispersion values must be in close range for laboratory scale reactor and that of large-scale reactor. Higher axial dispersion can be easily correlated to the longer reaction time so it becomes necessary to characterize the residence time distribution of the reactor at every scale. It is very difficult to exclude the effect of these parameters in the

real systems since these phenomena happen simultaneously. Also, the mass transfer and residence time distribution studies are usually performed using nonreactive systems, the obtained values/similarities are only the indicator of the performance since the phenomena happening in the presence of reaction is very complex and cannot be characterized easily. As obtained kinetics in the case of our reaction was lumped kinetics which included the effect of mass transfer and dispersion at laboratory scale improving on these processes will reduce the time to achieve the steady state. For the simulations it was assumed that the obtained kinetics were the true kinetics where effect of mass transfer and axial dispersion were minimum and then mass transfer and axial dispersion were added in the kinetics individually reducing the kinetics to get the time for steady state. It was clearly visible from (**figure 4.17**) the simulations that this parameter affects significantly in terms of achieving the steady state as time to achieve the steady state was prolonged. This simulation done under the assumption that process was isothermal and system was under the steady state of temperature and effect of temperature was not included.

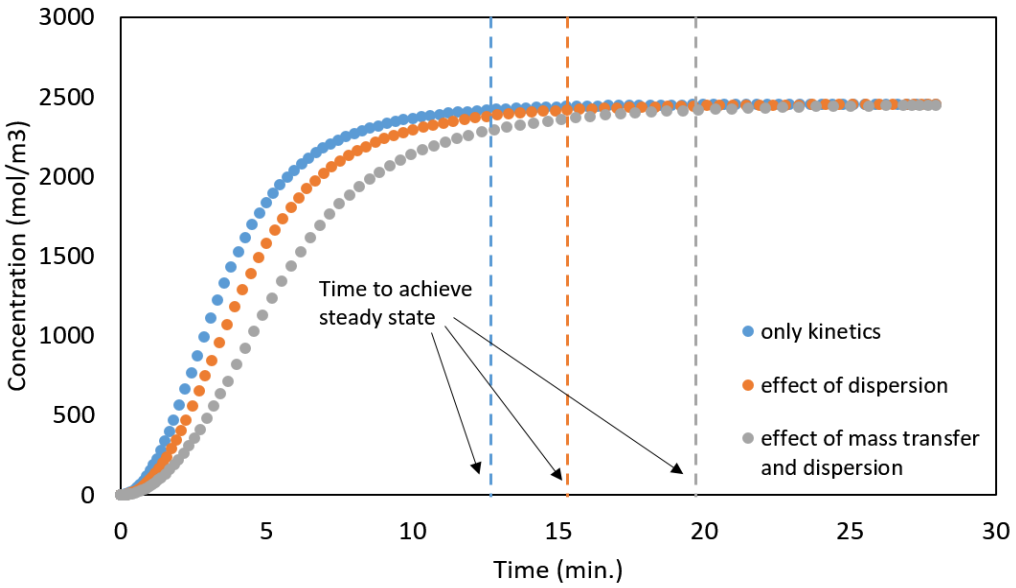


Figure 4.17 Predicted delay in time to achieve steady state including the effect of mass transfer and dispersion

To generate the effect of temperature and other parameters simultaneously happening at the large scale we monitored the running pilot plant and real time temperature data was recorded. It was hypothesized that effect of interaction of all the parameters in the system will directly affect the kinetics and in effect the heat released in the system so monitoring the time for reaching the temperature steady state is rate determining step for any system. To reach the temperature steady state following protocol was followed. Initially the reactor jacket was filled with water at the reaction temperature and solvent was pumped inside the reactor to flush the system with water. Immediately after flushing the system nitric acid was started in the system. Nitric acid was pumped till the temperature indicators located at reactor intervals showed desired reaction temperature. Once nitric acid reached the reaction temperature dosing of the organic reactant was started and temperature profile was recorded until the temperature at each indicator reached the desired reaction temperature. Deviating significantly from the expected thumb rule that it will take 2 times of mean residence time (volume/volumetric flow rate) to achieve state, the steady state was reached after 5 times of residence time. As there was no procedure to monitor the reaction conversion at the intermediate stages the sampling was done only after the system achieved the steady state. The temperature profile is shown below (**figure 4.18**). It can be seen that as reactant enters the reactor the temperature dropped significantly in the first reactor which was recorded as T1. Along the length as reaction mixture gets heated temperature start shooting up which were further monitored in the subsequent thermocouples attached in the intermediate stages. Though one reagent i.e. nitric acid was kept initially to the higher temperature and organic substrate were pumped at the room temperature the reduction in temperature can be attributed to the endothermic nature of the first reaction. Keeping this in mind the next experiments were done by preheating the reagents to the reaction temperature. There was no significant difference in the observed temperature profile. One other important thing to note here is that at lab scale syringe pumps were employed whereas at plant scale

piston pumps were used for continuous pumping. As in the piston pumps flow rate decides the frequency of piston strokes, synchronizing the pumps was essential which happened only few times over a run cycle due to the different flow rates. Also as mentioned earlier the flow rates from the pumps fluctuates (periodically due to piston movement) which may have contributed to the disturbance which was unavoidable.

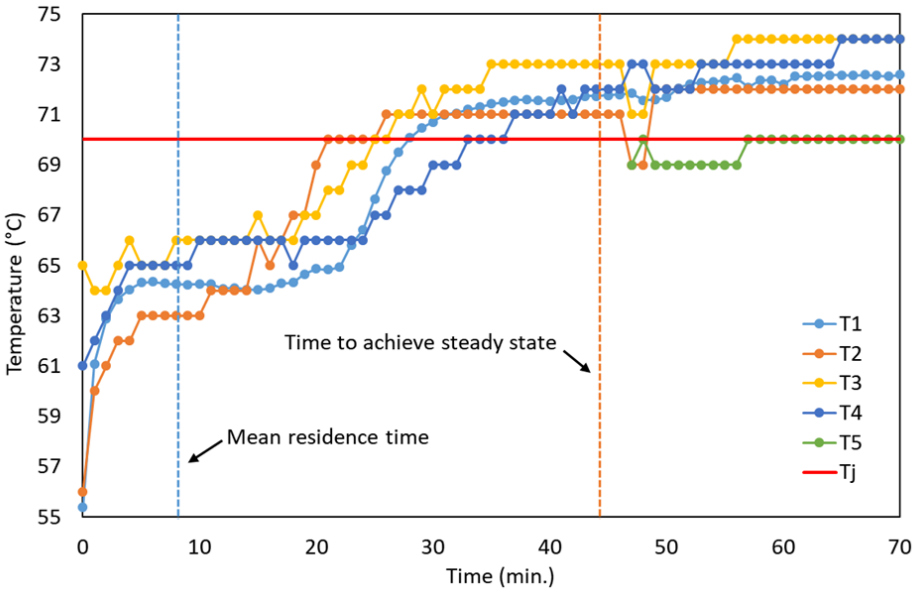


Figure 4.18 Time required to achieve steady state after start-up of the plant for the set temperature of 70°C

It is very important to characterize the time to achieve steady state since the kind of interactions happening in the reactor due to various phenomena occurring is very difficult to predict. In this scenario especially for scale up in flow synthesis assumption of linear scale up with the similar laboratory scale performance will become obsolete. Having intermediate pilot plant will help in terms of identifying the challenges in terms of steady states, interactions of different components, instrumentation, control loops and issues related to the operation at large scale which are generally not encountered at laboratory environment. It is recommended to fabricate the intermediate level pilot scale facility before going for full scale production since

this will reduce the time and effort in terms of solving unexpected challenges which can be known beforehand and with the developed protocol at the intermediate level production facility.

4.11 Conclusion

Scale-up of the di-nitration reaction for synthesis of selective herbicide pendimethalin using only nitric acid in continuous flow is presented in this work. This work showcases an approach for smooth scale-up for an herbicide for a production capacity of 50 kg/day using a pinched tube reactor. The approach begins with the batch experiments followed by flow synthesis using a 1/8-inch SS316 helical coil tube where kinetics of the di-nitration was determined and process optimization was done. Systematic approach was followed for quantification of heat transfer, mass transfer and residence time distribution and scale-up. Detailed scale-up methodology is presented with effect of relevant parameters for successful scale-up. Modular pilot plant with inline quenching, extraction and separation are some of the salient features presented in this work.

It is found that the time taken for achieving the steady state for large scale reactor is ~ 5 times that of residence time which is unusual. The probable causes for late attainment of steady state is explored and it is shown that simultaneous interaction of plant machinery, process parameters and transport process contribute in increasing the time for achieving the steady state after start up.

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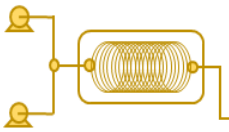
Chapter 5



Can Numbering-Up always be Economically Feasible

Manuscript is under preparation

Sharma, M. K.; and Kulkarni A. A.,

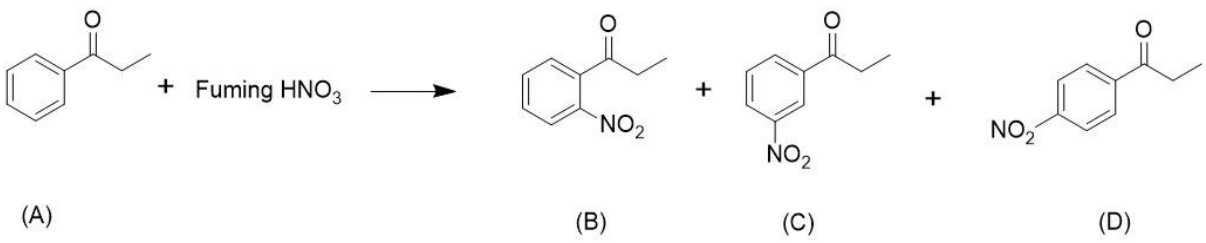
Capacity enhancement of continuous flow reactors by numbering-up is an established approach. This chapter evaluates the economic feasibility of the numbering-up approach for production of m-nitro propiophenone as a case study. For a range of operating conditions as well as the numbering-up strategies the CAPEX was found to increase with increasing volume fraction of the reactor made of smaller diameter tube. The CAPEX of the reactor with higher mole ratio of FNA and shorter residence time was much lesser, while the OPEX was always higher due to higher pressure drop and sometimes even higher load on utility to maintain isothermal condition in the reactor. The overall OPEX of reactor running at higher flow rates is found to be always higher. The variation of CAPEX was linear with respect to OPEX and the steepness in the dependence increased with increasing number of parallel reactors. It is worth noting that a reactor made from the combination of large and small sized tubes depending upon the relative rates of heat evolution during a reaction will achieve more profit and less payback period than having the entire reactor made of any single tube size.

5.1 Introduction

Continuous flow synthesis of high value intermediates and products has recently gained momentum after a large number of one step or one pot[1-4] kind of flow synthesis were demonstrated successfully at the laboratory scale. Some of the recent examples from the literature on end-to-end synthesis for valuable drugs on automated platforms highlights the importance and benefits of the state-of-the-art technology[5-9]. The key drivers for these successes in the continuous flow technology was the ability to induce rapid mixing, high heat and mass transfer rates, reduced levels of dispersion and new methods of conducting the reactions using a variety of energy sources[10-14]. Often these new environments/process parameters efficiently applied in small domains are termed as 'novel process windows'[15]. The novelty of continuous flow synthesis/processing is associated with very different operating conditions that help enhance the reaction rates and also to some extent the selectivity of the desired product in complex network of the reaction. One of the key issues in realizing the laboratory scale synthesis to a practicable production process is the selection of right kind of flow reactor and its operation. In the arena of different flow reactors[16-21] available in variety of materials of fabrication, capacities and a range of available hydrodynamic parameters, it is necessary to evaluate the feasibility of a laboratory scale synthesis in its "novel window" for its applicability to the large-scale production. In general, it is widely accepted that a laboratory scale flow synthesis developed at fairly intensified conditions resulting in better yields than conventional methods is always suitable for numbering-up. However, the lab-to-production approach has a lot more in between when the given product is to be produced continuously/manufactured in a sizeable quantity. As discussed in the literature it is possible to show the feasibility of a flow process through direct and indirect economic impacts[16]. However, it is possible to design a better reactor with a very different configuration and yet always check if a design makes a process feasible. Also, a given reactor geometry may not

always be applicable for all the reactions and inherently there should be a flexibility in the design procedure to achieve a design that meets all the design objectives and yet makes a process economical to be practiced in reality. In this paper we demonstrate on how different design concepts can still make one struggle to join all the pieces in a puzzle that aims to make an aromatic nitration commercially viable.

Nitration chemistry is an ideal candidate to be converted in continuous flow owing to its exothermicity and safety related issues, which has been studied for variety of substrates[22-25] One of the major challenges in the implementation of continuous flow technology has been the development and evaluation of an approach for scale-up based on the conditions optimized at the laboratory scale. Scale up approaches vary depending on the method, substrate properties, condition employed and reactor chosen at lab scale compared to conventional synthesis. Since the advantages of smaller dimensions are lost with conventional scale-up approach, major proponent of implementation of flow chemistry is the numbering-up approach. Though numbering up is an acceptable approach, it possesses its own challenges in terms of designing the suitable flow distributor where the significant amount of research is happening in the current scenario.



Scheme 5.1 Nitration of propiophenone

Propiophenone **(A)** nitration using fuming nitric acid (FNA) (**scheme 5.1**) results in the formation of nitro derivatives e.g. *o*-nitro-propiophenone **(B)**, *m*-nitro-propiophenone **(C)** and *p*-nitro-propiophenone **(D)**. Nitro-propiophenone derivatives are important intermediates for

the preparation of many drugs and organic compounds (e.g. ephedrine production, fragrance enhancer and polymer sensitizer). Nitro-propiophenones are one of the key intermediates for the synthesis of biologically active molecules (e.g. Radio sensitizers[26]). Nitro group on the aromatic ring can be reduced to respective amines which are important intermediates. Though being important in API synthesis, not much literature is available for the nitration of propiophenone. In the conventional approach, reaction is performed using mixed acid (mixture of nitric acid and sulfuric acid) at low temperatures (< 10°C) due to exothermic nature of the reaction. Also, presence of activating ethyl group results in the mixture of meta (*m*-) and para (*p*-) nitro-derivatives of propiophenone. Nitration also gives rise to many difficult to separate by-products, which decreases the overall yield of *m*-nitro-propiophenone **(C)**. Sulfuric acid enhances the overall reaction rate of nitration at the expense of utilization of large quantity of water for reaction quenching and subsequent neutralization of sulfuric acid generate large quantities of salt which needs to be disposed.

In the view of these issues, here we carry out nitration of propiophenone using FNA alone. Owing to the different rates of generation of nitronium ions, the conditions of nitration with only FNA will be different than that of nitration using mixed acids[27-29]. Reaction can be quenched by diluting it with water and organic phase can be extracted using any suitable organic solvent. By carefully optimized use of water for quenching, spent nitric acid of particular concentration can be obtained, which can be enriched for recycle and reuse. Since the rate of nitronium ion generation gets enhanced with temperature, higher temperature enhances the rate of nitration reaction.[30] In this chapter we bring out the economic analysis of different reactor configurations, based on range of conditions that yield better selectivity of **(C)**.

5.2 Experimental

5.2.1 Batch experiments

Initial experiments were carried out in batch mode via conventional procedure[26] with mixed acid (HNO_3: H_2SO_4 ~ 40/60 v/v). Concentrated (69-70 %) nitric acid was used for reaction and the mole ratio of propiophenone to nitric acid was varied from 1:1 to 1:3. Reactions were performed for 2 hours at 0^0C in a 250 ml jacketed glass stirred reactor. Reaction mixture was quenched in ice and the precipitated product was extracted with toluene and analyzed on GC. These experiments were reproduced from literature to observe the possible precipitation of the nitro derivatives and the associated time scales.

5.2.2 Flow experiments

The set-up comprised of Amar1 micromixer (Amar Equip. Pvt. Ltd., India) having an internal machined volume of 1 ml followed by a residence time tube (SS316 tube of 3.2 mm O.D. and 2.5 mm I.D.). The total volume of the assembly was 22.6 ml. The reactants, propiophenone and the nitrating agent (in SS316 syringes) were pumped to the micromixer with the help of syringe pump. Residence time tube was divided in four sections (of identical volumes), each having a sampling valve which helped to take samples along the length of the reactor. This assembly comprising of the micro mixer and residence time tube was immersed in a constant temperature bath (Julabo, Germany) to maintain the constant temperature for the whole unit. Experiments were carried out with mixed acid as well as with FNA as nitrating agent. Experiments were performed at different flow rates (to vary the residence time, 75 s to 1250 s) over a range of temperature (-10 ^{0}C to 20 ^{0}C) and for different mole ratio of the reactants (nitric acid to propiophenone ~ 1 to 12). Schematic of the experimental set-up is shown in **Figure 5.1**.

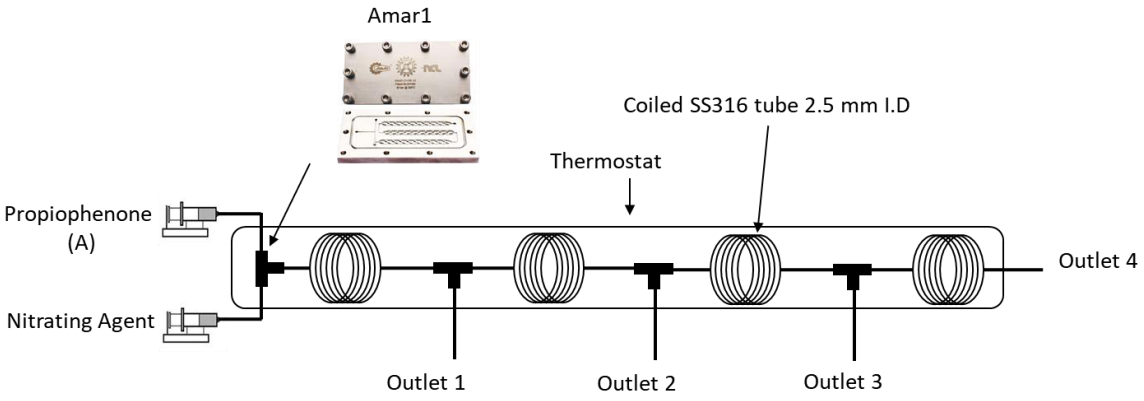


Figure 5.1 Schematic of the experimental set-up for nitration of propiophenone

Samples were collected for specific time to collect 5 ml organic phase in 30 g crushed ice from each sampling port. The organic phase was subsequently extracted in 3 parts using total 40 ml toluene. Water wash was given to the extracted organic phase to remove traces of acid. Washed organic phase was passed over bed of sodium sulphate to remove traces of water and this dry samples were analyzed on GC. Gas chromatograph was calibrated for different concentrations of propiophenone, and nitro-propiophenones using nitrobenzene as internal standard. Subsequently, known amount of internal standard was added in each sample during analysis and concentration was determined using previously obtained calibration chart. Each sample was analyzed thrice and obtained average concentration was used for further calculations.

5.3 Results and Discussions

5.3.1 Analysis of experimental data

Initially, batch experiments carried out at 0°C for 2 hours showed only 15% *m*-nitro-propiophenone (area % on GC) with several other peaks in the chromatogram. This data was used only for comparison with further continuous experiments. All further experiments were carried out in continuous mode using the set-up shown in **Figure 5.1**. The observations from

the continuous flow experiments are given in **Table 5.1**. It was observed that increase in mole ratio of nitric acid, residence time and temperature, all have positive impact on the overall conversion of propiophenone to nitro-propiophenone. However, performing the experiments at low mole ratio of nitric acid for longer residence time did not result in any improvement on conversion. The unavailability of sufficient nitronium ion in the absence of sulfuric acid was found to be the limiting condition during experiments at low mole ratio.

Table 5.1 Effect of parameter variation on conversion in continuous flow experiments for samples collected from the last outlet

Mol ratio $PhCOC_2H_5$: fuming HNO_3	Temperature (°C)	Residence time (Sec.)	Conversion (%)
1:2	10	300	18
1:4	10	300	34
	20		59
	30		60
	40		67
1:8	-10	300	98
	-5		99
	0		99
	10		99
1:12	0	1320	99
	10	1320	99
	10	300	99

For the mole ratio of 1:4 (propiophenone to FNA) increasing the residence time and temperature (**Figure 5.2**) resulted in improvement in conversion but the conditions were not sufficient for complete conversion.

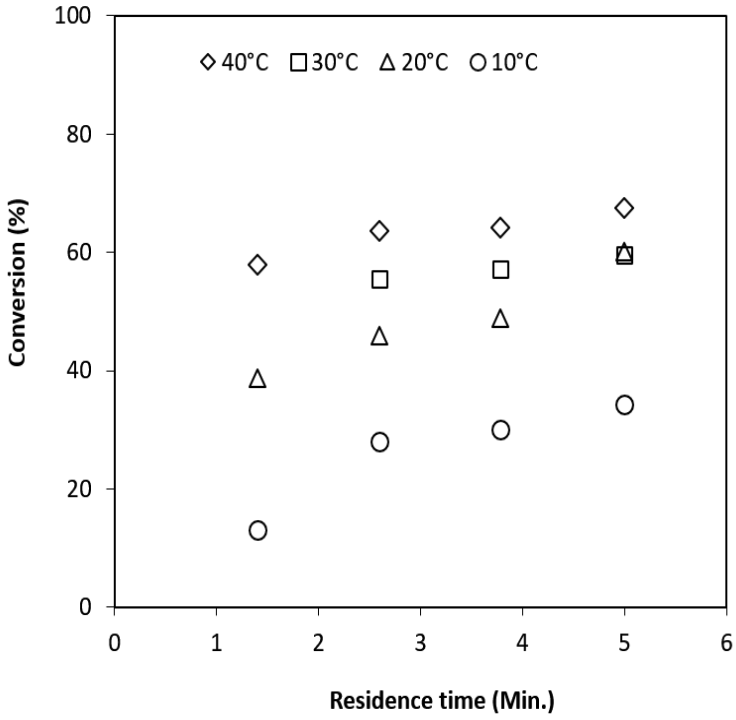


Figure 5.2 Effect of temperature and residence time on the conversion obtained for mole ratio of propiophenone to fuming nitric acid 1:4.

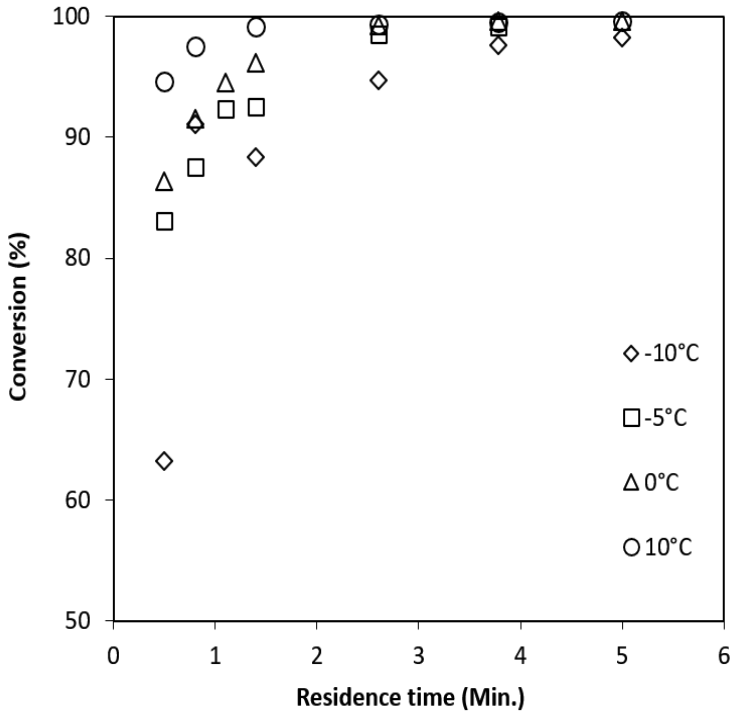


Figure 5.3 Effect of temperature and residence time on the conversion obtained for mole ratio of propiophenone to fuming nitric acid 1:8.

Reactions carried out at the mole ratio of 1:8 (propiophenone to FNA) also showed similar trend (**Figure 5.3**) where conversion increased after increasing the temperature and residence time. However, at 10°C, nearly complete conversion was obtained for mole ratio of 1:8 compared to that of 1:4 at significantly low residence time of 90 s. At very high mole ratio of 1:12 reaction was complete in less than 40 s. It is important to mention here that only two isomers *o*-nitro-propiophenone (**B**) and *m*-nitro-propiophenone (**C**) were formed when experiments were carried out using fuming nitric acid, whereas experiments using mixed acid resulted in several peaks during GC analysis, leading to very low yield of nitro-derivatives. The isomers obtained can be isolated easily based on the solubility in the organic solvents like methanol, ethanol etc.

Similar to other aromatic ketones, in propiophenone, *meta* position is more susceptible for nitration. At lower concentrations, nitric acid gets diluted (generation of water during the reaction reduces the nitronium ion generation), which decreases the rate and hence takes more time for the completion of the reaction. Also at higher concentrations of FNA the reaction is homogeneous in nature and as the reaction progresses, since the reactants and products are insoluble in water, water formed in the reaction makes the reaction heterogeneous where mass transfer and diffusion of nitronium ions to organic phase plays vital role.[31,32] Thus, depending up on the degree of mixing, lower mole ratio of reagents is not very effective for the conversion. As one part of the ketone group contains aromatic ring and the other is a propyl linkage due to positive inductive effect, the electron density on both ortho and meta position remains nearly the same hence some amount of the ortho isomer is also favored during the course of the reaction. Hence theoretically, for most of the conditions the *meta* to *ortho* isomer ratio should be between 1 to 1.1, which can change depending upon the reaction temperature. From the flow experiments in this work, the yield of *m*-nitro-propiophenone (**C**) was always higher than that

of *o*-nitro-propiophenone (**B**), and in specific cases the mole ratio of these isomers *m*:*o* was close to 1.75.

5.3.2 Reactor sizing and feasibility

The conventional process for nitration of propiophenone is based on the semi batch mode that needs significantly long reaction time at very low temperatures. Making this process continuous has its benefits in terms of intensifying the operation at much higher temperatures than the conventional batch mode, reducing the foot print of the reactor and also saving on utility. In the rest of this manuscript we have compared different reactor options to check its feasibility through the analysis of process economics for a fixed production capacity.

As a benchmark for comparison, we have considered the batch nitration data of propiophenone. The total heat duty was estimated based on the 84% conversion of propiophenone to nitro-propiophenone when nitration was carried out at -10 to -5°C. Mole ratio of nitric acid to propiophenone used was 4.23:1 with slightly higher ratio of sulfuric acid to nitric acid i.e. 1.23:1, which allows the reaction to complete in 30 minutes. The heat of reaction estimated on the basis of bond energy of product and the reactants is -133.96 kJ/mol.[33] Other properties of the reactants and products (viz. density, viscosity, specific heat capacity, thermal conductivity, etc.) were taken from the MSDS of individual compounds obtained from the suppliers. The heat release rate for the conditions reported in the literature[34] and quantity of substrate was estimated independently. In the presence of excess nitrating agent, reaction was found to be first order with rate constant 0.00254 (1/s) calculated from initial rates of reaction and the activation energy for reactions was 30.74 kJ/mol. This helped to estimate the heat generation rate for batch mode (as reaction proceeds) and was used for the design of a batch reactor for the production of 1000 kg per day of product (**C**). The details of the calculations are not given as these are standard text book methods.

5.3.2.1 Batch reactor

For the production of 1 ton per day (TPD) of *m*-nitro propiophenone in a batch reactor, it was assumed that 3 batches were operated every day with 8 hour of batch time (including charging of substrate, addition of chilled nitrating agent, reaction, quenching, product withdrawal and washing of the reactor). Initially the reaction rates will be high and to avoid the rapid heat generation the nitrating agent was added over the time (2 hours). The heat generation profile was estimated and corresponding cooling cost was also calculated to obtain the expenses on utility.

5.3.2.2 Continuous stirred tank reactor (CSTR)

Based on the reaction kinetics, checking the feasibility of the CSTR for this specific nitration, 4 equal volume (45 L) CSTR's were selected. Conversion at the outlet of each reactor was calculated using standard equation. Calculations were carried out to estimate the heat load under steady state condition for each CSTR.

5.3.2.3 Flow reactor/Tubular reactor

For the desired production rate, the reaction kinetics were used for estimation of total plug flow reactor of volume, which comes out to be 39 L under isothermal conditions. Length of the reactor in this case may vary depending on the reactor diameter. The standard sets of design equations were used for estimation of reaction time for achieving 85% conversion from the batch as well as CSTR. As expected, the overall cooling capacity needed as we go from batch to flow reactor decreases (owing to different heat transfer coefficients and heat transfer area in each case) and it plays a significant role in the operating costs as it will directly reflect in the utility requirement.

Table 5.2 Comparative performance of different ideal reactors at a fixed reactor temperature of -5°C and fixed jacket side utility flow rate (2000 L/hr.)

	Batch reactor	CSTR	Plug Flow reactor
Reactor volume (m3)	2.24	0.045	0.039
Number of reactors	1	4	1
Flow rate (L/min)	--	3.27	3.27
Batch/Residence time	8 Hr	39 Min	12 Min
Average heat release rate (kJ/s)	20.14 (Actually varies with time)	10.03 (can vary based on number of CSTRs in Series)	10.03 (varies along the length of reactor)

Since the plug flow reactor seems to be more efficient (also based on the flow synthesis experiments discussed earlier) among the three, here we present a detailed analysis of the economic feasibility of different tubular reactor configurations for the production of 1 TPD of *m*-nitro propiophenone (C) (i.e. about 700 g/min). Seamless SS316 tubes offer variety of configurations that can be used for fabricating a flow reactor[35-38]. The focus will be on the jacketed tubular reactor and we compare the effect of various design parameters on the economics of a flow reactor. The reaction conditions (residence time, temperature) that yields maximum selectivity for *m*-nitro propiophenone (C) was considered as the design basis[39]. As a simple system, it was considered that the reactor is to be fabricated using a combination of different sections made from SS316 tubes of $^{1}/_{8}$" outer diameter (2.5 mm inner diameter) and ¼" outer diameter (i.e. 6.3 mm inner diameter), which allows to have different heat transfer area values. Basic information brings out following three key indications: (i) the ¼" diameter tube is costlier by 1.26 to 1.4 times than that of the $^{1}/_{8}$" diameter tube, (ii) one would need 6.35 times longer tube of the $^{1}/_{8}$" diameter to occupy the same volume as the ¼" diameter tube and (iii) $^{1}/_{8}$" diameter tube offers twice the heat transfer area per unit length but with significantly higher pressure drop than the ¼" diameter tube. Thus, for producing a fixed quantity of *m*-nitro propiophenone, it is possible to design a reactor having specific residence time and the volume

such that it would have variable heat transfer area along its length, which would imply different ranges of pressure drop and hence the operating cost. Thus, depending upon the heat generation rate, which would be proportional to the differential reaction rate along the tube length, it is necessary to ensure that adequate heat transfer coefficient is ensured by providing the necessary heat transfer area as well as the Nusselt number (*Nu*) on tube as well as shell side. It is always possible to design a flow reactor that can take care of location specific heat duties as the reaction proceeds along the length of the reactor.

5.3.3 Assumptions

The analysis of economic feasibility is based on certain assumptions as follows: (i) For a fixed capacity and for a given condition the (%) selectivity is independent of the reactor design and hence the downstream processing costs will remain the same, (ii) The extent of variation in the axial dispersion is negligible for different reactor configurations, and (iii) For a given throughput the pumps will also have a possible narrow variation in the pressure drop and hence the cost of the pumps of specific material of construction will not vary significantly.

5.3.4 Approach

Considering the above assumptions and criteria, here we give a quick approach that allows one to evaluate the possible designs of a flow reactor and the relative variation in the costing. Some details on various reactor design approaches can be found in Joshi and Doraiswamy[40]. It is known that while the heat of reaction is an intrinsic property of a transformation, the overall heat release rate depends on the extent of conversion of the limiting reactant. For exothermic reactions as in this case, on the basis of the volume fraction of reactor that yields a specific heat duty (or heat generation rate), the length of reactor can be estimated depending upon the required heat transfer area (for specific tube diameters), which eventually

yields the cost of the specific section of the reactor. Depending upon the fraction of the reactor used for different heat loads, the total capital cost (CAPEX) of a reactor (including the cost of jacket depending upon the geometrical configuration of reactor, viz. coil, double coil, triple coil, etc.) can be obtained. The cost of the connectors, flow distributors as well as the peripheral equipment (pumping, utility, storage, etc.) and control system (pressure transmitters, temperature sensors, control loops, central data acquisition and control system) can be added to the capital cost (tubular reactor + jacket). The operating costs (OPEX) primarily include the cost of pumping due to pressure drop at a given flow rate in different sections of the reactor, the cost of utility and its pumping through the jacket and the cost of operating control system and its maintenance (usually a very small fraction). Usually, single long tubular reactors are uneconomical (due to excessive pressure drop that leads to higher operating costs, as well as reactor of higher thickness which increases the CAPEX), and hence are run by numbering up, which reduces the flow rate through each reactor and hence also the resulting pressure drop. Thus, while the capital cost of the reactor can be retained more or less the same, the operating costs can be reduced. Also, the capital costs and peripherals including the control system are one-time investment and it usually depreciates and also needs maintenance, which adds to the recurring costs of a plant.

A few such assemblies of tubular reactors can be seen in the literature[19,38,41-43]. In the present case, the typical costing was performed based on the present cost of the reactants, products and material of reactor obtained from various sources. The standard depreciation rates, escalation in prices of raw materials and products, maintenance and repair costs and the down-time costs of the reactor (for 300 days of operation in a year) were taken into account. The CAPEX investment was distributed over a period of 5 years, it is possible to compare the feasibility of different reactor options based on the variation in the different economic indices for a range of conditions that will lead to identical yield of the desired product.

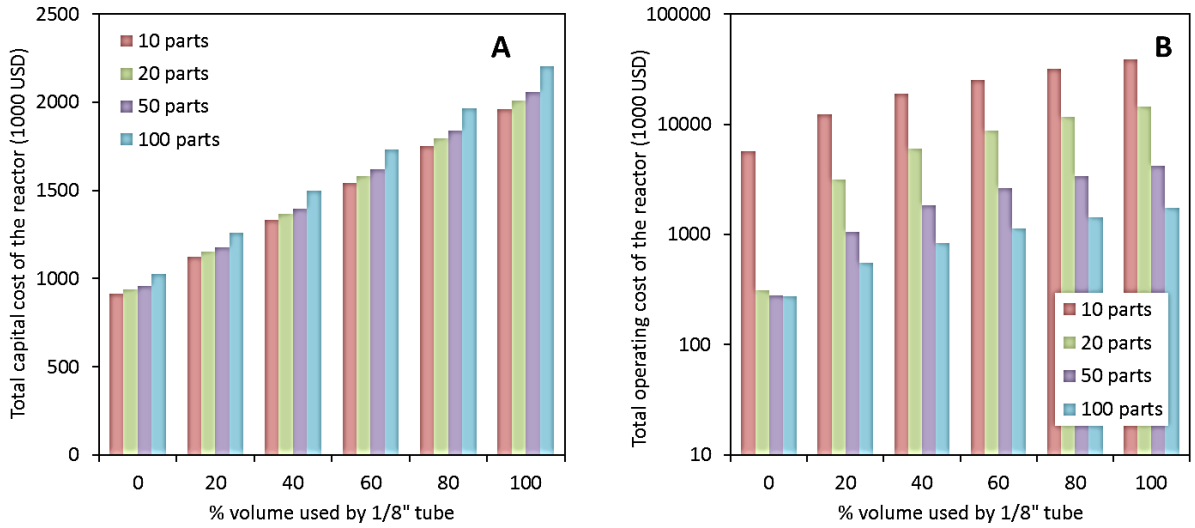


Figure 5.4 Economic analysis of the nitration of propiophenone using SS316 tubular reactors for nitric acid to propiophenone mole ratio of 4.5:1; (A) Variation in the CAPEX with the volume fraction of 1/8" o.d. tube; (B) Variation in the OPEX with the volume fraction of 1/8" o.d. tube; used for constructing a flow reactor (remaining volume is occupied by ¼" tube).

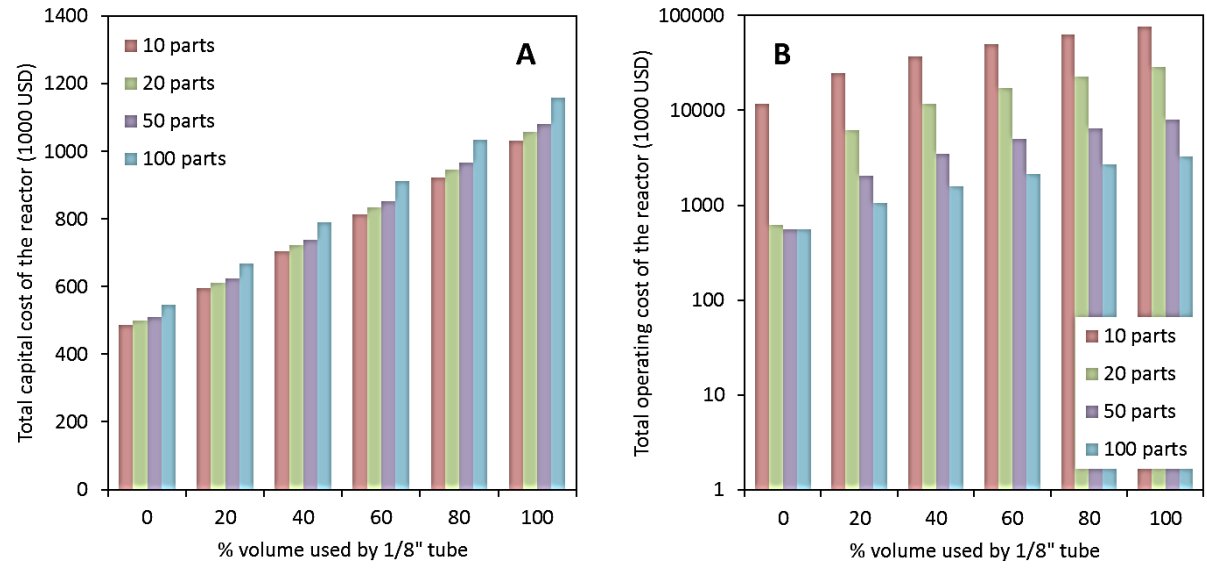


Figure 5.5 Economic analysis of the nitration of propiophenone using SS316 tubular reactors for nitric acid to propiophenone mole ratio of 8:1; (A) Variation in the CAPEX with the volume fraction of 1/8" o.d. tube; (B) Variation in the OPEX with the volume fraction of 1/8" o.d. tube; used for constructing a flow reactor (remaining volume is occupied by ¼" tube).

Independent of the mole ratio of the Fuming nitric acid to Propiophenone as well as the numbering-up strategy, the CAPEX continued to increase with increasing volume fraction of the reactor made out of smaller diameter tube (**Figure 5.4A, 5.5A**). This is quite expected as

the cost of reactor made from smaller size tubes will always be higher due to larger lengths needed to occupy the same volume. On the other hand, smaller diameter tubes would offer higher pressure drop and hence the power consumption as well as the pump specifications will also end up in higher investments. Use of less mole ratio of fuming nitric acid (**Figure 5.4A**) would need longer residence time and higher temperature for completion of the reaction, which would need a larger reactor volume and hence higher CAPEX when compared to the reactor operated with mole ratio of 8:1 (**Figure 5.5A**) even in shorter residence time (180 s) and lower temperatures (0°C). Thus, the contribution of the reactor cost to the variation in the CAPEX will always be more than the other fixed assets. Having different numbering-up strategies would help to reduce the length of individual tubular reactor and would demand a precise design for the flow distributor. Considering that the flow distributor can be designed with the help of adequate upstream pressure drop that yields uniform flow distributon in all the parallel tubes (in coil form), having more parallel streams makes the capital cost to increase independent of the operating conditions and stoichiometri ratio to achieve complete conversion of the substrate. Thus, the capital cost of the reactor depends not only on the residence time and flow rates of substrates but also the rate of heat removal by the utility fluid for a given tube diameter.

The operating cost is also important and may show non-monotonous linear increase with increase in the volume fraction of the reactor made of 2.5 mm i.d. tube. As expected the total OPEX decreased with increasing number of parallel reactors (**Figure 5.4B, 5.5B**). The overall OPEX of reactor running at higher flow rates is always higher. The gradient of reduction in OPEX decreased with increasing number of parallel units. Which implies that it is possible to identify a critical number of parallel reactors beyond which the OPEX will not change significantly. This observation is quite notieable when the most of the reactor is made out of larger tube size. However the total cost of the reactor i.e. CAPEX and OPEX over a period of

time would decide the most feasible design option and hence the variaton in OPEX as a function of CAPEX for all these cases will help to make such a preliminary choice.

In view of this, we considered the two cases (**Figure 5.4,5.5**) and plotted the CAPEX vs. OPEX for the reactor that allows to achieve complete conversion of propiophenone to nitro propiophenone (**Figure 5.6**). As discussed earlier, it is clear that for either cases the numbering-up strategy has a strong effect on the nature of this variation. The CAPEX of the reactor with higher mole ratio of fuming nitric acid and shorter residence time was much lesser, while the OPEX was always higher due to higher pressure drop and higher load on utility to maintain isothermal condition in the reactor. The variation of CAPEX was linear with respect to OPEX and the steepness in the dependence increased with increasing number of parallel reactors.

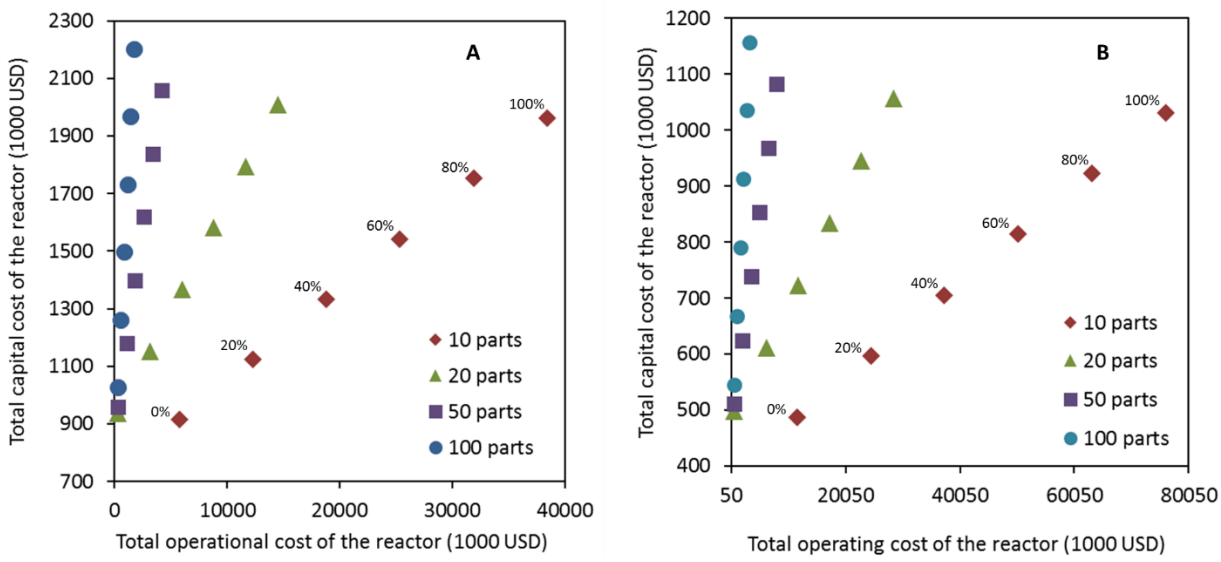


Figure 5.6 CAPEX vs OPEX for the reactor for complete conversion of propiophenone in flow reactor divided in number of parallel reactors (10-100 parts); (A) fuming nitric acid to propiophenone 4.5:1; (B) fuming nitric acid to propiophenone 8:1. [*Number on legends indicate the volume fraction of 1/8" o.d. tube used for making the reactor]

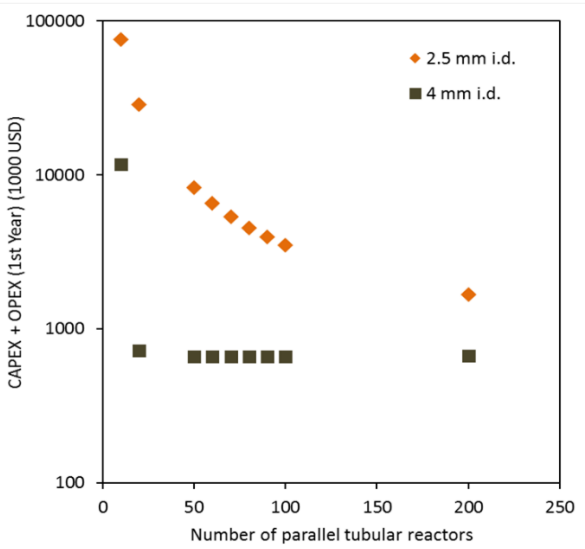


Figure 5.7 Variation in the CAPEX + OPEX (for 1st Year) as a function of the volume fraction of the reactor made of 2.5 mm i.d. SS316 tubes for complete conversion of propiophenone in flow.

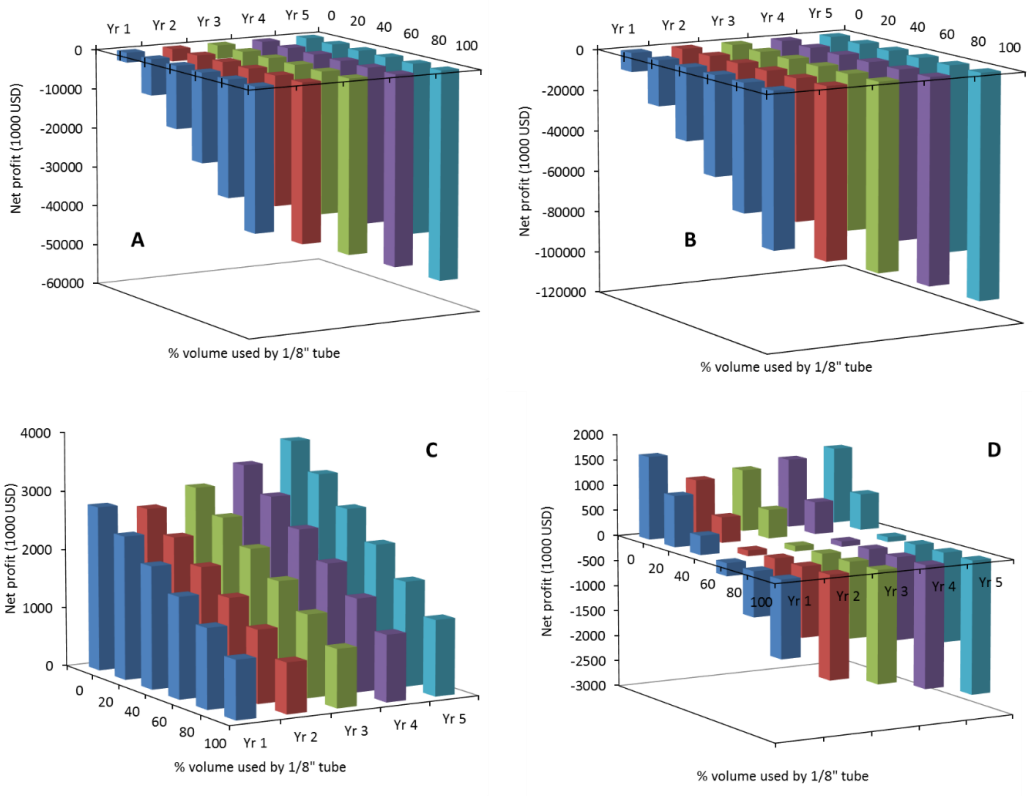


Figure 5.8 Effect of design and numbering-up approach on the annual net profit (in 1000 US$) from operating a continuous flow tubular reactor. (A) FNA:PP = 4.5:1, t = 600 s, 20°C with flow distributed in 10 parallel reactors, (B) FNA:PP = 8:1, t = 180 s, 0°C with flow distributed in 10 parallel reactors, (C) FNA:PP = 4.5:1, t = 600 s, 20°C with flow distributed in 100 parallel reactors, (D) FNA:PP = 8:1, t = 180 s, 0°C with flow distributed in 100 parallel reactors.

Upon plotting the total investment for the first year (**Figure 5.7**) (CAPEX + OPEX, considering that the CAPEX is distributed over 5 years) it can be seen that the reactor with larger diameter (4 mm) is always economical. Further analysis of the economic feasibility of such a reactor can be done based on the net annual profit from the reactor. The values of net annual profit as a function of the % volume of the reactor made of 2.5 mm i.d. tubes for various conditions (designs for specific operating conditions and numbering-up approaches) are shown in **figure 5.8**. It is clear that operating a reactor with only 10 parallel configurations at lower as well as higher mole ratio leading to a reaction time more than 180 s is never beneficial. However, if the number of parallel operating reactors is increased to 100, the same process becomes feasible with certain design constraints. Upon having a mole ratio of fuming nitric acid to propiophenone = 8:1, at 0°C and a residence time of 180 s, the reactor is always feasible if the % volume occupied by 2.5 mm tube is kept always less than or equal to 20%, preferably only at the inlet section where the heat generation rates are high due to higher concentrations and need higher heat transfer area.

5.4 Conclusions

Feasibility of a continuous flow tubular reactor for the nitration of propiophenone using fuming nitric acid is studied. The effect of concentration of fuming nitric acid, temperature, residence time and the diameter of the reactor on the conversion of propiophenone and the yield of desired m-isomer was studied. Lower concentrations of fuming nitric acid even at having longer residence time as well as higher temperature do not help to achieve complete conversion of the substrate. Higher mole ratio (> 4.5) is always favorable to achieve complete conversion within a few minutes.

The evaluation of the tubular reactor for manufacturing of 1TPD of m-nitro propiophenone was studied by designing different configurations of the reactors for a range of

mole ratio, residence time and temperature to achieve complete conversion of propiophenone. A single long tubular reactor is always uneconomical (due to excessive pressure drop that leads to higher operating costs as well as material of higher thickness which increases the CAPEX). While the capital cost of the reactor can be retained more or less same, numbering-up helps to reduce the OPEX.

For a range of operating conditions as well as the numbering-up strategies the CAPEX was found to increase with increasing volume fraction of the reactor made out of smaller diameter tube. The CAPEX of the reactor with higher mole ratio of FNA and shorter residence time was much lesser, while the OPEX was always higher due to higher pressure drop and higher load on utility to maintain isothermal condition in the reactor. The overall OPEX of reactor running at higher flow rates is always higher. The variation of CAPEX was linear with respect to OPEX and the steepness in the dependence increased with increasing number of parallel reactors.

In general, the reactor with larger tube diameter is always economical, however may not be always feasible in view of the variable heat load from inlet to the outlet. Hence for a given combination of initial small section made out of smaller diameter tube followed by larger tubes, and several such reactors run in parallel it is possible to choose the best combination on the basis of the net annual profit from the reactor. An order of magnitude increment in the number of reactors operated in parallel was seen to make the process feasible with large net profit. Thus, a combination of small residence time, manageable heat duty and large number of parallel network of reactors will allow an economical process. If the contribution of CAPEX for a given manufacturing capacity is significant (which can be the case for reactors involving significant machining/fabrication) and the overall heat duties can be managed in multiple sections, even the best performing flow reactor may not make a process economically feasible.

A detailed economic analysis of specific systems including the complete plant configuration for this system is in progress and will be presented separately.

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Multistep continuous flow synthesis of pharmaceuticals

National Chemical Laboratory (Pune) - INDIA

Chapter 6

Multistep synthesis of Edaravone in continuous flow

Manuscript is under preparation

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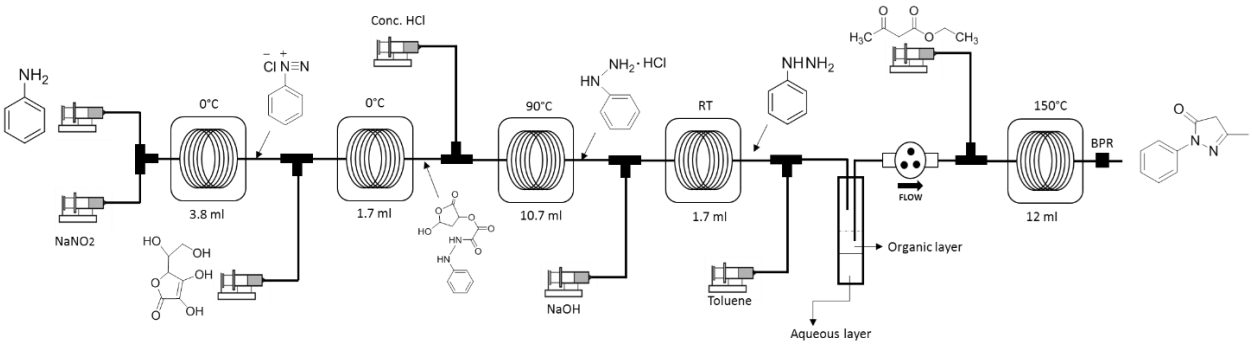


An integrated multistep continuous flow synthesis of drug Edaravone a free radical scavenger used for the treatment of amyotrophic lateral sclerosis (ALS) starting from aniline is presented in this chapter. Different aniline derivatives were used for the synthesis of respective hydrazines using their diazonium salts also synthesized in continuous flow. The hydrazine resulting from aniline is further used for the synthesis of the target drug. The multistep flow synthesis platform includes inline extraction, continuous separation, and microwave based flow synthesis. Very good yields (69 %) within short residence time were obtained compared to the batch synthesis protocol that needs hours.

6.1 Introduction

The pharmaceutical industry has been witnessing a radical change over the past decade by slowly adapting to distributed manufacturing while utilizing the benefits of flow chemistry for making the process more efficient[1-4]. Excellent heat and mass transfer, short reaction time, constant product yield and consistent product quality are a few of the well-known advantages of continuous flow synthesis [5-10]. Low processing volume provides safe handling of toxic and hazardous chemicals even at elevated process variables [11-13]. Elevated process parameters actually enhance the reaction rate, making reaction faster which increases the production capacity in a safe manner which is usually not the case in the conventional approach. To date, a large number of drug syntheses protocols have been transformed using flow synthesis making flow chemistry as the most promising tool for future pharmaceutical manufacturing [14-18]. Modular continuous process plants will offer benefits in terms of ease of assembly, logistics, and distributed production for the pharmaceutical industry where the final product is synthesized from several ingredients which are being synthesized at different locations in conventional mode. Such an approach involves high space-time demands for the final drug molecule to be synthesized [19]. To add to many drugs that are already synthesized using integrated multistep flow synthesis platforms [17,19-24], here we present the synthesis of Edaravone.

Edaravone has recently been approved by the US FDA as a drug which is a free radical scavenger used for the treatment of amyotrophic lateral sclerosis (ALS). ALS is a disease caused by an acute neural infection. This disease kills the nerve cells that control the voluntary muscles which are used for normal body function, a condition that gets worse over time. Most people with ALS die from respiratory failure, usually within three to five years from when the symptoms first appear. The control of such disease is very important and based on experience in Japan, the US FDA has approved this drug for treating ALS [25]. Edaravone is a pyrazolone

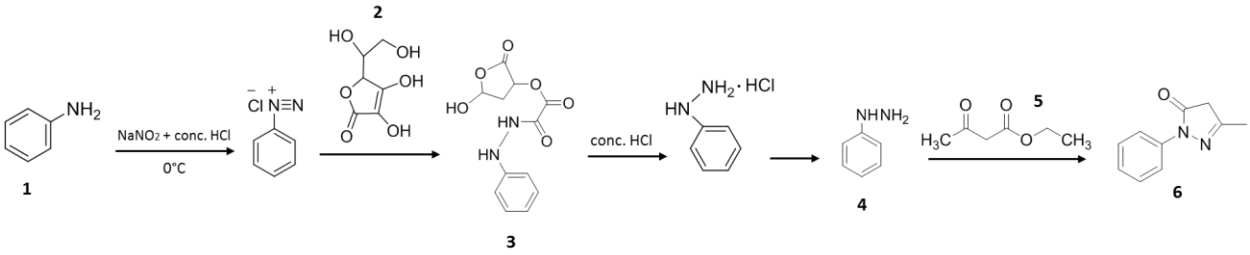
based drug, which is synthesized by reacting Phenyl hydrazine with Ethyl-acetoacetate [26]. Different methods for the synthesis are reported in the literature with various conditions (e.g. using ethanol as solvent [27], without solvent [28], with reflux [29] and at normal temperature [30]). The synthesis time varies according to the batch process conditions but is usually in the range of a few hours. Phenyl hydrazine is toxic and very corrosive to the skin [31] which is synthesized by diazotization of aniline and reduction with a suitable reducing agent [32-34]. It is well known that diazotization is a fast and exothermic reaction, which requires precise temperature control else it can undergo decomposition and is a potential hazard at a large scale [35]. To avoid the challenges associated with handling of phenyl hydrazine and utilization of flow chemistry for safely carrying out the diazotization chemistry, here we describe the synthesis of Phenyl hydrazine for various anilines in a continuous flow manner and later extend it to the integrated continuous flow multistep synthesis of Edaravone.

6.2 Results and Discussion

6.2.1 Flow synthesis of Phenyl hydrazine

As mentioned previously Edaravone was formed by the reaction of Phenyl hydrazine and Ethyl-acetoacetate. In batch, (**Scheme 6.1)** Phenyl hydrazine was prepared by diazotization of aniline **(1)** (1:1.2 Aniline/$NaNO_2$) and coupling it with L-ascorbic acid (1.05 moles) **(2)** at 0°C to form the lactone intermediate **(3)**. After the addition of L-ascorbic acid, the reaction mixture was allowed to come at room temperature over time which yields lactone intermediate that can be precipitated from the solution. In another protocol, the lactone intermediate was *in-situ* acidified and heated to 90°C, for two hours to obtain phenylhydrazine hydrochloride which on treatment with base precipitates Phenyl hydrazine **(4).** A protocol developed by Brown et al. was adapted and optimized further [36]. Lactone intermediate and Phenylhydrazine from two protocols were extracted in diethyl ether and analyzed on HPLC. The same batch procedure

was repeated for different aniline derivatives (e.g. *p*-anisidine, *p*-toudiene) and yield of lactone intermediate and Phenyl hydrazine was calculated after HPLC analysis.



Scheme 6.1 Reaction scheme for the synthesis of Edaravone starting from aniline

Diazonium salts are unstable at a higher temperature and can decompose, resulting in a lower yield of the product. Transforming diazotization and coupling in continuous flow overcomes the difficulties and helps to achieve better yields[35,37-40]. Diazotization in flow (**figure 6.1**) was carried out by pumping aniline (Aniline + conc. HCl) and aqueous $NaNO_2$ (10%) by using two independent syringe pumps to a Tee junction attached to Amar3 micromixer (0.3 ml). Flow rates were maintained accordingly to match the stoichiometry of batch synthesis. Reactant solutions were allowed to react in SS316 tube (1/8-inch inner diameter) connected to the Amar3 micromixer. The complete reactor assembly was dipped in the thermostat (Julabo, Germany) to maintain the reaction temperature to 0°C. At the reactor outlet another Tee junction was added where solution of *l*-ascorbic acid was pumped using another syringe pump. The resulting reaction mixture was allowed to react at the reaction temperature of 0°C in another SS316 tube (1/8-inch inner diameter) which was also dipped in same thermostat. The flow rates were maintained sufficiently high to ensure the constant flow of solids (if any) out of the reactor to avoid clogging. The purity of the lactone intermediate was determined on HPLC.

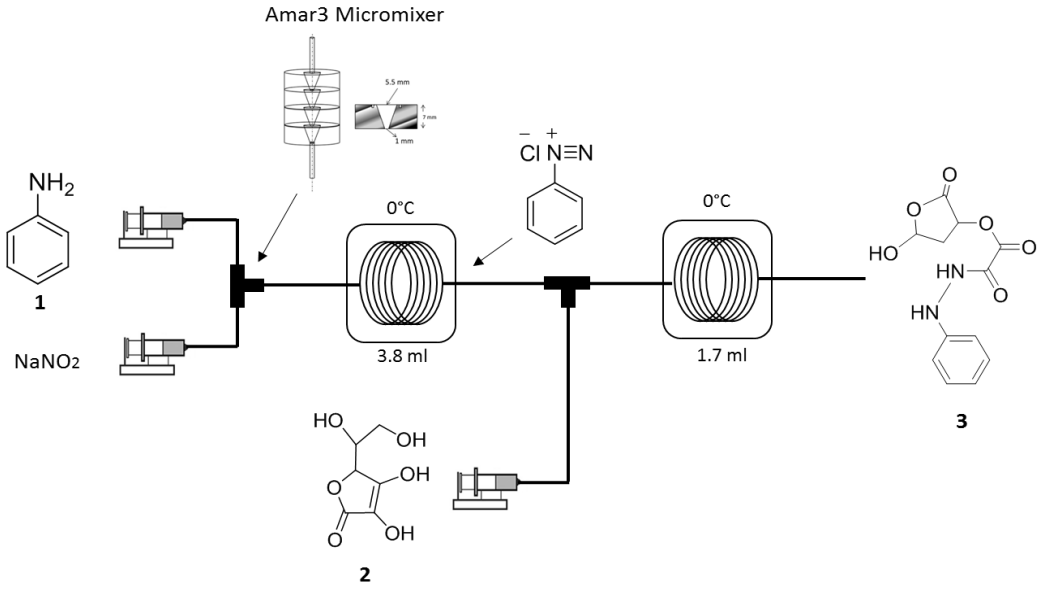


Figure 6.1 Synthesis of lactone intermediate in continuous flow

Reactions were performed for aniline and other aniline derivatives (*p*-anisidine, *p*-toudiene) for different residence time and conversion was monitored (**figure 6.2**). It was found that conversion increased for increasing the residence time from 2 to 15 min. for all the derivatives. The yield of respective lactone intermediate was calculated for all the substrates (**table 6.1**). In all the cases for the optimized condition yield of respective lactone intermediate was greater by 25-30% than obtained in the convention batch protocol. The maximum residence time in flow synthesis was 12 minutes, which was much smaller compared to the conventional batch synthesis method. After successfully converting the different anilines in the lactone intermediates, converting them to the corresponding hydrazine involved subsequent reactions with conc. HCl and aqueous NaOH, respectively in sequence. Two syringe pumps containing conc. HCl and aqueous NaOH solutions were connected at two different locations as shown in **figure 6.3**. Hydrazine hydrochloride was prepared by heating lactone intermediate in dilute HCl solution (concentrated HCl: water:: 11:5.5 mol/mol) at 90°C. The obtained reaction was subsequently neutralized with aqueous NaOH to yield Phenyl hydrazine. Same

procedure was followed for all other aniline derivatives. Yield and purity for hydrazine obtained from different aniline derivatives were determined on HPLC (**Table 6.2**). The yield of hydrazine derivatives in continuous flow mode was 10-30% better than in batch mode with a much lesser reaction time (compared to 2 hours in batch mode) without any in-line separation and isolation steps till hydrazine derivatives are formed.

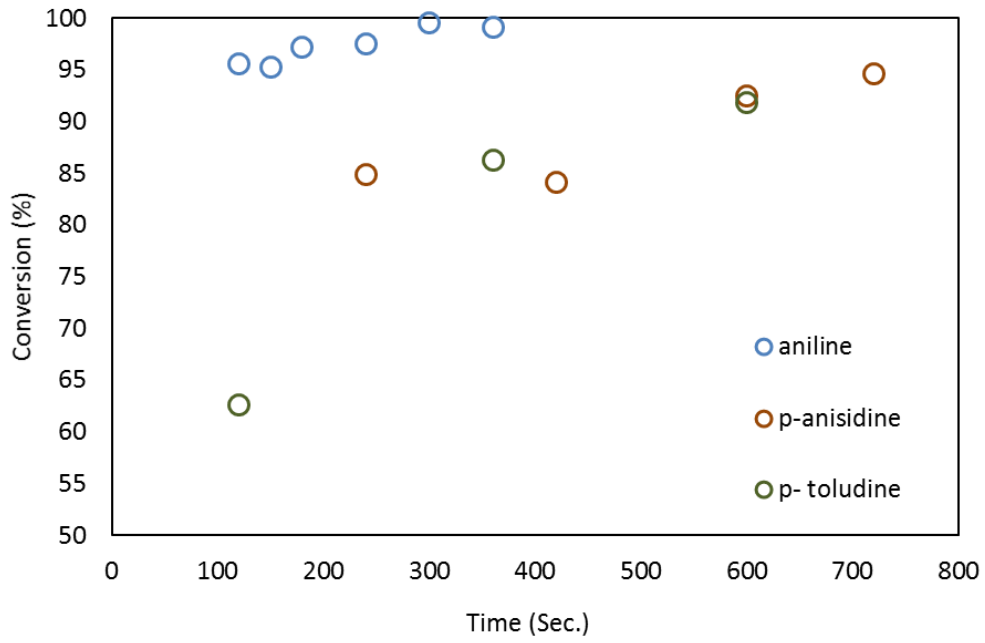


Figure 6.2 Conversion of aniline derivatives to corresponding lactone intermediates

Table 6.1 Optimized yield and purity of lactone intermediates

Compound	Residence time (s)	Lactone intermediate yield (%)	Lactone intermediate purity (%) HPLC
Aniline	300	75	99.9
p-anisidine	720	60	95.5
p-toludiene	600	38	92.3

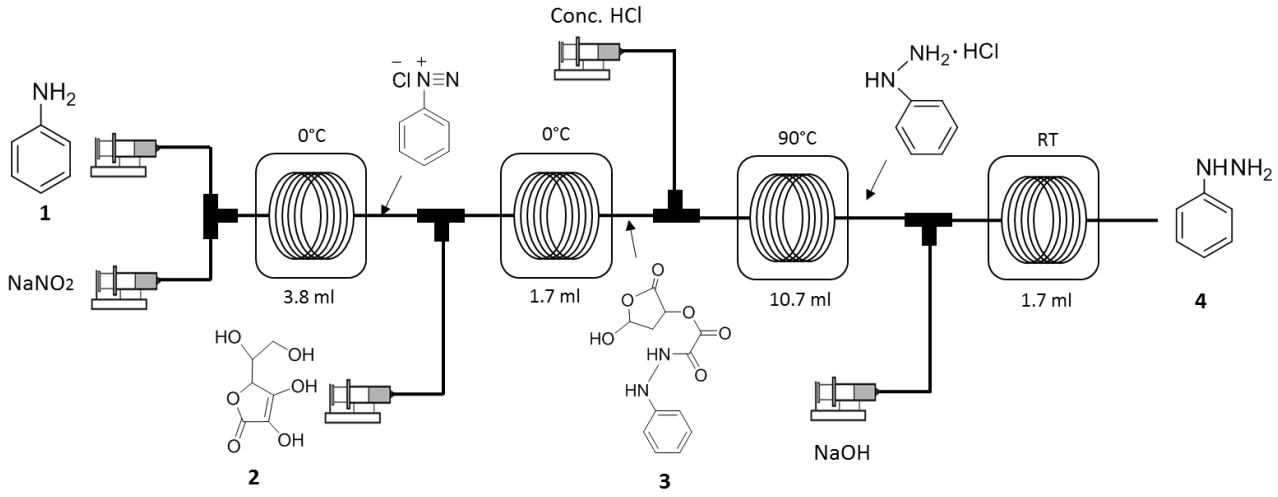


Figure 6.3 Synthesis of Phenyl hydrazine in flow starting from aniline

Table 6.2 Optimized yield and purity of hydrazine derivatives

Compound	Residence time (s)	Hydrazine derivative yield (%)	Hydrazine derivative purity (%) HPLC
Aniline	458	75	99.9
p-anisidine	801	42	94.5
p-toludiene	867	32	96.6

6.2.2 Flow synthesis of Edaravone

For synthesis of Edaravone in continuous flow, fresh Phenyl hydrazine (**4**) (50% in ethanol v/v) and Ethyl acetoacetate (**5**) (50% in ethanol v/v) were mixed continuously using Amar3 micromixer (0.3 ml) and were allowed to react in a 1/16" SS316 tube (in coil form) open to atmosphere (**figure 6.4** without BPR). The coil was dipped in a thermostat to maintain the reaction temperature at 75°C but almost all the experiments at different residence times (10 – 15 min) gave very low yield (5 - 8%) of the product Edaravone (**6**). Such a situation would arise either because of short residence time or lower reaction temperature.

These Initial flow experiments showed a strong need for carrying out batch experiments to monitor the reaction progress and product yield, which is not reported in the literature. For the batch experiment jacketed reactor was used. The reactants (without ethanol) were charged in the jacketed batch reactor heated to 95°C in the mole ratio of 1:1. A yield of 2.13%, 10.59%, and 40.11% was observed over 15, 30 and 60 minutes of reaction, respectively.

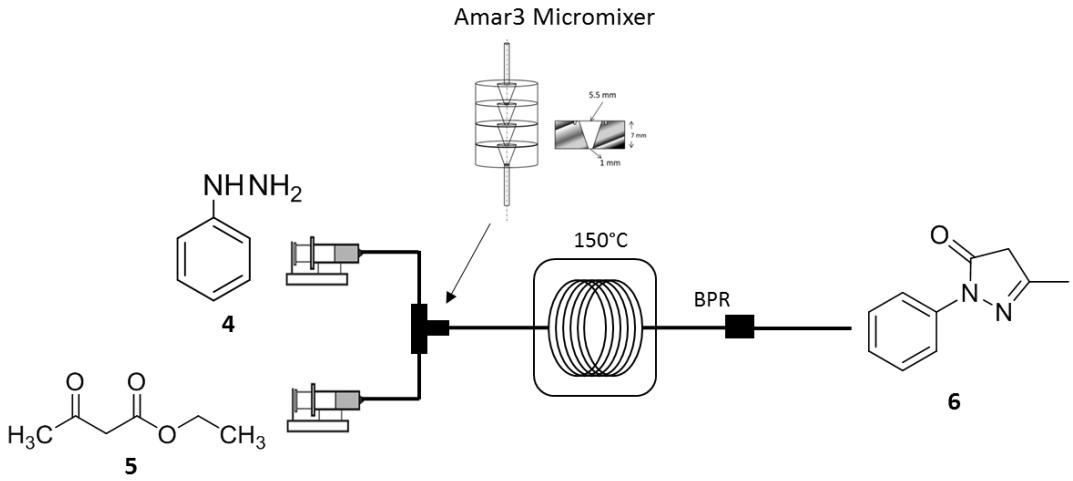


Figure 6.4 Edaravone synthesis in flow

Table 6.3 Yield of Edaravone in batch experiments using microwave

Time (min.)	Temperature (°C)	Pressure (Bar)	% yield HPLC
5	100	0	7
10	120	2-3	19
25	150	5-6	51
30	150	5-6	72

These observations indicated that the reaction itself was relatively slow and can be accelerated at a higher temperature and with higher reactant concentration. Further experiments

were planned at a higher temperature without using ethanol in a microwave reactor which is expected to reduce the reaction time through molecular heating. **Table 6.3** shows the reaction progress in the microwave.

The reaction progress was monitored over HPLC [41]. It is important to note here that the batch microwave which we have used (Anton-Paar monowave300 Germany) had a closed reaction chamber with the allowable pressure limit of 8 bar. So, with this constraint, we did not go for the higher temperature since that may have resulted in higher pressure, which may result in the explosion of the reaction chamber. However, the observations indicated a positive effect of reaction temperature on the yield, which led us to go for increased temperature in continuous flow.

The same experimental setup (**figure 6.4**) was used for the flow experiments at the higher reaction temperature i.e. 150°C. One initial experiment was done with the 1 hour residence time with 50% dilution with ethanol, without using back pressure regulator (BPR) which resulted in very low residence time due to the vaporization of solvent at higher temperature resulting in very low product yield. In order to achieve longer residence and prevent any evaporation, a BPR (Idex) was used for further experiments. At 2.5 bar back pressure on the reactor and at 150°C, only 8.7% yield was obtained at 50% dilution of reactant while with the neat reactant the yield was 31.2% with a residence time of 15 min. A further experiment was carried out at longer residence time as well as in a continuous microwave set-up with a BPR. With 30 min residence time under microwave 69% yield of the desired product was obtained.

After making the two synthesis steps continuous i.e. Phenyl hydrazine synthesis and Edaravone synthesis, process integration was the final aim to have the end to end continuous flow synthesis of drug Edaravone starting from aniline. It is very beneficial from the process point of view that if all the steps for the desired chemistry can be done in the same solvent or

without solvent to remove the necessary downstream processing steps, it will reduce the end-to-end synthesis time significantly. For the present case until the step of hydrazine formation, water was used as a solvent while the final drug was synthesized without any solvent. It is very important to avoid the water in this drug synthesis since it will quench the reaction and ethanol cannot be used as a solvent to extract the Phenyl hydrazine from the previous step. So, among the available solvents, we decided to use toluene for extraction of hydrazine and further reaction with ethyl acetoacetate since it is cheap, having a high boiling point and very less toxicity. In order to integrate the entire synthesis protocol, one batch experiment was carried out at optimized parameters where reaction till Phenyl hydrazine was carried out in water, Phenyl hydrazine was then extracted in toluene and subsequently reacted with Ethyl acetoacetate in microwave to get the drug Edaravone.

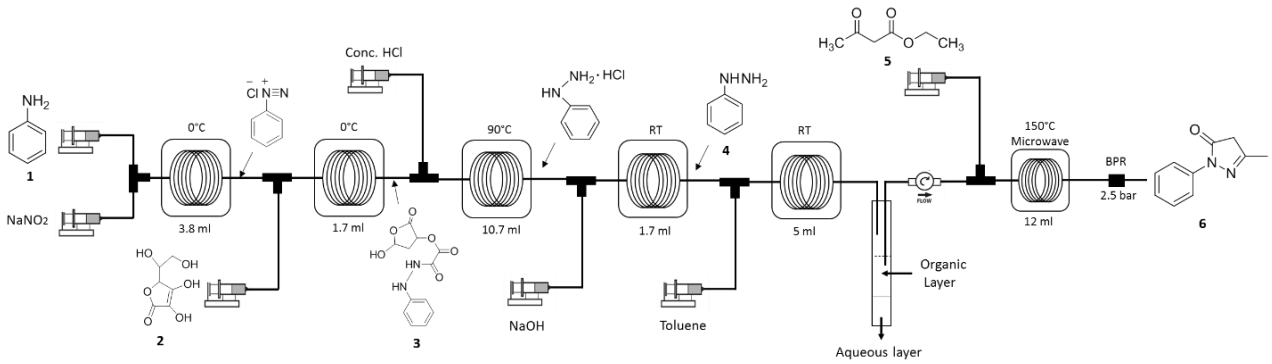


Figure 6.5 Multistep integrated flow synthesis of Edaravone

It is worth to highlight that, in multistep flow synthesis for all the reaction steps that fall in the category of 'one-pot-synthesis', the overall flow rate continues to increase as we go along the different reaction steps as different reactants enter the flow reaction system discretely towards the final outlet of the reactor network. This further implies that the actual residence time continues to decrease for a set-up having fixed reactor volume between two steps. In order to avoid such issues, care was taken to increase the reactor volume accordingly to have sufficient residence time as in the optimized conditions for respective reaction steps.

All the reaction steps were integrated to synthesize Edaravone after successfully carrying out all the steps in batch reactor. The overall experimental set-up is shown in **figure 6.5**. Different Phenyl hydrazine derivatives synthesized in this work can be used for the synthesis of respective pyrazolone derivatives.

6.3 Conclusion

We have successfully synthesized the Edaravone drug using integrated continuous flow multistep synthesis involving diazotization, coupling, inline solvent extraction and microwave under back pressure regulator. 3 different aniline derivatives were used for synthesis of respective hydrazine derivatives. Initially single step batch experiments were carried out and respective steps were optimized in continuous flow and then individual steps were integrated to give the final drug. Having inline separation stages helps to isolate the atmospheric pressure zones and microwave flow synthesis under pressure thereby avoiding maintaining high pressure in the entire system. In all ~ 30% improvement in yield was observed when batch procedure was converted to flow for much less residence time (~ 20 min). Integrated synthesis avoids the handling of Phenyl hydrazine which was inline extracted in toluene and used for synthesis of Edaravone. Molecular heating in microwave helps in fast achievement of temperature which reduced the reaction time significantly. Finally, Phenyl hydrazine made in continuous flow was reacted with Ethyl acetoacetate in microwave at 2.5 bar pressure and at 150°C for 30 min residence time which resulted in 69% yield of Edaravone.

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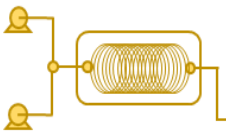
Chapter 7



Multistep synthesis of cystic fibrosis drug ivacaftor with inline separation

This chapter is based on:

Vasudevan, N., Sharma, M. K., Reddy, D. S. and Kulkarni A. A.,

A multi-step continuous flow synthesis of the cystic fibrosis medicine ivacaftor,

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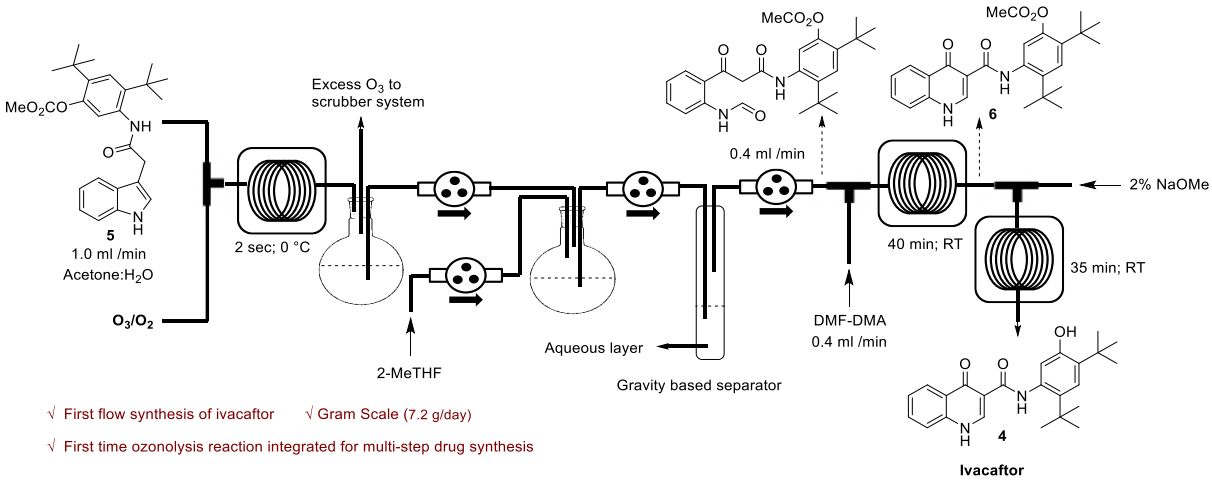


Continuous flow ozonolysis method combined with multi-step flow sequence is developed for the synthesis of drug ivacaftor for the first time is presented in this chapter. Safe ozonolysis, continuous flow quadruple reaction to construct quinolone scaffold, inline extraction followed by continuous phase separation are the key features of present work. Feasibility of using a continuous mixed flow reactor commonly referred as CSTR (continuous stirred tank reactor) is also investigated for the relatively slow reaction segment. The current integrated multi-step flow synthesis can produce 7.2 g/day of the drug ivacaftor at laboratory scale, which is sufficient to treat 50 patient per day. The present route can also be used as a general route for the synthesis of other related drugs such as quinolone antibiotics.

7.1 Introduction

In the recent years, continuous flow synthesis has received significant attention in academic as well as industrial research.[1-4] Several advantages offered by the miniaturized flow reactors such as rapid mixing, excellent heat & mass transfer rates, relatively narrow residence time distribution have given a novel platform that can handle hazardous and toxic materials, sensitive reagents and unstable intermediates.[5-8] These features allow us to carry out the reactions at close to intrinsic reaction kinetics which often gives improved yields and better selectivity over batch method. A vast body of literature is available on single step and two-step flow synthesis.[9-13] However implementation of continuous work-up or separation is essential to extend the approach to a truly multi-step flow synthesis. Preparation of medicinal drugs involves several synthesis steps and between two reaction steps the work-up involves many unit operations *viz.* phase separation, evaporation, extraction, crystallization and purification etc.[14-16]

Recently, this multi-step flow synthesis approach has been implemented to access moderately complex molecules with diverse architectures such as natural products and APIs.[17-20] Notably, Jamison's quinolone antibiotic ciprofloxacin[21], single dedicated platform for the multiple drug molecules[1] independently developed by Kobayashi[4] and Hessel[22], solid supported synthesis of Imatinib[23] by Steven Ley and end-to-end process for aliskiren hemifumarate[16] stand out as significant milestones in the area of multistep-flow synthesis. This approach helps manufacture these drug molecules in a distributed manner. It also helps in addressing the challenge of manufacturing of prescription drugs[24-26], which faces shortage in terms of availability. This has remained a top priority in FDA for a long time where multi-step flow synthesis will come to an aid as it can produce sufficient quantities with consistent quality, which will also boost decentralized manufacturing of important drugs. Along these lines, in this chapter we report a new approach for the multi-step continuous flow synthesis of drug

ivacaftor which include safe ozonolysis, quadruple reaction, continuous inline extraction and separation.

The ivacaftor is 4-quinolone-3- carboxylic acid ester-based drug, used for the treatment of cystic fibrosis. It is one of the most expensive drugs (US $300,000/year/patient) and the discovery of ivacaftor was celebrated as a breakthrough in cystic fibrosis research because it is the only drug available to treat this deadly disease.[27-29 30b] The pharmacophore of ivacaftor, 4-quinolone-3- carboxylic acid ester, is an privileged scaffold in drug discovery.[31-33] Besides quinolones are frequently found in many biologically active compounds and drugs for treatment of various diseases[31-33] as antibiotics, anti-malarial, anti-tumor etc. (**figure 7.1**).[11d] The commercial process[12a] developed by Vertex Pharmaceuticals involves Gould-Jacobs

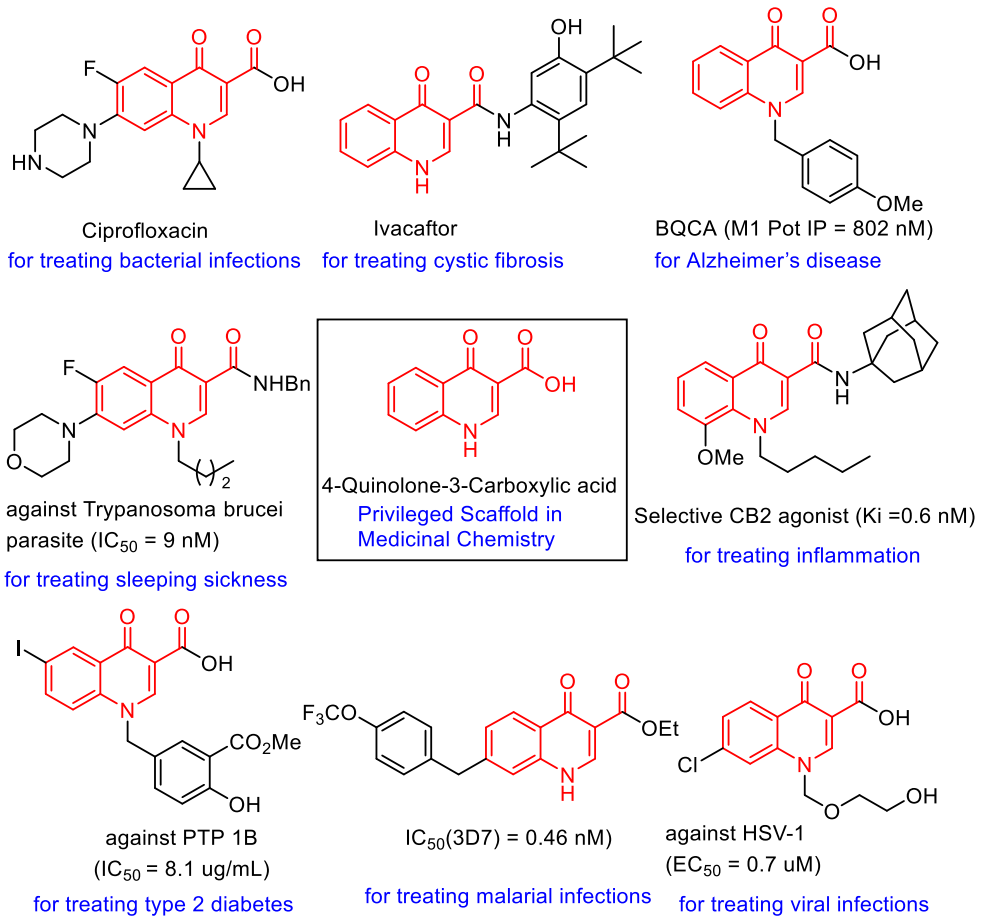


Figure 7.1 Selected compounds in clinics with 4-quinolone-3-carboxylic acid moiety

approach[12b,12c] for the synthesis of key intermediate quinolone carboxylic acid ester. Larus[12d] pharma and Yang *et. al.*[12e] reported independently the multistep synthesis of ivacaftor starting from o-nitro and o-halo benzoyl chloride respectively. We have previously reported[12f] concise synthesis of ivacaftor using Witkop-Winterfeldt oxidation (**figure 7.2**).[12]

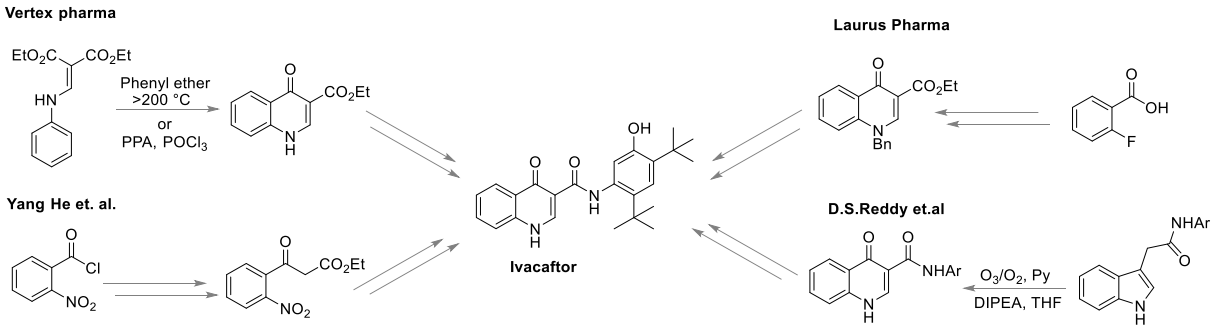


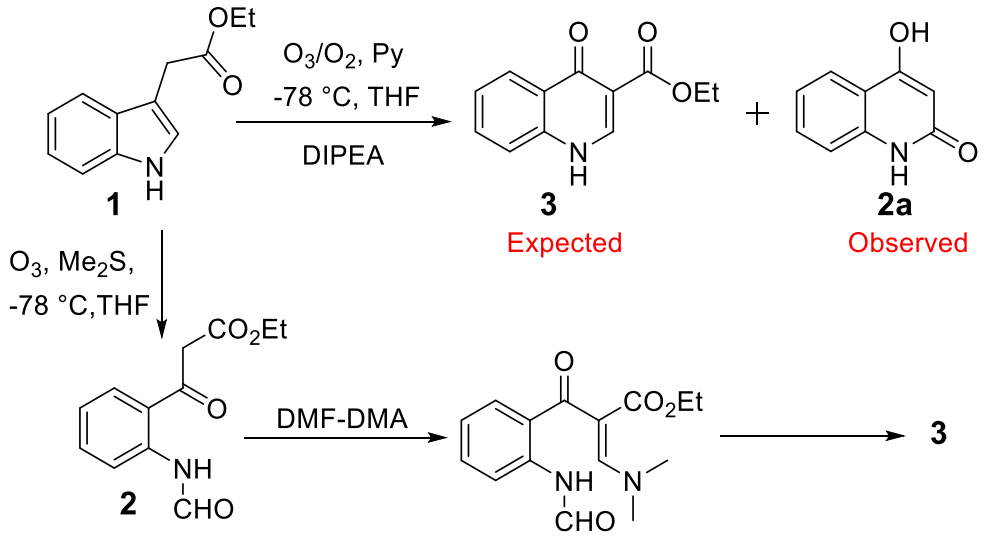
Figure 7.2 Approaches for ivacaftor synthesis

7.2 Results and discussion

Having this background, we have planned a general route to access ivacaftor, which is suitable for batch as well as continuous flow synthesis. Initially batch process is developed, followed by transformation of every step, in continuous flow synthesis along with its optimization and then finally to integrate all the steps on a single platform. Initial efforts for the construction of quinolone ring suggested that our laboratory scale protocol for the preparation of quinolone-3-carboxylic acid amides works well.[12f] However, the same method did not give corresponding esters, rather 2-quinolone **2a** was observed (**Scheme 7.1**). Hence a new protocol was designed and executed for the synthesis of quinolone core using batch and flow methods.

Attempts on oxidative-cleavage of indole moiety using $NaIO_4$ resulted in very good yield but it was always accompanied with significant amounts of solid byproduct. In order to reduce the work-up after every reaction step, multistep synthesis was aimed to be carried out with minimal solvent changes (so as to achieve close to one pot synthesis). Keeping this aspect in mind, a

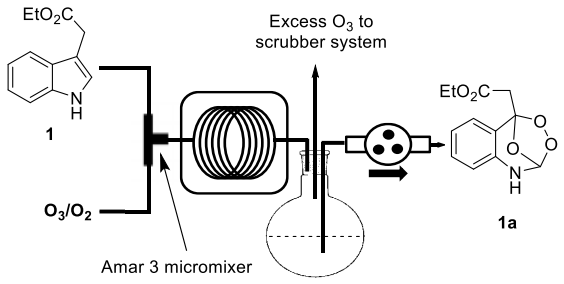
new route, which involved ozonolysis of indole moiety and subsequent cyclization (**Scheme 7. 1**) was developed using single solvent THF throughout the process with a moderate yield (47%). It is necessary to highlight that the desired compound **3** could be isolated without any chromatographic purification.



Scheme 7.1 One-pot batch optimization reaction for quinolone synthesis

As the developed protocol involves ozonolysis, eneaminone formation, aza-Michael addition-elimination and deformylation, this process can be regarded as one-pot quadruple reaction.[13] Ozonolysis is considered as an alternative to metal-based oxidants, where ozone gas is used as greener oxidizing agent and widely utilized for several functional group transformations in organic synthesis.[34-364] Although it is a very useful oxidation platform, its utility in large-scale synthesis is limited due to high exothermicity and the hazards associated with the ozonide intermediate. Jensen *et al*. demonstrated continuous flow ozonolysis in multichannel microreactor[15a], which is later explored by several other groups[15] for a broader

Table 7.1 Optimization for ozonide formation



Sr.No	Comp 1 (g)	Flow rate (mL/min)		RV (mL)	RT (sec)	T (°C)	Conversion
		Comp1	O_3/O_2				
1	0.5	1.0	1000	7.5	0.4	-60	Incomplete
2	0.5	0.5	1000	7.5	0.4	-60	Incomplete
3	0.5	0.5	500	28	3.3	-60	Incomplete
4	0.5	1.0	500	28	3.3	-60	100%
5	0.5	1.5	500	28	3.3	-60	Incomplete
6	0.5	1.0	500	28	3.3	-40	100%
7	0.5	1.0	500	28	3.3	-10	100%
8	1.0	1.0	500	28	3.3	-10	100%
9	1.0	1.0	500	20	2.4	-10	100%
10	1.5	1.0	500	20	2.4	-10	Incomplete
11	1.5	0.5	500	20	2.4	-10	100%
12	1.5	0.5	500	20	2.4	-10	100%
13	2.0	0.5	500	20	2.4	-10	100%
14	2.5	0.5	500	20	2.4	-10	Incomplete

*RT - Residence time; RV – Reactor volume; (a) In all cases compound 1 was dissolved in 50 ml THF; (b) Reaction was monitored by TLC for absence of starting material. For entries (1-3, 5, 10 and 14) conversion is given as ‘incomplete’ as quantitative off-line characterization in the presence of reactive unstable ozonoids in the solution was not sufficiently reliable. Only qualitative analysis using TLC was performed to check the presence of the limiting reactant.

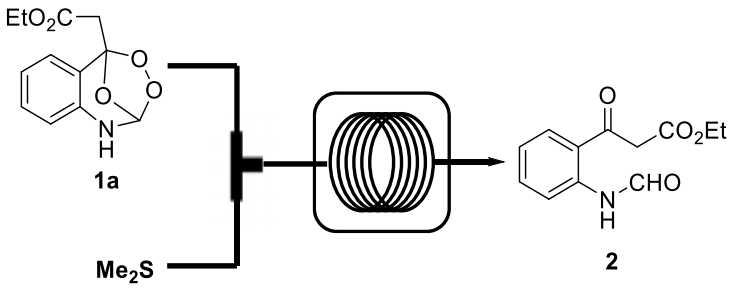
range of applications.[34,35] With this background we decided to translate the batch ozonolysis step into a continuous protocol.

Experiments were performed by varying flow rates, reactor volume and different reagent concentrations to arrive at the final condition (**table 7.1**). Initially the effect of increase in the temperature of ozonolysis reaction and reduction in the residence time was studied. For this reaction since the flow rate of the gas stream containing ozone was very high (500 mL/min with 0.0026 mole/min concentration of ozone) when compared to the substrate (1.0 mL/min), the overall residence time was very low. However, despite very low residence time, reaction was seen to get completed, which indicates ozonide **1a** formation to be a very fast reaction. After the optimization of ozonide formation step, in the next step quenching of ozonide **1a** with dimethyl sulfide (Me_2S) for the formation of β-keto ester **2** was explored (**table 7.2**).

Though the reaction time for quenching of ozonide **1a** was sufficiently long (12 h) in batch mode, we firmly believed that it is possible to reduce the reaction time in microreactor by enhancing the intrinsic kinetics by changing concentration and/or temperature. Initial experiments were performed using large excess of Me_2S in THF or with neat Me_2S (entry 1 to 8, Table 2) by varying flow rate of both reactants at ambient temperature. However, the concentration of Me_2S did not influence the reaction rate. The reaction progress was monitored using starch-KI strips (Sigma-Aldrich) for the completion of reaction which was confirmed by the disappearance of the blue color.[16] (***CAUTION!*** *As the most of ozonides and peroxides are potentially explosive, the reaction mass has to be subjected to further transformation/ workup only after NEGATIVE test with starch-KI or peroxide test strips*).

No significant improvement was observed by using pyridine as reducing agent before[17a] or after the ozonolysis (**Table 7.2, entry 9, 10**)[17b]. This implied that the determination of kinetics was essential for this step. Accordingly, batch experiments were planned at two different

Table 7.2 Reductive quenching of ozonide



Exp. No	Me_2S (mL)	Flow rate (mL/min)		RV (mL)	RT (min)	T (°C)	Conversion
		1a	Me_2S				
1[a]	10	0.5	0.5	15	15	-10	Incomplete
2	20	0.4	0.4	15	19	-10	Incomplete
3	20	0.2	0.4	15	25	-10	Incomplete
4	30	0.5	0.5	15	15	-10	Incomplete
5	30	0.5	0.5	50	50	-10	Incomplete
6	30	0.5	0.5	50	50	25	Incomplete
7	50 (neat)	0.5	0.5	50	50	25	Incomplete
8	50 (neat)	0.1	0.1	50	250	25	Incomplete
9[b]	50 (neat)	0.1	0.1	50	250	25	Incomplete
10[c]	50	0.1	0.1	50	250	25	Incomplete

*RT- Residence time; RV – Reactor Volume (a) Reaction was monitored by starch-KI strips (b) pyridine was used for quenching instead of Me_2S. (c) Pyridine (10 mL) was taken along with compound **1** before ozonization; 1-6 Me_2S was dissolved in 50 ml THF and all the case the concentration of **1a** was 0.1 M.

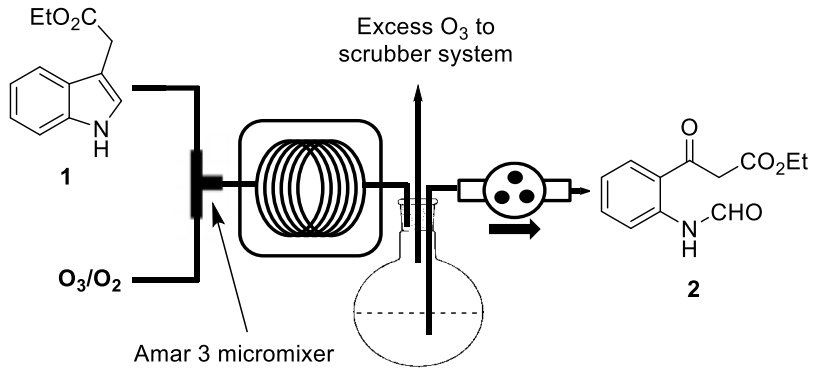
temperature i.e. 25°C and 30°C in a 50 ml jacketed reactor. Ozonide intermediates generated by the flow experiments were collected in the reactor at the same temperature as for the ozonolysis reaction. After collection for sufficient time, Me_2S (10 eq) was added and the reaction temperature was raised to 25°C. Once addition was over the reaction was monitored

for the consumption of ozonide by using starch-KI strips after an interval of every half an hour. The observations indicated that the reaction took 6 hours at 25°C, which decreased to 3.5 hour upon rising temperature (30°C) along with untraceable impurities. Experiments with higher mole ratios of Me_2S (25 eq) did not result in any significant improvement. From the findings from the batch experiments it is very clear that quenching of the ozonide is a slow reaction and for the flow reactor volumes used in this work (**Table 7.2**) the flow rates have to be very low, which will result in very low throughput. For higher throughput with the required flow rate the reactor volume has to be increased significantly and is not a viable option as it will result in a very long tubular reactor. For an inherently slow reaction, a continuous stirred tank reactor (CSTR) serves as a better alternative[18] where outlet from the ozonolysis step can be fed to a CSTR and Me_2S can be added simultaneously allowing the reduction of ozonide with sufficient residence time and product can be withdrawn continuously using a separate pump.

In view of this, an experiment was carried out in a CSTR (100 mL) for quenching of ozonide **1a** with 7-hour residence time and the product β-keto ester **2** was collected continuously at the outlet. It is important to note that all the known continuous flow ozonolysis methods[14-15] involve ozonide intermediate, which is eventually reduced/oxidized with a variety of reagents e.g. PPh_3, $NaBH_4$, H_2O_2, $P(OEt)_3$, solid supported reagents (thiourea, phosphines, and amines). Here we have purposely avoided all these reagents for ozonide quenching which needs additional purification step after the reaction. In search of an alternative method to traditional ozonolysis we found an interesting report[19] from Dussault and co-workers which involves in-situ capturing of the carbonyl oxide intermediates followed by decomposition to desired carbonyl compound. Recently this approach has been used in similar reactions.[15i-15k] Accordingly, a solution of indole acetic acid ester **1** in acetone: water (2:1 vol. /vol.) was pumped through our continuous flow reactor set up to get oxidized compound **2** without adding any additional additive or reagents (**fig. in Table 7.3**). The approach is found useful and we

were able to make the desired β-keto ester **2** along with some unreacted starting material **1** (**table 7.3, entry 1**). Further systematic fine-tuning of reaction conditions by changing concentration and reactor volume led us to the optimal conditions (**table 7.3, entry 6**). This ozonolysis reaction does not go through the potentially toxic/explosive ozonide intermediate and reaction completed within 2 seconds and can give an overall throughput of 84 g/day with simple bench top flow reactor (30ml) system.

Table 7.3 Safe ozonolysis optimization

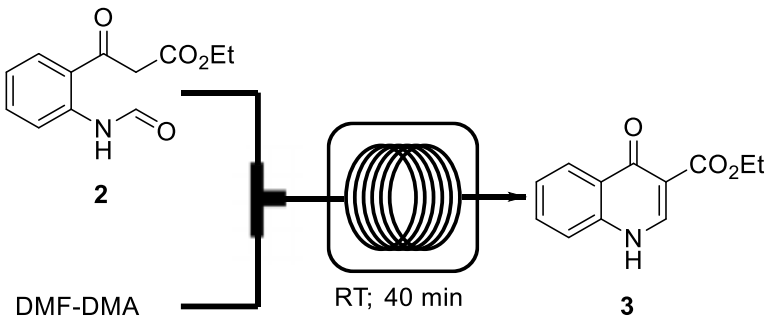


Sr. No	Comp. 1 (g)	Flow rate (mL/min) Comp. 1	RV (mL)	RT (sec)	Acetone:H_2O (2:1) (mL)	Conversion
1	1	1.5	15	1.0	60	Incomplete
2	2	1.0	15	1.0	60	100%
3	2	1.0	15	1.0	50	100%
4	2	1.5	15	1.0	50	incomplete
5	2	1.5	30	2.0	50	incomplete
6	3	1.0	30	2.0	50	100%
7	4	1.0	30	2.0	50	incomplete

*RT- Residence time; RV- Reactor Volume; (a) all the reactions were run at 0°C and flow rate for ozone (O_3/O_2) kept constant (1000 mL/min); In all cases Comp. 1 was dissolved in Acetone: water mixture. For entries (1, 4, 5 and 7) conversion is not given in terms of % (reported as incomplete) as quantitative off-line characterization in the presence of reactive unstable ozonoids in the solution was not sufficiently reliable. Only qualitative analysis using TLC was performed to check the presence of the limiting reactant.

The next step of cyclization reaction of β-keto ester **2** with DMF-DMA could be carried out successfully in a continuous flow tubular reactor where the reaction time was significantly reduced from 12 h to less than 1 h (**table 7.4, entry 1-3**). Increase in the concentration of DMF-DMA plays a key role for altering the residence time (**table 7.4, entry 4 to 7**).

Table 7.4 Optimization for Batcho-cyclization

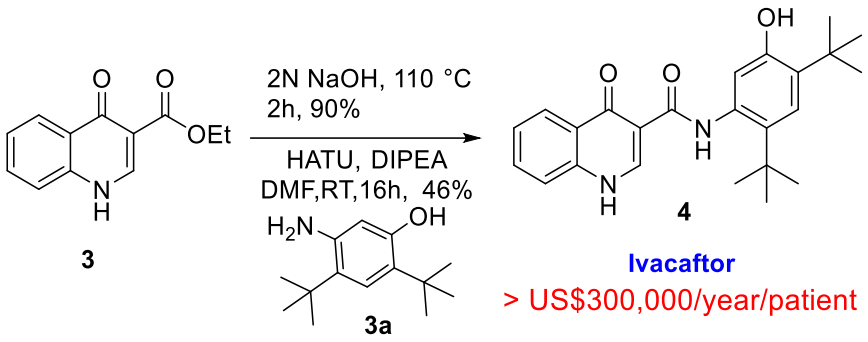


Exp. No	Amount		Flow rate (mL/min)		RT (Min)	Conv. (%)
	DMF-DMA (mL)	Comp. 2 (g)	Com. 2	DMF-DMA		
1	1.4 ml (5eq)	0.5	0.1	0.1	70	100%
2	4.2 ml (5eq)	1.5	0.1	0.1	50	100%
3	8.4 ml (5eq)	3.0	0.1	0.1	40	100%
4	2.8 ml (10eq)	0.5	0.1	0.1	60	100%
5	5.6 ml (20eq)	0.5	0.1	0.1	50	100%
6	7.0 ml (25eq)	0.5	0.15	0.15	40	100%
7[a]	7.0 ml (25eq)	0.5	0.4	0.4	40	100%

*RT- Residence time; for all cases comp. 2 and DMF-DMA was dissolved in 50 mL THF except entry 7; (a) Reaction were done in Ethyl acetate instead of THF.

In general, the reaction time was seen to decrease with increase in either the concentration of substrate **2** or the amount of reagent DMF-DMA. With available solvent options THF was discarded due to its high miscibility in water and instead ethyl acetate (EA)

was employed for cyclization (Table 7.4, entry 7). In the modified safe ozonolysis protocol water-acetone system in used where extraction of ozonized product is needed for cyclization with DMF-DMA. The suitability of EA was first verified through a batch experiment where intermediate from the first step was extracted in EA and DMF-DMA was added in the batch reactor and formation of product was confirmed. The completion of reaction confirmed the suitability of EA for further flow reaction. The complete process integration for producing quinolone core by ozonolysis of indole ester **1**, in-line extraction of compound **2** in EA, subsequent cyclization was carried out to obtain compound **3**.



Scheme 7.2 Gram-scale synthesis of ivacaftor

Integrated continuous experimental setup is shown in figure 2. Next, quinolone ester **3** thus obtained was subjected to ester hydrolysis followed by coupling of required aniline **3a** using HATU as coupling reagent, which allowed us to access ivacaftor on a gram-scale (**Scheme 7.2**). The spectral data of the synthesized drug is in complete agreement with that of reported one.[12a] It is worth highlighting that the present protocol for synthesis of quinolone ester is far more convenient than the commercial processes[12a] involving very high temperature (>250 °C) or corrosive reagents (PPA/$POCl_3$) with high boiling solvents such as diphenyl ether or dowtherm.[12b,12c] White[20a] and Lengyel[20b] group have individually reported flow synthesis of pyrimidinone and quinolone by Gould-Jacobs approach. However, these methods lack generality and gives poor yields.

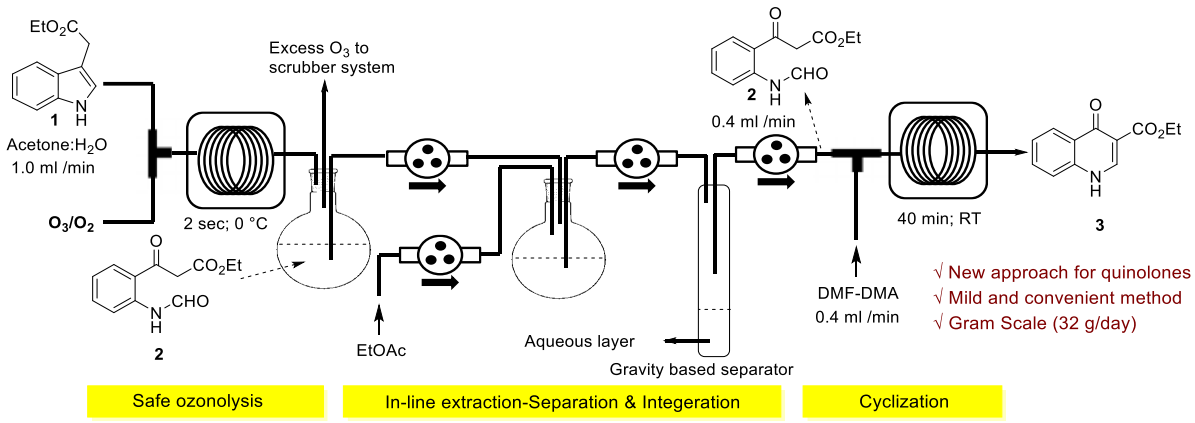


Figure 7.3 Integration of all steps with in-line extraction

With the protocol being established independently for each step, it was followed for the flow synthesis of the desired drug. Accordingly, the compound **5**, previously prepared[12f] in our laboratory was subjected to the optimized condition to get corresponding quinolone carboxylic acid amide **6**. The outlet of the set up (**Figure 7.3**) was connected to another tubular reactor (1/8“ Teflon tube of 40 ml volume) using a T-mixer (**Figure 7.4**) for the removal of phenolic protecting group in compound **6** using sodium methoxide solution (2% in MeOH, W/V) which directly produced the desired product ivacaftor **4**.[12a, 12f] Upon complete integration of all the continuous flow steps, the set-up was operated continuously and the bench top experimental setup is able to produce 450 mg in 90 minutes implying that it can synthesize 7.2 g/day (60% yield over 3 steps), which is actually sufficient to treat 50 patients/day.

To the best of our knowledge, this is the first example where safe ozonolysis is integrated in multi-step continuous flow synthesis of drug ivacaftor. Several commercial processes in particular many drugs such as oxandrolone, cefaclor, ceftibuten etc[14c] involve ozonolysis reaction.[14c] However, it has been carried out in semi-batch method due to difficulties in handling large volume of highly exothermic ozonides and additional reductive/oxidative work up procedure, which sometime also involves removal of quenching reagents such as PPh_3.

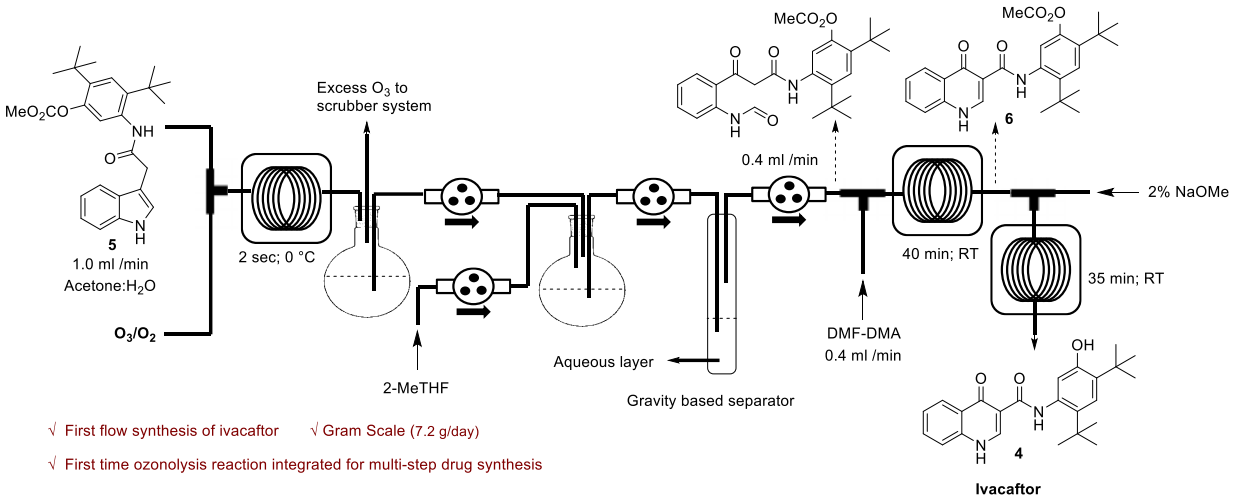


Figure 7.4 Continuous flow synthesis of ivacaftor

7.2 Conclusions

To summarize, here we are reporting mild and convenient method for the synthesis of quinolones via new one-pot quadruple reaction by batch as well as continuous flow process. The present method also paved the way for the two unique approaches for the synthesis of drug ivacaftor and ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate. We have successfully demonstrated that new chemistry route in combination with flow synthesis can result in significant reduction in reaction time with safe protocol. The developed synthetic route can produce 32 g/day of ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate and 7.2 g/day of drug ivacaftor using available bench-top infrastructure. The present approach is being used for similar quinolone-based drugs such as well-known fluoro-quinolone carboxylic acid-based antibiotics and will be reported separately.

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Chapter 8

Impact of deviation in optimized flow synthesis on scale-up

This chapter is based on:

Sharma, M. K.; Raval, J.; Gwang-Noh Ahn; Dong-Pyo Kim and Kulkarni, A. A.,

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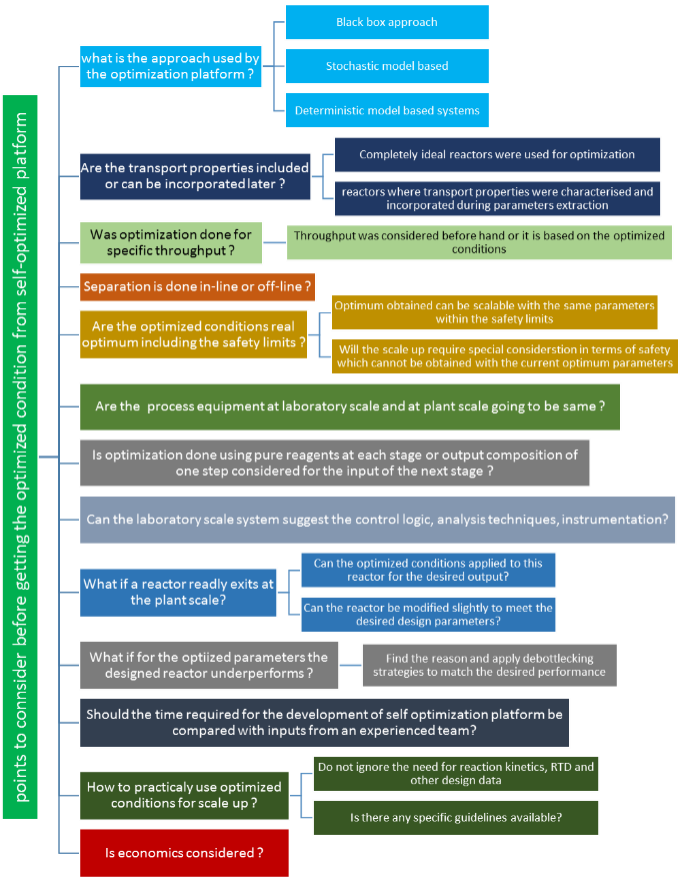

This chapter highlights the unavoidable connection between the manual or self-optimized flow synthesis protocols for multistep flow synthesis and its scale-up. We have used a case study of flow synthesis of Ivacaftor that is optimized at the laboratory scale and is subjected to specific deviations deliberately. The resulting effects are captured in terms of their effect on scale-up approach. The analysis shows that small deviations in performance viz. conversion or selectivity at every reaction step would lead to significant deviation in the process and the overall capital investment. Translating "Laboratory synthesis" into "Commercial scale manufacturing "needs careful differentiation between an optimized reaction step and realizing a commercially feasible process.

8.1 Introduction

Automated flow synthesis has become the new and latest buzzword in the field of flow synthesis primarily aiming at interfacing artificial intelligence with synthesis platforms. This approach has eventually led the concepts like 'dial-a-molecule'[1-4] or 'synthesis 4.0'[5] or 'intelligent retrosynthesis'[6-8], etc. These approaches have facilitated identification and rapid screening of synthesis protocols backed by very large data base of reactions, kinetics, analysis procedures, etc. for designing an efficient experimental setup suitable for a specified synthesis. Very often when broken down in a system's approach, the tasks are simple viz. synthesis, optimization of individual reaction steps, separation of reactants and products, etc. Advancement in reactor fabrication technologies e.g. 3D printing has made it easy to fabricate complex flow reactors as designed from CAD on the basis of simulated flow field using flow modelling tools where optimum performance of the synthesis can be attained by resolving the composition along the reactor length at various operating conditions. Furthermore, the system for multistep flow synthesis becomes much more complex on integrating various reaction steps/reactors. This demands a complementary system that banks on advancement of technology with experience of a process chemist/engineer to deliver a reliable and adaptable synthesis machine. While a very few efforts are seen to have a total reliance on the automated decisions, 99.999% of the manufacturing plants are still designed and operated based on experience or a combination of experience, empiricism and heuristics. So, with the proven set of examples that clearly suggest to adopt continuous manufacturing as the best way to synthesize high value specialty chemicals[9-15], it is especially certain that the pharma industry would make some moves to align with the flow synthesis. There are many examples in the literatures focusing on scale-up using flow synthesis [16-18], inline analysis for real time monitoring[19-20], printing of reactor for fabricating complex reactor geometries[21-22] and very recently utilization of smart algorithms for the automation. Yet it is very early stage of an

attempt on substantial integration of the individual system and process. Words like synthesis automation for increasing output, safety in manufacturing, spending time on important aspects of research rather than building setups and synthesize molecules seem lucrative but demonstration of such an integration is not very common since it requires many challenges to be addressed.

Reaction optimization at laboratory scale for single step synthesis or for the individual reaction steps is now a relatively easy task using the algorithms to handle. However, as complexity increases the task becomes more data driven, requiring more computing power and highly skilled personals having multidisciplinary background. The situation becomes even more critical in actual plant environment where system have several interconnecting segments and interact with other instrument thereby creating an interesting situation where the time scales of reaction are smaller than the time lags from the interacting system. Optimizing a reaction is very much different than optimizing a process, the latter being far more complex, needing significant engineering inputs. This chapter aims at taking a realistic view of moving from “Laboratory synthesis” to “Commercial scale manufacturing” for high value low volume chemicals in the fine and specialty chemicals sectors including the pharmaceutical drugs. Here we make an attempt to explore the viability of a process for commercial scale based on the laboratory scale optimization (equally applicable for self-optimized systems) of multistep flow synthesis.

8.2 State-of-the-art of scale-up of flow reactors/processes

The number of reports on commercial scale flow synthesis is less than 1% of the total number of publications on flow synthesis. In reality, the situation is changing, as in the recent time a large number of industries have been practicing flow synthesis at pilot and commercial scale. It becomes evident from the total number of large-scale flow reactors that are sold by

various manufacturers (viz. Corning Inc.[23], Chemtrix LLC.[24], Kobelco Ltd.[25], Ehrfeld Mikrotechnik BTS.[26], Amar Equipments[27], Himile Microrectors[28], AM Technologies[29], etc.) as otherwise they would not have sustained only based on the laboratory scale flow synthesis devices. Among the very early reports of using a microreactor of a flow reactor for commercial scale production, Mehrabi and co-workers have shown a reconfigurable system for adopting the varying manufacturing demands[30]. However, the reactor used is a horizontal flow reactor with capillaries at different levels. This approach would not work for reaction mass of lower viscosity due to the influence of gravity on distribution. May et al. have reported a continuous process for the 1H-4-substituted imidazole intermediate in two different approaches that use optimization and scale-up rapidly in plug flow reactor (PFR) and automated sampling, process analytical technology and inline separation for screening the best possible route for synthesis and scale-up, respectively[31]. Fitzpatrick et al. developed a software called Leylab for remote reaction monitoring and have demonstrated it for reaction optimization[32]. Laue et al.[26] performed the lithiation reaction of fluoro-aromatics in the microreactor under non-isothermal conditions while achieving a controlled precipitation. Fitzpatrick and Ley have reported a successful integration of the batch and flow experiments on a single platform with an automated system for synthesis of 5-methyl-4-propylthiophene-2-carboxylic acid[33]. They also incorporated automated downstream processing and solvent switching steps for freeing the more time for chemists from routine laboratory tasks. A sophisticated approach that involves reaction automation, inline analysis and feedback systems to drive the reaction systems to continuously generate new insights about the reaction has also been reported[3]. A continuous sequence for synthesis of benzoxazole building blocks involving flow synthesis set-up, getting the heat profile of the reactors and then finally combining the batch reactor, semi batch reactors and flow reactors to get the desired production is reported in a systematic manner[34]. Continuous manufacturing of drug prexasertib monolactate monohydrate on 24 kg scale involving 8 unit

operations has also been reported[13]. The effect of recycle in the reactor and in the crystallizer on the enhancement of yield and selectivity using dynamic simulations and optimization in an end-to-end continuous pharma manufacturing have also been studied[35].

Scale-up through numbering-up works exceptionally well for ultrafast reactions[36]. However, throughput limitations and complexities of flow distribution are major challenges that need case-by-case scrutiny before design. For example, Iwasaki et. al. have demonstrated the scale-up via numbering-up for radical polymerization using micro-flow system for producing methyl methacrylate up to 2.5 kg of the product per week[17]. Five parallel monolithic microreactors are used for synthesis of an intermediate of valsartan, a therapeutic agent for hypertension and diabetes[18]. Similar approach has been used for numbering-up of gas-liquid photocatalytic reactions[37]. As another example, it was shown that the productivity can be increased by parallelizing up to 32 visible light-mediated organic photocatalytic reactions in microfluidic reactors based on luminescent solar concentrators[38]. Very recently, Jang et. al. demonstrated ~4 g of drug production per hour. System comprises of a total of 10 photoreaction capillary reactors connected by 3D distribution modules needing a total residence time of 2.2 minutes from synthesis to product separation[39]. A similar approach has been demonstrated using an integrating flow distributor and a copper catalytic module for high productivity of 'Rufinamide'[16].

These reports in the published literature from the industry is the tip of an iceberg of the actual implementations. However, this brings out a very important question on deciding the viability of a "process for commercial scale" based on the "laboratory scale (self) optimization" of multistep flow synthesis. In general, since these two aspects are important yet unconnected, it is necessary to understand the reasons on how the former can help the later, which is the ultimate reason for all the efforts of a process development. In all the reported scale-up approaches which involve integration of multiple steps and integration of separation and inline

analysis involve thorough investigation of various parameters of the process. Once each step or sequence of operation is optimized and integrated, they can run continuously as there is no scope for any significant change to be incorporated at the large scale. Usually, scale-up approach is very specific to the chemistry under consideration. General scale-up procedure depends on the know-how available, physicochemical properties of the chemicals/materials involved, specific chemistry and the experience of individuals involved in the exercise. Using artificial intelligence (AI) in incorporating automation in developing methodology and devising the algorithms with decision making ability will help to predict the scalability. There is possibility of variations that can happen beyond the laboratory scale experiments when one uses them directly for scale-up. Efforts in development of self-optimization platforms will reduce the time and efforts which are necessary but they need to be coupled with reliable predictive scalability.

8.3 Self-optimization tools: Need, limits and scope towards predicable scalability

Continuous flow multistep synthesis coupled with online analysis can help rapidly test the effect of different reaction conditions on subsequent reactions. Self-optimising systems typically use a feedback control algorithm with automated process control. Automated systems can perform "black-box" optimization[40] wherein no prior knowledge of the reaction parameters is required provided the desired boundary conditions are already fed to the system. In general, such an approach becomes useful even when the kinetic data is limited or not available. Automated synthesis platforms can be used to monitor reaction parameters (primarily, temperature, pressure, residence time and the outlet composition). Precise control over reaction parameters can be achieved by continuous generation of data (real time analytics using Raman spectroscopy, IR spectroscopy, mass spectroscopy, Nuclear Magnetic Resonance, UV-Vis, etc.) and using precision sensors [41]. This would help to determine information like reaction

kinetics, yield and selectivity. Resulting conditions can be used for process optimisation that can lead to integration of chemistry and engineering.

One of the primary requirements a self-optimization system is an intelligent algorithm (**figure 8.1**). Data from every planned experiment is used as information for transforming into a knowledge base to take decisions based on heuristics and trends or imposed guidelines/constraints. In general, having rapid data acquisition is essential and can help minimisation of time in optimising any reaction. Smart algorithms will also account for any unforeseen changes in the input variables. The basic aim of any optimisation algorithm is to save labour/working hours. It creates a feedback loop wherein at any given point of time the reaction mixture is analysed and new set of conditions are generated based on the previous experimental data. As for self-optimisation, black-box approach is generally followed, the optimisation problem becomes a bound- constrained optimisation wherein only the objective function is known. Algorithms employed to solve such a problem are referred to as derivative-free algorithms (as it does not require any derivative information of the objective function).

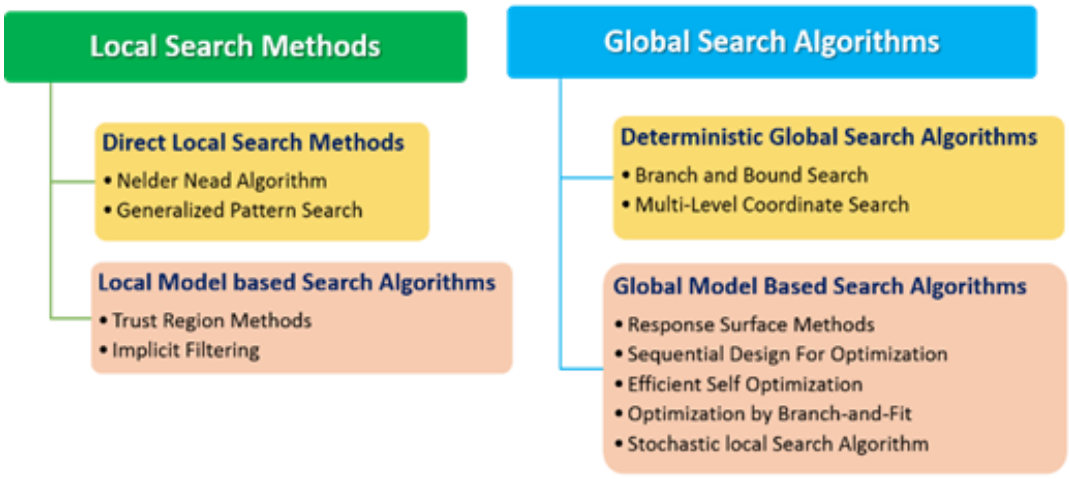

Figure 8.1 Classification of different decision/search algorithms

The reported literatures on self-optimisation in microreactors generally use the following algorithms (**Table 8.1**):

Nelder-Mead Simplex Algorithm (NMS): It is the simplest direct search algorithm used for multidimensional unconstrained optimisation. As no derivative of function is required, it becomes easy to use Nelder-Simplex for noisy problems.

Response Surface Methods (RSMs): This method optimises a function by examining relationship between the response and the factors affecting the response using regression models.

Optimisation by Branch-and-Fit: The algorithm combines global and local searching by branching and local fits. It provides a fast solution for bound-constrained noisy optimisation.

and

Hit-and-Run Algorithms: this approach can be used for getting global optimum values in the continuous optimisation problems under mild conditions. It generates an optimum value by comparing the current iterate value with a randomly generated candidate.

Table 8.1 Summary of different self-optimization algorithms (in comparison with NMS)

	Convergence	Optimizing chemical system with	
		Single optimum	Multiple optimum
Nelder-Mead Simplex Algorithm	fast	✓	×
Response Surface Methods	slow	✓	✓
Optimisation by Branch-and-Fit	slow	✓	✓
Hit-and-Run Algorithms	slow	✓	✓

The general approach involved in the development of self-optimizing system is shown in **figure 8.2**. Self-optimisation has been reported in literature since 2010. In a first such

attempt, Jensen et. al. used the Nelder-Mead Simplex Method coupled with an online HLPC analysis to maximise the yield of Heck Reaction[20]. It took 19 automated experiments to determine the optimum reaction conditions and the reaction was scaled-up to about 50 times using these conditions. Later they demonstrated optimization of Knoevenagel condensation reaction and oxidation of benzyl alcohol using different algorithms with inline HPLC monitoring[19]. A six-step system comprising of three synthesis steps and three workup stages for synthesis of 2-aminoadamantane-2-carboxylic acid has been reported and studied using advanced control strategies[42]. The applicability of self-optimised system using Supercritical CO_2 as solvent has also been demonstrated[43]. Nanoparticle synthesis using an autonomous "black-box" system has also been reported in literature[44].

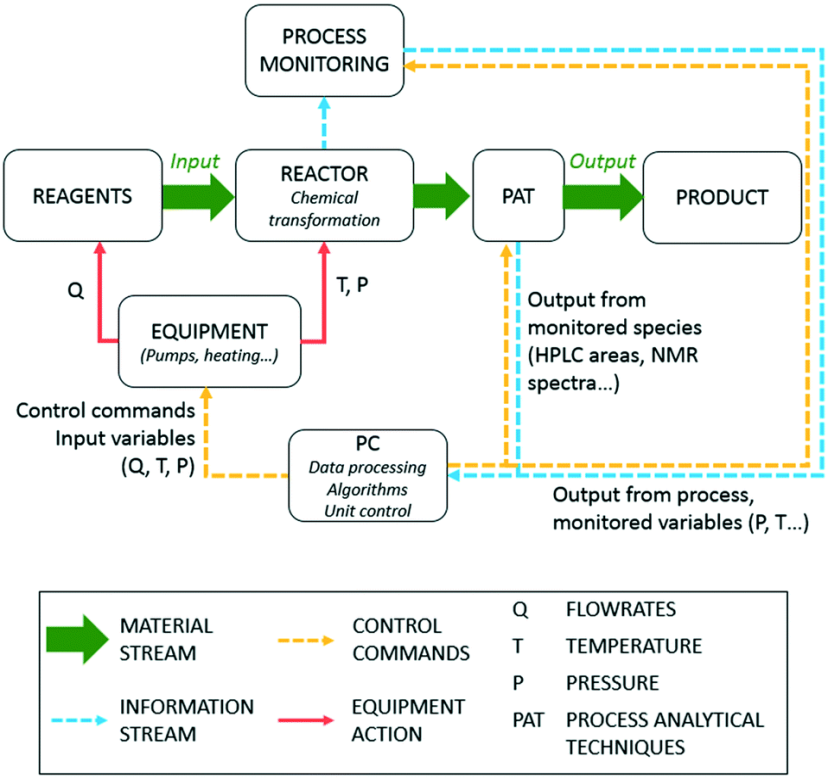

Figure 8.2 Overall process of self-optimized microreactor system

A parallel development of a modular, continuous, integrated, automated and remote-controlled reaction platform that sets up and performs the necessary unit tasks is also an

important milestone[45]. Li et al. presented a method for creating complex polycyclic structures involved in biochemistry and drug design based on carbon-based small molecules through deprotection, coupling, and purification modules, as well as reaction automation techniques[46]. Jensen and Jamison groups have built and miniaturized a refrigerator-sized continuous flow system for continuous and productive drug synthesis and presented an integrated set of modules[47]. In addition, a system was proposed that can perform various chemical reactions through optimization of temperature and concentration and feedback control that can greatly affect product yield[48]. In particular, in the recent time, a system has been proposed for molecular synthesis led by AI and performing it through a robotic arm to greatly reduce the efforts of experts in complex organic molecular synthesis. As a result, they succeeded in applying this strategy for a total of 15 active pharmaceutical ingredients (APIs)[49]. Other excellent efforts include modular robotic platforms that formulate and control the assembly of molecules, which has successfully synthesized three pharmaceutical compounds, including paediatric anticonvulsant Rufinamide[50], automated control system for photochemical chemistry with constant yields under rapidly changing light conditions[51], machine learning-based synthesis efficiency with human experimenter-led synthesis efficiency[52], development of systems to remotely monitor and integrate many chemical experiments on a large scale, viz. use of networked robots to explore azo-coupling reactions[53]. These efforts are moving the chemical synthesis beyond imagination and it is sufficiently matured to now take it ahead for transform synthesis into robust processes that would eventually lead to manufacturing.

8.4 Moving multistep flow synthesis beyond laboratory scale

Though these reports shed light on the future of manufacturing in terms of automation and machine learning, several criteria are ignored in the development of this methods or devices. Automated manufacturing involves the simultaneous monitoring and control of

important process parameters with very little human interaction when the process is operating at steady state or within the constraints. It also involves the development of logic and control algorithms in case of slight disturbance in the processing parameters at any stage. In rest of this section we discuss these aspects with greater detail more cautiously.

8.4.1 What is real optimum?

As mentioned earlier, the optimization studies involve the development of the search algorithms. This is a very tedious process and requires perfect logic coupled with necessary constraints in a highly trained algorithms to do that. For the automated feedback-based optimization (based on Black box approach/ Deterministic model-based system/ Stochastic models), the optimum may have variation[54]. This becomes crucial for multistep reaction sequence, where the need for more than one product optimization makes the approach very difficult upon integration of steps. While a well-trained algorithm can be used, a collaborative human intervention by involving an experienced chemical engineer or chemist becomes very helpful in deciding the critical parameters to define the bounds for optimal point.

8.4.2 Economic feasibility of versatile self-optimization system

A multipurpose self-optimization platform would help perform a very rapid assessment of optimal conditions for almost every reaction. It will reduce significant process costs but at the cost of development of such a platform. It will also need a lot of data in terms of physical properties of all the components and reaction mixtures (which is usually unavailable for complex reactions). It should also have almost every possible in-line or on-line analytical instrument attached to it to ensure that every single experiment gives the maximum information that becomes useful for optimization, scale-up, and sometimes even for formulation. When we

consider the total time required by those platforms for optimization it will significantly depend on the desired residence time and analysis time for any reaction.

8.4.3 Post processing of the data and sensitivity analysis

The final aim of the generated data from the optimization platform is its utilization for scale-up, which depends on many aspects viz. reactor chosen for optimization, critical parameters assumed, time of analysis, method of analysis etc. Since in the chemical engineering literature it is well documented that scale-up is not so straightforward and it involves rigorous quantitative estimations and many other engineering aspects. Hence while the objective of scale-up is to achieve the same performance as optimized by the laboratory scale system, a lot more information which was not relevant at the laboratory scale becomes important. Hence, it is not necessary that the optimum at lab scale would be optimal only in terms of reaction performance. The usefulness of this data for predictability of scale-up approach is going to be an important step in the decision-making process.

8.4.4 Process economics

Success of any process for synthesis depends on overall process economics which usually not only dependent on the actual process but also on the nature and quantum of downstream processing. It is always possible that the optimum obtained in case of lab scale studies would need specific downstream processing equipment that may not be available for higher capacities. For example, standard equipment viz. wiped film evaporator is never seen in any published literature where solvent recovery is needed before moving for the next step. The matching of time scale for downstream processing operation with the reactor condition also becomes critical, which does not seem to be the criteria of consideration in the current scenario. Also, slight deviation from the optimized set of conditions may have huge impact in the

downstream processing which may reflect in the overall costing. This can have minor or major implications on the overall viability of the process. In the current scenario from the literature on multistep flow synthesis, development of a clear understanding on economic viability of an optimized laboratory protocol needs more careful analysis.

With the above gap in the existing literature that, if addressed would help in moving from "Laboratory synthesis" to "Commercial scale manufacturing" and brings out a need for a "comprehensive process evaluation cum decision making tool" having predictive scalability.

8.5 Flow synthesis of Ivacaftor: Sensitivity analysis

Ivacaftor is used for the treatment of cystic fibrosis and it is one of the most expensive drugs. The analogues of this drug including deuterated versions are also being explored for efficacy in treating the decease. Laboratory scale multistep flow synthesis of Ivacaftor is considered[49] and a process flow diagram is built based on the optimal condition reported in the previous chapter (**Figure 8.3**). The process consists of three reactors, two separators and a scrubber for the synthesis of Ivacaftor **(Figure 8.4)** and certain assumptions were made to show how an optimised process can change even with very small variations in the optimised parameters.

Three different cases are considered to show how small changes in performance could affect the overall process flow. It was assumed that the optimised conditions for the process give 1g of pure Ivacaftor per unit time. For initial base conditions previously reported[49] experimentally optimized conversions were used for all three reaction steps based on which rate constants were calculated[49]. At every step, since one of the reactants was always in excess all the three reactions were considered to follow first order kinetics, based on which the rate constant *k* for each reaction was obtained. The volumes for the liquid-liquid separator, gas-liquid separator, and the scrubber were estimated considering 30 minutes residence time for

separating the reaction mixture if all of them were working at 100% efficiency. In order to assess the effect of temperature variation, three reaction temperatures were considered with difference of 10°C. As a thumb rule, it was assumed that the rate doubles with every 10°C rise in the reaction temperature. These assumptions have helped to get certain parameter values for the synthesis of 1g of Ivacaftor.

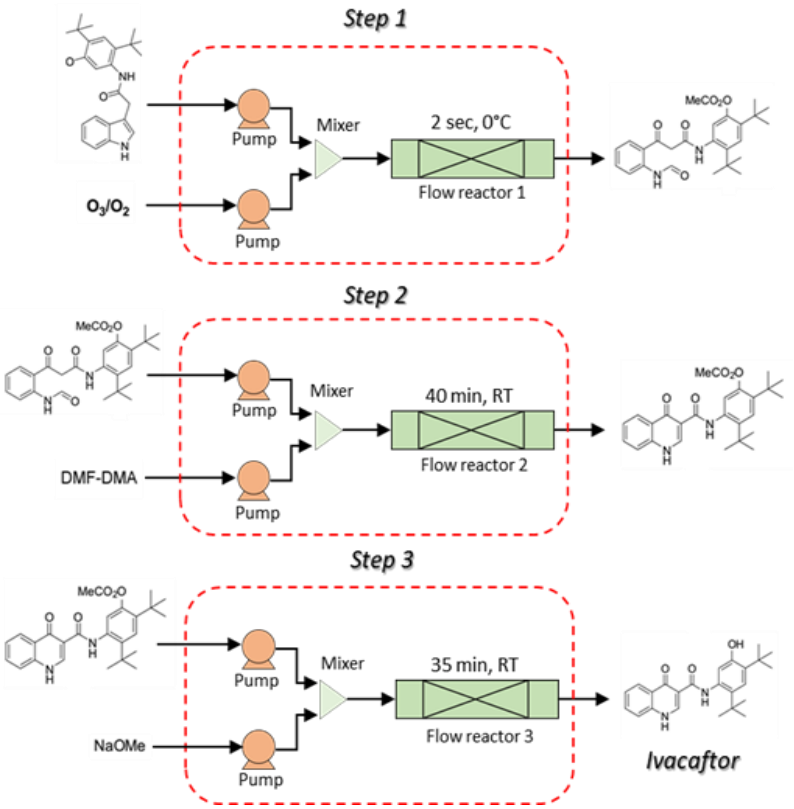

Figure 8.3 Typical schematic of the experimental set-up for optimizing individual reaction steps in flow synthesis.

Based on the laboratory optimised values for 1g of the process, the values for scaling up the process by 1.5, 2 and 10 times were obtained. A 5% change in the conversion in the individual reactors was assumed to show how the reactor volume changes drastically during scale-up with small change in conversion while all the other parameters remain unchanged.

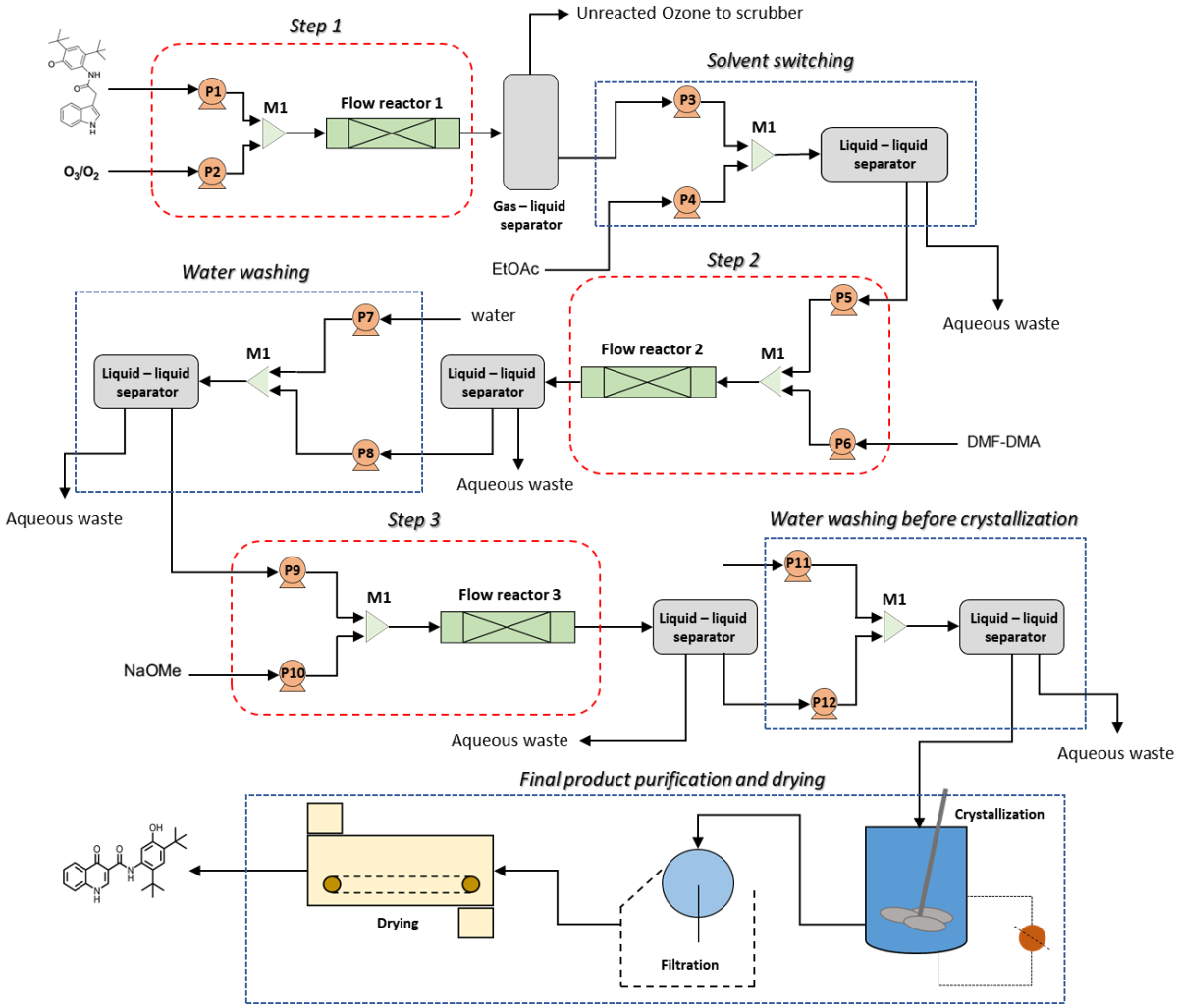

Figure 8.4 A typical possible process Flow Diagram for flow synthesis of Ivacaftor

The resulting values are tabulated in **Table 8.2**, assuming 100% efficiency of all the separators and scrubber. However, if separation/purification equipment do not work at 100% efficiency, the conversion and hence the yield of final product would be lower than expected. In order to see the sensitivity of this effect during scale-up, a 5% variation was assumed in the efficiency of the separators and scrubber and subsequent yield of Ivacaftor was calculated. The effect of these variations on the overall process is described subsequently.

Table 8.2 Change in reactor volume based on the effect of variation of throughput and kinetics in synthesis of Ivacaftor

Temperature (°C)	Reactor	1 g scale		1.5 g scale		2 g scale	
		Reactor volume(ml)	K	Reactor volume (ml)	K	Reactor volume (ml)	K
25	R1	30	0.153	45	0.153	60	0.153
	R2	30	0.021	45	0.021	60	0.021
	R3	40	0.012	60	0.012	80	0.012
35	R1	15	0.307	22.5	0.307	30	0.307
	R2	15	0.042	22.5	0.042	30	0.042
	R3	20	0.025	30	0.025	40	0.025
45	R1	7.5	0.614	11.2	0.614	15	0.614
	R2	7.5	0.084	11.2	0.084	15	0.084
	R3	10	0.050	15	0.050	20	0.050

8.5.1 Effect of throughput variation in combination with other reaction parameters

The optimized conditions for a specific reaction step are usually valid only for a specific throughput within the desired parameter constraints. Any variation in the throughput will need a different reactor to match the desired residence time. However, there will be consequences beyond only change in the reactor volume as the heat transfer rates, mass transfer rates and mixing efficiency can change and thus would need a new set of optimal conditions, which can be different than that of the initial one and can be different from the real optimum with the available reactor volumes. One of the ways to compensate for such variations can be through changing temperature, provided the reaction kinetics are known or by ensuring certain values

of transport coefficients. It also puts an important constraint of retaining a fixed outlet composition as the downstream unit operations including subsequent reactions are designed for a specific inlet composition.

Conventionally, a multistep flow synthesis goes through an individual step optimization followed by integration of the separation stages. In the presented exercise, the experimentally measured reaction kinetics were used for estimating the reactor volume for each step, and corresponding temperature in each reactor for the final desired output of Ivacaftor (**Table 8.2**). The best-case scenario is the optimum obtained from the literature [55] and reaction rates were varied for 3 different temperatures which will enhance the reaction rate and reduce the reactor volume. For an expected output of 1g/min, there are 3 sets of reactor combination for all the three reactions. Thus, if the self-optimization platform consists of reactors of the volumes 10ml, 10ml and 13ml, each for the first, second and the third reaction step, respectively, then, for an expected throughput of 1g, the stoichiometry and inlet concentration would result in specific flow rates at 45°C.

For enhancing the production rate beyond 1g would need larger reactor volume. However, for the same production rate, if we go for the lowest temperature and the highest reactor volume, (i.e. 30 ml, 30 ml, 40 ml) the same reactor combinations can achieve 2g output at higher temperature at increased flow rates. However still it would be oversized by 25% in each step and can actually achieve the design specific production capacity only at another set of conditions. This would lead to an unending loop where change in one parameter would lead to the change in the optimal condition only within a small range. Such a situation leading to *on-site optimization* can be avoided through a detailed modelling exercise involving intrinsic kinetics, transport coefficients, the extent of dispersion for a specific throughput.

8.5.2 Optimization at large scale based on optimized conditions

Enhancing the production capacity from a flow reactor (i.e. scale-up) can be achieved either by numbering up (where a number of geometrically and dimensionally similar units are run in parallel at identical conditions) or through conventional scale-up by changing the reactor dimensions. If the production capacity in the present case is to be enhanced by 10 times, the required reactor volumes would be 300ml, 300ml and 400ml. The numbering up approach would need 10 reactors of the same dimension running in parallel, while the second approach would demand identical rates of heat transfer and mixing as at smaller scale. Any deviations from the desired hydrodynamics would reduce the conversion at the outlet of specific reactor.

Table 8.3 Change in reactor volume based on the effect of variation of conversion on scale-up process compared to initial laboratory scale optimized condition to obtain 10g yield of the ivacaftor

Temperature (°C)	Reactor for specific reaction step	Rate constant	Reactor volume for 10 g production scale	
			Optimal condition (ml)	5% reduction in the conversion in all the reactors (ml)
25	R1	0.153	300	390.3
	R2	0.021	300	341.6
	R3	0.012	400	455.5
35	R1	0.307	150	195.2
	R2	0.042	150	170.8
	R3	0.025	200	227.7
45	R1	0.614	100	130.3
	R2	0.084	100	113.9
	R3	0.050	133	151.8

In order to quantitatively evaluate this effect, from the known kinetic data we identified the conditions that would result in lower conversion in each reaction step by 5% individually as well as an overall 5% lower productivity at the outlet of the sequence of reactors. A quantitative analysis of the final yield is given in **Table 8.3**, where the change in volume required for change in the conversion in the individual reactor as well as for their combinations is given. If any of the reactor underperforms then to meet the overall throughput the new reactor has to be of higher capacity to get the required input for the feed at the next stage, which is very much expected. In all these cases the overall volume was seen to increase by almost 18%, which will also add to the capital cost and also slightly to the operational costs.

8.5.3 Design of separation stages/ Change in operating conditions of the separation stages

As discussed earlier usually the laboratory scale process development does not include the design of a continuous separation stage as the type of separation depends on the reaction. In general, in the recent time a lot of examples are seen, where liquid-liquid separation is demonstrated using membrane separator or using simple gravity-based layer separation. Using a membrane separator demands the solutions to be completely homogeneous in term of dissolved solids. This also implies that using excess solvent might be needed to facilitate easy separation of two immiscible phases. However, when going for the scale-up, separation strategy needs to be carefully designed to match the desired output for the input of the subsequent step. In general, while one can still accept slight variations in the residence time in the reactor, then variation in the residence time in a continuous separator may or may not be acceptable due to specific time scales relevant to the mechanism of separation. In general, no literature reports any deviation from optimal performance would add more process equipment to the plant adding to higher capital cost, higher operational cost and such operational issues although they hold a key to the plant design. In the cases where reactors are already designed

for a specific production capacity, if it underperforms for the parameters obtained from optimized conditions the separation approach would change completely as one has to then even plan to separate unreacted reactants from the product, both probably in the same phase. Situation completely rests on the design of the separation stages to incorporate the feed composition change for certain capacity, which is not an easy task. For the separations involving distillation, change in the feed composition can be handled using the change in column operating conditions but for the separation involving the liquid-liquid extraction change in the feed composition can completely change the separation dynamics which may result in the one phase contaminated with the other. It might also need a second level of separation to take care of such issues. In order to see such an effect, i.e. change in separation efficiency affecting the complete plant design, we have varied the separation efficiency at each stage by 5% and the observations are shown in **Table 8.4.**

Table 8.4 Yield variation as efficiency of Gas-Liquid Separator, Liquid-Liquid Separator and Scrubber changes bigger plant foot

Condition with relevance to the optimal	Yield (g)	Additional process equipment to meet the desired production capacity
At optimum condition	10	-
5% reduction in the GLS efficiency	9.03	1
5% reduction in the LLS efficiency	9.5	1
5% reduction in the scrubber efficiency	9.5	1
5% reduction in the efficiencies (all three)	8.14	3

It can be seen that every separation step must work close to the desired efficiency as else it can affect the performance drastically, although all reactors would work at optimal conditions.

The approach involves several points to be addressed and evaluate the feasibility of a decision on the entire process. We have given one such set of questionnaires that would help anyone who wants to go for assessing the efficacy of an optimized synthesis protocol towards its realization into a commercially viable process (**Figure 8.5**).

8.6 Conclusions and Recommendations

In summary, it is well understood that utilization of advanced algorithms and self-optimization platforms are critical requirements of future chemical synthesis plant at laboratory scale and production scale. However, significant input in terms of development and assessment of critical parameters for each individual synthesis steps or complete process for chemical synthesis is necessary. Every chemical synthesis step cannot be generalized but can be incorporated in specifically designed algorithms with advanced processing techniques with the help of experienced professionals in the field or through the incorporation of AI tools. It is also shown that having assessed the parameters at the laboratory scale for any synthesis is just the first step in overall plant design in terms of anticipating and preparing for the probable deviations during scale-up which does not avoid the knowledge of experienced personals (chemist/chemical engineer) in the field.

We have shown that as small as 5% change in conversion or change in performance of separation stages may result in 18% change in throughput which results in manipulation of other parameters or utilization of additional equipment to meet the quality criteria. Using laboratory scale optimization also, it is shown that throughput and available reactor size put constraints on the optimized parameters which can change if different reactors are available as

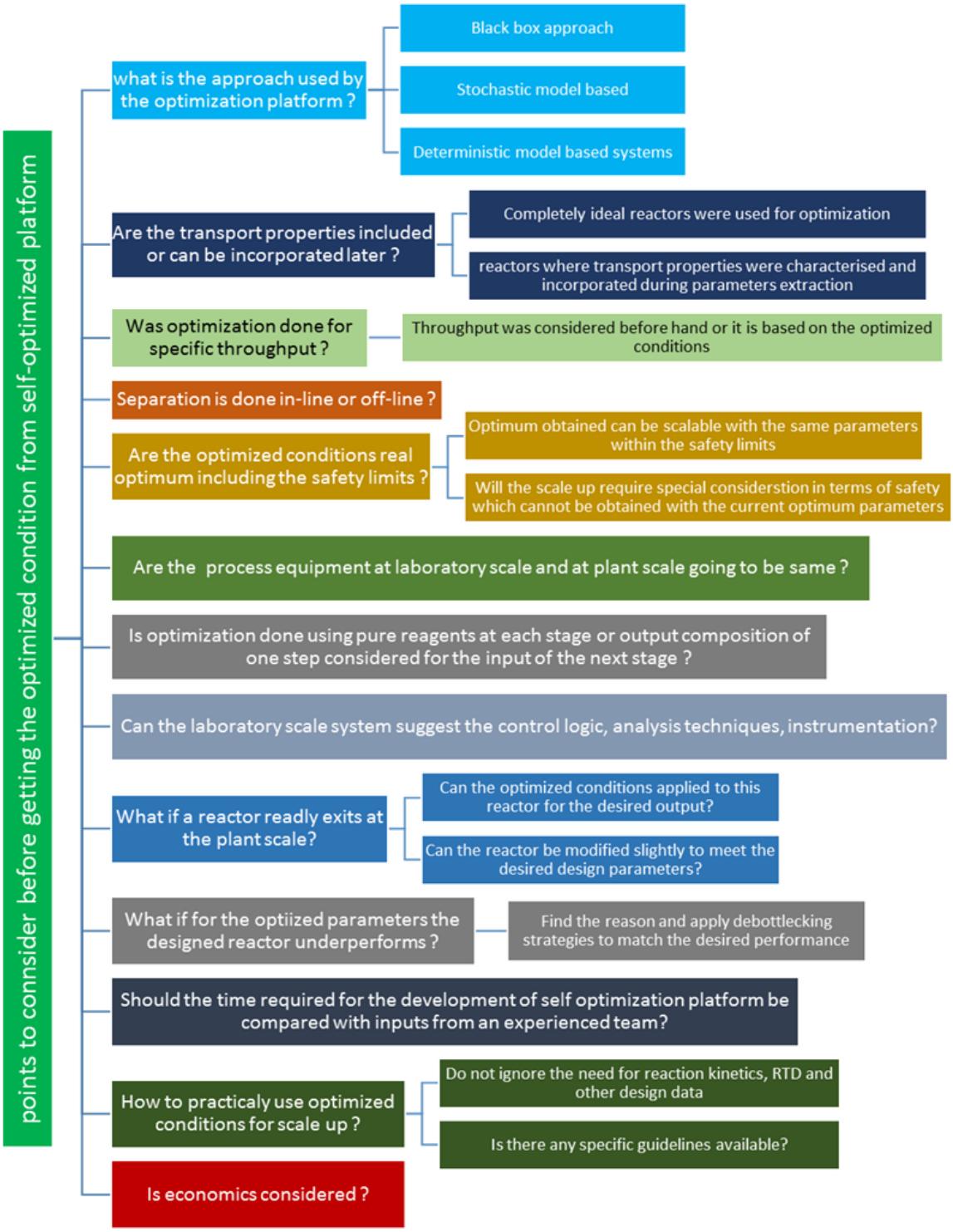

Figure 8.5 A model questionnaire cum flow chart for moving from a (self) optimized system predicted synthesis condition to a scalable manufacturing scale process involving multistep flow synthesis.

options. Upon reaching the plant scale, it almost impossible to accept any deviations in any parameters (conversion, temperature variation, efficiency of separation stages etc.) which may change the process flow diagram and add additional burden to the capital investment.

It is envisaged that for any manufacturing, advanced algorithms with automated synthesis platform and knowledge of experienced personals will go hand in hand to design better plants and efficient manufacturing techniques. Realizing self-optimization and automation in laboratory synthesis will require many challenges to be addressed (apart from technical issues mentioned here) in terms of result interpretation, decision on final optimum parameters, troubleshooting, generating know-how to develop and utilize advance synthesis platforms, utilization of new information for the modification or incorporation in existing process etc. all of which require significant human intervention. Addressing all the above challenges would help successful translation of "Laboratory synthesis" into "Commercial scale manufacturing".

A large body of organic synthesis and reaction engineering community is working on automation of synthesis, optimization, data analysis, integration of PAT tools in the system, etc. In such a situation it might be useful to look at the state of the art of automation in petrochemical refineries, bulk chemicals and polymers as a few decades ago these industries have made revolutionary changes in manufacturing involving flammable products. Maybe, it will help the community to save time in re-inventing some parts of the wheel.

Another important point that needs to be addressed in the entire endeavour is planning for imparting multiple complementary skills to the next generation, which significantly deviates from the erstwhile generation of chemists and engineers. Including AI for property estimation, python-based programming, making chemists use self-optimization tools, etc. will bring the community closer than before. This will definitely make everyone work on more challenging and more relevant problems of sustainability.

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Chapter 9

Unified multistep flow synthesis platform
A perspective

This chapter is based on:

Sharma, M. K., Acharya, R. B., Shukla, C. A. and Kulkarni A. A.,

Assessing the possibilities of designing a unified multistep continuous flow synthesis platform,

Beilstein J. Org. Chem. 2018, 14, 1917-1936.

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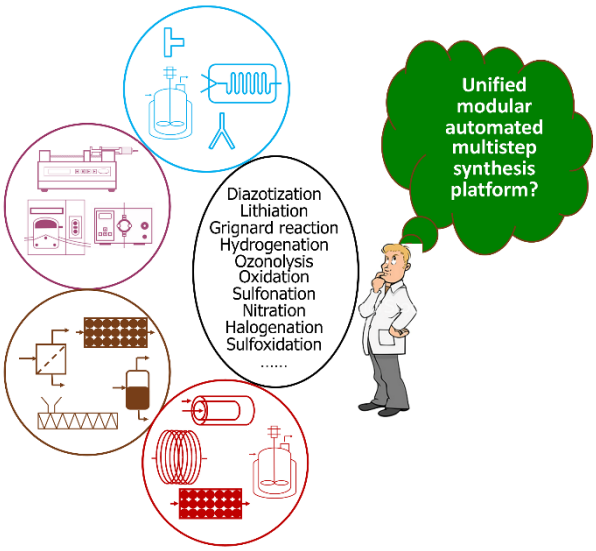
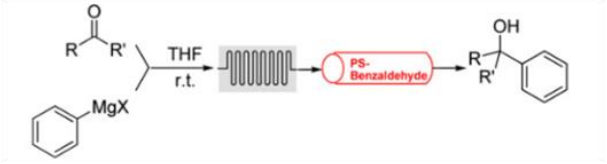
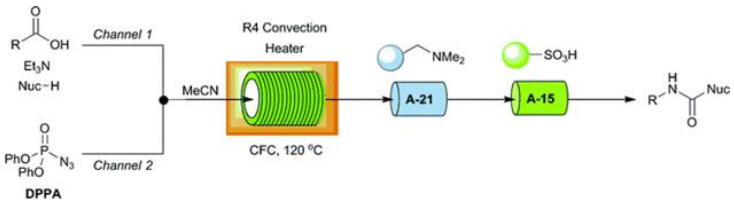
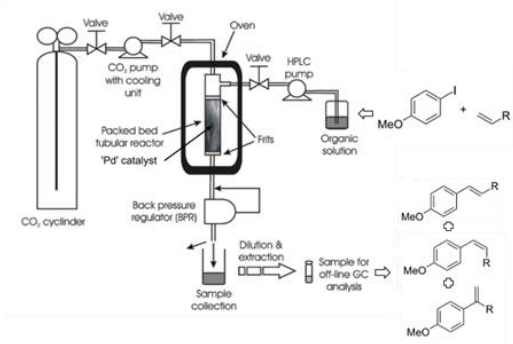
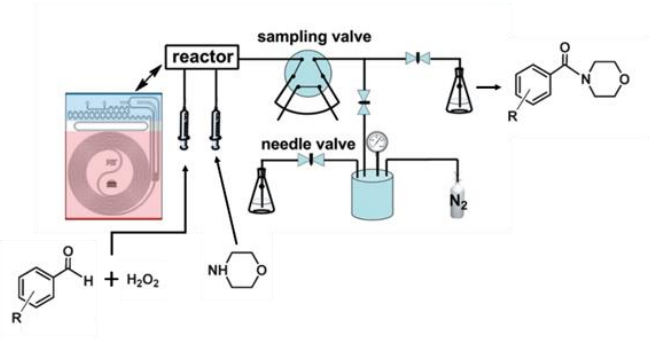
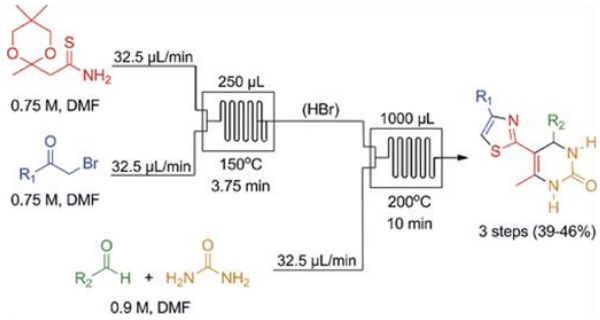


In this chapter we give a more 'engineering' look at the possibility of developing a 'unified multistep flow synthesis platform'. A detailed analysis of various scenarios is presented considering 4 different classes of drugs already reported in the literature. The possible complexities that an automated and controlled platform needs to handle are also discussed in detail. Three different design approaches are proposed: (i) one molecule at a time, (ii) many molecules at a time and (iii) cybernetic approach. Each approach would lead to the effortless integration of different synthesis stages and also at different synthesis scales. While one may expect such a platform to operate like a 'driverless car' or a 'robo chemist' or a 'transformer', in reality, such an envisaged system would be much more complex than these examples.

10.1 Introduction

Flow chemistry is now seen as a reliable approach for the synthesis of simple organic compounds[1-6], complex large molecular weight medicinal drugs[7-12], polymeric materials[13-15], nanomaterials (metallic, bimetallic, composites, metal oxides, etc.)[16-18], catalysts [7, 19] etc. In the recent times, the applicability of this tool has been extended for the synthesis of high value drugs involving multiple reaction steps including separation protocols [8-9, 20]. A vast range of useful molecules that are synthesized in flow has also helped integrate the complex synthesis with fine engineering to make the systems completely automated[9, 20]. Flow chemistry gains its benefits from excellent heat and mass transfer rates and rapid mixing which is not possible in the case of conventional synthesis modes[21]. In general, the continuous flow synthesis aims at conducting the reactions at intrinsic kinetics. This helps to have reactors having smaller volumes making them inherently safer. Due to low processing volumes and reactions at intrinsic rates without much of human intervention it is possible to carryout hazardous reaction and the reaction at much higher temperature which is not possible with the conventional method[22-23]. Automated flow synthesis approach also reduces the labor costs significantly and operation can go on for a long time without any interruptions or significant downtime for the maintenance[9, 20]. Many reactions have been performed in flow synthesis and are shown to be better than conventional synthesis[24-27]. A few examples of experimental set-ups of successfully demonstrated multistep flow synthesis encompassing various kinds of reactions from the literature are given in **Table 9.1** Single step approaches were useful in terms of evaluating the concepts in continuous flow synthesis. However, since synthesis of any fine chemical or medicinal drug or agrochemical compound involves a sequence of reaction as well as several unit operations, by making only one process step continuous does not make much impact in terms of overall efficiency, economics and operation time. Thus, the flow synthesis made its mark in terms of improving the product quality and reducing the environmental impact, albeit

Table 9.1 Reactions and corresponding flow synthesis set-up from the literature

Reaction name and Flow set up
Grignard Reaction[31] 
Curtius Rearrangement[32] 
Heck Reaction[33] 
Cannizzaro Oxidation Reaction[34] 
Biginelli Reaction[35] 

only for single reactions. This also helped understand the safety related issues of flow synthesis and even helped to study the effect of operating parameters (viz. flow rates, temperature, pressure, pH, etc.) and design parameters (viz. mixing, heat transfer, mass transfer, dispersion, etc.), which together helped in developing reactor selection protocols and safer intensification window for its continuous operation. Over the time even the process control structures also got evolved for specific kind of experimental set-ups and even automated self-optimizing platforms were also tested[28]. The natural evolution was towards the multistep flow synthesis. The integration of in-line separation has taken the confidence of the synthesis community one step ahead [21, 29-30]

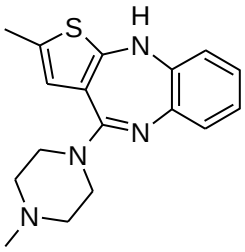
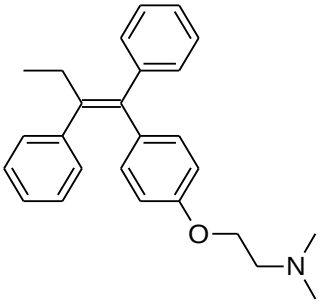
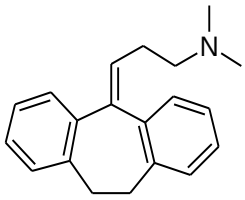
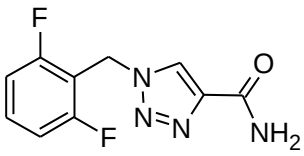
In parallel to this, in-line analytical techniques have also been used for on-line measurement and characterization[31-33]. Multistep flow synthesis is a significant milestone in practice of organic synthesis. In the recent time, there has been a visible surge in the number of publications on multistep flow synthesis with specific target molecules[26, 34]. **Table 9.2** shows a few drugs which are synthesized using multistep flow synthesis. Multistep flow synthesis approach has the capability of replacing the conventional synthesis methods. It involves many unit operations also made to operate continuously to truly harness the benefits of flow chemistry which is not an easy task.

The utilization of the same approach for the synthesis of a wide range of products is very challenging since each product in the chemical synthesis involves different synthesis procedures, different conditions, different phases and different isolation protocols. However, the approaches adopted for several multistep flow synthesis still lack from seamless extrapolation to other synthesis platforms, including the non-availability of specific unit operation in continuous mode at the throughputs suitable for laboratory scale.

Though, the multistep continuous flow synthesis approach is very promising for the synthesis of important chemicals having applications as medicinal drugs, agrochemicals,

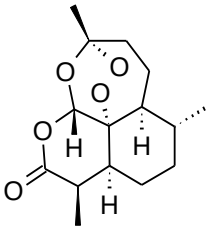
perfumery compounds etc., in general, the components/equipment in a flow synthesis platform are almost identical and this paves the way to think of developing a unified flow synthesis platform that can facilitate multistep synthesis involving a wider reaction scope over a varied range of conditions.

Table 9.2 A few important drug molecules synthesized in multistep continuous flow

Molecules and reaction/separation steps	End Product	Remarks
Olanzapine (Zyprexa)[11] • 4 reaction steps • 2 separation steps		• antipsychotic drug • Inductive heating was used • Starting materials used: aryl iodide, aminothiazole Pd_2dba_3, Xantphos, Bu_4NOAc, Et_3SiH, HCl, piperazine
Tamoxifen[12] • 5 reaction steps		• Breast cancer drug • Telescope synthesis • Moisture sensitive reagents were used • Starting material used: Weinreb amide, PhMgBr, Aryl bromide, nBuLi, aq. HCl, TFAA, Et_3N
Amitriptyline[10] • 6 reaction steps		• Antidepressant drug • Moisture sensitive reagents were used • Tube-in-tube reactor was used • Inductive heating was used • Starting material used: benzyl bromide, nBuLi, CO_2, Grignard reagent, EtOH
Rufinamide[35] • 3 reaction steps		• Anticonvulsant drug • Telescope synthesis • Copper tubing was used as reactor and catalyst • Starting material used: Aryl bromide, NaN_3, methyl propiolate, aq. NH_3

Artemisinin[36]

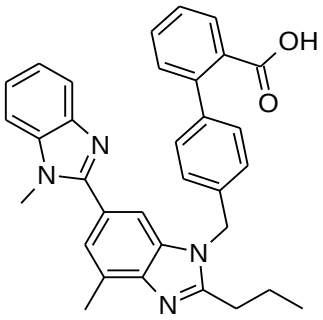
- 3 reactions steps
- 4 separation steps



- Anti-malarial drug
- The pressure was monitored to avoid unsafe backpressure due to clogging
- Starting material used: Dihydroartemisinic Acid, TFA, toluene, O_2, TMOF / TEOF/succinic anhydride

Telemisartan[37]

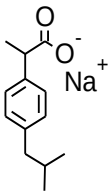
3 reaction steps



- Hypertension drug
- Telescope synthesis
- Starting material used: benzimidazole derivative, tBuOK, bromide derivative, aq. KOH, bromobenzimidazole

Ibuprofen[38]

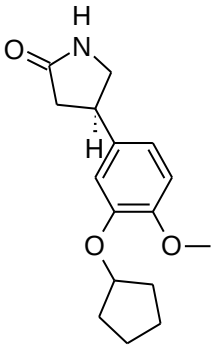
- 3 reaction steps
- 1 separation step



- Nonsteroidal anti-inflammatory drug
- Three minutes residence time
- Starting material used: isobutylbenzene, propionyl chloride, AlCl3, TMOF, ICl, NaOH, 2-mercaptoethanol

(S)-rolipram[7]

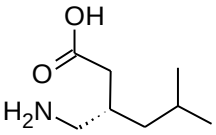
1. 4 reaction steps



- anti-inflammatory drug and selective phosphodiesterase 4 (PDE4) inhibitor
- Heterogeneous Catalysts
- Starting material used: Aldehyde derivative, Nitromethane, malonate, Et_3N, H_2, water and o-xylene

(±)-Pregabalin[39]

- 3 reaction steps



- Used as a therapeutic agent for nervous system disorders such as epilepsy, anxiety disorder, and neuropathic pain
- Heterogeneous Catalysts
- Starting material used: isovaleraldehyde, methyl malonate, nitromethane, 1-PrOH, H_2, HCl, NaOH

Such a platform would help reduce the time in setting-up of experimental set-ups for individual reaction(s) or sequence and will also help to do a seamless integration of experimental conditions with smaller laboratory footprint. In addition to the most obvious purpose of having such a platform that will facilitate the synthesis of any molecule including several intermediate stages, it will help in terms of the following:

End-to-end synthesis: Total synthesis of various molecules involving multiple chemical transformations (homogeneous or reactions involving multiple phases) at various optimal conditions including work-up/purification in continuous mode.

Screening: Rapid screening of operating conditions and development of a library of molecules from similar initial substrates.

Convenience: Selection of the specific parts of the set-up for a given synthesis step or for selecting a sequence of reaction steps reduces the time to disassemble and reassemble the set-up for different products. So, operating the set-up and deciding the parameters for each step becomes convenient using a unified platform.

Modularity in true sense: Making the reaction platform having plug-and-play approach would make it modular in true sense.

Adaptability: Having components with multiple functions will reduce the overall number of equipment/instruments on the synthesis platform.

Automation: Reduced human intervention facilitated by in-line measurements, automated optimization programs and continuous operation for a controlled set of conditions will be the unique features that will make such platforms attractive and efficient.

Reproducibility: Development of individual reaction steps and their optimization at various locations of an organization can become reproducible upon integration through such platforms.

While the concept of a unified synthesis platform looks fascinating and useful to reach the targets like 'Dial-a-molecule'[40], in reality, it can be very challenging. Some of the challenges are as follows:

10.1.1 A varied range of conditions

A multistep synthesis platform developed for one target molecule cannot always be utilized for different products since each product either requires different chemistry or a different set of unit operations or unit operation sequences. In some cases, synthesis chemistries can be very different such that totally different set of flow reactors (including material of construction) and operating conditions has to be employed. e.g. Flow chemistry literature shows the use of wide variety of flow reactors e.g. tube-in-tube gas permeable membrane reactor[41-43], High-pressure reactors utilizing back pressure regulator[44-46], reactors with different heating and cooling modes (e.g. inductive heating[11, 47], microwave[48-50] etc.) and many more, incorporating such special reactor[51] involve other difficulties which needs to be taken care. Also reactions vary in terms of conditions such as utilization of novel process windows[52-54] where high temperature and pressure is utilized which needs special attention in terms of safety and other criteria compared to the reactions requiring ambient conditions and low to moderate temperatures.

9.1.2 Matching of time scales

Residence time associated with a specific operating condition in each reactor and in a separation protocol (i.e. unit operation) in sequence has to be matched properly to get the desired final product which needs to be optimized every time if the throughput in the start or anywhere else gets changed in the sequence. This is very important for synthesis steps where downstream processing is also in sequence. Usually time scales for work up procedures like

extraction, crystallization, solvent switch etc. are longer compared to the main reaction and for any particular reaction in sequence the time scale for all other steps has to be either fixed or it gets fixed based on the initial step. One option is to have more pumps and collect the reaction mass at some point to change the flow rate for matching of time scale.[7-9, 20]. However such an arrangement, is complex and makes it difficult very difficult to vary for each new scenario which require special skill set or modification in chemical step.

9.1.3 Suitability of control structure and sensitivity

Multistep flow synthesis approach possesses challenges in terms of controls where a slight change anywhere in the process sequence can hamper the product output or will require very different kind of control strategy in the subsequent steps. For example, the reaction can be sensitive towards mixing, mass transfer/flow regime, temperature, etc. Slight variation in pump flow rate or coolant flow rate/temperature can change the relative time scales of the process affecting its selectivity. For such cases, the control system should quickly bring the process to steady state to maintain the desired selectivity. Shukla and Kulkarni have reported control structure for few synthetically important drug molecules and discussed challenges involved in developing such control process[55].

9.1.4 Monitoring

Utilization of inline analysis techniques and constant monitoring of the product also requires specialized equipment to be used and relative ‘analysis time’ in the whole process sequence is much greater compared to the reaction time. During utilization of such inline techniques like HPLC, UV and IR etc. where analysis time is greater than reaction provision has to be provided for intermittent sampling to monitor the reaction progress in those instances

it is the analysis time that dictates the control structure and parameters to be varied in case of any disturbance at/during any stage of operation [56-57].

9.1.5 Optimization

In continuation to the 1st point above, since every reaction step would have a different set of optimal conditions, the availability of a varied range of utility (i.e. the heating or cooling systems) and their suitability for integration on a single platform would be challenging for configuring the entire platform. Moreover, even after realizing such a platform, optimal conditions for each step would be different this might need significant reconfiguration for making a real 'plug-and-play' kind of system. This means that the unified synthesis platform should have as less number of utility variations as possible.

9.1.6 Compatibility

The material of construction or make of the process components may not be always suitable for a given set of reactants/products/solvents/by-products. Even the change in the sequence should be adaptable such a system can be very expensive as well.

9.1.7 Skills

With the advent of many flow synthesis tools available in the market much of the above issues may be taken care of. However, the automation in multistep synthesis needs careful selection. In general, setting-up of a multistep flow synthesis platform is very time consuming and needs multidisciplinary skills or a bigger team as it gets reflected in a few excellent works from the literature[8-9, 20, 58].

9.2 Motivation

In this chapter, we have explored the feasibility of having a unified multistep flow synthesis platform which can help do almost any flow synthesis. Such a platform, if developed would resolve most of the above-stated challenges and will reduce the time and other resources whenever new chemistry has to be developed in continuous flow manner. The proposed platform will contain all the necessary components of a multistep synthesis unit that will be sufficient to perform a number of chemical syntheses with wide variation in synthesis steps. With the developed platform it will be very easy to do a screening of different chemistries and save a lot of time for beginner chemist in terms of locating and assembling the setup. The proposed approaches are more as a guideline and will need elaborate engineering analysis before actually building them. However, we have also given specific recommendations in that direction. Before presenting and evaluating various approaches for building a unified multistep synthesis platform in **Table 9.3** we have given definitions of a few terms used throughout the chapter and their relevance.

Table 9.3 Definition of the specific terms used in the chapter

Terms as used	Meaning/relevance
Reactor	The section of the platform used for carrying out reactions. Usually, reactors are followed by separators (for extraction, distillation, chromatographic separation, crystallization, etc.).
Instrument	Wireless or cabled electronic unit that interfaces with the Reactor and separator to facilitate monitoring and/or measurement and/or control.
Equipment	An electronic unit that facilitates dosing of gas, liquid and solid.
Component	Connecting joints between Reactor(s), instruments and equipment. These will include fittings, connectors, valves, etc.
Module	An assembly of all the above segments to facilitate flow synthesis along with monitoring and control (1-4).

Variables and parameter	Set of conditions (set points or variables) that are used for optimizing a specific reaction section or the entire sequence of reactions.
Stage	Individual unit operations (viz. pre-heating, mixing, reaction, quenching, separation, etc.)
Number of steps	Number of reactions (chemical transformations) in a sequence to reach to the final product.
Synthesis sequence	A sequence of reactions and unit operations (stages) in the synthesis path for the specific final product.

9.3 Design complexity

General flow chemistry setup requires some basic equipment's like pumps, reactors (usually a flow reactor (tube of required length and diameter or a microchannel reactor having various geometries or a static mixer) or a continuous stirred tank reactor or a fixed bed reactor or other intensified process equipment viz. spinning disc reactor, impinging jet reactor etc.) and a thermostat which will maintain the reaction temperature and components viz. valves, measurement devices and so on. As mentioned earlier, a list of various terms used in this article is given in **Table 9.3**. Functionality and nature of setup can change with the chemistry under investigation and the experience of an individual involved in handling simple to complex synthesis containing a large number of stages and components. This demands more attention to address a few important aspects of such a unified synthesis platform.

9.3.1 Component selection

Component selection is the most important task for designing any synthesis set up that targets a specific product. For a typical multistep flow synthesis involving several reaction stages, the system will require several components, reactors, and equipment. One can definitely identify some class of reaction where the same kind and number of components can be utilized

but a slight change in synthesis route/chemistry will require a new component to be added extra or for the same component the suitable material of construction might be different than before. This can lead to a bulky system having complex flow path.

9.3.2 Choice of parameters

Choice of a range of operating conditions/parameters is a very crucial aspect while designing a unified synthesis platform. In a multistep synthesis route, each stage will have its own set of operating conditions for getting the optimum yield. A set of reactors and components designed for a specific reaction would require optimization in terms of operating conditions to match the throughput or residence time when used for another reaction. Moreover, once the system or synthesis platform is built, any minor variation needed at one stage due to possible variation in the purity of reactants will require manipulation at each stage in the sequence.

9.3.3 Number of steps

The number of reaction steps and subsequent downstream processing for the synthesis of any final drug molecule or an agrochemical is usually different. Therefore, the components needed for a specific synthesis protocol will also vary. Thus, a unified multistep flow synthesis platform may not be adequate and cannot be complete for the synthesis of any and every molecule. For example, a few synthesis steps need very specific type of equipment (viz. ozonolysis), which is not needed in every routine synthesis.

9.3.4 Sequencing of components

For a unified synthesis platform to become adaptive to any kind of reaction sequence (reaction followed by separation and purification) is one of the most important design challenges. As the component in a platform would be fixed, for every synthesis either some

components must be bypassed or connected in a loop, which would increase the dead volume in the overall system. This would enhance the residence time, demand more safety features and also need more inventory. Larger dead volume has its own challenges.

9.3.5 Control strategy

Devising a control strategy for a unified synthesis platform itself will be the most complex task. The complexity will originate from the varied control structures needed for individual synthesis sequence. For every reaction sequence verification of the sensitivity bounds on the specific control, strategy has to be developed for optimum performance of the setup.

9.3.6 Scale of operation

Throughput for any targeted molecule may vary based on the user requirement. Choosing a component to be operated in up-scaling and down-scaling mode at several throughputs with a wide range of operating conditions is very difficult. More than the effect of residence time, the hydrodynamics for the same reactor would vary depending upon the throughput and will affect the performance severely. In such a case, the plug-and-play mode might work provided the change of component is limited and absolutely necessary.

9.3.7 Troubleshooting

As unified platform will involve lots of components for a chosen multistep synthesis flow path, the standard protocols for start-up, operation and shut-down will vary depending upon the reaction sequence. Thus, the interlocks and control structure should be updated accordingly. For example, among the presently available automated flow synthesis platforms, the limitation always comes from non-availability of troubleshooting protocols.

9.3.8 Simultaneous use for synthesis of different molecules

Having a unified platform will serve the purpose only if all the units on the platform are utilized all the time which may not be the case always. Utilizing all the components simultaneously for different synthesis sequence will need isolation of one flow path from the other and since the whole system is integrated, this will introduce complex operational challenges.

9.3.9 Utility optimization

The operating conditions for individual reactions in a sequence are usually different and the reaction temperature can vary from -78°C < T < 200°C. In such a situation, it cannot be a viable option to have different utility for individual reaction steps.

The mentioned specific points need to be taken into account while planning for a unified synthesis platform for flow synthesis. Thus, depending upon the set of targeted molecules or functional group transformations it is possible to propose several design/assembly options.

9.4 How do we use it for drug synthesis?

The proposed options of unified synthesis platform will serve as a convenient tool at lab scale. Many new chemistries that are parts of a multistep flow synthesis route are to be performed with slight changes in the component/layout. The platform will serve as a single destination for the multistep flow synthesis whenever a reaction has to be optimized or new screening has to be done. It is expected that with slight modifications, a user will be able to 'choose' a multistep synthesis flow path in the unified platform.

9.5 Approach

For designing such system, we have analyzed the literature on multistep flow synthesis of API through complex chemistry. We have shortlisted the papers which contained different equipment's used in the pharmaceutical manufacturing to cover most of the functional groups which can be organized on the single platform and can be utilized for a number of chemical syntheses.

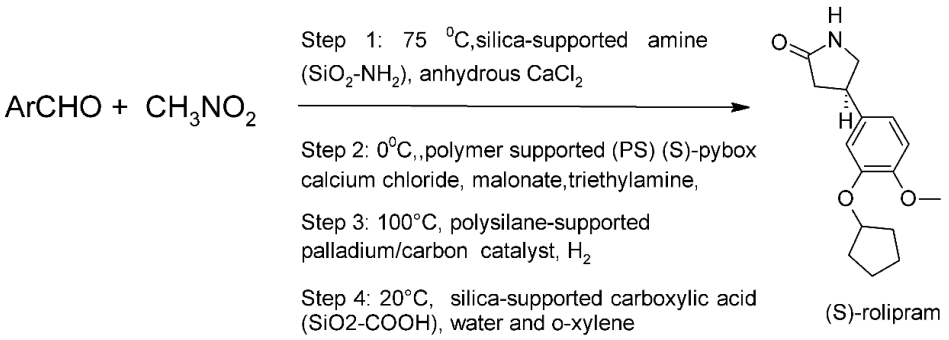
After identification of specific molecules to be used for developing a unified synthesis platform we have identified the number of components associated with a synthesis and then optimized the number of component which will be sufficient to do all the identified reactions. Once the components were chosen the optimal sequencing which will be efficient to do the reactions without much difficulty has been developed and sequencing was done. In order to evaluate the feasibility of the above concept, we have considered different multistep syntheses as case studies. Number of steps, starting material and other conditions are listed in **Table 9.4.** For these few cases we have evaluated three different approaches that can be used for developing a single synthesis platform. Every approach is based on a different logic of making a unified multistep flow synthesis platform. **Figure 9.1** shows comparison between different approaches.

9.6 Approach 1: One molecule at a time

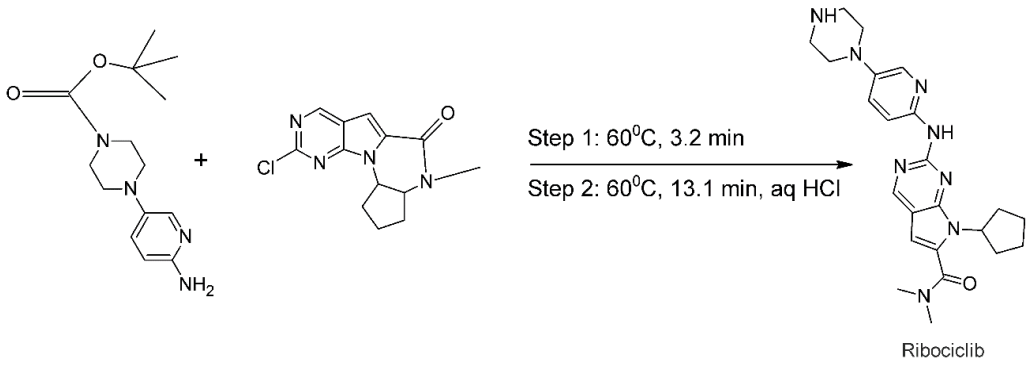
The first approach towards development of a unified flow synthesis platform mainly aims at minimizing the number of components and to perform the reactions in a single system without much change of components (**figure 9.2**). Here the components are fixed on one platform and the synthesis of a specific compound is carried out by choosing the path which is required for the reaction and other paths are blocked by using automated valves. This approach is good for relatively simple reactions and for some complicated reactions the number of

Table 9.4 Multistep synthesis case studies selected for the article

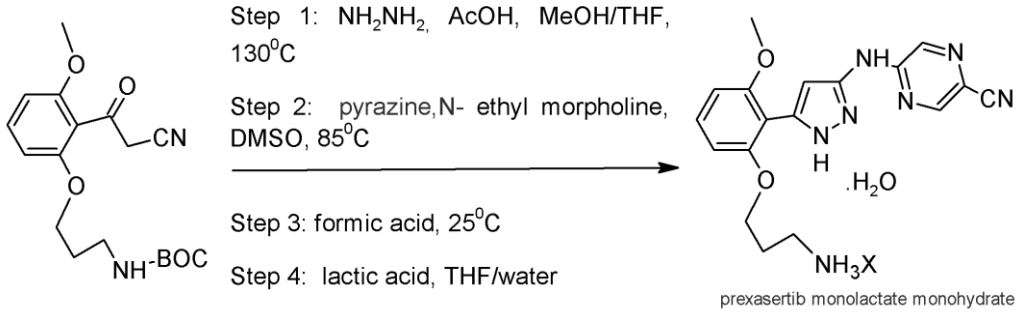
(S)-rolipram[7]:



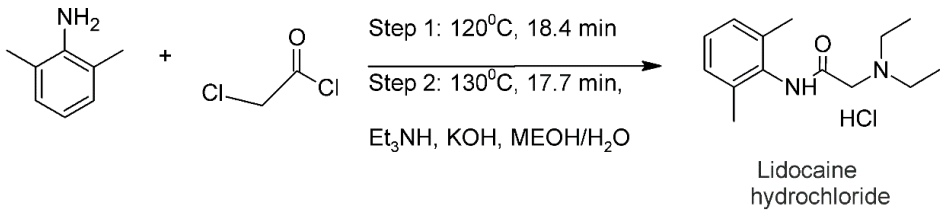
Ribociclib[59]:



Prexasertib monolactate monohydrate[8]

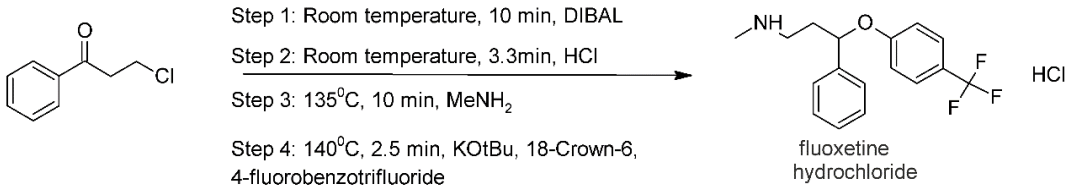


Lidocaine hydrochloride[9]



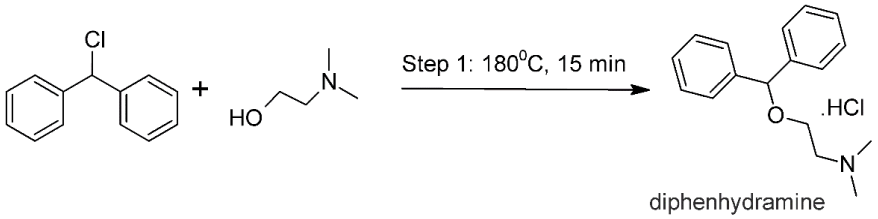
Lidocaine hydrochloride

Fluoxetine hydrochloride[9]



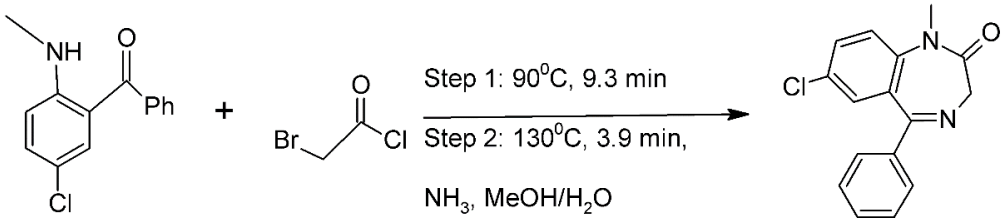
fluoxetine hydrochloride

Diphenhydramine hydrochloride[9]



diphenhydramine hydrochloride

Diazepam[9]



diazepam

components increase that lead to a large number of connections and a complex control structure. **Table 9.5** shows the path for the synthesis of different products based on Approach

1 and **Table 9.6** shows a list of components required for synthesis of above products using Approach 1.

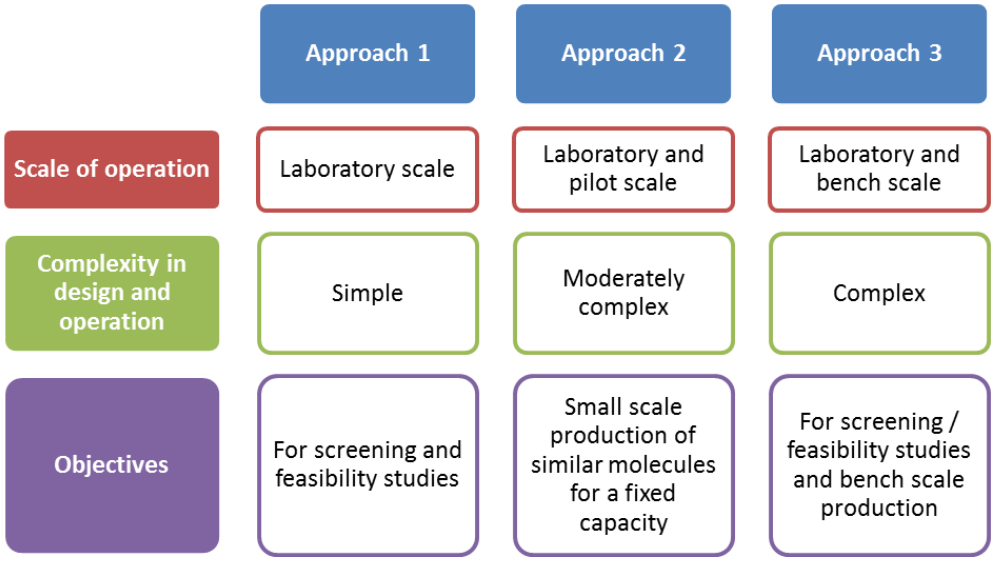


Figure 9.1 Key features of different approaches for unified multistep synthesis platform

Table 9.5 Conventional path for the synthesis of different intermediates based on Approach 1

Intermediate	Multistep synthesis flow path
Prexasertib monolactate monohydrates	P1+P2→HE1→TR1→E1→TR2→TR3→RE1→T2→ TR4→F1→T1
Aliskiren hemifumarate	P1+P2→R1→S1→S2→TR4→S1→PBC→C1→S2→T2
Diphenhydramine	P1+P2→R1→H1→BPR→CH→S1
Lidocaine hydrochloride	P1+P2→R1→R2→BPR→CH→S1
Diazepam	P1+P2→R1→R2→BPR→CH→S1
Fluoxetine hydrochloride	P1+P2→R1→R2→S1→S2→R3→S1→H1→R2→T1
Ricociclib	P1+P2→R1→R2→S1→R4→T1
Rolipram	P1+P2→PBR1→X→TR1→PBR2→PBR3→Y→Z→T3

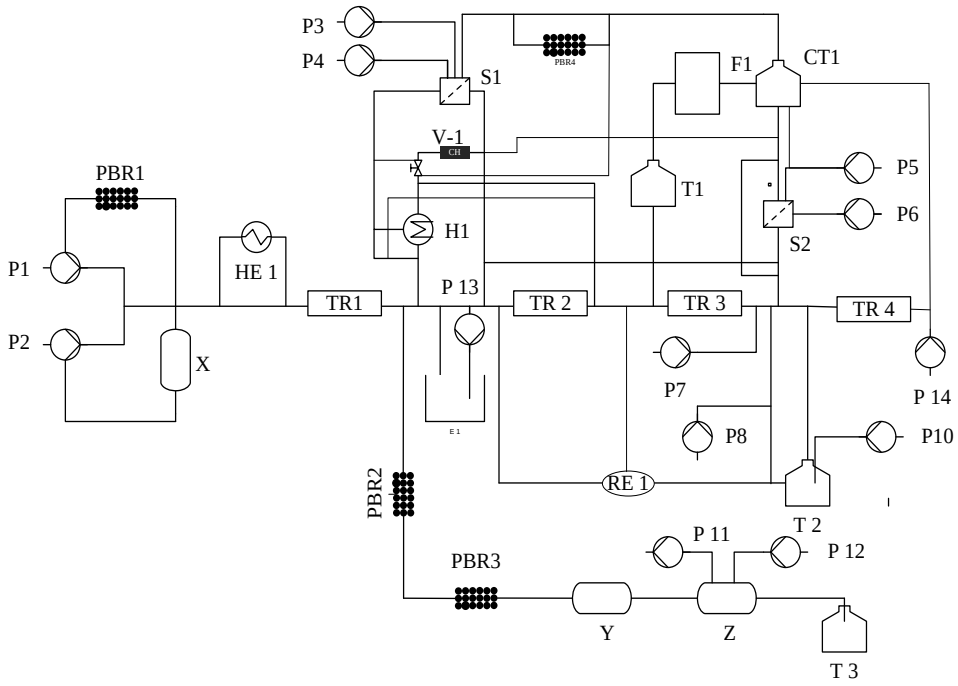


Figure 9.2 Schematic representation of Unified platform for the flow synthesis (P1-P14 Pumps, PBR Packed Bed Reactor, HE1 Heat Exchanger, H1 Heater, S1 S2 Separator, E1 Extractor, TR1-TR 3 Tubular Reactor, CH Charcoal, CT 1 Crystallization Tank, T1-T3 Tanks, F1 Filtration.)

Table 9.6 Components required for the synthesis of the above API's [Pumps (P), Reactor (R), Heat exchanger (HEx), Heater (H), back pressure regulator (BPR), Packed/Fixed Bed Reactor (PBR/FBR), Separator (S), Charcoal adsorption cartridge (CA, Liquid-liquid extractor (LLEx)]

Name of API's	P	R	HEx	H	BPR	PBR/FBR	S	CA	LLEx
Diphenamine hydrochloride	4	1	-	1	1	-	1	1	-
Lidocaine hydrochloride	5	2	-	-	1	1	1	-	-
Diazepam	4	2	-	-	1	1	1	1	-
Fluoxetine hydrochloride	11	4	-	1	4	-	4	-	-
Aliskiren hemifumarate	14	2	-	-	-	1	5	-	-
Ricociclib	4	2	-	-	-	-	2	-	2
Rolipram	7	1				5			
Prexasertib monolactate monohydrate	20	3	1		-	-	1	-	2

Figure 9.2 involves the platform for the synthesis of API's listed in **table 9.5**. One example has chosen from Table 5 to explain Approach 1. The description for the synthesis of Prexasertib monolactate monohydrates based on Approach 1 in Figure 2 is explained as follows: The synthesis of Prexasertib monolactate monohydrates involves four steps a) condensation b) aromatic nucleophilic substitution reaction, c) deprotection and d) formation of lactate salt. Details of the same are given below: -

- **Condensation**: Condensation takes place in a first reactor TR1 between nitrile and hydrazine at high temperature and under pressure. Here, nitrile was dissolved in a THF and hydrazine was dissolved in a mixture of solvents such as methanol, acetone, and water. Nitrile was pumped using pump P1 and hydrazine was pumped through P2 into the tubular reactor TR1 maintained at a temperature of 130°C and residence time of 60 minutes to obtain pyrazole. Pyrazole having the impurities were removed by passing to the continuous countercurrent extraction E1. Here solvent exchange process takes place between toluene and water. Pyrazole was then concentrated using automated rotary evaporator RE1. The concentrated product was diluted with DMSO using pump P13.
- **Aromatic nucleophilic substitution**: Nucleophilic substitution reaction takes place between pyrazole and N-ethyl morpholine. Pyrazole of step 1 in extractor was pumped through P13 and N-ethyl morpholine through P3 into the reactor TR2 to form the arylated product of pyrazole. Here reactor was maintained at a temperature of 70°C-100°C for 1 - 3 hours. The product was crystallized in CT1 with anti-solvent methanol pumped through P4 into crystallization tank. The crystallized product was filtered and separated in S2.
- **Deprotection:** The second stage product from the separator enters into the tubular reactor TR3 at temperature 20-40°c with the residence time of 4hours. Into this reactor

nitrogen gas was pumped through pump (peristaltic pump) P7 and formic acid using pump P8. In TR3 gas-liquid reaction takes place.

- **Formation of lactate salt:** In step four, lactic acid was pumped through pump P3 to form the final lactate salt of product. Here excess of formic acid and lactic acid was removed by the rotary evaporator RE1, then passes through TR4 into the crystallization tank CT1. the solid product formed was filtered in F1 and stored in a tank T1.

9.6.1 Challenges in performing multiple reactions in a single platform as given above

The number of valves needed to select the desired set of equipment is much higher. The reactions which take place only in a packed bed reactor and which do not involve separator, filter, crystallizer etc., the path required for the synthesis is same as that of synthesizing it individually so that the number of components required will remain unchanged be same as that of individual synthesis.

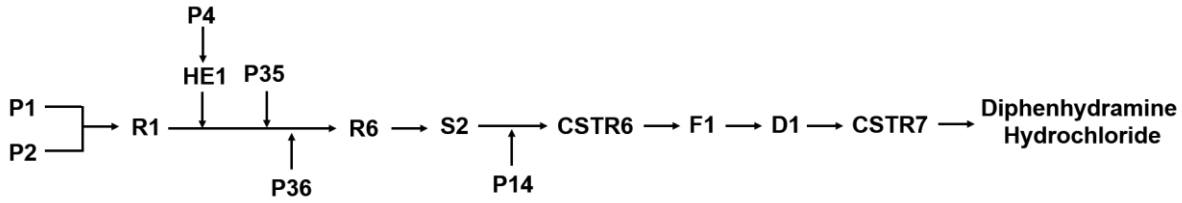
9.7 Approach 2: Multimolecular operation (more than 1 molecule at a time)

This approach consists of identifying and optimizing a minimum number of components for performing flow synthesis of different molecules. The developed platform will contain all the necessary components for synthesis (flow reactors, packed columns etc.) to the downstream processing (extractor, separator, crystallizers, dilution tank etc.). Some of these components can be used for different chemistries just by changing the flow rates or the operating conditions specific to the chemistry. The components will be arranged on a platform where the order of arrangement can be varied in terms of processing needed for chemical synthesis just by connecting the components via tubes. The designed platform will be provided with some accessories which will include at least one component of all types on the platform (of different or same volume, or suitable to the different operational parameters) with an exactly

same dimension which will make replacement of component easy in case of failure or whenever needed. This platform will be plug-and-play kind of system where the user will just have to choose the specific order of component arrangement, select the operating parameters before starting any experiment. The platform can be used for specific synthesis step optimization or for performing the optimized multistep synthesis. The plug and play approach makes it very useful in the sense that if some or any component on the platform is not being utilized for any synthesis that component can be removed and used for another purpose or simultaneous synthesis of different molecules can be done using components which are not being utilized for the ongoing synthesis. The components like dilution tanks, crystallization tanks, and gravity-based liquid-liquid separators can serve different purposes if planned properly before experiment so that same component can be used interchangeably with different chemistries reducing the need for different components still further. **Figure 9.3** shows the unified platform based on the approach 3 which contains the optimum component-based details extracted from the literature of selected case studies. The sequence of components was arranged according to the described setup in the case studies selected. **Figure 9.4** depicts 4 processes in one chart and the components in blue color are the common components, which will take part in the synthesis of any or every molecule chosen from the case studies. That reduces the quantity of the same kind of components by 4 times. The number of components for each unit operation is quite large, however, that helps to carry out the synthesis of all the identified products in the chart.

To have a view of the platform as in approach 2 one example of diphenhydramine hydrochloride is covered here from the case studies, where two reactants 2-dimethylaminoethanol and neat chlorodiphenylmethan is being pumped from P1 and P2 to reactor R1 where it is getting heated at temperature 180°C at a pressure of 1.7 MPa. The molten salt which comes out of reactor R1 is then treated with aqueous NaOH through pump P4 which

is heated to 140°C through HE1. Inline extraction and purification happen in packed bed column reactor R6 by water and hexane which are pumped through pump P35 and P36. Resulting biphasic solution passes through gravity operated liquid-liquid separator S2 with automatic level control. In the downstream section API was precipitated with HCL through pump P14 and the precipitate is dissolved in ethanol and crystallized in CSTR6 maintaining temperature 5C. After crystals being filtered through F1 and dried in D1, the final product was dissolved in water in CSTR7. The final product diphenhydramine hydrochloride is collected in the form of a solution. The overall process follows the path as shown in the sequence below



With this approach, it is very easy to reduce the number of components significantly to perform a number of different chemical steps of varying nature (except very different chemistries where very specific equipment is required). The platform developed using this approach will have the following key features:

- **Useful for a limited number of molecules**

This approach will be very useful if a similar set of chemical transformation is to be performed which will reduce the number of components significantly, however, the approach discussed above is not unique since everyone can come up with an optimum number of components based on the chemistries involved and level of expertise.

- **Volume of each component**

Choosing the right component volume plays a very critical role here since that is going to fix the residence time and the overall throughput. For the same synthesis route, the volume of a component will vary if the throughput is going to increase or decrease. It becomes very

important before designing such platform to define the scale of operation and the type of chemistry that will be used since much of the selection criteria will depend on the aforesaid two parameters.

- **A number of components**

As components can be interchanged and reused, defining the number of components is not critical but one has to take this into account since this will depicts the overall cost of building such a platform. Though one can have a large number of accessories, adding each one on the synthesis platform will increase the cost.

- **Connection for components**

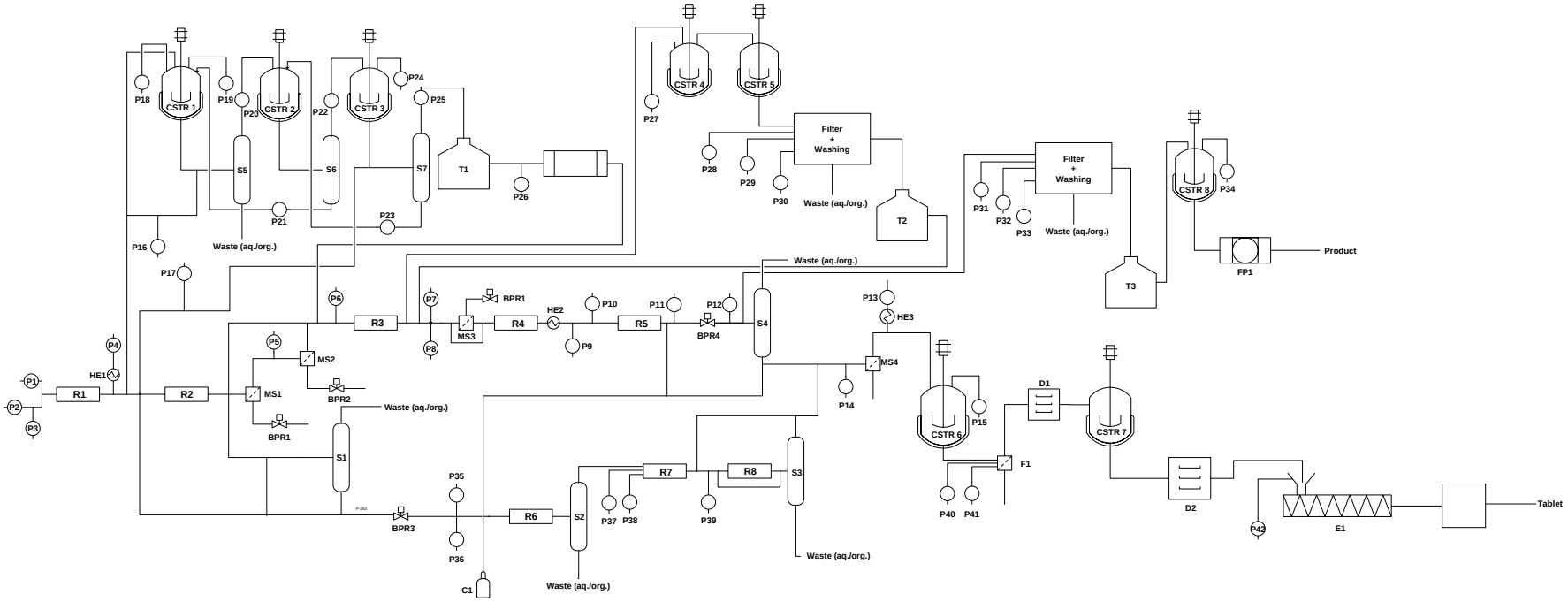
Connecting the components in proper sequence is required for success in any multistep flow synthesis including work-up. Making connection before and after each operation will add an extra volume to the existing process volume, which needs to be taken care off. In this approach, the connection is not fixed rather the plug-and-play kind of approach can bring the components close to each other reducing the need for intermediate heating/cooling or requirement of added utility to maintain the reaction temperature in the tubes.

- **Instrumentation**

Here, we have not explicitly considered any instrumentation (other than in-line analysis or measurements for monitoring a given reaction/purification) but that can be added at the specific steps wherever needed.

- **Utility**

At this point of time it is assumed that for each reaction step the heating or cooling arrangement (also referred as ‘utility’ in the chemical process engineering and plant operation) is arranged individually.



R – Coil reactor/Packed bed reactor/scavenger, **P** – Pump, **HE** – Heat exchanger, **CSTR** – Stirred tank reactor/Crystallizer/dilution tank, **T** – Storage tank, **F** – Filter, **S** – Gravity based separator, **D** – Dryer, **FP** – Filter press, **MS** – Membrane separator, **E** – Extruder, **BPR** – Back pressure regulator

Figure 9.3 Layout of a unified synthesis platform (including all the component) for multiple drug molecules (Approach 2)

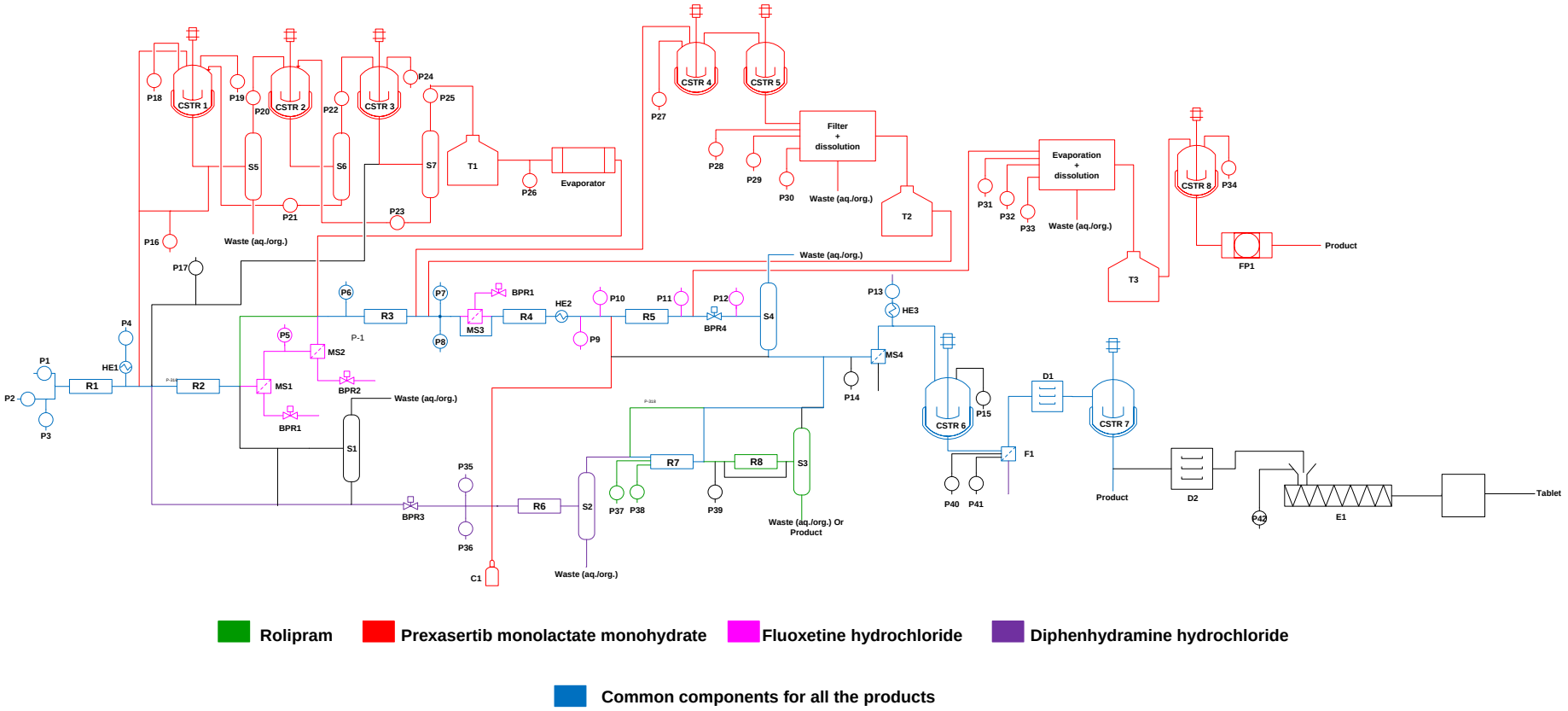


Figure 9.4 Layout for synthesis of 4 molecules on a single platform (Approach 2)

9.8 Approach 3: A Cybernetic approach

The third approach can be based on the need for a versatile and extremely flexible system. **Figure 9.5** shows the concept of a unified platform (Approach 3) for multistep synthesis in a continuous flow. The platform can have three basic modules which are interconnected.

The first, reactor module includes different reactors types that are commonly used in the synthesis of APIs viz. tubular reactor (R1-R4), packed bed reactor (R5-R8) and stirred tank reactor (R9). The reactors are equipped with a jacket for maintaining the reaction temperatures. Additionally, multiple temperature zones can also be provided if required. The reactor module also includes mixers (M1-M9) that are commonly used in flow chemistry [60-61]. Continuous flow reactor can also be equipped with inline static mixing elements[59].

The second module includes the intermediate storage tanks (T1-T8) with an agitator and a jacket for maintaining the temperature. The intermediate storage tanks can be used for multiple purposes viz. preheating/ precooling any reaction intermediate, mixing reagents, quenching the reaction, dilution, crystallization, reaction and can be operated in batch or continuous mode (CSTRs). Preheating and precooling are essential for getting reproducible and reliable experimental data.

The third and final module includes separators viz. membrane separators/filters, scavengers or adsorption column (packed column), extractors/gravity separators, dryers, extruders, etc. These three modules can be fixed in a 3D space on a skid. However, the tubings, valves and back pressure regulators need not be fixed and can remain connected to individual module units as per process requirements. Avoiding the tubing will add more flexibility to the unified platform similar to pipeless plants[62]. The entire platform has separate tanks for storing the feed, product, solvent/ buffer solution for extraction and waste collection. The feed storage tanks will be equipped with temperature control for any preheating or precooling any reagent

before mixing. Moreover, the unified platform can be integrated into any commercial separation and analytical system. This approach is analogous to cybernetics[63].

Table 9.7 shows the process components required and the sequence of unit operations for producing various pharmaceutical products using Approach 3. These unit modules can be connected in the desired sequence by connecting tubing. Additionally, valves and back pressure regulators can be used whenever required. The unit operations which are not required for the process under consideration will not be connected. This approach allows connecting any unit operation in any desired sequence making it a unified platform for multistep synthesis. Such a platform can be integrated with chromatography purification systems, inline analytical instruments, a mold for tablet making and various commercial instruments.

As suggested, a priory information should be known regarding kinetics of various processes (reaction/ drying/ crystallization/ adsorption/ desorption), solubility data (extraction/ crystallization), etc. This approach is useful for testing proof of the concept for a continuous process of various drugs which are in clinical trials. However, this approach may not be feasible for pilot or production scale as the scale of operation is different and reactors and separators should be designed accordingly. The ideal use of this platform is to evaluate the possibility of the synthesis concept of various processes along with automation having a variety of unit operations and operating conditions and collect useful data for further plant design or for using it for a specific period of time to meet the production needs and then switch to another molecule, making it a flexible production platform. Eventually, at the pilot or production scale, it will be analogous to Approach 2. Key features of this approach can be given as follows: (i) truly unified multistep flow synthesis platform, (ii) intermediate tanks can be used for preheating/precooling, isolating different pressure zones and intermediate storage, (iii) the system will have all the necessary components like back pressure regulator, check valve, control valve, temperature and pressure sensors, etc., (iv) the stirred tank reactor can be used

for reaction and also for crystallization, (v) the reactor jacket can have multiple temperature zones to offer more flexibility, (vi) the fixed bed/packed columns can be used as reactors as well as scavenging columns depending on the requirement or even as a mixer if the packing is inert.

While such a unified platform would offer enormous flexibility in operation, it would be challenging to develop such a platform. A few challenges can be given as follows: (i) too many connections, (ii) arrangement of various components in 3D space is critical, (iii) needs very complex control strategy, (iv) minimizing the pipeline length during component assembly is challenging to optimize the residence time variation and will handle more chemicals than conventional systems, (v) relatively large amount feed material will be required when compared (to compensate dead volume) to single dedicated experimental setup and (vi) automation will be complex as well as expensive.

9.8.1 Simultaneous synthesis of (S) – Rolipram and Ribociclib by approach 3

Aldehyde and nitromethane are dissolved in toluene separately and kept in the feed storage tanks for preheating (**see Figure 9.5**). The reagents can be pumped with suitable pump (viz. peristaltic pump, piston pump, diaphragm pump etc.) into the mixer M5 and subsequently to reactor R5 which is packed with SiO_2-NH_2 and $CaCl_2$. The intermediate nitroalkane obtained is cooled to 0°C in intermediate storage tank T5. The reaction mixture can pass through separator S1 (adsorption column) which is packed with MS4A to remove the by-product water. A solution of malonate and triethylamine in toluene are precooled to 0°C in feed storage tanks and pumped to mixer M6 where it mixes with nitroalkane stream. The reaction stream can then be passed through reactor R6 which is packed with polymer-supported (S)-pybox–calcium chloride and maintained at 0°C. The reaction stream can be further passed to

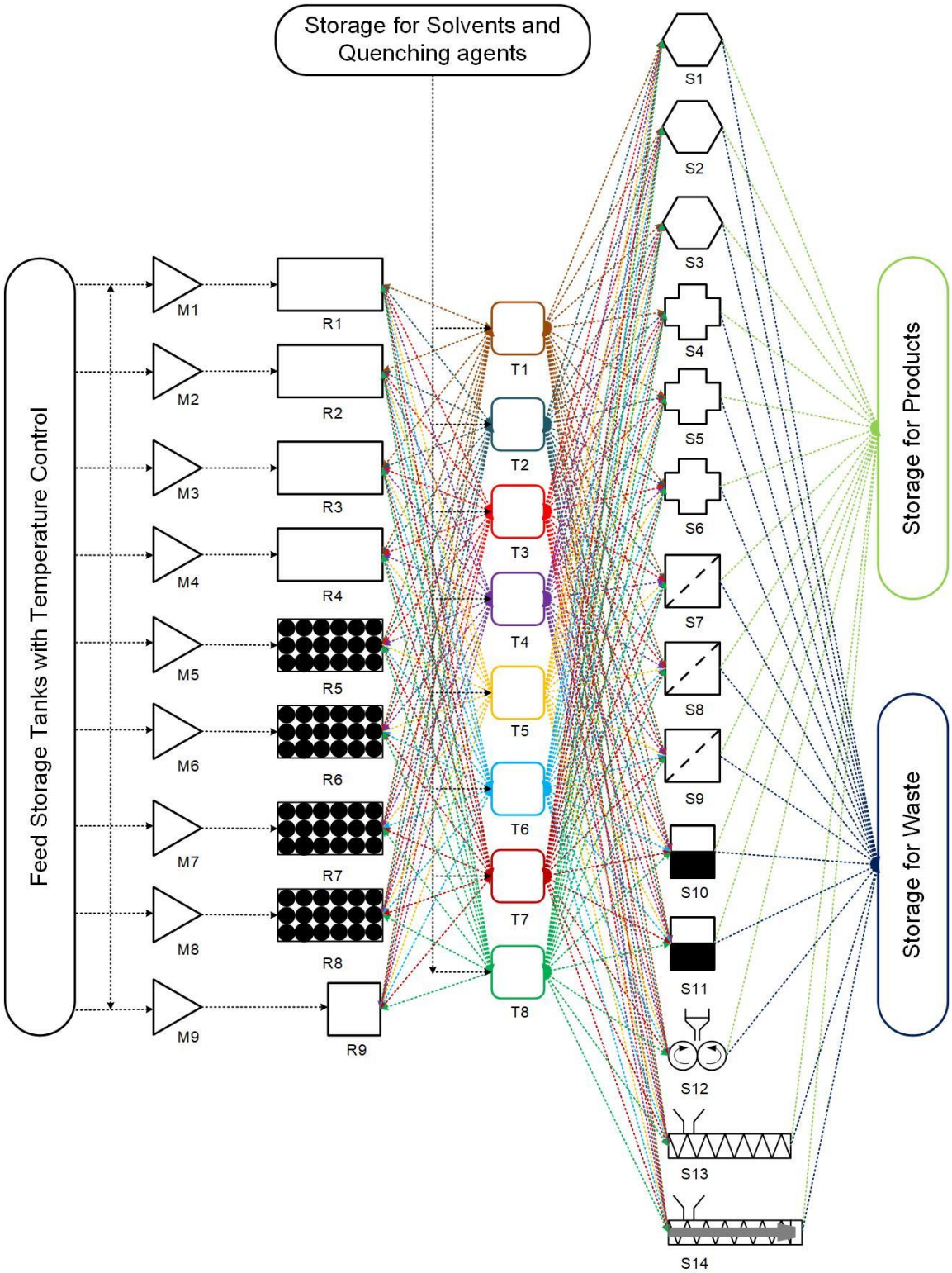


Figure 9.5 Approach 3 for a unified platform for multistep synthesis. M1-M9 = Mixers, R1-R4 = Tubular reactors, R5-R8 = Packed bed reactor, R9 = Stirred tank reactor, T1-T8 = Intermediate storage tanks, S1-S3 = Adsorption columns, S4-S6 = Extraction columns/Gravity based separator, S7-S9 = Membrane separator/Filter, S10-S11 = Evaporator, S12= Rotary drum dryer, S13 = Vacuum screw dryer, S14= Extruder

Table 9.7 Sequence of unit operations for various pharmaceutical products by approach 3

Reference	Product	Reactors/Equipment/ Components (number)	Sequence of unit operations as per Approach 3 (see Figure 5)
Tsubogo et al.[7]	(R) - and (S) - Rolipram	• Packed bed reactor (4) • Adsorption column (3)	M5→R5→T5→S1→M6→R6→T6→M7→R7→T7→S2→T8→S3→R8
Pellegatti et al.[59]	Ribociclib	• Flow reactor (2) • Extractor (2) • Stirred tank reactor (1)	M1→R1→M2→R2→S4→T1→M3→R3→S5→R9
Cole et. al[8]	Prexasertib monolactate monohydrate	• Flow reactors (4) • Extractors (3) • Evaporators (2) • Crystallizers + tanks (9) • Filter (3)	M1→R1→T1→S4→T2→S5→T3→S6→T4→S10→M2→R2→T5→T6→S7→S8→T7
Adamo et al.[9]	Fluoxetine hydrochloride	• Flow reactor (4) • Membrane/Filter (3) • Extractor (1) • Adsorption (1)	M1→R1→T1→S7→T2→S8→R2→T3→S10→A1→T4→R3→T5→S4→Downstream
	Diazepam	• Flow reactor (2) • Packed column (1) • Extractor (2) • Adsorption column (1)	M1→R1→M2→R2→T1→R5→S4→S1→T2→S5→ Downstream
	Lidocaine hydrochloride	• Flow reactor (2) • Packed bed column (1) • Extractor (1)	M1→R1→N2→R2→T1→R5→S4→ Downstream
	Diphenhydramine hydrochloride	• Flow reactor (1) • Packed bed column (1) • Extractor (1) • Adsorption column (1)	M1→R1→T1→R5→S4→S1→ Downstream
Mascia et al.[20]	Aliskiren hemifumarate	• Flow reactors (2) • Membrane/ Filter (3)	M1→R1→T1→S4→T2→T3→S7→T4→M2→R2→T5→S5→S8→

	• Extractor/Settler (3) • Adsorption column (1) • Dryer (2) • Crystallizers + Tanks (6)	S1→T6→T7→S9→T8→S12→S13→S14→Moulding Machine

intermediate tank T6 where it can be preheated to 100 ^{0}C. The reaction stream containing Michael addition product is mixed with hydrogen gas (from H_2 cylinder) in mixer M7. The resulting two-phase mixture can be passed to reactor R7 packed with Pd/DMPSi-C catalyst and maintained at 100 ^{0}C. The reaction stream can then be passed in intermediate tank T7 where unreacted hydrogen gas is vented and recycled and the liquid stream is preheated to 120°C. The liquid stream then can pass through separator S2 (adsorption column) packed with Amberlyst-15 Dry to remove impurities. Water and o-xylene can be preheated and pumped from the feed storage tanks into intermediate storage tank T8 where it is mixed with the reaction mixture. The process stream can be further passed through separator S3 (adsorption column) packed with Celite. The reaction mixture can pass through reactor R8 packed with silica-supported carboxylic acid and maintained at 120°C to obtain the product (s)-rolipram. In the above example, intermediate storage tanks T1-T4 can also be used instead of T5-T8 as every unit module (reactors, intermediate storage tanks, and separators) can be connected in any desired sequence by simple tube fittings. However, the choice of unit modules should be done on the basis of lower tubing volume.

Chloropyrimidine and aminopyridine derivative are dissolved in THF and can be preheated to 60°C in the feed storage tank. LiHMDS solution in THF also can be preheated to 60°C in the feed storage tank. Both the solutions can be pumped with suitable pumps in the mixer M1 and then through reactor R1 which is maintained at 60°C. The product stream can be mixed with preheated HCl in mixer M2 and then passed through reactor R2 which is also maintained at 60°C. The reaction mixture can then be passed to separator S4 (extractor) to

separate the aqueous and organic phases. The organic waste can be collected in the waste storage and the aqueous phase is mixed with sodium hydroxide in intermediate storage tank T1 to quench the HCl. The reaction mixture can be mixed with THF in mixer M3 and passed through reactor R3. The process stream can be further passed to separator S5 (extractor) to separate the aqueous waste and organic phase. The organic phase can be further passed to reactor 9(stirred tank) where it can be mixed with succinic acid for further batch crystallization to obtain the product Ribociclib.

In this way, we can operate two synthetic processes simultaneously in the unified platform (approach 3). However, many unit modules still remain unused (viz. M4, R4, T2-T4, and S6-S14). **Table 7** shows the unit module sequences for various products for approach 3.

9.9 Summary

For the multistep flow synthesis approach, the next evolution is obviously towards a combination of automation, monitoring, screening, optimization, artificial intelligence and instrumentation. It has changed the conventional synthesis approaches through significant improvement in the product quality, efficiency, and smaller environmental foot print. Utilizing the benefits of multistep flow synthesis is not easy and it requires experienced professionals and ready-to-use tools for effortless integration of different synthesis stages. Developing the unified platform which will reduce the effort in setting up the experiments and integration of different component which will definitely help to speed up the overall process to truly harness the advantages of flow synthesis. Based on different objectives viz. reaction screening, library generation, bench/pilot scale synthesis for various molecules we have shown three approaches to make a unified multistep flow synthesis platform which can be made keeping the interest of individual or organization for future. These approaches show the unique and promising ways to make the unified platform to realize the concepts like dial a molecule. Realising the concept

of unified flow synthesis platform possess some challenges but those can be taken care based on the need and planning beforehand. Once this platform is built it will act as ‘driverless car’ or a ‘robot chemist’ where an only instruction has to be given and platform will take care of synthesis of the desired molecule based on the specific chosen flow path. The next level of such a platform can only go in the direction of self-regulated automatic 3D configurable synthesis platforms, just like an advanced version of ‘Transformers’. With growing machine intelligence, it is expected that the synthesis platforms would harness big data sets as a source of knowledge, artificial intelligence for decision-making abilities at various levels and self-optimization. Developing such a unified integrated multistep flow synthesis platform will be the new thing for organic synthesis to explore the unexplored chemistry.

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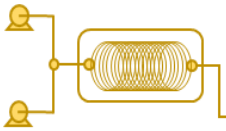
Conclusion



Conclusion

We have shown that the simple reactor designs can be very effective in terms of cost and fabrication with no compromise on performance. The utilization of gravity can be beneficial for handling large concentration of solid suspensions in flow. Conversion of batch synthesis to continuous flow results in safe processes with significant reduction in plant footprint. However, obtaining the steady state as early as possible is very important in any plant and careful determination of time to achieve steady state becomes necessary. Maintaining similar hydrodynamics at the laboratory scale and plant scale is very important and results in similar quality of product at large scale. Flow synthesis is also beneficial for end to end synthesis of drug which can help in reducing the cost and shortage. Though flow chemistry is very beneficial it has to cover a long journey where AI driven systems can take over the routine synthesis to make processes more efficient in controlled environment.

Part-II (Novel flow reactor designs)

The novel pinched tube flow reactor was design and fabricated in SS316. The detailed characterization of the reactor for mixing, pressure drop, residence time distribution and mass transfer coefficient were done and the suitability of reactor was analyzed for performing the exothermic reaction. It was found that the pinching and continuous change in the direction of pinch induces rapid mixing. Effect of pinching is higher at higher flow rates which reduces at low flow rates. At low flow rates pinched tubes of smaller diameter can be used. Higher number of pinched sections does not result in the higher pressure drop and the pressure drop remains nearly same as that of straight tube. The good mixing at the pinched sections makes pinched tubes ideal for reactions where mass transfer coefficient obtained was much higher compared to that of the straight tubes. Two prominent Dean Vortices are observed in case of pinched helical coil tube at high flow rates as compared to the helical coil tube and for the same flow rates. The pinched tube reactor was used for nitration of benzaldehyde and the results obtained indicated that the proposed reactor can be used for exothermic reactions which require good mixing.

In an attempt to solve the challenge of handling solids in flow the novel flow reactor was designed which contained no moving parts and uses only pressure energy for suspending solids during flow. Geometry and the dimension of the reactor were optimized using COMSOL simulations. The optimized geometry of reactor was fabricated in acrylic and SS316. Reactor was characterized for hydrodynamics and tested for variety of solids suspension. The reactor has unique shape cavities which do not allow solids to settle inside the reactor during operation. The pressure energy is only utilized for flow and solids flow in the direction of gravity. COMSOL simulations suggested that aspect ratio of 1.53 with the outlet diameter of 0.2D and outlet positioned at 0.3D from the center positioned at 180° from the previous outlet are better for mixing and handling suspension. Obtained mass transfer coefficient was comparable to the

existing flow reactors. After successfully checking the solid handling capacities for variety of solids, reactor was checked for neutralization reaction and it was found that the proposed reactor design was suitable for handling solids up to 22% (w/v) concentration.

Part-III (Scale-up using flow reactors)

The conventional batch synthesis of pendimethalin (herbicide) was converted to continuous flow processes. The challenges associated with batch synthesis (use of mixed acid, long reaction time, safety and large quantity of solvent) were removed in the developed continuous flow process. The new process involves use of only nitric acid, very less solvent with very short reaction time (in minutes). Based on the optimized conditions the detailed step by step analysis and procedure was followed to scale-up the continuous process for the production capacity of 2 kg/hr. The pilot plant was constructed for the proposed production capacity and demonstrated for more than 100 hours run. The findings from the pilot plant was reported. When going for scale up using flow processes it was observed that the time to achieve steady state for reaction and temperature is different. That may result due to interaction of heat transfer, mass transfer and reaction rates. This phenomenon is very important since it governs the start-up time of the plant. The start-up time is important in cases of high throughput and costly materials. Based on this observation it becomes important to devise the operating strategy of the plant. Which material to be pumped first, what kind of data to be monitored and the control structure required for any disturbance in the system. It was proposed that seamless scale-up for the flow chemistry is not usually the case and it goes through many stages and strategies for the same need to be formulated.

Also, with the help of propiophenone nitration the economics of numbering up was studied and shown that the numbering up is economically viable only after suitable dimension

enlargement. The dimension enlargement has to be done maintaining the similarity of the hydrodynamic parameters without hampering the product quality and safety.

Part-IV (Multistep flow synthesis of pharmaceuticals)

The drug for the treatment of cystic fibrosis and amyotrophic lateral sclerosis was first synthesized in batch mode. Modifications were then implemented to the batch synthesis procedure in terms of chemistry, while going from batch to flow. The developed flow synthesis method involves the ozonolysis, diazotization, coupling, inline solvent switching, extraction, microwave and separation before final product formation. Throughput obtained from developed bench top flow synthesis set-up was sufficient to treat 50 patients per day.

In the area of flow synthesis, the next evolution will be towards a combination of automation, monitoring, screening, optimization, artificial intelligence and instrumentation. Though implementation of flow synthesis has changed the way conventional synthesis has been performed, utilizing the full benefits is not easy and it requires experienced professionals and ready-to-use tools for effortless integration of different synthesis stages. Developing the unified platform which will reduce the effort in setting up the experiments and integration of different component which will help to speed up the overall process to truly harness the advantages of flow synthesis. Realizing the concept of a unified flow synthesis platform possesses some challenges but those can be taken care based on the need and planning beforehand. Developing such a unified integrated multistep flow synthesis platform will be the new thing for organic synthesis to explore the unexplored chemistry.

A large body of the organic synthesis and reaction engineering community is working on automation of synthesis, optimization, data analysis, integration of PAT tools in the system, etc., primarily for medicinal chemistry. In such a situation it might be useful to look at the state of the art of automation in petrochemical refineries, bulk chemicals and polymers as a few

decades ago these industries have made revolutionary changes in manufacturing involving flammable products. Maybe, it will help the community to save time in re-inventing some parts of the wheel. Another important point that needs to be addressed in the entire endeavor is planning for imparting multiple complementary skills to the next generation, which significantly deviates from the erstwhile generation of chemists and engineers. Including AI for property estimation, python-based programming, making chemists use self-optimization tools, etc. will bring the community closer than before. This will make everyone work on more challenging and more relevant problems of sustainability

ABSTRACT

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Faculty of Study: Engineering Science **Year of Submission:** 2021
AcSIR academic centre/CSIR Lab: NCL-Pune **Name of the Supervisor:** Dr. Amol A. Kulkarni

Title of the thesis: Selectivity engineering of exothermic multistep reactions using flow reactors

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Revolutionizing the way of chemical synthesis, flow micro-reaction technology has manifested its benefits in terms of reducing the reaction times, environment footprint, increasing the yield and selectivity while making the processes safe. Excellent heat and mass transfer with small channel dimension are principal attributes of flow micro-reaction technology which has resulted in the development of various micromixer designs, translation of many batch chemistries in continuous flow, automated machines for synthesis and safe manufacturing plant which have evolved over time. However, the efficient micro-mixers/micro-reactors/flow reactor designs with easy fabrication and with ease of scale-up is still under development and challenge of flowing solids is yet to be solved completely.

Pinched tube flow reactor for performing the exothermic liquid-liquid reactions and flow reactor for handling solids is presented in this thesis. The proposed designs are easy for fabrication and does not contain any moving parts. The designs were optimized using computational fluid dynamics simulations and fabricated to analyse the hydrodynamic parameters. Reactors were shown to perform on par with the existing commercial reactors through exothermic nitration reaction and precipitation reaction. The detailed methodology for scale-up is presented using pinched tube reactor for exothermic di-nitration reaction, where pilot plant was fabricated for production capacity of 50kg/day of the product in modular fashion. The built pilot plant was successfully operated for the proposed capacity in safe manner continuously for days. Two important molecules Edaravone and Ivacaftor were synthesized using multistep continuous flow synthesis involving inline quenching, extraction and separation, mitigating the hazardous synthesis steps and toxic chemicals involved. The developed bench top synthesis set-up was producing final drug molecule in enough quantities to treat 50 patient/day. The effect of variations in the optimized parameters on the scale-up was analysed and unified platform for synthesizing multiple molecules using flow synthesis is envisaged with detailed discussion on challenges involved for developing such a platform. In all, presented thesis contains the complete guidelines for going from batch to flow and an approach for scale-up using reactors which are easy to fabricate and safe to operate.

List of publications

1. Sharma, M. K., Potdar, S. B. and Kulkarni, A. A., Pinched tube flow reactor: Hydrodynamics and suitability for exothermic multiphase reactions, ***AIChE journal,*** 2017, 63, 358-365

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Pinched Tube Flow Reactor: Hydrodynamics and Suitability for Exothermic Multiphase Reactions

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A novel tubular flow reactor where a straight tube is modified by pinching it periodically at a fixed pitch and at different angles is presented. Pinched tubes (straight tube as well as helical coils) with different pitch and angles between successive pinching are studied. This work reports a detailed hydrodynamic study involving single and two-phase flow. Mixing experiments showed that having an angle of 90° between successive pinchs achieves the shortest mixing length when compared to lower angles. Pressure recovery along with sequence of high and low shear zones and change of flow direction imposed better mixing. Residence time distribution studies showed that higher number of pinch sections decreases the extent of dispersion, yet it deviates from plug flow. The performance is evaluated by carrying a homogeneous and two-phase aromatic nitration and also liquid-liquid extraction. Pinched tube presents an economical option as a flow reactor for conducting exothermic reactions. © 2016 American Institute of Chemical Engineers *AIChE J*, 63: 358–365, 2017

Keywords: pinched tube flow reactor, pressure drop, residence time distribution, mass transfer, reactions

Introduction

Development of compact continuous flow reactors is an important component of process intensification.[1,2] Having compact reactors helps to achieve decentralized/spot synthesis, smaller chemical foot print, enhanced safety and distributed production. Such reactors need to be efficient in terms of mixing, lower axial dispersion, better heat transfer and enhanced interfacial mass transfer. The nature of operation depends on the mode of energy supply, that is, kinetic energy (spinning disk reactor, Holl tube in tube rotating reactor, Higee reactor, rotating packed bed contactor, etc.), pressure energy (static mixers, coil inverters, etc.), and new forms of energy supply (viz. ultrasound,[3] microwave, plasma, etc.). Details on these concepts can be found in the literature.[4] This article focuses on the second category of pressure energy driven systems, which includes excellent examples, oldest being the static mixers. One of the primary ways to achieve rapid mixing in such flow reactors is using smaller dimensions and/or spatial variations in the cross-sectional area and/or spatial splitting and recombining the flow and/or imposing tortuous path to enhance chaotic advection or shear. Depending on the system under consideration and the objective behind design, it is necessary to design a flow reactor that has one or many of the above features.

Among a few known designs, Corning's Advanced Flow Reactor[5] is an excellent example of a sequence of two-dimensional converging zones with an internal flow splitting and recombining mechanism and high heat transfer area that allows rapid mixing as well as generation of very fine fluid–fluid dispersion. Conversely, 3D-Flow Reactor[6] comprises of a sequence of three-dimensional (axisymmetric or non-axisymmetric) converging units with or without flow splitting that further allows enhancement in the capacity with a marginal loss of heat transfer area and also a relatively lower pressure-drop due to pressure recovery mechanism. In an early example, Wilhite et al.[7] have demonstrated the use of a microfabricated supersonic converging nozzle for intensification of mixing for continuous generation of singlet oxygen. Their sequence of microscopic converging units included a pressure recovery system that helped avoiding generation of shock waves and choking of nozzles. The orifice microreactor for a two-phase exothermic reaction showed that having orifices allows enhancing the throughput without a linear enhancement in pressure drop.[8] Su et al.[9] have demonstrated the use of a packed microchannel reactor for conducting a mixing limited exothermic reaction. The use of inert packing helps to create a tortuous path while handling very low liquid quantities, which helps to retain the heat generation rates in the desirable limits.

Most of these reactors need specific fabrication methods viz. micromachining, lithography, glass embossing, and so forth and it makes the accessibility limited to some extent. Conversely, static mixers although can be inserted in straight tubes/pipes, that limits the overall geometrical configuration of the reactor. In view of this, here we propose pinched tube flow reactor as an option that uses pinching of straight tubes in

Additional Supporting Information may be found in the online version of this article.

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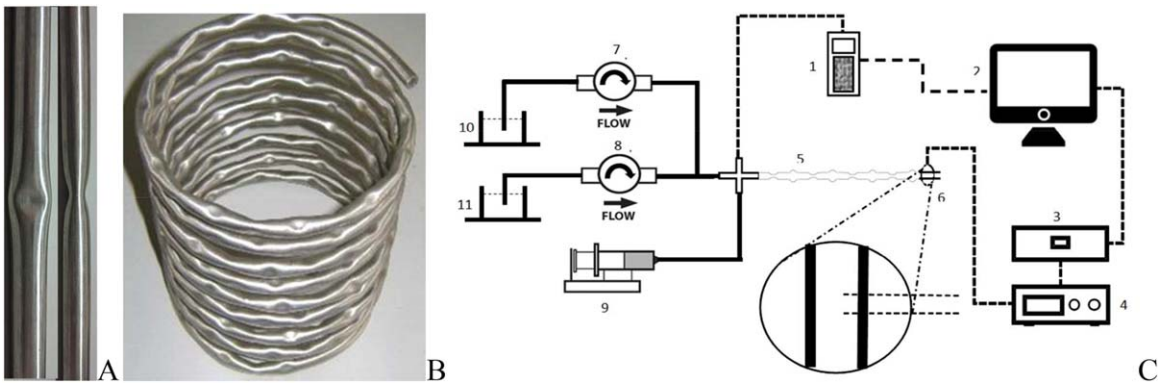

Figure 1. (A) Photographs of pinched tube from top and side, (B) Pinched helical coil, (C) Schematic of the experimental set up [1. digital manometer, 2. Computer, 3. data acquisition system, 4. conductivity meter, 5. pinched tube reactor, 6. conductivity probes, 7,8. peristaltic pumps, 9. syringe pump, 10. water, and 11. kerosene,].

[Color figure can be viewed at wileyonlinelibrary.com]

various ways and then the straight pinched tubes/pipes can be given any form to fit in the smallest possible space without getting limited by the change in the cross-sectional area at various locations. Use of pinched tubes is not new in refrigeration or oil cooling in radiators where pinched tubes are inserted in straight tubes to enhance the local velocities periodically to improve the heat transfer.[10,11] In variety of cases, the flow takes place through the periodically changing cross-section of an annulus or in the partly-pinched capillary tubes, which can be used as a flow reactor or microreactor.[12]

There is abundant literature on the use of microreactor for carrying out variety of single-phase and two-phase reactions (viz. sulfoxidation,[13] halogenations,[14] ozonolysis,[15] nitration,[16,17] catalytic hydrogenation,[18] Grignard exchange reaction,[19] synthesis of caprolactam,[20] production of high performance polymers,[21] etc.). The two-phase flow tubular reactors shows different regimes viz. drop flow, slug flow, stratified flow, annular flow, and so forth. Generation of a two and three-phase flow using a double T-junction is a classical method. In a recent analysis, Wang et al.[22] have shown that bubble and droplet volumes depend on their generation frequency and the operating criteria. Thus, to make a device independent of these parameters and yet have consistent extent of transport rates it is necessary for the dispersed phase to continuously undergo break-up and shear rather than just having a slug flow throughout the capillary. In view of the above introduction, here we propose a high throughput pinched tube flow reactor for process intensification to carry out fast and exothermic reactions. After the Introduction, we have given experimental details on the set-up, measurement of hydrodynamics of pinched tube reactor to support the observations. The analysis of the hydrodynamics and its performance as a reactor are discussed in the section on Results and Discussion, which is followed by conclusions of this work.

Experimental

Experiments were carried out for the measurement of hydrodynamics of a pinched tube reactor. The parameters like pressure drop, mass transfer coefficient, residence time distribution (RTD) and mixing were measured. Details are given as follows:

Making a pinched tube

A normal straight tube of small diameters (viz. inner diameter, $d = 1$–5 mm) usually gives a parabolic velocity profile under laminar flow condition and the extent of dispersion increases with increasing tube length. This extent of dispersion can be reduced by breaking the nature of flow and making it undergo continuous spatial mixing. To achieve the same, the tube was pinched periodically at a fixed pitch (P). Pitch is estimated as the ratio of distance between successive pinches and the inner diameter of the tube. In the present study with $d = 4.5$ mm inner diameter tube, the pitch (P) was varied between 2.2 and 11. The pinching was done using a motorized system that allowed maintaining specific pitch between two successive pinches. The angle of pinch was changed by changing the axis of pinching and the mechanized approach helped to maintain accuracy in angle between successive pinches. Initially, to finalize the most optimal angle between successive pinching (θ) pinched tubes (1 m long) were made in glass with θ of 30°, 45°, and 90°, respectively. As compared to the gradual variation in θ of 30° and 45°, pinched tube with $\theta = 90°$ would force the liquid to change the flow direction after a short distance. Once a straight tube is pinched, it can be oriented in any form to achieve a helical coil or serpentine shape or even a spiral form to reduce the overall space occupancy. In the present work, once the angle between successive pinching is fixed, 15 different pinched tubes were made having 5 different P values and three geometries (helical coils of diameter 50 mm, 100 mm and straight tubes). Typical geometries of the pinched tube and pinched coil are shown in Figure 1. Different pinched tube configurations are shown in the Supporting Information.

Experimental set-up

Pinched tube flow reactors were made using 1/4" o.d. ($d = 4.5$ mm) SS316 tubes of 1 m length each. The experiments were carried out by placing the straight tubes as well as the coil axis horizontally. Normal tap water was used for the single-phase experiments. For two-phase experiments, two immiscible liquid system water ($\rho = 998.2$ kg/m^3, $\mu = 0.001$ Pa s) and kerosene ($\rho = 786$ kg/m^3, $\mu = 0.00162$ Pa s) were used. The interfacial tension (σ) for this system is 0.05 kg/s^2. All the fluid properties are at 25°C. A Schematic of the experimental setup is shown in Figure 1. For the experiments for measuring the hydrodynamic properties, liquids

were pumped in the reactor through two peristaltic pumps at equal flow rates. Flow rates of each fluid were varied over a range from 1 to 100 mL/min. For each experimental condition and for each parameter, the data was recorded at least 3 times and the average value was used for further calculations.

Mixing

Mixing experiments were performed using a pinched tube flow reactor made in glass (tube inner diameter = 3 mm). Three different glass tubes with different angle of pinching (30°, 45°, and 90°) were used for the mixing characterization. Commercially available water soluble red and blue inks were used as colors for monitoring mixing. All the experiments were performed using aqueous solution of inks (10 mL ink dissolved in 400 mL water). Solutions were pumped with the help of a syringe pump at equal flow rates over a range of 10–60 mL/min. Images were recorded at pinched sections 1, 4, and 5 starting from the inlet with the help of a DSLR camera (Sony Corp.) and then analyzed to monitor the uniformity in color over the tube diameter.

Pressure drop measurements

Pressure drop over the reactor length was measured for single-phase and two-phase flow using a digital manometer (HTC instruments, China) for the flow rate range of 2–200 mL/min. The data was recorded online and then subjected to statistical analysis.

Residence time distribution

Pulse input method was used for the measurement of RTD for every reactor over the entire flow rate range. Tracer solution was prepared by dissolving 14 g common salt in 100 mL water and a pulse of 100 μL was given in 0.1 s using a syringe pump. The conductivity of the fluid at the outlet was recorded with the help of pre-calibrated conductivity meter. The concentration vs. time data was subjected to further analysis to obtain an E-curve and then to quantify the dispersion.

Mass transfer coefficient

Kerosene-water-propionic acid system was chosen for the determination of overall mass transfer coefficient. Transfer of propionic acid from kerosene to water was monitored to determine the overall mass transfer coefficient ($k_L a$). Stock solution was prepared by dissolving 12 mL propionic acid in 1000 mL kerosene and this stock solution was used for every experiment. Both the liquids were pumped to the pinched tube using two peristaltic pumps at equal flow rates (1–100 mL/min). At the outlet solutions were allowed to get separated in a separating funnel and conductivity of the aqueous phase was measured. For the determination of concentration in aqueous phase calibration chart was prepared by measuring the conductivity of water at different known concentrations of propionic acid in water. Mass transfer coefficient was estimated as $K_L a = (1/t)\ln[(C_{in} - C^*)/(C_{out} - C^*)]$, where C_{in}, C_{out}, and C^* are the concentration of propionic acid in water at the inlet, outlet and the equilibrium concentration respectively and t is the mean residence time. Details on how to determine equilibrium concentration can be found in the literature.

Result and Discussion

The measured hydrodynamic properties for different configurations of pinched tube were analyzed to explore the feasibility of this concept as a flow reactor. The observations are discussed as follows with support from flow patterns at appropriate locations.

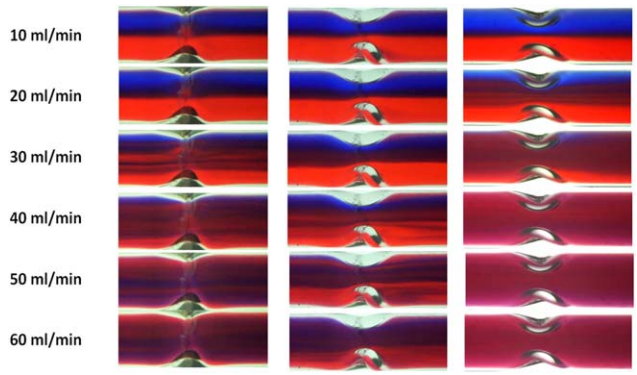

Figure 2. Effect of angle between successive pinches on mixing in a pinched tube flow reactor for a range of flow rates. Images are taken at the 5th pinch point from the inlet. (Left column) $\theta = 30°$ (Middle column) $\theta = 45°$, (Right column) $\theta = 90°$.

[Color figure can be viewed at wileyonlinelibrary.com.]

Mixing

Periodically varying cross-sectional area and also the flow direction at the pinch point result in a spatially periodically varying shear field along the tube length. This kind of a flow will also help in achieving rapid mixing of miscible fluids. In general, with increase in the inlet velocity by two times, for a fixed cross-sectional area at pinch point there is an enhancement in the axial velocity by 2.29 times. This observation was consistent over a wide range of flow rates. At the pinch points the contribution of pressure energy would decrease and that of kinetic energy would increase. Thus, a sequence of pinched sections with alternate pinching in directions perpendicular to each other is expected to enhance mixing in the reactor much significantly than a normal tube. Experiments were performed as discussed before. The effect of pinching angles on the extent of mixing was monitored and the observations are shown in Figure 2. The images indicate that although increasing the flow rates helps to achieve better mixing, an angle of 90° between successive pinching gives much shorter mixing length than angles of 30° and 45°. While the extent of shear at every pinch point is almost identical, the alternate perpendicular pinching forces the fluid streams to break away from relatively lesser variations in the change of direction and hence intensifies mixing when $\theta = 90°$. The observations on how the mixing patterns change from inlet to the 5th pinch point are shown in Supporting Information (S3). Mixing was monitored at different pinch points that is, 1st, 3rd, and 5th pinch point (which for $P = 15$ mm, would be 15 mm, 45 mm, and 75 mm, respectively) from the inlet. For $\theta = 90°$, at lower flow rates ($Q < 20$ mL/min) the fluids flow almost in parallel for some length. With increasing flow rates the striations of individual color were observed to get thinner, which with change of pinching plane almost diminished. These observations showed that it was possible to achieve very good mixing over a length less than 16 times the tube diameter without using any static mixers. The mixing length can be further decreased by at higher flow rates or for higher flow rates tubes of larger size can be used with similar pinching profile ($P < 3d$). Thus, short pinched tubes can be used for mixing of reactants or reagents

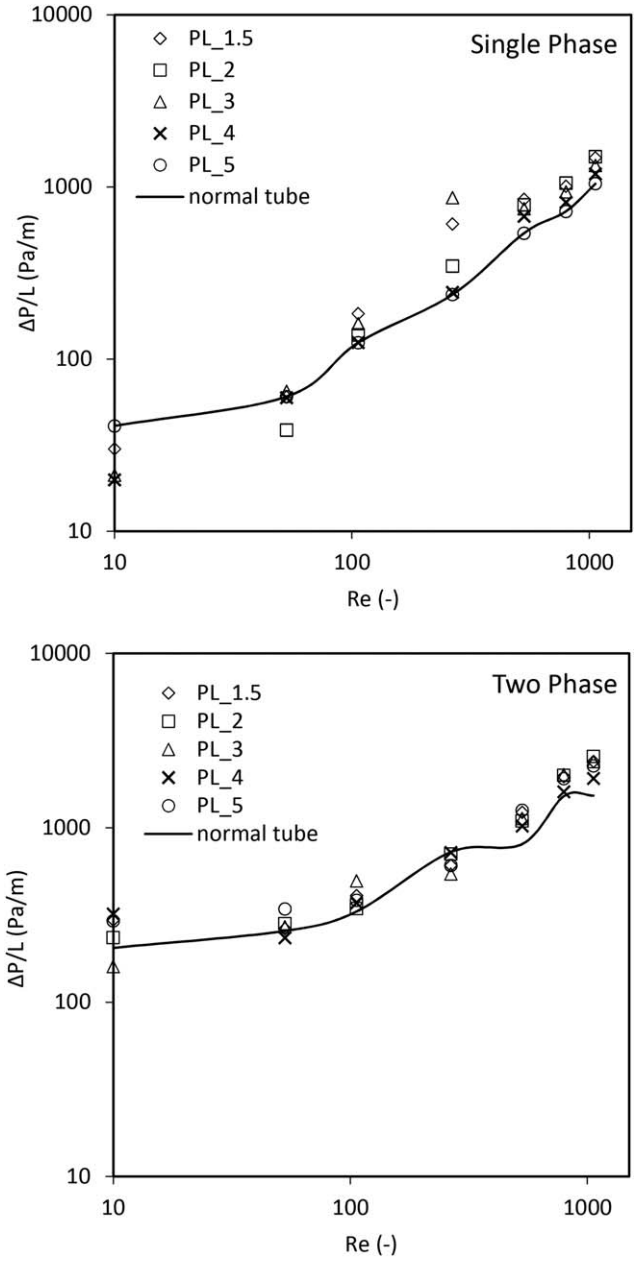

Figure 3. Pressure drop for pinched tube (1/4" o.d.) in the coil form (coil diameter = 5 cm).

(A) Single phase flow and (B) two phase flow. Lines are for coil made from a normal tube.

before the reaction mixture enters in sections of reactor where only longer residence time is needed for a reaction to get completed. If the range of flow rates is below 20 mL/min, it is better to use pinched tubes of smaller diameter (< 3 mm). In view of the excellent mixing performance with $\theta = 90°$, in rest of the manuscript we have done all the further experiments using pinched tubes having successive pinches perpendicular to each other.

Pressure drop over the pinched tubes and helical coils

Pressure drop (ΔP) measured for a pinched tube reactor (having different pitch and geometry) for single-phase and two-phases flow was analyzed. The observations are shown in Figure 3A, B. In general, there was a standard deviation of $\pm 3.4\%$ over the entire flow rate range. The values of ΔP for the pinched tube flow reactors of different pitch showed trends similar to the normal straight tube. For $Re < 100$, the normal tube showed higher pressure drop as compared to pinched tubes and depending on the pitch (or number of pinch per unit length) pressure drop increased. However for $Re > 100$, despite having as number of pinch sections over a range from 20 to 66, the extent of rise in the pressure drop varied at the most by 1.4–3 times. As discussed in the previous section, each pinched section is comprised of a sequence of straight portion, a reducing section, an expanding section and again a straight section. The length of straight section changes depending on the pitch while the geometry of reducing and expanding sections was maintained identical in all the cases. This implies that every pinch section would behave similar to a venturi and there would be a finite pressure recovery after every pinched section. The estimated values of pressure recovery over a range of flow rates for different P values show that at higher flow rates loss coefficient reaches to that of a normal venturi. The pressure drop data for single-phase flow indicates that around $Re \sim 100$ there could be change of flow regime.

The pressure drop for two-phase flow was significantly higher compared to single-phase flow experiments and the pressure drop in coils was higher than in the straight tubes. Literature on the analysis of two-phase pressure drop in converging and diverging sections indicates that both, converging as well as diverging sections act differently in enhancing the pressure drop. The continuous shearing effects with change of pinch direction by 90° are expected to break the dispersed phase droplets continuously thereby generating fine dispersion. Generation of smaller droplets from inlet to outlet (observed from the flow visualization experiments from pinched tubes made in glass, shown in the Supporting Information) will lead to enhancement in the interfacial area and hence the frictional resistance between the two phases. This would enhance the pressure drop by as much as 2 times when compared to single-phase flow. On estimating the pressure drop for two-phase flow using the Lokhart–Martinelli method,[23] it was observed that Chisholm parameter (C) does not follow the values as for standard straight tubes and to take care of the pressure recovery in pinched tubes, the values of C need to be given as a function of the two-phase Re as $C = 118.2\ Re^{(-0.66)}$. This observation was consistent even for small diameter pinched tubes. Incidentally, the two-phase pressure drop for pinched tube varied over a narrow range even for various pitch values and hence the above value of C can be used independent of pitch.

Residence time distribution

The extent of dispersion in pinched tube reactor was estimated using concentration in the form of conductivity data measured at the reactor outlet. Open-open boundary condition was used for analyzing the data and axial dispersion model was used for estimation of the dispersion coefficient. E-curves for the pinched tube flow reactor with 50 and 15 mm distance between successive pinch points are shown in Figure 4A, B. It can be observed that with more number of pinch sections the extent of dispersion decreases and the system behaves closer to a plug flow. The data is not strictly Gaussian and it show features of continuous stirred tank reactor in series with some dead volumes resulting in a longer tail. To quantify the extent of dispersion, vessel dispersion number ($N_{VD} = D/uL$) was estimated for all the configurations over a

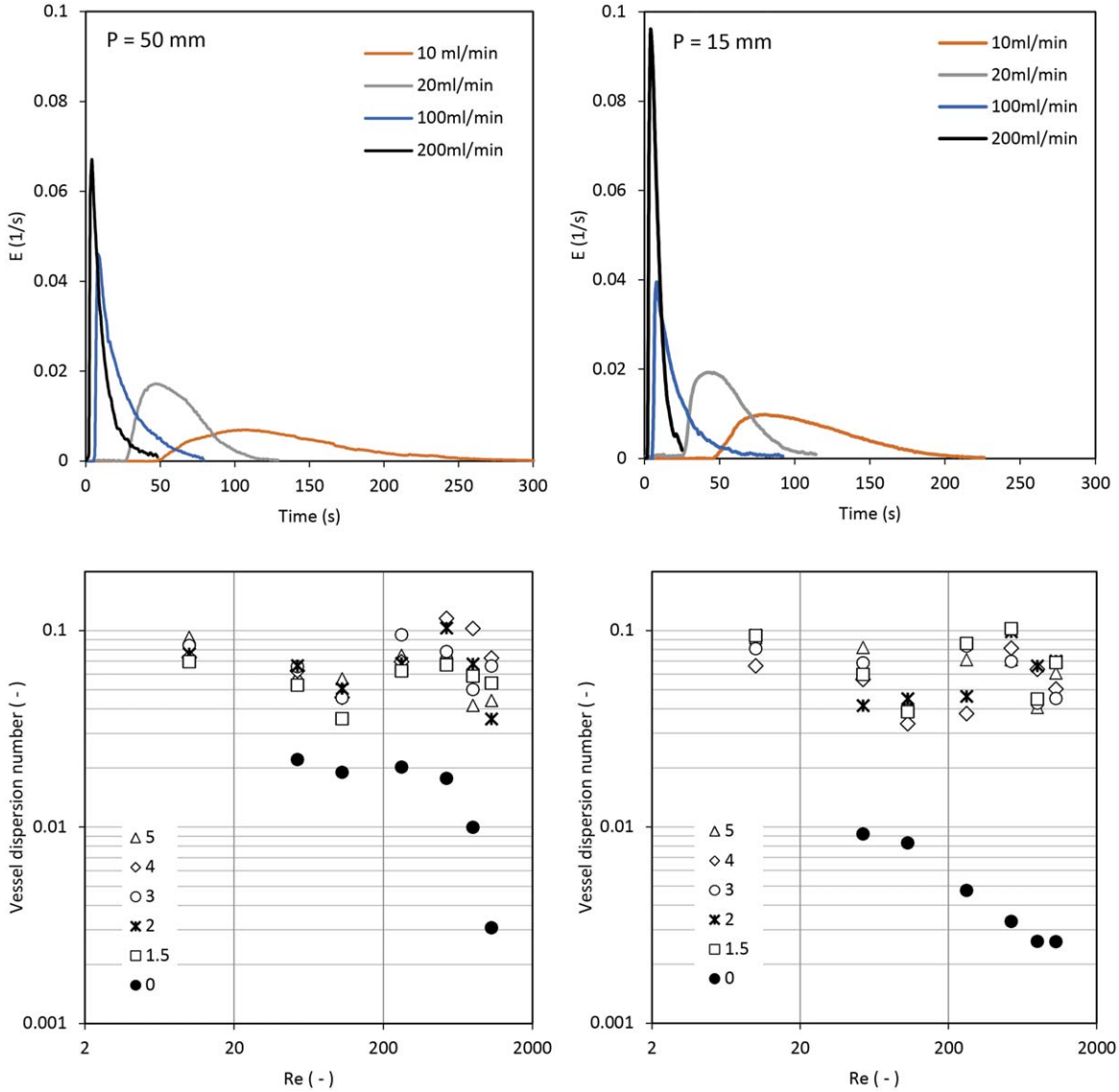

Figure 4. RTD analysis of pinched tubes.

(A, B) E-curves for pinched tube with 50 mm and 15 mm pitch between two successive pinch sections, (C, D) vessel dispersion number vs. Re for 1 m long straight tube and helical coil with and without pinch. Legends show the pitch (in mm) for pinch sections. [Color figure can be viewed at wileyonlinelibrary.com.]

range of flow rates (2–200 mL/min) and the observations are shown in Figure 4C, D.

The estimated values of N_{VD} were greater than 0.01, indicating large deviation from plug flow and a significant dispersion compared to the straight tube and coil of same diameter without pinch. These findings indicate that pinching the straight tube improves the mixing performance but also enhances the dispersion to some extent. Thus, these types of reactors are suitable for reactions that need rapid mixing or mass transfer but which do not have any sequential reactions.

Mass transfer

The interfacial liquid-liquid mass transfer is an essential hydrodynamic parameter that is often chosen to identify the right design and operating condition for a two-phase flow synthesis. The overall mass transfer coefficient ($k_L\underline{a}$) for liquid-liquid dispersions was measured as described in the experimental procedure over the range of Re (10–1060). The $k_L\underline{a}$ values for different configurations of pinched tube flow reactors (pitch values, straight tube, coils of different coil diameters, etc.) were compared with that of the normal tube or helical coil. It was observed that pinching has always resulted in higher mass transfer rates. In general, $k_L\underline{a}$ for helical coil with smaller radius of curvature was higher. At identical power consumption per unit volume (P_w), the values of $k_L\underline{a}$ due to pinching were higher by 8–9 times that of straight tube without pinching and can increase further at higher flow rates (shown in the Supporting Information). Enhancement in $k_L\underline{a}$ can be attributed to sequential reduction and enhancement in the cross sectional area, which accelerates and decelerates the flow thereby improving mixing and contacting between the phases. The secondary flow generated due to the coil shape also has a positive effect. The mass transfer coefficient obtained in the pinch tube reactor is comparable to the different flow reactors and microreactors available in the literature (Figure 5). It was observed from the analysis of pinched tube reactors of 2.5 mm and 4.5 mm diameters that the values of $k_L\underline{a}$ follow a power law behavior with P_w and can be given as

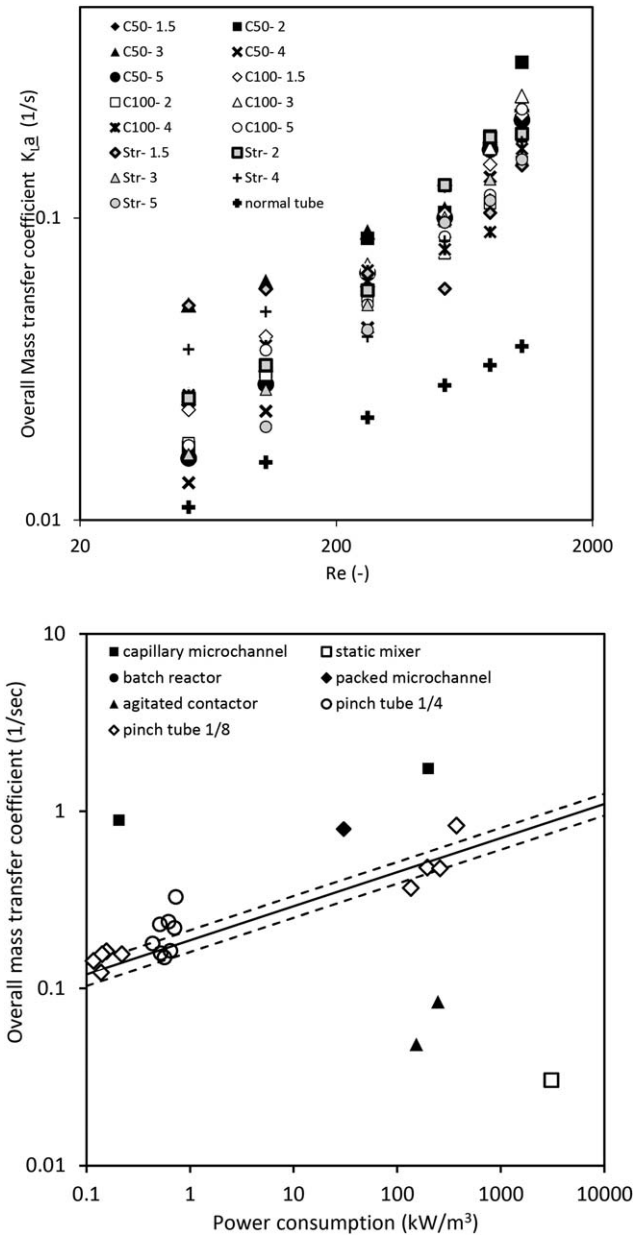

Figure 5. (A) Overall mass transfer coefficient measured for straight pinched tube, pinched coil of 50 mm and 100 mm coil diameter and unpinched normal straight tube of 4.5 mm i.d., (B) Comparison of overall mass transfer coefficient values for pinched tube and different flow reactors.

$\mathrm{Log}(k_L a) = 0.186\ [(\log(Pw)]^{0.192}$ with an error of less than $\pm 7.2\%$. Thus a simple geometry made out of commonly available tubes yield an excellent flow reactor with simpler fabrication.

Performance evaluation of pinched tube reactor

On the basis of above hydrodynamic experiments and RTD studies, which recommends the use of pinched tubes for reactions that need rapid mixing or mass transfer but which do not have very fast sequential reactions, here we have chosen a single phase and a two-phase aromatic nitration reaction, where the activation energy for secondary nitration is higher than the mono-nitration. Exothermic homogeneous nitration of bromobenzene ($\Delta H = -86.94$ kJ/mol) with mixed acid and nitration of benzaldehyde ($\Delta H = -172$ kJ/mol) with fuming nitric acid were chosen for performance evaluation of pinched tube reactor and compared with normal tubes of same volume and diameter. Finally we also demonstrate the use of pinched tube flow reactor for liquid-liquid extraction.

Bromobenzene Nitration. Nitration of bromobenzene in batch mode was done by adding bromobenzene in solution of pre-cooled mixed acid (40:60 v/v nitric acid to sulfuric acid) over a period of 2 h maintaining the reaction at room temperature.[24] Once addition is complete temperature was raised to 60–80°C with precise temperature control to avoid dinitration reaction. Reaction progress was monitored by monitoring the concentration of bromobenzene using gas chromatography (GC). After completion of reaction the reaction mass was dumped into ice to recover the solid product which is mixture of para and ortho-nitrobromobenzene. Bromobenzene nitration done in batch mode helped in deciding the operating condition for continuous flow nitration. The batch experiments indicated that in the absence of a suitable acidic solvent one of the nitro-isomers precipitates and it can eventually block the flow reactor. To avoid such a situation acetic acid was used as the solvent. For continuous flow experiments in pinched tube flow reactor, the two reagents, mixed acid and solution of bromobenzene in acetic acid (1:5 v/v) was used. Mixed acid solution (40:60 v/v nitric acid to sulfuric acid) was prepared using concentrated nitric acid (69%) and sulfuric acid (98%). After the solution preparation was done, solutions were loaded in two different syringes and were pumped into the reactor from a tee mixer connected at the inlet section of the helical coil reactor made from normal tubing as well as pinched tube. The volume of tee mixer was less than 0.2% of the reactor volume. Reactions were done at 80°C and for a residence time of 600 s. Product at the outlet was quenched in 50 g ice and extracted with 30 mL toluene in three parts (15, 10, and 5 mL). Extracted product was washed two times with water and then with a bicarbonate solution to remove traces of acid and later dried over sodium sulfate before subjecting to analysis using GC. The conversions at the outlet of helical coil made out of normal tube and pinched tube ($P = 20$ mm) were 76% and 92.7%, respectively. The isomer ratio of mononitro derivatives was identical.

Benzaldehyde Nitration. Nitration of benzaldehyde with fuming nitric acid was chosen to evaluate the performance of pinched tube reactor. Two syringe pumps were used to pump benzaldehyde and fuming nitric acid through Tee mixer connected at the inlet of the reactor. Helical coil was immersed in a circulating water bath maintained at 40°C. Reactions were carried out at three different residence times (viz. 450, 90, and 45 s). For every residence time, experiments were carried out at two different values of the mole ratio of nitric acid to benzaldehyde, that is, 1.24:1 and 7:1, respectively. At lower concentration of nitric acid the reaction will be limited by the kinetics while for the second condition it is expected to remain limited by interfacial mass transfer. The experiments were carried out using helical coils (tube i.d. = 4.5 mm) of 50 mm coil diameter made out of pinched tube ($P = 15$ mm) and normal tubes ($P = 0$). The samples of fixed volume were collected at the reactor outlet and sample preparation process as explained for the previous example was followed. Samples were analyzed on GC to measure the conversion and selectivity. The results are shown in Figure 6. At identical set of conditions pinched coil always showed higher conversion compared to

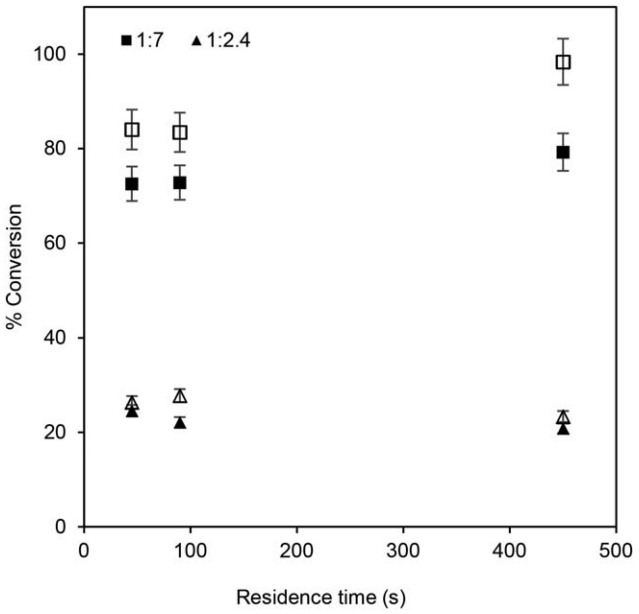

Figure 6. Comparison of performance of helical coil reactors made out of pinched tube (□) and unpinched normal tube (■) at different residence time and concentrations of nitric acid.

that of normal coil without pinching. In all the cases, the isomer mole ratio (i.e., m-nitrobenzaldehdye to o-nitrobenzaldeyde) was almost same (2.9:1–3.1:1). Both the inlet flow rates of the reactants would result in different flow regimes. Using pinched tube always helps to achieve a better liquid-liquid dispersion as compared to a segmented flow that is expected in a normal tube. This specific feature helps to achieve better conversion and hence higher yield of the desired isomer when using a pinched tube.

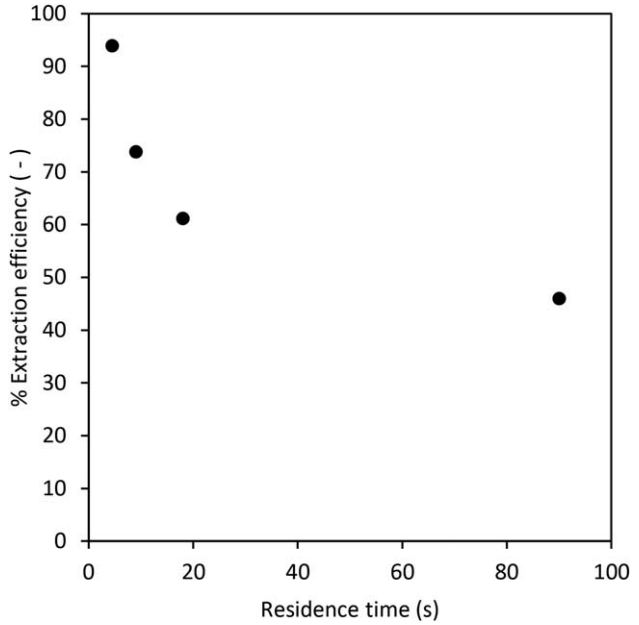

Figure 7. Variation in the extraction efficiency of a pinched tube flow reactor (length = 1 m, volume = 12 mL) as a function of residence time ABC.

Liquid-Liquid Extraction. With relatively higher mass transfer coefficient values, the pinched tube flow reactor can also be used for liquid-liquid extraction, which is one of the most common separation steps in flow synthesis. To verify the usefulness of pinched tube for L-L extraction, a model system comprising of toluene, n-butanol and water was chosen for the liquid extraction experiments.[25] 18% (wt/wt) stock solution of n-butanol in toluene was prepared and used for the liquid extraction experiments. Distilled water was used for extraction of n-butanol from toluene. Experiments were done at 4 different flow rates (10, 50, 100, and 200 mL/min) where stock solution and water were pumped at equal flow rate. A pinched tube flow reactor made from SS316 tube (6.32 mm outer diameter and 4.5 mm inner diameter) with pitch of 50 mm between successive pinches for pinching and $\theta = 90°$ was used for the experiments. Experiments were conducted at different flow rates. The flow rates of phases were maintained identical. Samples were collected at the outlet of the reactor and the toluene phase was analyzed after layer separation for quantifying the amount of n-butanol remaining in toluene. The balance would get extracted in water. Analysis of organic phase was done using GC with bromobenzene as internal standard. Equilibrium concentration of n-butanol in toluene was determined by stirring the equal volume of stock solution and water for 2 h. The observations are shown in Figure 7. Increasing the flow rate increase the extraction of n-Butanol from toluene to water. This can be attributed to the high shear rate at pinch points, which would result in very high interfacial area for mass transfer. Importantly, the extraction efficiency continued to increase when the residence time was less than 5 s. This implies that the interfacial area generated in the dispersion as well as the enhancement in true mass transfer coefficient due to high shear was sufficient to overcome the limitation of small residence time. Result indicates that pinched tube flow reactor can be successfully utilized for liquid-liquid extraction.

Conclusions

A novel concept of pinched flow tubular reactor is proposed and analyzed in terms of hydrodynamics and performance for a reaction. A large number of experiments were carried out for pinched tubes of different tube diameter, angle between successive pinching, pitch between pinch sections, coils diameters and the flow rates.

Change in flow pattern with continuous enhancement and reduction in the axial velocity as well as shear across every pinch location helped to achieve rapid mixing. Effect of pinching was prominent for higher flow rates resulting in small mixing lengths. Since the observations and the extent of enhancement is a function of the number of pinch points, geometry with alternate perpendicular pinching sections is recommended.

In general, at a given Re, higher number of pinch sections per unit length does not result in a proportional increase in the pressure drop. The estimated values of pressure recovery over a range of flow rates for different P values show that the pressure loss coefficient reaches to that of venturi at higher flow rates. The pressure drop for two-phase flow was significantly higher than the case of single-phase flow.

The RTD studies showed that with more number of pinch sections the extent of dispersion decreases and the system behaves closer to a plug flow. The number of tanks in series correlates positively with the number of pinch sections. Excellent local mixing at pinch points indicate that the pinched

tubes are more suitable for reactions that need rapid mixing or mass transfer but which do not have very fast sequential reactions.

In general, $k_L\underline{a}$ for helical coil with smaller radius of curvature was higher. At identical power consumption per unit volume (P_w), the values of $k_L\underline{a}$ due to pinching were significantly higher than straight tube without pinching. Highly exothermic nitration reactions could be carried out in pinched tube flow reactor with much better conversion and yield of the desired isomers. Pinched tube resulted in better liquid-liquid dispersion as compared to a segmented flow in a normal tube. The pinched tube flow reactor also proves as an excellent option for efficient L–L extraction. Thus a simple geometry made out of commonly available tubes yield an excellent flow reactor with simpler fabrication approach.

Acknowledgments

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Assessing the possibilities of designing a unified multistep continuous flow synthesis platform

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Review

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Abstract

The multistep flow synthesis of complex molecules has gained momentum over the last few years. A wide range of reaction types and conditions have been integrated seamlessly on a single platform including in-line separation as well as monitoring. Beyond merely getting considered as ‘flow version’ of conventional ‘one-pot synthesis’, multistep flow synthesis has become the next generation tool for creating libraries of new molecules. Here we give a more ‘engineering’ look at the possibility of developing a ‘unified multistep flow synthesis platform’. A detailed analysis of various scenarios is presented considering 4 different classes of drugs already reported in the literature. The possible complexities that an automated and controlled platform needs to handle are also discussed in detail. Three different design approaches are proposed: (i) one molecule at a time, (ii) many molecules at a time and (iii) cybernetic approach. Each approach would lead to the effortless integration of different synthesis stages and also at different synthesis scales. While one may expect such a platform to operate like a ‘driverless car’ or a ‘robo chemist’ or a ‘transformer’, in reality, such an envisaged system would be much more complex than these examples.

Review

Introduction

Flow chemistry is now seen as a reliable approach for the synthesis of simple organic compounds [1-6], complex large molecular weight medicinal drugs [7-12], polymeric materials [13-15], nanomaterials (metallic, bimetallic, composites, metal oxides, etc.) [16-18], catalysts [7,19], etc. In the recent times, the applicability of this tool has been extended for the synthesis of high value drugs involving multiple reaction steps including separation protocols [8,9,20]. A vast range of useful molecules

that are synthesized in flow has also helped integrate the complex synthesis with fine engineering to make the systems completely automated [9,20]. Flow chemistry gains its benefits from excellent heat and mass transfer rates and rapid mixing which is not possible in the case of conventional synthesis modes [21]. In general, the continuous flow synthesis aims at conducting the reactions at intrinsic kinetics. This helps to have reactors having smaller volumes making them inherently safer. Due to low processing volumes and reactions at intrinsic rates without much of human intervention it is possible to carry out hazardous reactions and a reaction at much higher temperature which is not possible with conventional methods [22,23]. An automated flow synthesis approach also reduces the labor costs significantly and operation can go on for a long time without any interruptions or significant downtime for the maintenance [9,20]. Many reactions have been performed in flow synthesis and are shown to be better than conventional synthesis [24-27]. A few examples of experimental set-ups of successfully demonstrated multistep flow synthesis encompassing various kinds of reactions from the literature are given in Table 1.

Table 1: Reactions and corresponding flow synthesis set-up from the literature.

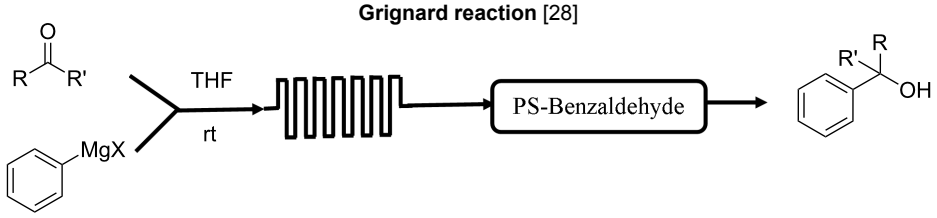
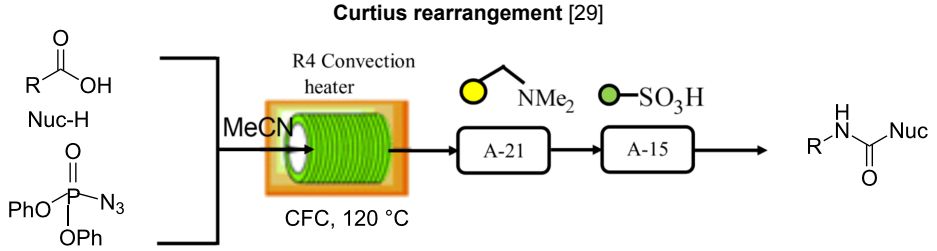
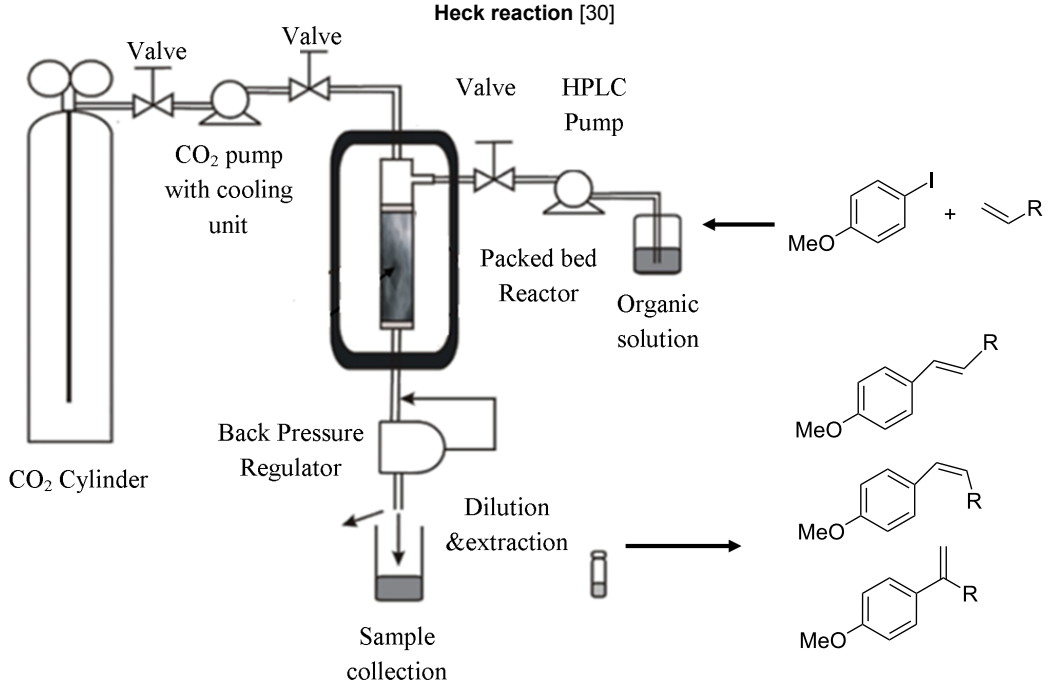
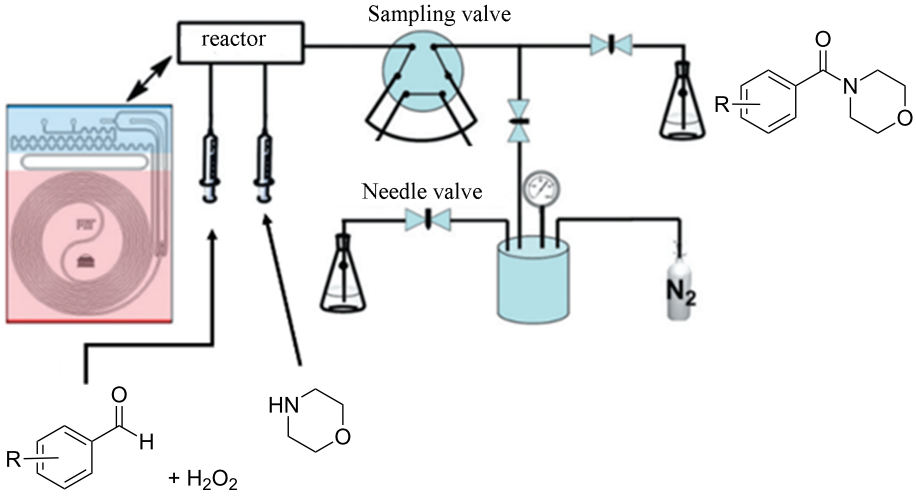
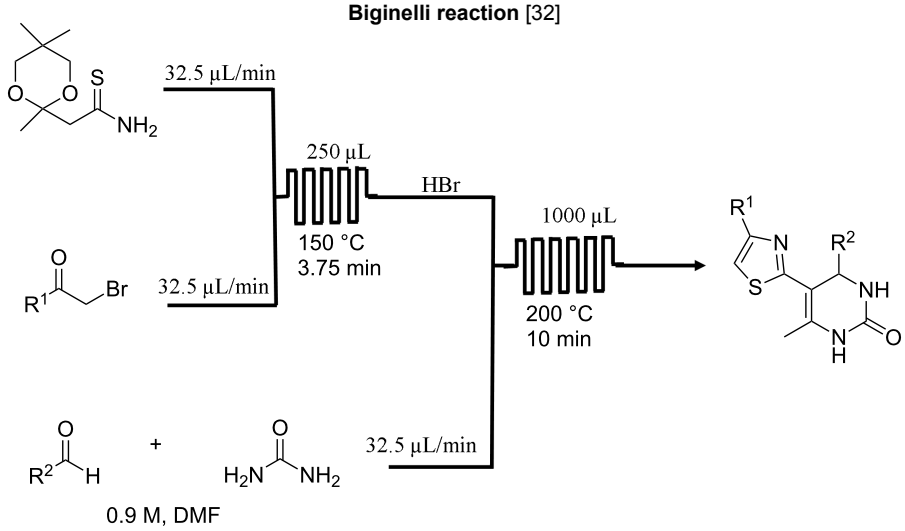
reaction name and flow set-up
Grignard reaction [28] 
Curtius rearrangement [29] 
Heck reaction [30] 

Table 1: Reactions and corresponding flow synthesis set-up from the literature. (continued)

Cannizzaro oxidation reaction [31]



Biginelli reaction [32]



Single step approaches were useful in terms of evaluating the concepts in continuous flow synthesis. However, since synthesis of any fine chemical or medicinal drug or agrochemical compound involves a sequence of reactions as well as several unit operations, by making only one process step continuous does not make much impact in terms of overall efficiency, economics and operation time. Thus the flow synthesis made its mark in terms of improving the product quality and reducing the environmental impact, albeit only for single reactions. This also helped to understand the safety related issues of flow synthesis and even helped to study the effect of operating parameters (viz. flow rates, temperature, pressure, pH, etc.) and design parameters (viz. mixing, heat transfer, mass transfer, dispersion, etc.), which together helped in developing reactor selection protocols and safer intensification window for its continuous operation. Over the time even the process control structures also got evolved for specific kind of experimental set-ups and even automated self-optimizing platforms were also tested [33]. The natural evolution was an archetype for the multistep flow synthesis. The integration of in-line separation has taken the confidence of the synthesis community one step ahead [21,34,35]. In parallel to this, in-line analytical techniques have also been used for on-line measurement and characterization [36-38]. Multistep flow synthesis is a significant milestone in practice of organic synthesis. In the recent time, there has been a visible surge in the number of publications on multistep flow synthesis with specific target molecules [26,39]. Table 2 shows a few drugs which are synthesized using multistep flow synthesis. Multistep flow synthesis approach has the capability of replacing the conventional synthesis methods. It involves many unit operations also made to operate continuously to truly harness the benefits of flow chemistry which is not an easy task.

Table 2: A few important drug molecules synthesized in multistep continuous flow.

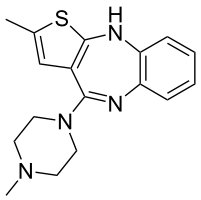
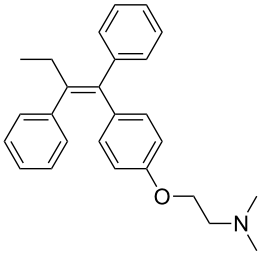
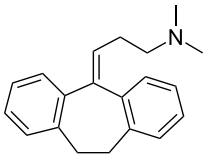
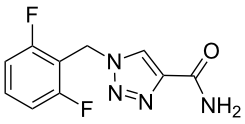
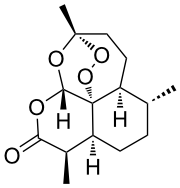
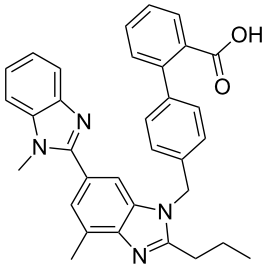
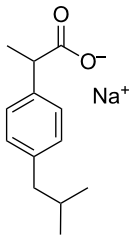
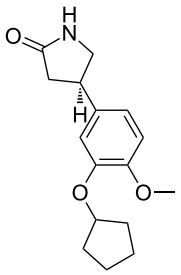
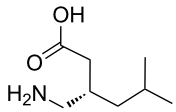
molecules and reaction/separation steps	end product	remarks
olanzapine (Zyprexa) [11] • 4 reaction steps • 2 separation steps		• antipsychotic drug • inductive heating was used • starting materials used: aryl iodide, aminothiazole Pd_2dba_3, xantphos, Bu_4NOAc, Et_3SiH, HCl, piperazine
tamoxifen [12] • 5 reaction steps		• breast cancer drug • telescope synthesis • moisture sensitive reagents were used • starting materials used: Weinreb amide, PhMgBr, aryl bromide, *n*-BuLi, aq HCl, TFAA, Et_3N
amitriptyline [10] • 6 reaction steps		• antidepressant drug • moisture sensitive reagents were used • tube-in-tube reactor was used • inductive heating was used • starting materials used: benzyl bromide, *n*-BuLi, CO_2, Grignard reagent, EtOH
rufinamide [40] • 3 reaction steps		• anticonvulsant drug • telescope synthesis • copper tubing was used as reactor and catalyst • starting materials used: aryl bromide, NaN_3, methyl propiolate, aq NH_3
artemisinin [41] • 3 reaction steps • 4 separation steps		• antimalarial drug • the pressure was monitored to avoid unsafe backpressure due to clogging • starting materials used: dihydroartemisinic acid, TFA, toluene, O_2, TMOF/TEOF/succinic anhydride
telemisartan [42] • 3 reaction steps		• hypertension drug • telescope synthesis • starting materials used: benzimidazole derivative, *t*-BuOK, bromide derivative, aq KOH, bromobenzimidazole
ibuprofen [43] • 3 reaction steps • 1 separation step		• nonsteroidal anti-inflammatory drug • three minutes residence time • starting materials used: isobutylbenzene, propionyl chloride, $AlCl_3$, TMOF, ICl, NaOH, 2-mercaptoethanol

Table 2: A few important drug molecules synthesized in multistep continuous flow. (continued)

(*S*)-rolipram [7] • 4 reaction steps		• anti-inflammatory drug and selective phosphodiesterase 4 (PDE4) inhibitor • heterogeneous catalysts • starting materials used: aldehyde derivative, nitromethane, malonate, Et_3N, H_2, water and *o*-xylene
(±)-pregabalin [44] • 3 reaction steps		• used as a therapeutic agent for nervous system disorders such as epilepsy, anxiety disorder, and neuropathic pain • heterogeneous catalysts • starting materials used: isovaleraldehyde, methyl malonate, nitromethane, 1-PrOH, H_2, HCl, NaOH

The utilization of the same approach for the synthesis of a wide range of products is very challenging since each product in the chemical synthesis involves different synthesis procedures, different conditions, different phases and different isolation protocols. However, the approaches adopted for several multistep flow synthesis still lack from seamless extrapolation to other synthesis platforms, including the non-availability of specific unit operation in continuous mode at the throughputs suitable for laboratory scale. Though, the multistep continuous flow synthesis approach is very promising for the synthesis of important chemicals having applications as medicinal drugs, agrochemicals, perfumery compounds etc., in general, the components/equipment in a flow synthesis platform are almost identical and this paves the way to think of developing a unified flow synthesis platform that can facilitate multistep synthesis involving a wider range of reactions over a varied range of conditions. Such a platform would help to reduce the time in planning of experimental set-ups for individual reaction(s) or sequences and will also help to do a seamless integration of experimental conditions with smaller laboratory footprint. In addition to the most obvious purpose of having such a platform that will facilitate the synthesis of any molecule including several intermediate stages, it will help in terms of the following:

1. **End-to-end synthesis:** Total synthesis of various molecules involving multiple chemical transformations (homogeneous or reactions involving multiple phases) at various optimal conditions including work-up/purification in continuous mode.
2. **Screening:** Rapid screening of operating conditions and development of a library of molecules from similar initial substrates.
3. **Convenience:** Selection of the specific parts of the set-up for a given synthesis step or for selecting a sequence of reaction steps reduces the time to disassemble and re-assemble the set-up for different products. So, operating the set-up and deciding the parameters for each step becomes convenient using a unified platform.
4. **Modularity in true sense:** Making the reaction platform having plug-and-play approach would make it modular in true sense.
5. **Adaptability:** Having components with multiple functions will reduce the overall number of equipment/instruments on the synthesis platform.
6. **Automation:** Reduced human intervention facilitated by in-line measurements, automated optimization programs and continuous operation for a controlled set of conditions will be the unique features that will make such platforms attractive and efficient.
7. **Reproducibility:** Development of individual reaction steps and their optimization at various locations of an organization can become reproducible upon integration through such platforms.

While the concept of a unified synthesis platform looks fascinating and useful to reach the targets like ‘Dial-a-molecule’ [45], in reality, it can be very challenging. Some of the challenges are as follows:

1. **A varied range of conditions:** A multistep synthesis platform developed for one target molecule cannot always be utilized for different products since each product either requires different chemistry or a different set of unit operations or unit operation sequences. In some cases, synthesis and chemistries can be very different

such that totally different set of flow reactors (including material of construction) and operating conditions has to be employed, e.g., flow chemistry literature shows the use of a wide variety of flow reactors, e.g., tube-in-tube gas permeable membrane reactors [46-48], high-pressure reactors utilizing back pressure regulators [49-51], reactors with different heating and cooling modes (e.g., inductive heating [11,52], microwave [53-55] etc.) and many more, also very special reactors [56] with other difficulties that need to be taken care. Also reactions are varied in terms of conditions such as the utilization of novel process windows [57-59] where high temperature and pressure is utilized which needs special attention in terms of safety and other criteria compared to the reactions requiring ambient conditions and low to moderate temperatures.

2. **Matching of time scales:** Residence time associated with a specific operating condition in each reactor and in a separation protocol (i.e., unit operation) in sequence has to be matched properly to get the desired final product which needs to be optimized every time if the throughput in the start or anywhere else gets changed in the sequence. This is very important for synthesis steps where downstream processing is also in sequence. Usually time scales for work-up procedures like extraction, crystallization, solvent switch etc. are longer compared to the main reaction and for any particular reaction in sequence the time scale for all other steps has to be either fixed or it gets fixed based on the initial step. One option is to have more pumps and collect the reaction mass at some point to change the flow rate for matching of time scale [7-9,20]. However, such an arrangement is complex and makes it very difficult to vary for each new scenario which requires special skill set or modification in chemical step.
3. **Suitability of control structure and sensitivity:** A multistep flow synthesis approach possesses challenges in terms of controls where a slight change anywhere in the process sequence can hamper the product output or will require very different kind of control strategies in the subsequent steps. For example, the reaction can be sensitive towards mixing, mass transfer/flow regime, temperature, etc. Slight variation in pump flow rate or coolant flow rate/temperature can change the relative time scales of the process affecting its selectivity. For such cases, the control system should quickly bring the process to steady state to maintain the desired selectivity. Shukla and Kulkarni have reported a control structure for a few synthetically important drug molecules and discussed challenges involved in developing such a control process [60].
4. **Monitoring:** Utilization of in-line analysis techniques and constant monitoring of the product also requires specialized equipment to be used and relative 'analysis time' in the whole process sequence is much greater compared to the reaction time. During utilization of such in-line techniques like HPLC, UV and IR etc. where analysis time is greater than reaction, provision has to be provided for intermittent sampling to monitor the reaction progress. In those instances it is the analysis time that dictates the control structure and parameters to be varied in case of any disturbance at/during any stage of operation [38,61].
5. **Optimization:** In continuation to the first point above, since every reaction step would have a different set of optimal conditions, the availability of a varied range of utility (i.e., the heating or cooling systems) and their suitability for integration on a single platform would be challenging for configuring the entire platform. Moreover, even after realizing such a platform, optimal conditions for each step would be different this might need significant reconfiguration for making a real 'plug-and-play' kind of system. This means that the unified synthesis platform should have a number of utility variations as low as possible.
6. **Compatibility:** The material of construction or make of the process components may not be always suitable for a given set of reactants/products/solvents/byproducts. Even the change in the sequence should be adaptable such a system can be very expensive as well.
7. **Skills:** With the advent of many flow synthesis tools available in the market much of the above issues may be taken care of. However, the automation in multistep synthesis needs careful selection. In general, setting-up of a multistep flow synthesis platform is very time consuming and needs multidisciplinary skills or a bigger team as it gets reflected in a few excellent works from the literature [8,9,20,62].

Motivation

In view of the above introduction, in rest of this manuscript, we have explored the feasibility of having a unified multistep flow synthesis platform which can help to do almost any flow synthesis. Such a platform, if developed would resolve most of the above-stated challenges and will reduce the time and other resources whenever new chemistry has to be developed in continuous flow manner. The proposed platform will contain all the necessary components of a multistep synthesis unit that will be sufficient to perform a number of chemical syntheses with wide variation in synthesis steps. With the developed platform it will be very easy to do a screening of different chemistries and save a lot of time for beginner chemists in terms of locating and

assembling the setup. The proposed approaches are more as a guideline and will need elaborate engineering analysis before actually building them. However, we have also given specific recommendations in that direction. Before presenting and evaluating various approaches for building a unified multistep synthesis platform in Table 3 we have given definitions of a few terms used throughout the manuscript and their relevance.

Design complexity

A general flow chemistry setup requires some basic equipment like pumps, reactors (usually a flow reactor tube of required length and diameter or a microchannel reactor having various geometries or a static mixer) or a continuous stirred tank reactor or a fixed bed reactor or other intensified process equipment viz. spinning disc reactor, impinging jet reactor etc.) and a thermostat which will maintain the reaction temperature and components viz. valves, measurement devices and so on. As mentioned earlier, a list of various terms used in this article is given in Table 3. The functionality and nature of the setup can change with the chemistry under investigation and the experience of an individual involved in handling simple to complex synthesis containing a large number of stages and components. This demands more attention to address a few important aspects of such a unified synthesis platform.

Component selection: Component selection is the most important task for designing any synthesis set-up that targets a specific product. For a typical multistep flow synthesis involving several reaction stages, the system will require several components, reactors, and equipment. One can definitely identify some class of reaction where the same kind and number of components can be utilized but a slight change in synthesis route/chemistry will require a new component to be added extra or for the same component the suitable material of construction might be different than before. This can lead to a bulky system having a complex flow path.

Choice of parameters: Choice of a range of operating conditions/parameters is a very crucial aspect while designing a unified synthesis platform. In a multistep synthesis route, each stage will have its own set of operating conditions for getting the optimum yield. A set of reactors and components designed for a specific reaction would require optimization in terms of operating conditions to match the throughput or residence time when used for another reaction. Moreover, once the system or synthesis platform is built, any minor variation needed at one stage due to possible variation in the purity of reactants will require manipulation at each stage in the sequence.

Number of steps: The number of reaction steps and subsequent downstream processing for the synthesis of any final drug molecule or an agrochemical is usually different. Therefore the components needed for a specific synthesis protocol will also vary. Thus a unified multistep flow synthesis platform may not be adequate and cannot be complete for the synthesis of any and every molecule. For example, a few synthesis steps need very specific type of equipment (viz. ozonolysis), which is not needed in every routine synthesis.

Sequencing of components: For a unified synthesis platform to become adaptive to any kind of reaction sequence (reaction followed by separation and purification) is one of the most important design challenges. As the component in a platform would be fixed, for every synthesis either some components must be

Table 3: Definition of the specific terms used in the article.

terms as used in this article	meaning/relevance
1. reactor	the section of the platform used for carrying out reactions. Usually, reactors are followed by separators (for extraction, distillation, chromatographic separation, crystallization, etc.).
2. instrument	wireless or cabled electronic unit that interfaces with the reactor and separator to facilitate monitoring and/or measurement and/or control.
3. equipment	an electronic unit that facilitates dosing of gas, liquid and solid.
4. component	connecting joints between reactor(s), instruments and equipment. These will include fittings, connectors, valves, etc.
5. module	an assembly of all the above segments to facilitate flow synthesis along with monitoring and control (1–4).
6. variables and parameter	set of conditions (set points or variables) that are used for optimizing a specific reaction section or the entire sequence of reactions.
7. stage	individual unit operations (viz. pre-heating, mixing, reaction, quenching, separation, etc.).
8. number of steps	number of reactions (chemical transformations) in a sequence to obtain the final product.
9. synthesis sequence	a sequence of reactions and unit operations (stages) in the synthesis path for the specific final product.

bypassed or connected in a loop, which would increase the dead volume in the overall system. This would enhance the residence time, demand more safety features and also need more inventory. A larger dead volume has its own challenges.

Control strategy: Devising a control strategy for a unified synthesis platform itself will be the most complex task. The complexity will originate from the varied control structures needed for individual synthesis sequence. For every reaction sequence verification of the sensitivity bounds on the specific control, strategy has to be developed for optimum performance of the setup.

Scale of operation: Throughput for any targeted molecule may vary based on the user requirement. Choosing a component to be operated in up-scaling and down-scaling mode at several throughputs with a wide range of operating conditions is very difficult. More than the effect of residence time, the hydrodynamics for the same reactor would vary depending upon the throughput and will affect the performance severely. In such a case, the plug-and-play mode might work provided the change of component is limited and absolutely necessary.

Troubleshooting: As a unified platform will involve lots of components for a chosen multistep synthesis flow path, the standard protocols for start-up, operation and shut-down will vary depending upon the reaction sequence. Thus, the interlocks and control structure should be updated accordingly. For example, among the presently available automated flow synthesis platforms, the limitation always comes from non-availability of troubleshooting protocols.

Simultaneous use for synthesis of different molecules: Having a unified platform will serve the purpose only if all the units on the platform are utilized all the time which may not be the case always. Utilizing all the components simultaneously for different synthesis sequence will need isolation of one flow path from the other and since the whole system is integrated, this will introduce complex operational challenges.

Utility optimization: The operating conditions for individual reactions in a sequence are usually different and the reaction temperature can vary from −78 °C < T < 200 °C. In such a situation, it cannot be a viable option to have a different utility for individual reaction steps.

The above mentioned specific points need to be taken into account while planning for a unified synthesis platform for flow synthesis. Thus, depending upon the set of targeted molecules or functional group transformations it is possible to propose several design/assembly options. In rest of this article, we bring out a few different ways in which it would be possible to design a unified flow synthesis platform. A few case studies from the literature on multistep flow synthesis of very specific drug molecules are used to explore and evaluate the design approach for building a single synthesis platform that can help produce all of those drug molecules, each having a very different synthesis route.

How do we use it for drug synthesis?

The proposed options of a unified synthesis platform will serve as a convenient tool at lab scale. Many new chemistries that are parts of a multistep flow synthesis route are to be performed with slight changes in the component/layout. The platform will serve as a single destination for the multistep flow synthesis whenever a reaction has to be optimized or new screening has to be done. It is expected that with slight modifications, a user will be able to 'choose' a multistep synthesis flow path in the unified platform.

Approach

For designing such a system we have analyzed the literature on multistep flow synthesis of API's through complex chemistry. We have shortlisted the papers which contained different equipment's used in the pharmaceutical manufacturing to cover most of the functional groups which can be organized on the single platform and can be utilized for a number of chemical syntheses.

After identification of specific molecules to be used for developing a unified synthesis platform we have identified the number of components associated with a synthesis and then optimized the number of component which will be sufficient to do all the identified reactions. Once the components were chosen the optimal sequencing which will be efficient to do the reactions without much difficulty has been developed and sequencing was done. In order to evaluate the feasibility of the above concept, we have considered different multistep syntheses as case studies. Number of steps, starting material and other conditions are listed in Table 4.

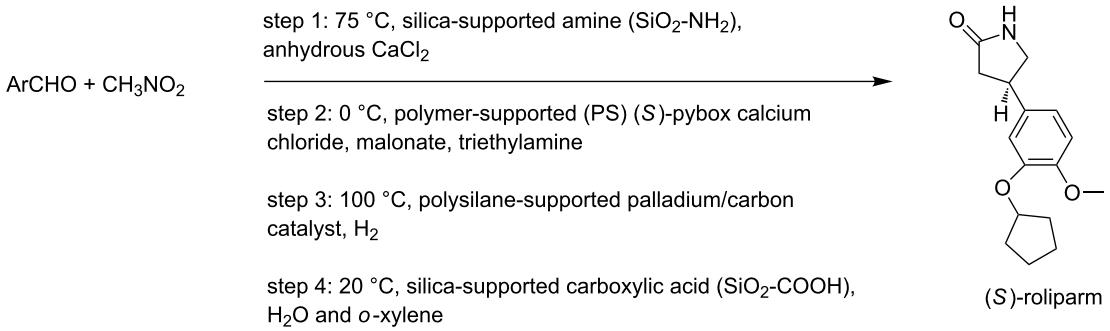
For these few cases we have evaluated three different approaches that can be used for developing a single synthesis platform. Every approach is based on a different logic of making a unified multistep flow synthesis platform. Figure 1 shows a comparison between the different approaches.

Approach 1: Unimolecular synthesis (one at a time)

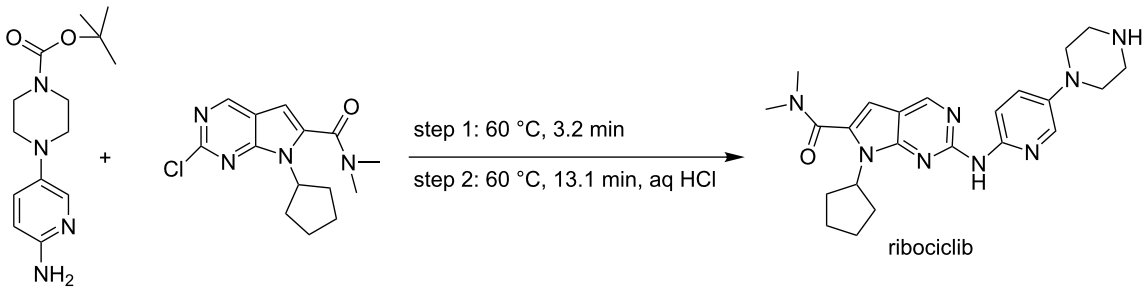
The first approach towards development of a unified flow synthesis platform mainly aims at minimizing the number of components and to perform the reactions in a single system without much change of components (Figure 2). Here the components

Table 4: Multistep synthesis case studies selected for the article.

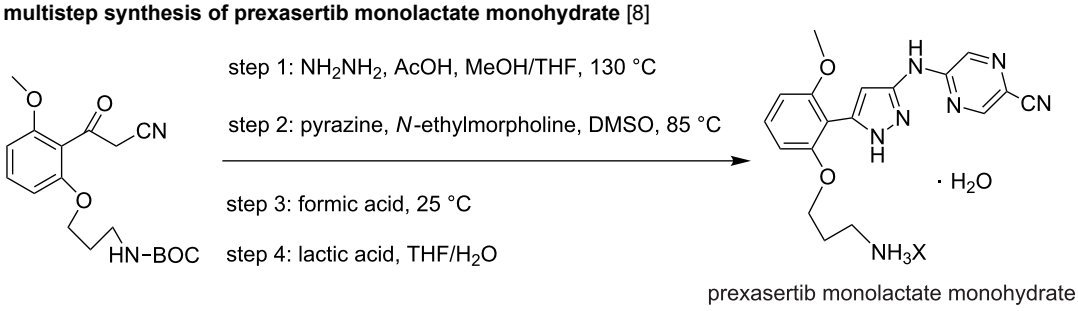
multistep synthesis of (*S*)-rolipram [7]



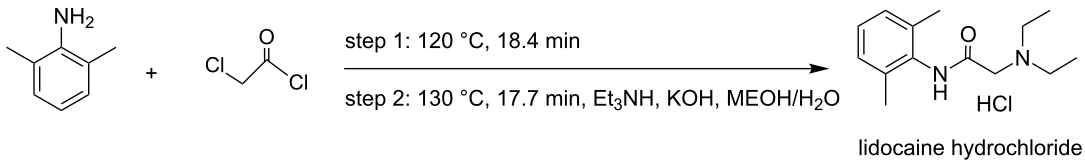
multistep synthesis of ribociclib [63]



multistep synthesis of prexasertib monolactate monohydrate [8]



multistep synthesis of lidocaine hydrochloride [9]



multistep synthesis of fluoxetine hydrochloride [9]

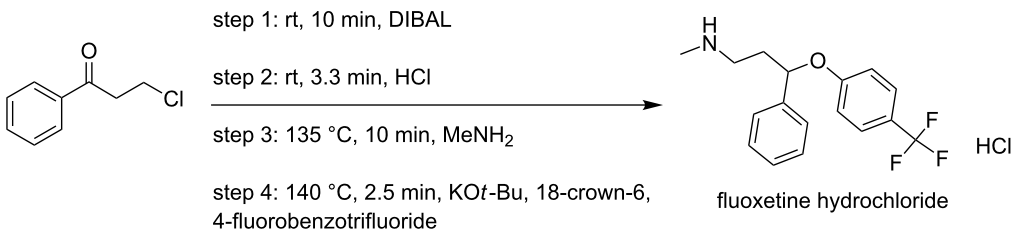
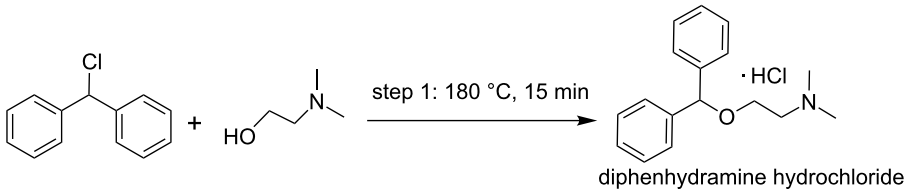


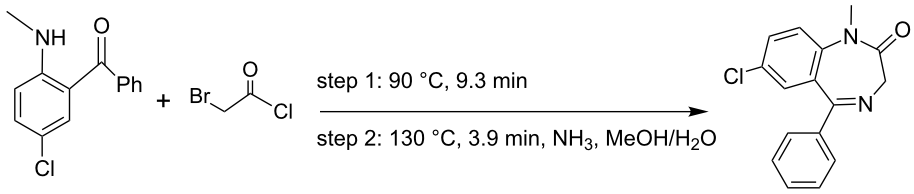
Table 4: Multistep synthesis case studies selected for the article. (continued)

multistep synthesis of diphenhydramine hydrochloride [9]



diphenhydramine hydrochloride

multistep synthesis of diazepam [9]



diazepam

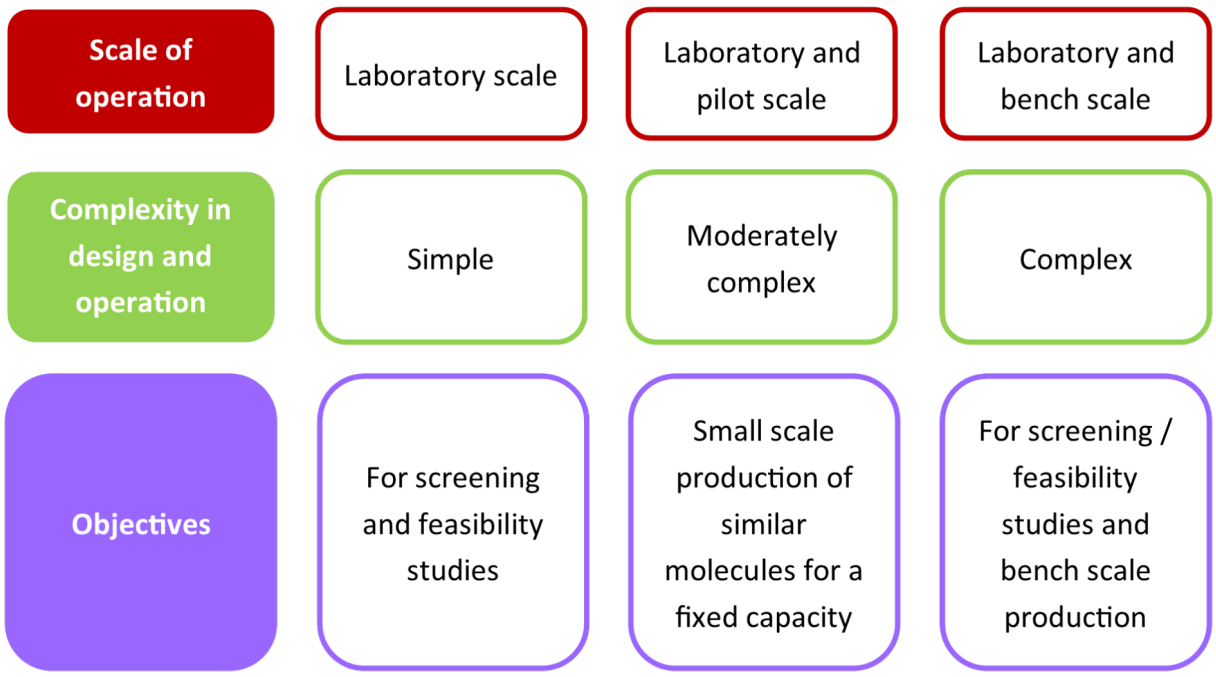


Figure 1: Key features of different approaches for unified multistep synthesis platform.

are fixed on one platform and the synthesis of a specific compound is carried out by choosing the path which is required for the reaction and other paths are blocked by using automated valves. This approach is good for relatively simple reactions and for some complicated reactions the number of components increases that lead to a large number of connections and a complex control structure. Table 5 shows the path for the synthesis of different products based on approach 1, Table 6 shows a list of components required for the synthesis of the above products using approach 1.

Figure 2 involves the platform for the synthesis of API's listed in Table 5. One example has chosen from Table 5 to explain approach 1. The description for the synthesis of prexasertib monolactate monohydrates based on approach 1 in Figure 2 is explained as follows: The synthesis of Prexasertib monolactate

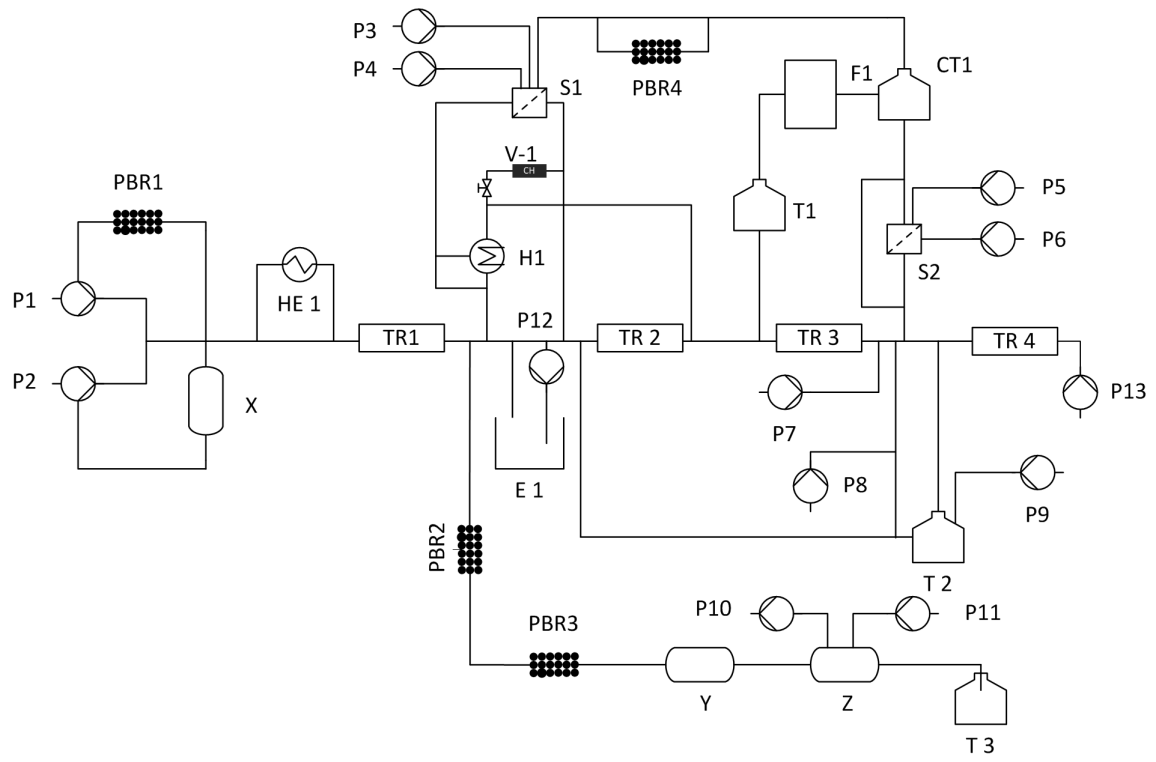


Figure 2: Schematic representation of a unified platform for the flow synthesis (P1–P14 pumps, PBR packed bed reactor, HE1 heat exchanger, H1 heater, S1 and S2 separator, E1 extractor, TR1–TR4 tubular reactor, CH charcoal, CT1 crystallization tank, T1–T3 tanks, F1 filtration).

Table 5: Conventional path for the synthesis of different intermediates based on approach 1.

intermediate	multistep synthesis flow path
prexasertib monolactate monohydrate	P1+P2→HE1→TR1→E1→TR2→TR3→RE1→T2→TR4→F1→T1
aliskiren hemifumatate	P1+P2→R1→S1→S2→TR4→S1→PBC→C1→S2→T2
diphenhydramine hydrochloride	P1+P2→R1→H1→BPR→CH→S1
lidocaine hydrochloride	P1+P2→R1→R2→BPR→CH→S1
diazepam	P1+P2→R1→R2→BPR→CH→S1
fluoxetine hydrochloride	P1+P2→R1→R2→S1→S2→R3→S1→H1→R2→T1
ricociclib	P1+P2→R1→R2→S1→R4→T1
rolipram	P1+P2→PBR1→X→TR1→PBR2→PBR3→Y→Z→T3

Table 6: Components required for the synthesis of the above API's [pumps (P), reactor (R), heat exchanger (HEx), heater (H), back pressure regulator (BPR), packed/fixed bed reactor (PBR/FBR), separator (S), charcoal adsorption cartridge (CA), liquid–liquid extractor (LLEx)]

name of API's	P	R	HEx	H	BPR	PBR/FBR	S	CA	LLEx
diphenhydramine hydrochloride	4	1	–	1	1	–	1	1	–
lidocaine hydrochloride	5	2	–	–	1	1	1	–	–
diazepam	4	2	–	–	1	1	1	1	–
fluoxetine hydrochloride	11	4	–	1	4	–	4	–	–
aliskiren hemifumarate	14	2	–	–	–	1	5	–	–
ricociclib	4	2	–	–	–	–	2	–	2
rolipram	7	1				5			
prexasertib monolactate monohydrate	20	3	1		–	–	1	–	2

monohydrates involves four steps a) condensation b) aromatic nucleophilic substitution reaction, c) deprotection and d) formation of lactate salt. Details of the same are given below:

- **Condensation:** Condensation takes place in a first reactor TR1 between the nitrile and hydrazine at high temperature and under pressure. Here, the nitrile was dissolved in a THF and hydrazine was dissolved in a mixture of solvents such as methanol, acetone, and water. The nitrile was pumped using pump P1 and hydrazine was pumped through P2 into the tubular reactor TR1 maintained at a temperature of 130 °C at residence time of 60 minutes to obtain the pyrazole. The impurities of the pyrazole were removed by passing it to the continuous countercurrent extraction E1. Here a solvent exchange process takes place between toluene and water. The pyrazole was then concentrated using automated rotary evaporator RE1. The concentrated product was diluted with DMSO using pump P13.
- **Aromatic nucleophilic substitution:** The nucleophilic substitution reaction takes place between the pyrazole and *N*-ethylmorpholine. Pyrazole of step 1 in the extractor was pumped through P13 and *N*-ethylmorpholine through P3 into the reactor TR2 to form the arylated product of the pyrazole. Here the reactor was maintained at a temperature of 70–100 °C for 1–3 hours. The product was crystallized in CT1 with the anti-solvent methanol pumped through P4 into the crystallization tank. The crystallized product was filtered and separated in S2.
- **Deprotection:** The second-stage product from the separator enters into the tubular reactor TR3 at a temperature of 20–40 °C with a residence time of 4 hours. Into this reactor nitrogen gas was pumped through peristaltic pump P7 and formic acid using pump P8. In TR3 gas–liquid reaction takes place.
- **Formation of the lactate salt:** In step four, lactic acid was pumped through pump P3 to form the final lactate salt of the product. Here the excess of formic acid and lactic acid was removed by the rotary evaporator RE1, then passes through TR4 into the crystallization tank CT1. The solid product formed was filtered in F1 and stored in a tank T1.

Challenges in performing multiple reactions in a single platform as given above: The number of valves needed to select the desired set of equipment is much higher. The reactions which take place only in a packed bed reactor and do not involve a separator, filter, crystallizer, etc. The path required for the synthesis is the same as that of synthesizing it individually so that the number of components required will remain unchanged and it is the same as that of an individual synthesis.

Approach 2: multimolecular operation (more than 1 molecule at a time)

This approach consists of identifying and optimizing a minimum number of components for performing flow synthesis of different molecules. The developed platform will contain all the necessary components for synthesis (flow reactors, packed columns etc.) to the downstream processing (extractor, separator, crystallizers, dilution tank etc.). Some of these components can be used for different chemistries just by changing the flow rates or the operating conditions specific to the chemistry. The components will be arranged on a platform where the order of arrangement can be varied in terms of processing needed for chemical synthesis just by connecting the components via tubes. The designed platform will be provided with some accessories which will include at least one component of all types on the platform (of different or same volume, or suitable to the different operational parameters) with an exactly same dimension which will make replacement of a component easy in case of failure or whenever needed. This platform will be a plug-and-play kind of system where the user will just have to choose the specific order of the component arrangement and to select the operating parameters before starting any experiment. The platform can be used for a specific synthesis step optimization or for performing an optimized multistep synthesis. The plug-and-play approach makes it very useful in the sense that if some or any component on the platform is not being utilized for any synthesis that component can be removed and used for another purpose or simultaneous synthesis of different molecules can be done using components which are not being utilized for the ongoing synthesis. The components like dilution tanks, crystallization tanks, and gravity based liquid–liquid separators can serve different purposes if planned properly before the experiment so that the same component can be used interchangeably with different chemistries reducing the need for different components still further.

Figure 3 shows the unified platform based on the approach 2 which contains the optimum component based details extracted from the literature of selected case studies. The sequence of components was arranged according to the described setup in the case studies selected. Figure 4 depicts 4 processes in one chart and the components in blue color are the common components, which will take part in the synthesis of any or every molecule chosen from the case studies. That reduces the quantity of the same kind of components by 4 times. The number of components for each unit operation is quite large, however, that helps to carry out the synthesis of all the identified products in the chart.

To have a view of the platform as in approach 2 one example of diphenhydramine hydrochloride is covered here from the case

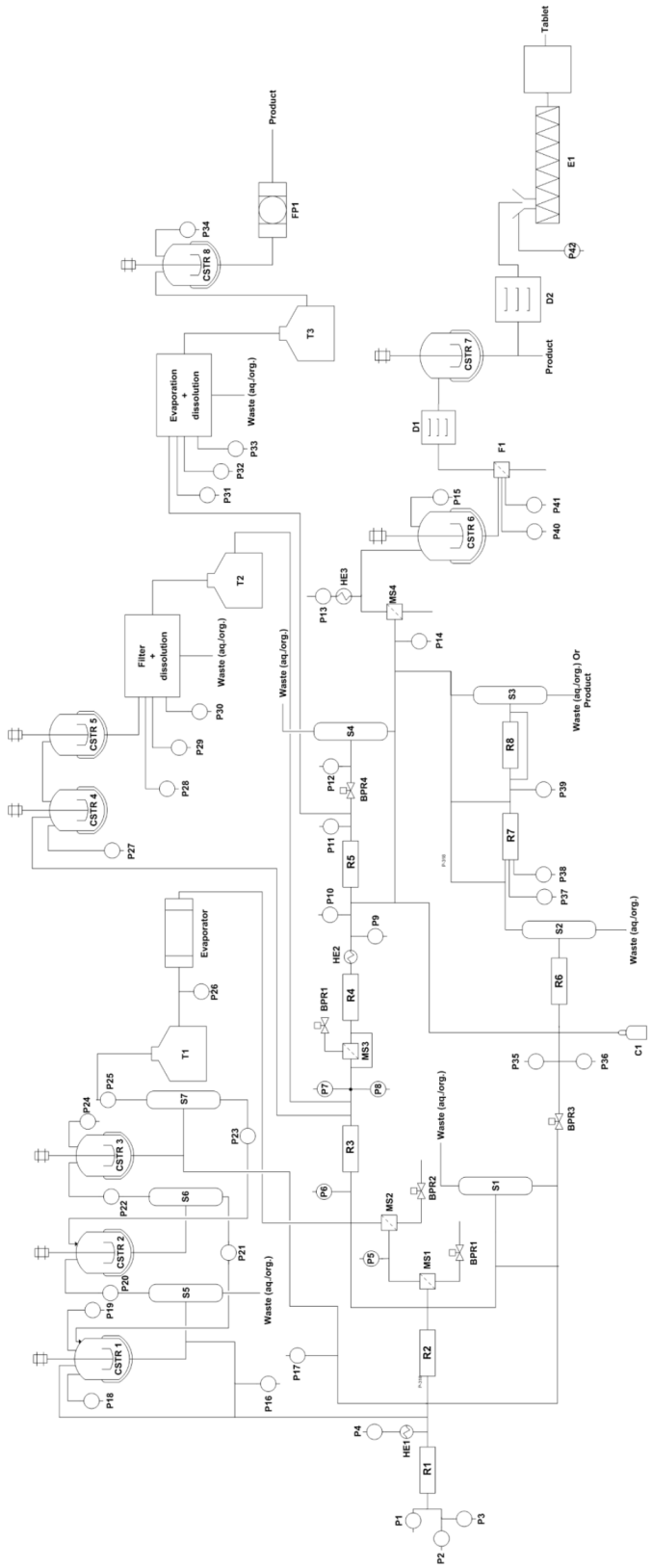


Figure 3: Layout of a unified synthesis platform (including all the component) for multiple drug molecules (approach 2) R – coil reactor/packed bed reactor/scavenger, P – pump, HE – heat exchanger, CSTR – stirred tank reactor/crystallizer/dilution tank, T – storage tank, F – filter, S – gravity-based separator, D – dryer, FP – filter press, MS – membrane separator, E – extruder, BPR – back pressure regulator.

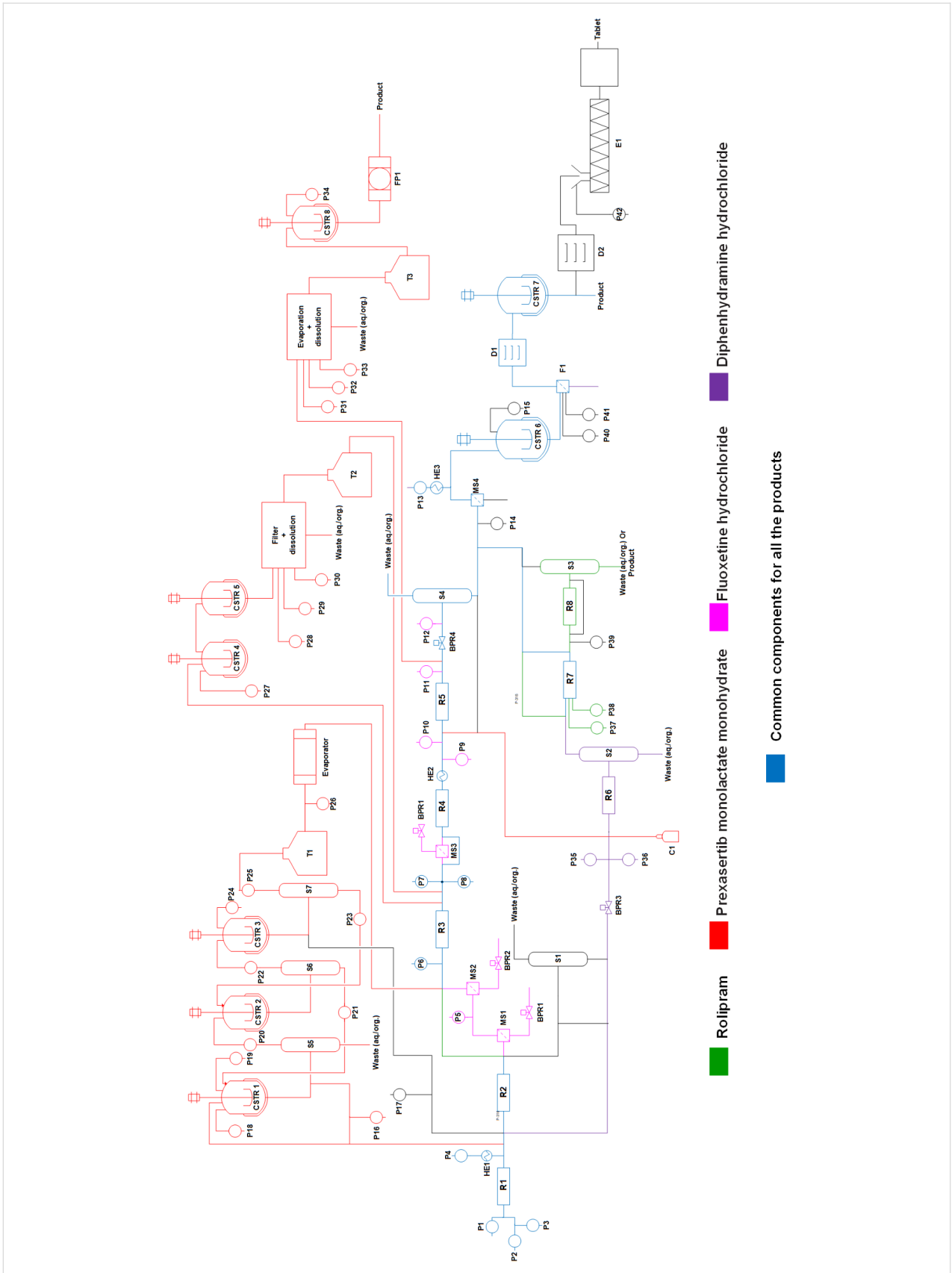


Figure 4: Layout for synthesis of 4 molecules on a single platform (approach 2).

studies, where two reactants 2-dimethylaminoethanol and neat chlorodiphenylmethan is being pumped from P1 and P2 to reactor R1 where it is getting heated at a temperature of 180 °C at a pressure of 1.7 MPa. The molten salt which comes out of reactor R1 is then treated with aqueous NaOH through pump P4 which is heated to 140 °C through HE1. In-line extraction and purification happen in packed bed column reactor R6 by water and hexane which are pumped through pump P35 and P36. The resulting biphasic solution passes through gravity operated liquid–liquid separator S2 with automatic level control. In the downstream section the API was precipitated with HCL through pump P14 and the precipitate is dissolved in ethanol and crystallized in CSTR6 maintaining temperature at 5 °C. After the crystals are being filtered through F1 and dried in D1, the final product was dissolved in water in CSTR7. The final product diphenhydramine hydrochloride is collected in the form of a solution. The overall process follows the path as shown in the sequence of Scheme 1.

With this approach, it is very easy to reduce the number of components significantly to perform a number of different chemical steps of varying nature (except very different chemistries where very specific equipment is required). The platform developed using this approach will have the following key features:

1. **Useful for a limited number of molecules:** This approach will be very useful if a similar set of chemical transformation is to be performed which will reduce the number of components significantly, however, the approach discussed above is not unique since everyone can come up with an optimum number of components based on the chemistries involved and the level of expertise.

2. **Volume of each component:** Choosing the right component volume plays a very critical role here since that is going to fix the residence time and the overall throughput. For the same synthesis route, the volume of a component will vary if the throughput is going to increase or decrease. It becomes very important before designing such a platform to define the scale of operation and the type of chemistry that will be used since much of the selection criteria will depend on the aforesaid two parameters.

3. **A number of components:** As components can be interchanged and reused, defining the number of components is not critical but one has to take this into account since this will depict the overall costs of building such a platform. Though one can have a large number of accessories, adding each one on the synthesis platform will increase the cost.

4. **Connection for components:** Connecting the components in proper sequence is required for success in any multistep flow synthesis including work-up. Making a connection before and after each operation will add an extra volume to the existing process volume, which needs to be taken care off. In this approach, the connection is not fixed rather the plug-and-play kind of approach can bring the components close to each other reducing the need for intermediate heating/cooling or the requirement of an additional utility to maintain the reaction temperature in the tubes.

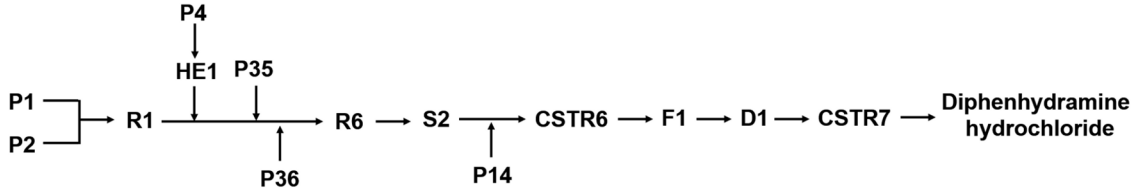
5. **Instrumentation:** Here, we have not explicitly considered any instrumentation (other than in-line analysis or measurements for monitoring a given reaction/purification) but that can be added at the specific steps wherever needed.

6. **Utility:** At this point of time it is assumed that for each reaction step the heating or cooling arrangement (also referred as 'utility' in the chemical process engineering and plant operation) is arranged individually.

Approach 3: a cybernetic approach

The third approach can be based on the need for a versatile and extremely flexible system. Figure 5 shows the concept of a unified platform (Approach 3) for multistep synthesis in a continuous flow. The platform can have three basic modules which are interconnected.

The first, reactor module includes different reactors types that are commonly used in the synthesis of APIs viz. tubular reactor (R1–R4), packed bed reactor (R5–R8) and stirred tank reactor (R9). The reactors are equipped with a jacket for maintaining the reaction temperatures. Additionally, multiple temperature zones can also be provided if required. The reactor module also includes mixers (M1–M9) that are commonly used in flow



Scheme 1: The overall process for the synthesis of diphenhydramine hydrochloride.

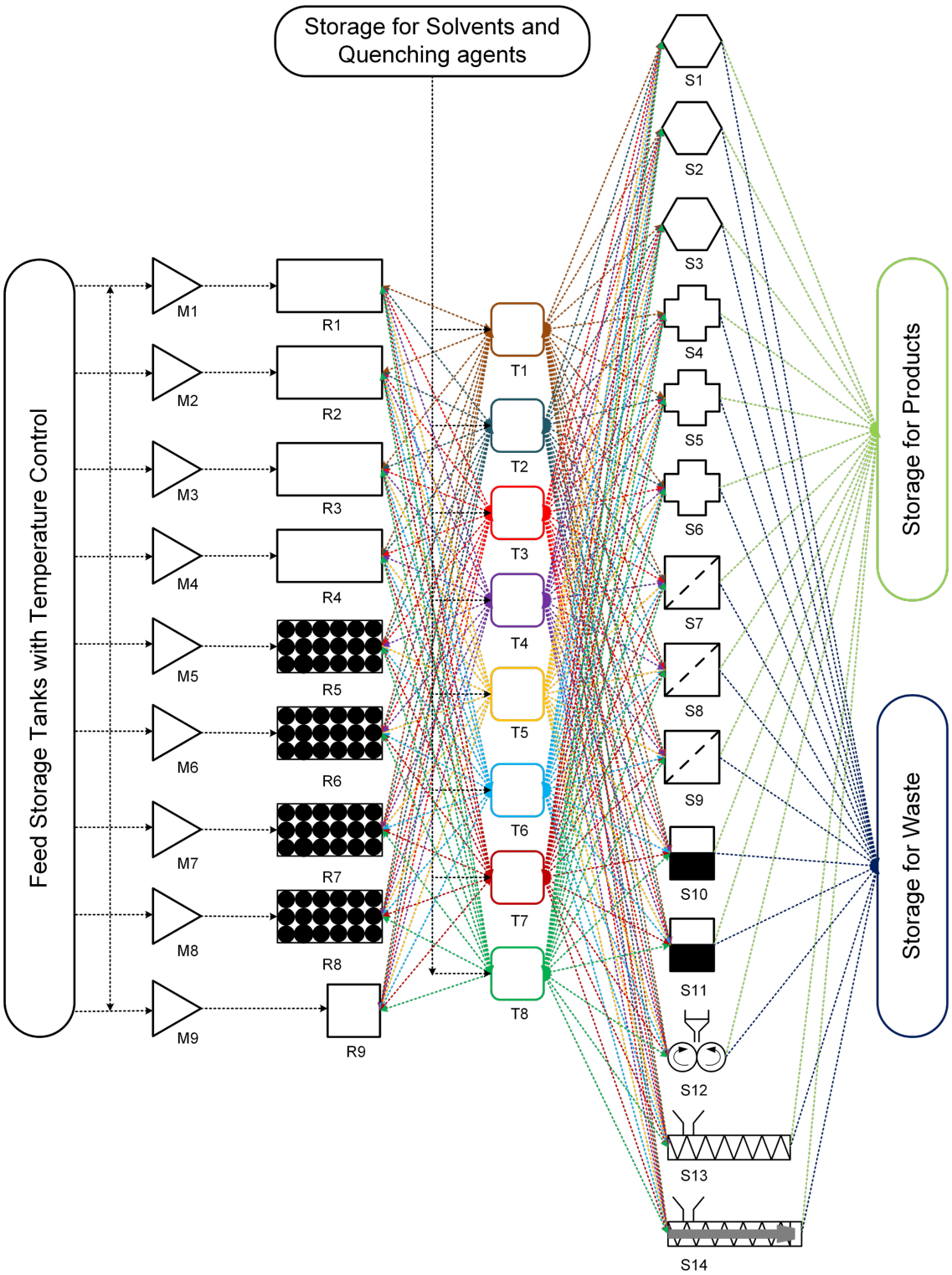


Figure 5: Approach 3 for a unified platform for multistep synthesis. M1–M9 = mixers, R1–R4 = tubular reactors, R5–R8 = packed bed reactor, R9 = stirred tank reactor, T1–T8 = Intermediate storage tanks, S1–S3 = adsorption columns, S4–S6 = extraction columns/gravity-based separator, S7–S9 = membrane separator/Filter, S10–S11 = evaporator, S12 = rotary drum dryer, S13 = vacuum screw dryer, S14 = extruder.

chemistry [64,65]. The continuous flow reactor can also be equipped with in-line static mixing elements [63].

The second module includes the intermediate storage tanks (T1–T8) with an agitator and a jacket for maintaining the temperature. The intermediate storage tanks can be used for multiple purposes viz. preheating/precooling any reaction intermediate, mixing reagents, quenching the reaction, dilution, crystallization, reaction and can be operated in batch or continuous mode (CSTRs). Preheating and precooling are essential for getting reproducible and reliable experimental data.

The third and final module includes separators viz. membrane separators/filters, scavengers or adsorption column (packed column), extractors/gravity separators, dryers, extruders, etc. These three modules can be fixed in a 3D space on a skid. However, the tubings, valves and back pressure regulators need not be fixed and can remain connected to individual module units as per process requirements. Avoiding the tubing will add more flexibility to the unified platform similar to pipeless plants [66]. The entire platform has separate tanks for storing the feed, product, solvent/buffer solution for extraction and waste collection. The feed storage tanks will be equipped with temperature control for preheating or precooling of any reagent before mixing. Moreover, the unified platform can be integrated into any commercial separation and analytical system. This approach is analogous to cybernetics [67].

Table 7 shows the process components required and the sequence of unit operations for producing various pharmaceutical products using approach 3. These unit modules can be connected in the desired sequence by connecting the tubing. Additionally, valves and back pressure regulators can be used whenever required. The unit operations which are not required for the process under consideration will not be connected. This approach allows connecting any unit operation in any desired sequence making it a unified platform for multistep synthesis. Such a platform can be integrated with chromatography purification systems, in-line analytical instruments, a mold for tablet making and various commercial instruments.

As suggested, a priory information should be known regarding kinetics of various processes (reaction/drying/crystallization/adsorption/desorption), solubility data (extraction/crystallization), etc. This approach is useful for testing proof of the concept for a continuous process of various drugs which are in clinical trials. However, this approach may not be feasible for pilot or production scale as the scale of operation is different and reactors and separators should be designed accordingly. The ideal use of this platform is to evaluate the possibility of the synthesis concept of various processes along with automation having a variety of unit operations and operating conditions and collect useful data for further plant design or for using it for a specific period of time to meet the production needs and then switch to another molecule, making it a flexible production platform. Eventually, at the pilot or production scale, it will be analogous to approach 2. Key features of this approach can be given as follows: (i) truly unified multistep flow synthesis platform, (ii) intermediate tanks can be used for preheating/precooling, isolating different pressure zones and intermediate storage, (iii) the system will have all the necessary components like back pressure regulator, check valve, control valve, temperature and

Table 7: Sequence of unit operations for various pharmaceutical products by approach 3.

reference	product	reactors/equipment/components (number)	sequence of unit operations as per approach 3 (see Figure 5)
Tsubogo et al. [7]	(*R*)- and (*S*)-rolipram	• packed bed reactors (4) • adsorption columns (3)	M5→R5→T5→S1→M6→R6→T6→M7→R7→T7→S2→T8→S3→R8
Pellegatti et al. [63]	ribociclib	• flow reactors (2) • stirred tank reactor (1)	M1→R1→M2→R2→S4→T1→M3→R3→S5→R9
Cole et al. [8]	prexasertib monolactate monohydrate	• flow reactors (4)	M1→R1→T1→S4→T2→S5→T3→S6→T4→S10→M2→R2→T5→T6→S7→S8→T7
Adamo et al. [9]	fluoxetine hydrochloride	• flow reactors (4)	M1→R1→T1→S7→T2→S8→R2→T3→S10→A1→T4→R3→T5→S4→downstream
	diazepam	• flow reactors (2)	M1→R1→M2→R2→T1→R5→S4→S1→T2→S5→ downstream
	lidocaine hydrochloride	• flow reactors (2)	M1→R1→N2→R2→T1→R5→S4→downstream
	diphenhydramine hydrochloride	• flow reactor (1)	M1→R1→T1→R5→S4→S1→downstream
Mascia et al. [20]	aliskiren hemifumarate	• flow reactors (2) • crystallizers + tanks (6)	M1→R1→T1→S4→T2→T3→S7→T4→M2→R2→T5→S5→S8→S1→T6→T7→S9→T8→S12→S13→S14→moulding machine

pressure sensors, etc., (iv) the stirred tank reactor can be used for the reaction and also for crystallization, (v) the reactor jacket can have multiple temperature zones to offer more flexibility, (vi) the fixed bed/packed columns can be used as reactors as well as scavenging columns depending on the requirement or even as a mixer if the packing is inert.

While such a unified platform would offer enormous flexibility in operation, it would be challenging to develop such a platform. A few challenges can be given as follows: (i) too many connections, (ii) arrangement of various components in 3D space is critical, (iii) needs very complex control strategy, (iv) minimizing the pipeline length during component assembly is challenging to optimize the residence time variation and will handle more chemicals than conventional systems, (v) relatively large amount feed material will be required when compared (to compensate dead volume) to a single dedicated experimental setup and (vi) automation will be complex as well as expensive.

Simultaneous synthesis of (*S*)-rolipram and ribociclib by approach 3

The aldehyde and nitromethane are dissolved in toluene separately and kept in the feed storage tanks for preheating (see Figure 5). The reagents can be pumped with a suitable pump (viz., peristaltic pump, piston pump, diaphragm pump, etc.) into the mixer M5 and subsequently to reactor R5 which is packed with SiO_2-NH_2 and $CaCl_2$. The intermediate nitroalkane obtained is cooled to 0 °C in the intermediate storage tank T5. The reaction mixture can pass through separator S1 (adsorption column) which is packed with MS 4 Å to remove the byproduct water. A solution of malonate and triethylamine in toluene are precooled to 0 °C in feed storage tanks and pumped to mixer M6 where it is mixed with the nitroalkane stream. The reaction stream can then be passed through reactor R6 which is packed with polymer-supported (*S*)-pybox–calcium chloride and maintained at 0 °C. The reaction stream can be further passed to intermediate tank T6 where it can be preheated to 100 °C. The reaction stream containing Michael addition product is mixed with hydrogen gas (from H_2 cylinder) in mixer M7. The resulting two-phase mixture can be passed to reactor R7 packed with Pd/DMPSi-C catalyst and maintained at 100 °C. The reaction stream can then be passed in intermediate tank T7 where unreacted hydrogen gas is vented and recycled and the liquid stream is preheated to 120 °C. The liquid stream then can pass through separator S2 (adsorption column) packed with Amberlyst-15 Dry to remove impurities. Water and *o*-xylene can be preheated and pumped from the feed storage tanks into intermediate storage tank T8 where it is mixed with the reaction mixture. The process stream can be further passed through separator S3 (adsorption column) packed with Celite. The reaction mixture can pass through reactor R8 packed with silica-supported carboxylic acid and maintained at 120 °C to obtain the product (*S*)-rolipram. In the above example, intermediate storage tanks T1–T4 can also be used instead of T5–T8 as every unit module (reactors, intermediate storage tanks, and separators) can be connected in any desired sequence by simple tube fittings. However, the choice of unit modules should be done on the basis of a lower tubing volume.

Chloropyrimidine and aminopyridine derivatives are dissolved in THF and can be preheated to 60 °C in the feed storage tank. LiHMDS solution in THF also can be preheated to 60 °C in the feed storage tank. Both the solutions can be pumped with suitable pumps in the mixer M1 and then through reactor R1 which is maintained at 60 °C. The product stream can be mixed with preheated HCl in mixer M2 and then passed through reactor R2 which is also maintained at 60 °C. The reaction mixture can then be passed to separator S4 (extractor) to separate the aqueous and organic phases. The organic waste can be collected in the waste storage and the aqueous phase is mixed with sodium hydroxide in intermediate storage tank T1 to quench the HCl. The reaction mixture can be mixed with THF in mixer M3 and passed through reactor R3. The process stream can be further passed to separator S5 (extractor) to separate the aqueous waste and organic phase. The organic phase can be further passed to reactor 9 (stirred tank) where it can be mixed with succinic acid for further batch crystallization to obtain the product ribociclib.

In this way, we can operate two synthetic processes simultaneously in the unified platform (approach 3). However, many unit modules still remain unused (viz., M4, R4, T2–T4, and S6–S14). Table 7 shows the unit module sequences for various products for approach 3.

Conclusion

For the multistep flow synthesis approach, the next evolution is obviously towards a combination of automation, monitoring, screening, optimization, artificial intelligence and instrumentation. It has changed the conventional synthesis approaches through significant improvement in the product quality, efficiency, and smaller environmental foot print. Utilizing the benefits of multistep flow synthesis is not easy and it requires experienced professionals and ready-to-use tools for effortless integration of different synthesis stages. Developing the unified platform which will reduce the effort in setting up the experiments and integration of different component which will definitely help to speed up the overall process to truly harness the advantages of flow synthesis. Based on different objectives viz. reaction screening, library generation, bench/pilot scale synthesis for various molecules we have shown three approaches to

make a unified multistep flow synthesis platform which can be made keeping the interest of individual or organization for future. These approaches show the unique and promising ways to make the unified platform to realize the concepts like dial a molecule. Realising the concept of a unified flow synthesis platform possesses some challenges but those can be taken care based on the need and planning beforehand. Once this platform is built it will act as 'driverless car' or a 'robot chemist' where an only instruction has to be given and platform will take care of the synthesis of the desired molecule based on the specific chosen flow path. The next level of such a platform can only go in the direction of self-regulated automatic 3D configurable synthesis platforms, just like an advanced version of 'Transformers'. With growing machine intelligence, it is expected that the synthesis platforms would harness big data sets as a source of knowledge, artificial intelligence for decision-making abilities at various levels and self-optimization. Developing such a unified integrated multistep flow synthesis platform will be the new thing for organic synthesis to explore the unexplored chemistry.

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License and Terms

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Exploring the Steady Operation of a Continuous Pilot Plant for the Di-Nitration Reaction

Continuous-flow synthesis of the selective herbicide pendimethalin was demonstrated in both a laboratory-scale and a pilot-scale reactor using only concentrated nitric acid as nitrating agent. The di-nitration reaction follows second-order kinetics where the reaction is first order with respect to both reactant and nitric acid. The pinched-tube reactor was chosen for pilot-scale reactor fabrication due to its excellent mixing and mass transfer characteristics compared to a straight-tube reactor. The estimated mass transfer coefficient showed similar nature in the laboratory-scale and the pilot-scale pinched-tube reactor, ensuring similar performance at the pilot scale. Di-nitration in continuous flow, inline quenching, extraction, and phase separation are some of the salient features of the developed pilot plant. The importance of the start-up time for achieving steady state in the flow system at the large scale is highlighted.

Keywords: Continuous manufacturing, Di-nitration, Reactor design, Scale-up, Steady state

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1 Introduction

Continuous manufacturing using miniaturized flow reactors is now a well-established process intensification tool for modern chemical production procedures. Short lead time, reduction in labor, and reduction in plant and environmental footprints are some of the distinct advantages that have led to continuous manufacturing becoming popular in today's world [1–7]. Processes involving hazardous chemistry and harsh process conditions demand efficient and rigid control over the process parameters; they are usually recommended to be carried out in continuous mode because of the relative ease of operation to maintain a steady state. Among many, the advantages obtained in continuous manufacturing include easy access and control over the parameters, with the accessible tenability of the parameters in case of slight disturbances, which is very difficult to achieve in the case of conventional batch procedures. Due to the aforesaid benefits, continuous manufacturing has attracted huge interest in industry and academia, resulting in a large number of process conversions from batch to continuous mode [4, 6, 8–14]. Although the laboratory-scale procedure looks very attractive, transforming an existing batch process to continuous mode or commercialization of a new molecule via a continuous process depends on many parameters (e.g., process chemistry, critical parameters to be controlled, scale-up strategy, stability criteria for the plant, etc.). For the process at large scale (production > 500 kg day^{-1} of fine and specialty chemicals and intermediates), the suitability of the operating conditions to produce the desired output in a safer and controlled manner becomes very important, which is the function of the steady state obtained in the process.

It is well understood that, to obtain maximum safety and conversion from a reactor, it is very important to choose the right steady state among the possible multiple steady states in a reactor. Incidentally, while continuous stirred-tank reactors (CSTR) show multiple steady states and plug flow reactors (PFR) may not, continuous-flow reactors that do not strictly follow either of these two ideal reactors would show a complex behavior. The multiplicity arises out of the simultaneous interaction of reaction, process parameters, and transport processes inside the reactor. An extensive literature is available in terms of the nature of the steady state in a reactor, including the understanding of their bifurcation analysis under various conditions [15–17]. Although it is assumed that a general-purpose PFR operates under steady state, it is possible to have a runaway condition due to spatiotemporal imbalance in the energy (heat generation rate vs. heat removal rate) due to operational failures, disturbances in the system parameters (e.g., varying pumping rates of reactants or utility), or the start-up/shut-down protocol, which are dynamic/unsteady in nature [18]. The thermal safety limit is another important parameter that needs to be characterized before scale-up of any process [12].

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Various models have been developed for understanding different steady states in a reactor, but the time to achieve those steady states after start-up or after any perturbation is rarely reported. The time to achieve a steady state is actually the time required for a continuous system to go through several different steady states before reaching the one having a much longer time scale suitable for a set of specific operating conditions. In the present work, we studied exothermic nitration at the pilot scale for the production of an herbicide. A fully operational pilot-scale reactor was built and operated to check the time to achieve steady performance.

With the above introduction, which gives a brief idea about the intent of this work, this manuscript is organized as follows: In the next section, a description of the di-nitration reaction and of the operation of the pilot plant is given. Then, the results on the reaction kinetics, the reactor design, and the hydrodynamics of the reactor are discussed. With the help of characteristic time scales that correspond to these segments, the various steady states that were observed in the pilot plant are then discussed as well as the importance of knowing them. Finally, the important findings from this study are summarized.

2 Process Description

N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitroaniline (pendimethalin) is a widely used selective herbicide for the reduction and control of grassy weeds and broad-leaf weeds, which was introduced in the market in the year 1974. It is classified as di-nitroaniline-based herbicide and is available in many formulations in the retail market. It is also used in combination with other herbicides, e.g. pendimethalin + imazethapyr. The most popular and practiced manufacturing approach for pendimethalin is by di-nitration of *N*-(1-ehtyl propyl)-3,4-dimethyl aniline (EPDMA) (Fig. 1), where di-nitration can be done in a single step or in two steps with mixed acid or with only nitric acid as nitrating agent. The conventional batch synthesis procedure involves in situ mono-nitration followed by di-nitration using mixed acid with a large quantity of solvent (40–60 %) in a single reactor. The temperature is kept low, usually less than 40 °C. Reaction also generates the by-product *N*-nitroso-*N*-(1-ethylpropyl)-3,4-dimethly-2,6-dinitroaniline (nitroso), which can be further converted into pendimethalin via a separate procedure, which is not the scope of this work. An increase in temperature, a high molar ratio of nitric acid, and a long reaction time have a positive impact on the amount of nitroso formed in the reaction [19].

In the conventional batch synthesis approach, a large quantity of solvent leads to dilution, with the subsequent reduction in reaction rates, and operation at low temperature ultimately results in long reaction times, which is necessary for the safe operation for large-scale manufacturing. The estimated heat of reaction for the two reaction steps are 98 and −198 kJ mol^{-1}, respectively. For large-scale manufacturing, say for 1 t per batch, the overall heat generation will be 355 800 kJ per batch. Considering 1 batch every 16 h (excluding batch reactor preparation, washing, discharge, etc.) and considering the fact that this is a two-phase reaction that is usually limited by mass transfer, the design and operation is always focused around the efficient heat removal and completion of the di-nitration reaction. Efficient heat removal can include multiple strategies, including (i) slow addition of one of the reactants, (ii) using a large excess of sulfuric acid that helps rapid absorption of the water released in the generation of nitronium ions and also provides high heat capacity, (iii) using cooled reactants, and (iv) external heat removal using the plant utility. However, in general, the reaction is carried out such that the reactor temperature never exceeds 40 °C. Selectivity is another issue in the di-nitration case, owing to the dilute reaction conditions and long reaction time, which may lead to the oxidation of the product. Approximately 16–20 h are required for one successful batch operation for pendimethalin synthesis, starting from reagents charging and final product discharge after achieving the desired product quality. The low heat and mass transfer capabilities of conventional batch reactors thereby enforce purposeful reduction in the inherent reaction rates by slow heat generation for better control over the process and having a safer operation. Another major issue is the disposal of aqueous waste, which arises due to the presence of sulfuric acid in the effluent and which, when neutralized, generates solid waste. Moreover, the organic layer after layer separation is given a water wash to remove residual traces of dissolved acidic moieties. The solvent used in the process needs to be recovered and recycled for reuse, which involves an efficient solvent removal facility and, in consequence, adding extra machinery, increasing the plant footprint and leading to the proportional release of volatile matter.

The literature suggests that this di-nitration can be done utilizing only nitric acid at different concentrations in two sepa-

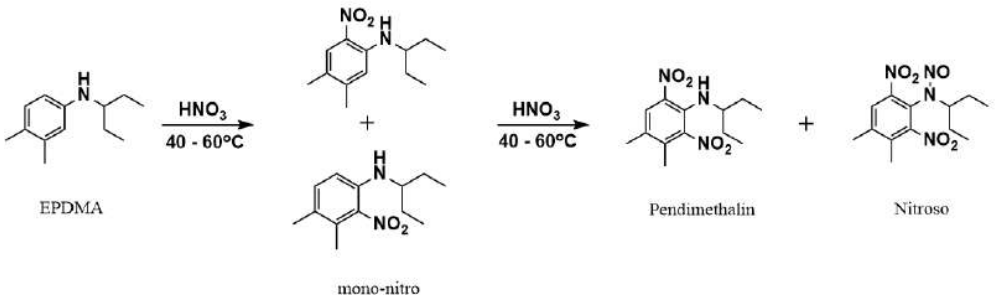

Figure 1. Reaction scheme for the synthesis of pendimethalin starting from dimethyl aniline (EPDMA) using only concentrated nitric acid (generated water in each step is not shown).

rate stages of batch operation [20]. In the first step, mono-nitration is done using a low concentration of nitric acid (~50 %), followed by di-nitration using a high concentration of nitric acid (69 %) in the second step. After the second step, the remaining aqueous phase, which is mostly nitric acid at ~50 % concentration, can be utilized for the mono-nitration in step one with slight adjustment, utilizing almost the complete aqueous phase. Although this process seems lucrative, it poses the same challenges as conventional batch operation, except for the issue of disposal of sulfuric acid. One way to surpass the challenges associated with the existing conventional process is to use the continuous-flow synthesis technology [19]. The microreactor system utilized has a volume of only 0.2 mL and a variety of conditions were evaluated for a range of aniline derivatives. The authors have used a 16-channel microreactor system for the scale-up of the process and suggest that the throughput can be enhanced to the multiple of 100 in the same manner. Scale-up by numbering up has its own challenges in terms of equal distribution of immiscible reagents in all the channels and developing methods to quantify the effect of variations in phase distribution on the product yield. Hence, it was preferred to initially increase the tube dimensions without compromising on the safe operation based on the energy balance in the reactor [21]. Here, we aim to go for scale-up by increasing the channel diameter for the production capacity of 2 $kg\,h^{-1}$ and understanding the complexities in operating such a plant with a specific outlet composition, i.e., complete conversion of the reactant, less than 1 % mono-nitro derivatives and the rest being the desired product (although it would contain some nitroso compounds which, after de-nitrosation, give the desired product).

In the present work, we used concentrated nitric acid (69 %) for the single-step di-nitration of EPDMA to yield pendimethalin. Reactions were done in a 1/8-inch coiled SS316 tubular reactor in the laboratory environment for the initial feasibility study and optimization, to attain a product quality similar to that of the industry standard. Two syringe pumps were used to inject the EPDMA and concentrated nitric acid into the tubular reactor. A three-dimensional (3D) flow reactor (as a static mixer) was connected at the inlet of the tube reactor to provide good mixing (Fig. 2). The 3D flow reactor was used for all laboratory-scale experiments and the whole setup was immersed in a constant-temperature water bath to achieve and maintain the desired reaction temperature [22]. Although the overall reaction is exothermic, it progresses in two steps, where the mono-nitration step is endothermic and the di-nitration step is exothermic, with some initial temperature needed to kick off the reaction, which was found to be > 40 °C. Consequently, all experiments were planned to be done above 40 °C. Methodical parametric analyses for mole ratio, temperature, solvent concentration, and residence time were done and the kinetics was determined. The determined kinetics was further used for the reactor selection, design, and scale-up.

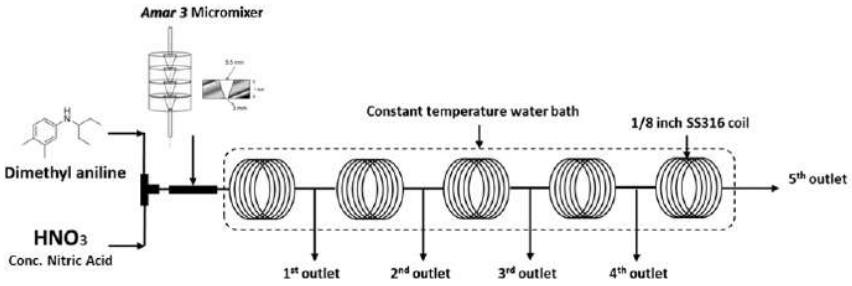

Figure 2. Laboratory setup for kinetics determination divided into five sections.

3 Reactor Design and Scale-Up

3.1 Reaction Kinetics

To deduce the reaction kinetics, the 1/8-inch SS316 tube reactor, which was used in the laboratory for initial screening and process optimization, was divided into five sections (Fig. 2), with a sampling valve between two sections. The samples were quenched in ice-cold water, followed by the extraction of the organic phase in ethylene dichloride (EDC). In a few experiments, the organic reactant was dissolved in EDC. Gas chromatography (GC) was used for determining the conversion and yield of the product. Since the by-product nitroso is not detectable on the selected GC column, a separate analysis method, i.e. the high-performance liquid chromatography (HPLC) technique, was used for capturing the amount of nitroso formed.

In order to obtain the information about the reaction kinetics, experiments were performed for the combination of three different EPDMA concentrations diluted with EDC (40, 50, and 60 wt %) and at three different temperatures (40, 50, and 60 °C). As the reactor was divided into five parts, every set of experiments resulted in five data points over the length of the reactor that would correspond to different residence times (50, 80, 140, 225, and 285 s). An increase in temperature enhances the rate of reaction whereas an increase in solvent reduces the rate. An increase in residence time always has a positive impact on the conversion of EPDMA and yield of pendimethalin, but also results in an increase in the quantity of the by-product nitroso. In general, the reaction follows second-order kinetics where the reaction is first order with respect to both the reactant EPDMA and nitric acid [23].

The rate constants were determined based on the curve fitting for the second-order rate expression. K_1, K_2, and K_3 (Tab. 1) represent the rate constants for the formation of the mono-nitro product, pendimethalin, and the by-product nitroso, respectively. After several efforts, it was found that the two isomers formed for the mono-nitro product were not separable and, after di-nitration, they both generated pendimethalin irrespective of the isomers; hence, K_1 is determined as combined rate constant for the mono-nitro product formation step one. The rate constants reported in Tab. 1 are lumped values, which include the effects of mass transfer and dispersion, if any. The role of the mass transfer and dispersion in the reaction kinetics and performance are elaborated later. Rate constants

Table 1. Experimentally obtained kinetic parameters.

Temperature [°C]	K_1 [L mol^{-1}S^{-1}]	K_2 [L mol^{-1}S^{-1}]	K_3 [L mol^{-1}S^{-1}]
40	1.7E-06	7.7E-07	1.7E-08
50	2.4E-06	1.6E-06	3.9E-08
60	4.8E-06	2.7E-06	1.7E-07

were determined assuming that the reaction is completely isothermal, since the complete setup was immersed in a constant-temperature water bath having at least 800 times a higher volume than the reactor volume and a circulation rate of at least three orders of magnitude higher than the flow rates of the reactants. The data was subsequently used in the model equations and validation of the laboratory experiment data.

3.2 Model Equations and Model Validation

Typically, in the di-nitration reaction, in the first step one mole of nitric acid (C_b) reacts with the reactant EPDMA (C_a) and a second mole of nitric acid reacts with the mono-nitro product (C_c) formed in first step to yield pendimethalin (C_e) and the nitroso (C_f) by-product simultaneously. Model equations were formulated as, in essence, the complete reaction involves formation of mono-nitro derivatives and the desired product pendimethalin in series, and formation of pendimethalin and nitroso compound in parallel. Eqs. (1)–(6) correspond to the rate equations for EPDMA, nitric acid, the mono-nitro product, water that gets generated during formation of nitronium ions, pendimethalin, and nitroso formed, respectively.

$$\frac{dC_a}{dt} = -K_1 C_a C_b \tag{1}$$

$$\frac{dC_b}{dt} = -K_1 C_a C_b - K_2 C_c C_b - K_3 C_c C_b \tag{2}$$

$$\frac{dC_c}{dt} = K_1 C_a C_b - K_2 C_c C_b - K_3 C_c C_b \tag{3}$$

$$\frac{dC_d}{dt} = K_1 C_a C_b + K_2 C_c C_b + K_3 C_c C_b \tag{4}$$

$$\frac{dC_e}{dt} = K_2 C_c C_b \tag{5}$$

$$\frac{dC_f}{dt} = K_3 C_c C_b \tag{6}$$

C_d represents the concentration of the water formed during reaction.[1)]

With the formulated model equations and obtained kinetic data, a MATLAB code was written to solve the model equations simultaneously to predict the reaction outcome, which subsequently validated the acquired experimental data. The predicted values and experimental results were comparable (Fig. 3), demonstrating the reliability of the obtained reaction kinetics and formulated model equations, which were further used for predicting the reaction performance at the large scale. However, at this point, the energy balance was not considered since the reactions were conducted isothermally. During scale-up consideration, energy balance equations were also formulated for the reactor (Eq. 7) and the jacket (Eq. 8) to predict temperature variations along the length of the reactor during reaction.

$$\frac{dT_r}{dt} = \frac{(K_1 C_a C_b - K_2 C_c C_b - K_3 C_c C_b)(-Hr) - UA(T_r - T_a)}{\left(\begin{array}{l} C_a Cp_a + C_b Cp_b + C_c Cp_c + C_d Cp_d + \\ C_e Cp_e + C_f Cp_f + C_{sol} Cp_{sol} \end{array}\right) Q} \tag{7}$$

$$\frac{dT_j}{dt} = \frac{UA(T_r - T_j)}{QCp_{water}} \tag{8}$$

3.3 Reactor Design for Scale-Up

Selection of the tube diameter for the flow reactor is an important design parameter towards scale-up. The throughput requirement with the optimum residence time sets the volume required for the reactor (mass balance). The excellent heat and mass transfer obtained in the laboratory reactor are not easily achievable in reactors of larger dimensions. Selecting the optimum diameter would dictate the heat transfer (energy balance) and pressure drop (directly related to the pumping cost) across the large-scale reactor. For getting the same performance at the

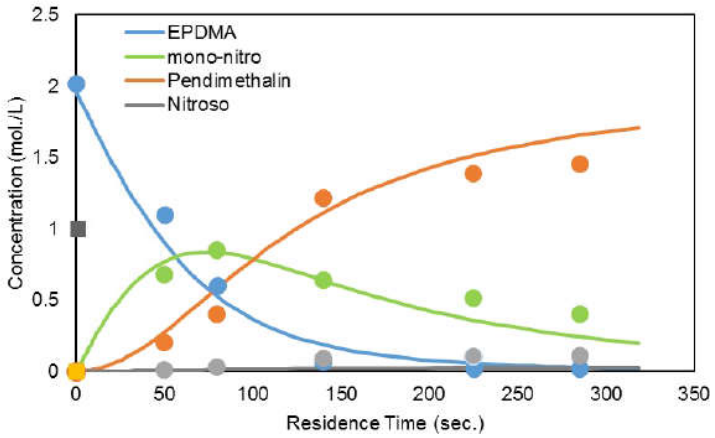

Figure 3. Comparison of the model prediction and experimental results for 60 % EPDMA concentration (diluted with EDC).

1) List of symbols at the end of the paper.

larger scale, some parameters like the residence time distribution and the mass transfer coefficient have to be similar as in the laboratory reactor. The mass balance with reaction kinetics at optimum conditions recommended the reactor volume to be 380 mL for the proposed pilot plant capacity of 2 kg h^{-1} production of pendimethalin. Since the same capacity can be built using tubes with different diameters, selecting the optimum tube diameter for getting optimum performance in terms of heat and mass transfer is of principal concern. The model equations (Eqs. (1)–(8)) were solved using the kinetics (Tab. 1) simultaneously to get the temperature profile and concentration profiles along the reactor length. Radial dispersion was neglected. Simulations were carried out for three tube diameters and the results were compared. With an increase in tube diameter, the tube length required to occupy the same volume decreased significantly. For a constant throughput, increasing the diameter would reduce the pressure drop and also the overall heat transfer rates (due to a lower heat transfer area per unit volume and also a lower tube side heat transfer coefficient due to lower velocities).

To select the optimum tube diameter among tube sizes that are commercially available, we simulated the temperature profile and concentration profiles inside the reactor for three different tube diameters of sizes 1/4, 3/8, and 1/2 inch. The model equations for concentration and temperature were solved simultaneously for the above-stated tube diameters with the same initial conditions and the results were compared.

For a constant jacket temperature of 60 °C, it was observed (Fig. 4c) that a tube with 10 mm in diameter does not reach the desired temperature whereas a tube with a diameter of 4 mm required a lesser volume for achieving the required temperature inside the reactor at the steady state. This difference in the temperature profile will control the conversion inside the reactor since the temperature can influence the reaction kinetics. Achieving the desired temperature inside the reactor at a much smaller tube length with the required residence time is highly necessary for the desired conversion. For the case of the tube of diameter 10 mm, an extra volume needs to be provided to achieve the desired conversion. An increase in volume will result in increased capital cost. When the concentration profile was plotted, it was clearly visible that the conversion achieved in the 10-mm-diameter tube is 10 % less than in the tube of 4 mm in diameter (Fig. 4a, b).

The indicated results showed that 4 mm is the optimum diameter for the pilot-scale reactor. Since we did not consider the effect of dispersion (in lumped kinetics), 15 % extra volume was included in the plant-scale reactor to account for any effect of axial dispersion. The simulations were done for the higher reactor volume to constitute for the axial dispersion effect at the higher scale and also the reactor was fabricated for the same volume to compensate for the extra residence time, if at all needed.

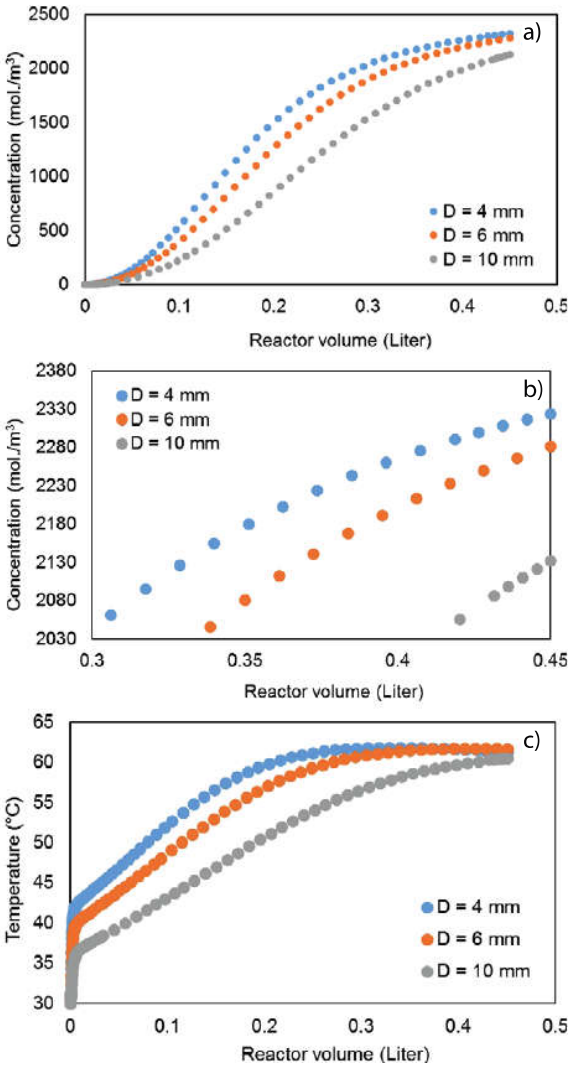

Figure 4. Predicted concentration and temperature profile along the reactor for three different tube diameters. (a) Concentration profile for 450 mL reactor volume, (b) difference in product concentrations at the reactor outlet, (c) temperature profile along the reactor for 450 mL with an initial temperature of 30 °C.

4 The Scaled up Reactor

4.1 Pinched-Tube Reactor

In order to compensate for the loss of effective performance due to the increase in tube diameter, instead of normal tubes, a pinched tube of the same diameter was used for fabrication of the reactor at the pilot scale [24]. A pinched-tube reactor is made by pinching the tube at different locations along the tube length at various angles (Fig. 5). This pinching provides a reduction in cross-section area, which helps to improve mixing due to the increase and decrease in velocity at each pinch. Having changing angles in the successive pinchings changes the direction of the flow and enhances mixing. Pinched-tube reactors have been shown to perform better compared to straight tubes of the same dimension. While the extent of dispersion is relatively more leading to stirred-tank behavior, the values of the mass transfer coefficient are comparable to those of static

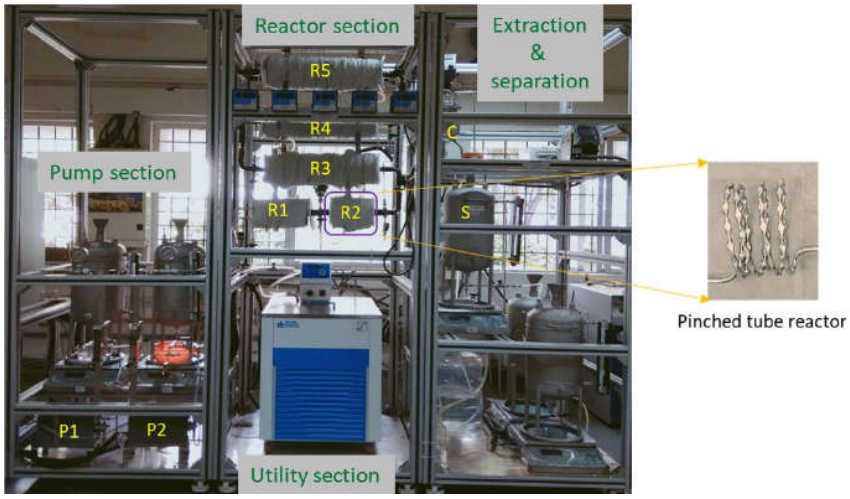

Figure 5. Developed pilot plant for the production capacity of 2 kg h^{-1}. (P1, P2) Pumps, (R1–R5) pinched tube reactors connected in series, (C) CSTR for quenching and extraction, (S) continuous gravity separator.

mixers. The detailed hydrodynamics and performance evaluation is studied in our previous publication [24].

For the pilot-scale reactor, a pinched tube of 36 m in length and of 1/4 inch in diameter (volume 450 mL, compensating for the reduced volume at the pinch points) was used, with a distance between successive pinchings of 3 cm. The tube length was divided into five sections of lengths 3, 3, 6, 12, and 12 m, respectively. Individual reactors were constructed making the tube in helical shape and jacketing each tube for heating through a constant-temperature water circulation unit. The reactors made with the above tubes were connected in series. At each intermediate connection point between the reactors, a provision for sampling was made and also a temperature indicator was added for temperature monitoring along the reactor length.

The inlet was provided at the first reactor, where reactant and nitric acid is to be added with the help of a piston pump. Reaction continued to happen in each reactor sequentially (from 1 to 5) and the outlet was let into a CSTR, where chilled water and solvent were added continuously to quench and extract the product from the reaction mixture. After quenching and extraction, the solution was subjected to continuous gravity separation where the bottom layer (organic phase) was collected in the product tank and the upper layer (aqueous phase) was collected in the tank for waste disposal. The procedure for quenching, extraction, and separation was applied only at the fifth outlet; however, samples collected at the intermediate reactors were analyzed in terms of conversion, with the same procedure of quenching, extraction, and separation done offline.

4.2 Mass Transfer Coefficient

The water/propionic acid/EDC system was used for determining the mass transfer coefficient for the laboratory-scale flow reactor as well as the pilot-scale flow reactor. A stock solution of propionic acid in water was made, where propionic acid was transferred from water to EDC. Flow rates were calculated for keeping the total residence time of 5 and 10 min in the laboratory-scale reactor and 7, 8, 9, and 10 min in the pilot-scale reactor. These residence times were decided based on the throughput, which was fixed according to the plant production capacity. Two different phase ratios were chosen according to the ratio of organic phase and acid phase during the experiment at two extremes. For each case, the phase ratio did differ slightly from 1:1. The transfer of propionic acid from water to EDC was monitored with the help of a pre-calibrated conductivity meter. The data was recorded and the mass transfer coefficient was determined for the residence times mentioned above. It is important to highlight that, for the laboratory experiments, the Reynolds numbers (*Re*) obtained were significantly low (22 and 44) compared to the range observed at the pilot scale ($267 \leq Re \leq 281$), for the specified throughput. The mass transfer coefficient values obtained in all the pilot-scale experimental throughputs were seen to be identical to that of the laboratory scale (Fig. 6a, b). This indicated that an increase in the scale of operation does not have any effect on the mass transfer obtained and the fabricated reactor is on par with the laboratory-scale tube reactor. The overall mass transfer coefficient was seen to decrease continuously with increasing residence time, which indicated it to be a strong function of the flow velocity. Further, increasing the mole ratio of nitric acid to substrate to 3.5 was seen to help enhance the overall mass transfer coefficient by 100 %, due to higher throughput for achieving the same productivity of pendimethalin (Fig. 6b).

5 Evaluating the Role of Process Equipment in Steady Operation

A large number of experiments were performed before running the pilot plant at the optimized conditions obtained from the simulation. Different combinations of residence time (20–7 min), temperature (50–80 °C), mole ratio (2.5–3.8), and reactant composition (60–90 %) were checked at the pilot scale. Each reactor was operated sequentially in combination with the previous one till it reached the steady state. The primary aim was to check the functionality of the instrumentation involved and also to identify any challenges associated (e.g., pulsation in pumps, reactor clogging, pressure monitoring, efficiency of separation, etc.) before operation at full capacity. For operation of the scaled up reactor, the developed laboratory protocol was followed where the reactor was initially filled with

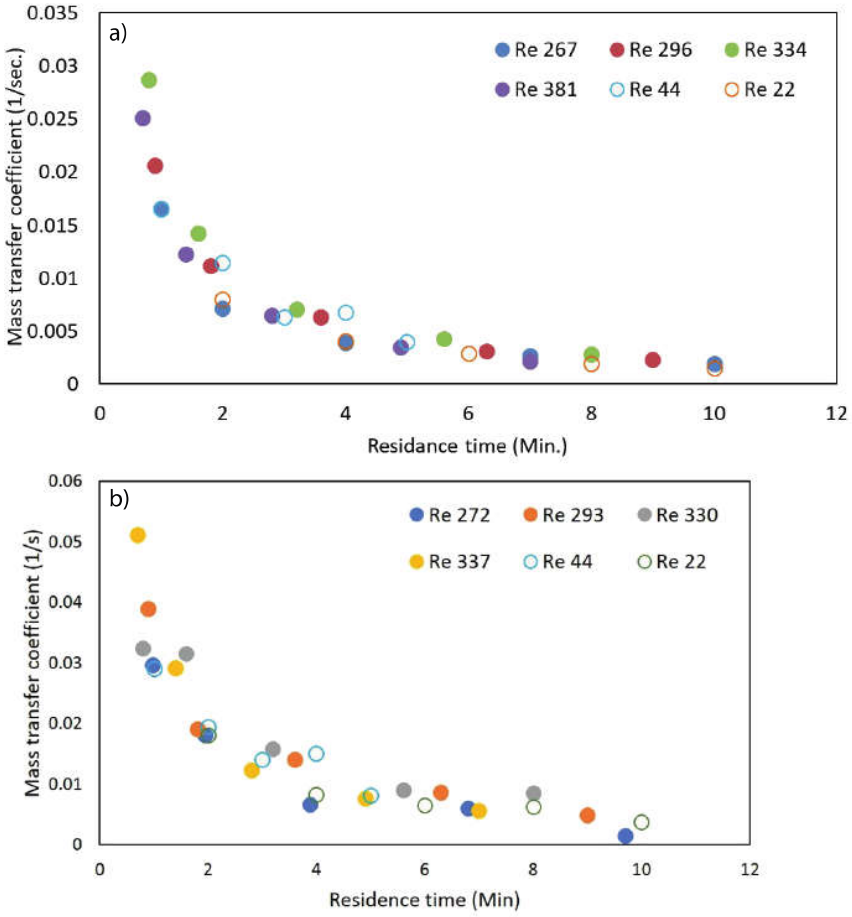

Figure 6. Mass transfer coefficient comparison for the laboratory-scale reactor and the pilot-scale reactor for two different phase ratios: (a) mole ratio of 1:2.75, (b) mole ratio of 1:3.5 (filled symbols for the pilot-scale reactor and hollow symbols for the laboratory-scale reactor).

6 Steady-State Operation of the Pilot Plant

Conventionally, a batch reactor operates under the transient/dynamic conditions where concentrations inside the reactor change continuously over time, whereas CSTR and flow reactors operate under the steady-state condition where the concentration remains constant at the outlet of the reactor, and the conditions at which the reactor is to be operated are decided by the steady-state conversion. In general, for any continuous reactor, operations such as the start time, the run time, and the shut-down time are unavoidable. The run time of a reactor is what is usually monitored carefully as this aims at achieving a reproducible and consistent performance in terms of the production rate. However, the start time is equally important as it helps overcome all the limitations before the system reaches a steady state. For any reactor or process to reach a steady state, the slowest phenomenon governs the specific time that ensures smooth operation of a pilot plant, and that time decides the end of the start-up protocol. The time taken to achieve the steady state can be different and may vary for the same reactor or process even under different conditions. Usually, material produced before achieving steady state may or may not be useful as, while it does not comply with the nitric acid and the temperature was allowed to reach the desired reaction condition. Once the temperature was obtained, the reactants were pumped into the reactor and the reactors were allowed to achieve the steady state in terms of temperature. When the temperatures were stabilized (shown by the temperature indicators installed between the reactors), the samples were taken and analyzed according to the procedure mentioned previously. Experiments done under the initial performance evaluation conditions showed that (Fig. 7), for any combination of parameters, the product yield obtained was above 80 %, with by-product and other impurities below 20 %, which can be further converted into the product via a separate procedure.

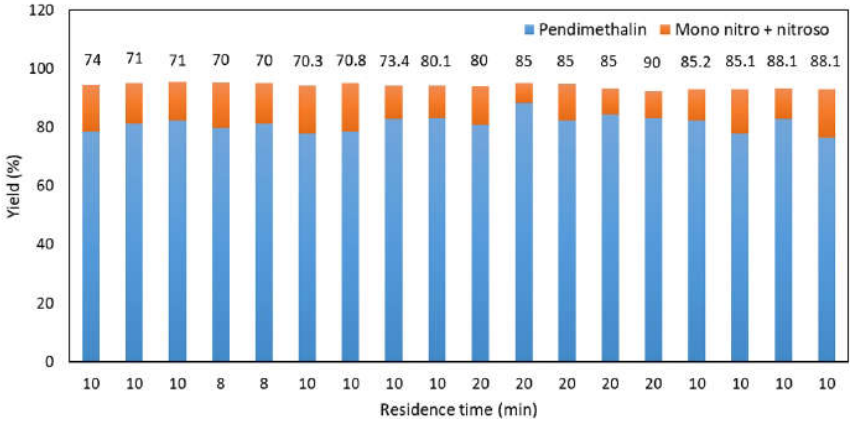

Figure 7. Reactions done at the pilot-scale facility for the mole ratio of 1:3.65 (EPDMA/nitric acid) in the temperature range of 70–90 °C (the temperature is shown at the top of the legend).

quality parameters, sometimes it can be recycled. So, the time required to achieve steady state will also correspond to the loss of production before getting the consistent output from the reactor. In general, it is assumed that, for a CSTR, the time required to achieve the steady state is more than three times the residence time; for a PFR and its variants, the time is two times the residence time. These assumptions/thumb rules of steady-state time are acceptable at the laboratory-scale operation where the loss of material is not significant. Moreover, under laboratory-scale conditions, the time for achieving steady state is considered, usually neglecting the time to achieve the steady state of temperature, since at the smaller dimension it is assumed that the reactor is completely isothermal. At very small scales, the transport processes happening are usually better compared to systems at larger scales. As the characteristic length scales (e.g., reactor volume, tube diameter, etc.) increase, the diffusion paths for mass, momentum and heat also increase significantly. This further implies that the relevant phenomena become less efficient and they add to the time needed to reach steady state. Usually, the temperature steady state is ignored; however, sometimes, being the slowest, it has greater implications on the concentration steady state. In general, reactors are designed assuming a certain steady-state performance (sometimes even considering a temperature profile) along the reactor length. Since the temperature has a positive effect on the kinetics, needing a longer time for reaching the required temperature results in the loss of material quality for that duration. While these phenomena are inevitable, it is necessary to understand the role of the different phenomena that lead to a steady condition of a reactor.

For bulk materials, where the costs are low and where the reactor is going to be operated for several years after start-up, this time required for reaching steady state does not matter much, but still adds to the waste generated if the time for reaching steady state is considerable, since the operational flow rates are usually high. For the cases where outputs are low and the reactor is to be operated as and when demand arises, every start-up time and shut-down time play a critical role in deciding the effective profit from that operation. This issue can be very important in case of pharmaceuticals and nanomaterials where production capacities are low and material costs are very high [25–31].

In a pilot plant and a large-scale commercial-scale continuous production plant, the complexity of the system and various interaction cycles between different instruments/streams/phenomena happening in the system cause delays in reaching the steady state. Key characteristic time scales relevant for mixing, mass transfer and reactions in a reactor include the residence time (τ), the reaction time (τ_R), the dispersion time (τ_D), the mixing time (τ_{mix}), the time scale of mass transfer (τ_m), the time scale of heat transfer (τ_h), etc. Effective rates of reactions and therefore effective conversion occurring in the reactor $X = f(\tau, [\tau_D, \tau_R, \tau_{mix}, \tau_m], C_{A0}, T)$ may therefore depend on these characteristic time scales and are largely controlled by the longest scale or the slowest phenomenon. In order to be able to realize the full benefits of the intrinsic reaction rates, it is essential that the time scales of mixing, heat transfer, and mass transfer are smaller than the characteristic time scale for reaction (which is in turn smaller than the residence time). The interfacial mass transfer is particularly important for the case of multiphase reactions, as in the present case. In addition to these time scales there are different instrument-related time scales and their interactions. Together, this forms a complex situation that may not follow the thumb rules. For example, the assumption that pumps operate under steady state is not always true. Pumps are the backbone of any flow plant; any fluctuation in the flow (including long-term issues like slow deposition or erosion in the pump head) and the mechanism of operation also results in a disturbance in the system, which directly affects the performance, thereby sometimes even deviating from the steady state even during operation. The other instruments that are located in the flow path of the reaction mixture also interact very differently (e.g., the valves). As any disturbance in the flow path results in very different flow profiles, this affects the performance to some extent. All of these effects together can delay the time to reach the desired steady state of a plant.

It is highly necessary to study this effect in separation since this phenomenon is very important to be quantified at the larger scale. One way to approach the problem is to do a complete system-wide simulation, but this may be quite complicated and will require the handling of large amounts of data and will be very time consuming. Also as the plant requirements do vary depending upon the process, no general solution is possible for each case. We tried to simulate the reactor performance including only the effects of mass transfer and dispersion, as these parameters significantly affect the system at the large scale. Mass transfer is a very important phenomenon for the case of two-phase reaction and, as the scale increases, dispersion effects also become important. A reduction in the mass transfer coefficient will result in a reduction in the reaction rate since, for fast reactions, the transport of a species from one phase to another will govern the kinetics. Maintaining a similar residence time distribution at every scale of operation is very crucial to have the same residence time for the conversion desired at every scale. This means that the obtained axial dispersion values must be in close range for the laboratory-scale reactor and the large-scale reactor. Higher axial dispersion can be easily correlated to a longer reaction time; so, it becomes necessary to characterize the residence time distribution of the reactor at every scale. It is very difficult to exclude the effect of these parameters in the real systems since these phenomena happen simultaneously. Also the mass transfer and residence time distribution studies are usually performed using nonreactive systems, the obtained values/similarities are only an indicator of the performance since the phenomena happening in the presence of reaction are very complex and cannot be characterized easily. The reaction kinetics were obtained using the laboratory setup where the reactor made of a 1/8-inch tube was used and where the mass transfer rates were much higher than for the 1/4-inch tube for an identical residence time. Usually, for the smaller-diameter tubes/channels, the mass transfer coefficient is much higher than for the larger tubes. Moreover, the extent of dispersion will be negligible for a two-phase flow (segmented flow) system and, hence, the kinetics obtained will have a very small contribution of these two parameters. As the scale increases, the effects of these parameters become significant (mainly because, with increasing tube size, the nature of the

two-phase flow will deviate from that of the segmented flow, even at identical residence time), which needs to be incorporated into the kinetics equation. These parameters affect the overall reaction rate differently and thereby add to the time for reaching steady state. Accordingly, these effects were incorporated in the kinetics and the data was simulated. At identical residence time and temperature, the reaction rate that was monitored at the pilot scale was found to reduce by 25 %, primarily because of the mass transfer rates and the effects of dispersion and heat transfer. The purpose of the simulation was to study the effects of these parameters in terms of increase in time for reaching steady state; so, the values for a reduction in kinetics are the average values that were assumed after seeing the effect in the pilot-scale reactor. It was clearly visible from the simulations (Fig. 8) that these parameters significantly affected the steady state, as the time needed to achieve the steady state was prolonged. These simulations were done under the assumption that the reactor was isothermal.

To monitor the effect of heat transfer and other parameters simultaneously happening at the large scale, we monitored the running pilot plant and the real-time temperature data was recorded. Since the interaction of all these parameters will directly affect the kinetics subsequently affecting the heat release rate in the reactor, monitoring the time for reaching the temperature steady state (which is independent of mass transfer and dispersion) is the rate-determining step for an exothermic system. In order to study this phenomenon (i.e. reaching a steady temperature profile), the following protocol was followed. Initially, the reactor jacket was filled with water at the reaction temperature and solvent was pumped inside the reactor to flush the system with water. Immediately after flushing, the system nitric acid was started in the system. Flushing of water was monitored by periodically measuring the pH at the outlet. Nitric acid was pumped till the temperature indicators located at reactor intervals showed the desired reaction temperature. Once the nitric acid reached the reaction temperature, dosing of the organic reactant was started and the temperature profile was recorded until the temperature at each indicator reached the desired reaction temperature. Deviating significantly from the expected thumb rule that it will take two times the mean residence time (volume/volumetric flow rate) to achieve steady state, the steady state was reached after five times the residence time. As there was no procedure to monitor the reaction conversion at the intermediate stages, the sampling was done only after the system achieved the steady state. The temperature profile is shown in Fig. 9. It can be seen that, as reactant entered the reactor, the temperature dropped significantly in the first reactor, which was recorded as T1. Along the length as the reaction mixture gets heated, the temperature started shooting up, which was further monitored in the subsequent thermocouples attached in the intermediate stages.

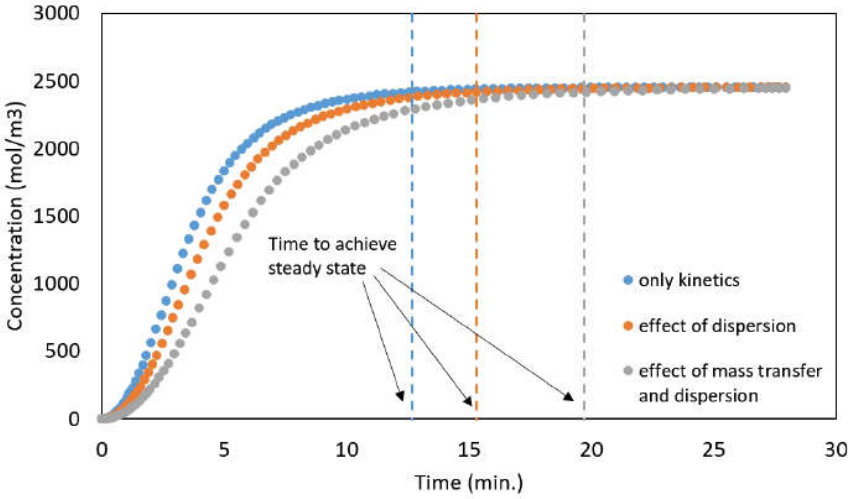

Figure 8. Predicted delay in time to achieve steady state including the effects of mass transfer and dispersion.

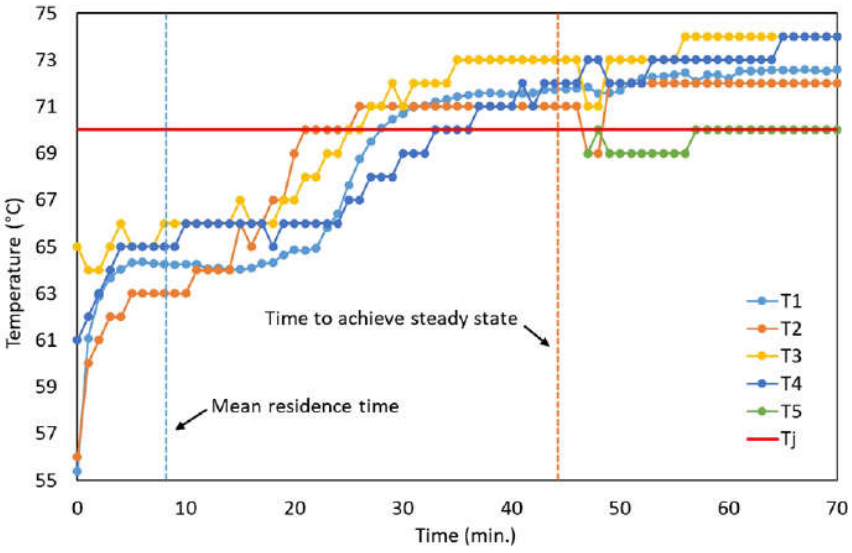

Figure 9. Time required to achieve steady state after start-up of the plant for the set temperature of 70 °C.

Although one reagent, i.e. nitric acid, was kept initially at the higher temperature and organic substrate was pumped at room temperature, the reduction in temperature can be attributed to the endothermic nature of the first step of the reaction. Keeping this in mind, the next experiments were done by preheating the reagents to the reaction temperature. There was no significant difference in the observed temperature profile. One other important thing to note here is that, at the laboratory scale, syringe pumps were employed whereas, at the plant scale, piston pumps were used for continuous pumping. As in the piston pumps the flow rate decides on the frequency of the piston strokes, synchronizing the pumps was essential, which happened only a few times over a run cycle due to the different flow rates. Also, as mentioned earlier, the flow rates from the pumps fluctuate (periodically due to the piston movement), which may have contributed to the disturbance, which was unavoidable.

It is very important to characterize the time to achieve steady state since the kind of interactions happening in the reactor due to various phenomena occurring simultaneously and yet progressively is very difficult to predict. In this scenario, especially for scale-up in flow synthesis, the assumption of linear scale-up with the similar laboratory-scale performance will become obsolete. Having an intermediate-scale pilot plant will help in terms of identifying the challenges in terms of steady states, interactions of different components, instrumentation, control loops, and issues related to the operation at large scale that are generally not encountered in the laboratory environment. Moreover, the start-up and shut-down protocols, which also are deviations from steady-state operation, need careful planning when it comes to exothermic and fast reactions. Work is in progress to develop systematic protocols for such systems so as to avoid any thermal, inertial and reaction shocks in the systems, and will be reported separately. It is recommended to fabricate the intermediate-level pilot-scale facility before going for full-scale production, since this will reduce the time and efforts in terms of solving unexpected challenges which can be known beforehand.

7 Conclusions

The highly exothermic di-nitration reaction for pendimethalin synthesis is successfully carried out in a pilot-scale reactor (production rate 2 kg h^{-1}). The lumped reaction kinetic data is used as a basis for validating the model equations, which showed that using a 1/4-inch-diameter tube as continuous reactor is sufficient for the desired output while meeting the heat transfer requirements. A pinched tube is used for the pilot-scale facility with similar mass transfer coefficient as that of the laboratory reactor. The pilot plant for continuous synthesis is constructed having reaction, quenching, extraction, and separation inline to give the final product. It is observed that the pilot-scale reactor took five times the residence time to achieve the steady operation (based on the outlet conversion and the product quality) compared to that of the laboratory reactor, which took only two times the residence time. It is also found that the time to achieve temperature steady state was the controlling factor when compared to the overall time to achieve steady state. Heat losses due to the larger scale of the system, the large number of connections, slightly reduced transport rates due to heat losses, interaction of different instruments/electronic components installed in the complete setup are some of the reasons that lead to such delays in reaching the steady state. In general, while the relative rates of heat generation, heat removal, and heat loss lead to the longest time to reach the steady-state condition, the pulsation in the pumps also plays a key role in maintaining a specific range of variation in the productivity. In view of this, it is always necessary to take such possible variations in selectivity or yield from such plants into account while designing the plants and deciding on the control system. More work on exploring the effects of dynamic variation in the performance due to perturbations in specific instruments are under progress and will be reported separately.

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Symbols used

A	[m^2]	area for heat transfer
C	[mol m^{-3}]	concentration
C_p	[J $kg^{-1}K^{-1}$]	specific heat capacity
D	[m]	tube diameter
H_r	[kJ mol^{-1}]	heat of reaction
K_1,K_2,K_3	[L $mol^{-1}s^{-1}$]	rate constants
Q	[$m^3 s^{-1}$]	flow rate
T_a	[K]	ambient temperature
T	[K]	temperature
T_1–T_5	[K]	temperatures at the intermediate outlets in the pilot reactor
t	[s]	time
U	[W $m^{-2}K^{-1}$]	heat transfer coefficient

Greek symbols

τ	[s]	residence time
τ_R	[s]	reaction time
τ_D	[s]	dispersion time
τ_{mix}	[s]	mixing time
τ_m	[s]	time scale for mass transfer
τ_h	[s]	time scale for heat transfer

Subscripts

a	reactant (EPDMA)
b	nitric acid
c	mono-nitro
d	water
e	pendimethalin

f	nitrosopendimethalin
j	jacket
r	reaction
sol	solvent
water	water

Abbreviations

CSTR	continuous stirred-tank reactor
EDC	ethylene dichloride
EPDMA	*N*-(1-ehtyl propyl)-3,4-dimethyl aniline
PFR	plug flow reactor

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A multistep continuous flow synthesis of cystic fibrosis medicine Ivacaftor

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Continuous flow ozonolysis method combined with multi-step flow sequence is developed for the synthesis of drug ivacaftor for the first time. Safe ozonolysis, continuous flow quadruple reaction to construct quinolone scaffold, inline extraction followed by continuous phase separation are the key features of present work. Feasibility of using a continuous mixed flow reactor commonly referred as CSTR (continuous stirred tank reactor) is also investigated for the relatively slow reaction segment. The current integrated multi-step flow synthesis can produce 7.2 g/day of the drug ivacaftor at laboratory scale, which is sufficient to treat 50 patient per day. The present route can also be used as a general route for the synthesis of other related drugs such as quinolone antibiotics.

Introduction

In the recent years, continuous flow synthesis has received significant attention in academic as well as industrial research.[1] Several advantages offered by the miniaturized flow reactors such as rapid mixing, excellent heat & mass transfer rates, relatively narrow residence time distribution have given a novel platform that can handle hazardous and toxic materials, sensitive reagents and unstable intermediates.[2] These features allow us to carry out the reactions at close to intrinsic reaction kinetics which often gives improved yields and better selectivity over batch method. A vast body of literature is available on single step and two-step flow synthesis.[3] However implementation of continuous work-up or separation is essential to extend the approach to a truly multi-step flow synthesis. Preparation of medicinal drugs involves several synthesis steps and between two reaction steps the work-up involves many unit operations *viz.* phase separation, evaporation, extraction, crystallization and purification etc.[4]
Recently, this multi-step flow synthesis approach has been implemented to access moderately complex molecules with diverse architectures such as natural products and APIs.[5] Notably, Jamison's quinolone antibiotic ciprofloxacin[6], single dedicated platform for the multiple drug molecules[1a] independently developed by Kobayashi[1d] and Hessel[7], solid supported synthesis of Imatinib[8] by Steven Ley and end-to-end process for aliskiren hemifumarate[4c] stand out as significant milestones in the area of multistep-flow synthesis. This approach helps manufacture these drug molecules in a distributed manner. It also helps in addressing the challenge of manufacturing of prescription drugs[9], which faces shortage in terms of availability. This has remained a top priority in FDA for a long time where multi-step flow synthesis will come to an aid as it can produce sufficient quantities with consistent quality, which will also boost decentralized manufacturing of important drugs. Along these lines, herein we report a new approach for the multi-step continuous flow synthesis of drug ivacaftor which include safe ozonolysis, quadruple reaction, continuous inline extraction and separation.
The ivacaftor is 4-quinolone-3- carboxylic acid ester based drug, used for the treatment of cystic fibrosis. It is one of the most expensive drugs (US $300,000/year/patient) and the discovery of ivacaftor was celebrated as a breakthrough in cystic fibrosis research because it is the only drug available to treat this deadly disease.[11 11b] The pharmacophore of ivacaftor, 4-quinolone-3- carboxylic acid ester, is an privileged scaffold in drug discovery.[10] Besides quinolones are frequently found in many biologically active compounds and drugs for treatment of various diseases[10a] as antibiotics, anti-malarial, anti-tumor etc. (SI, Fig. 1).[11d] The commercial process[12a] developed by Vertex Pharmaceuticals involves Gould-Jacobs approach[12b,12c] for the synthesis of key intermediate quinolone carboxylic acid ester. Larus[12d] pharma and Yang *et. al.*[12e] reported independently the multistep synthesis of ivacaftor starting from o-nitro and o-halo benzoyl chloride respectively. We have previously reported[12f] concise synthesis of ivacaftor using Witkop-Winterfeldt oxidation (Fig. 1).[12]

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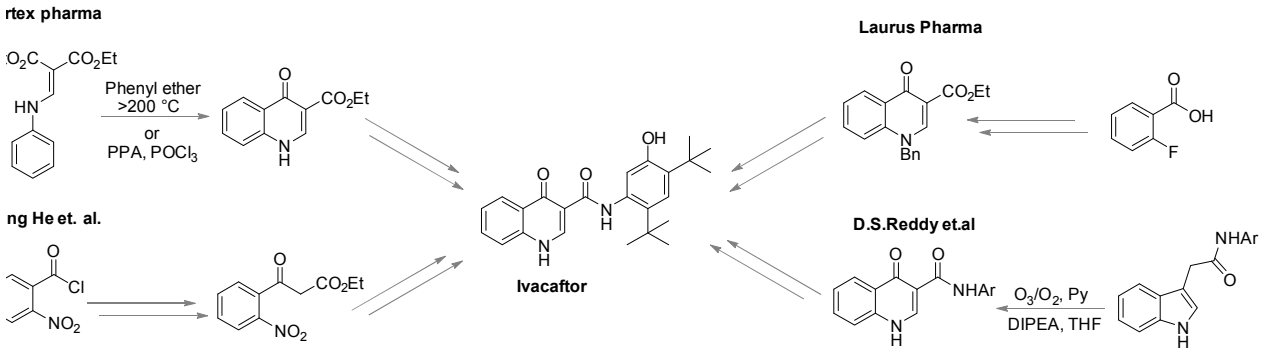
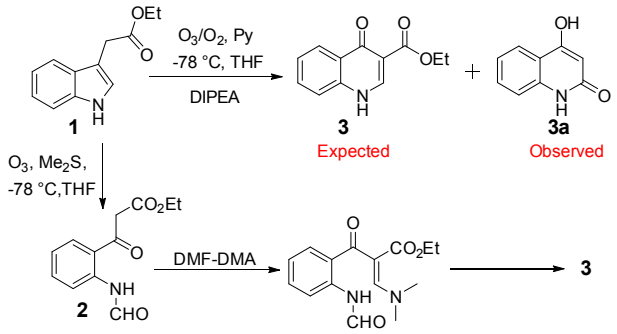


Figure 1. Approaches for ivacaftor synthesis

Results and discussion

Having this background, we have planned a general route to access ivacaftor, which is suitable for batch as well as continuous flow synthesis. Initially batch process is developed, followed by transformation of every step in continuous flow synthesis along with its optimization and then finally to integrate all the steps on a single platform. Initial efforts for the construction of quinolone ring suggested that our laboratory scale protocol for the preparation of quinolone-3-carboxylic acid amides works well.[12f] However, the same method did not give corresponding esters, rather 2-quinolone **3b** was observed (Scheme 1). Hence a new protocol was designed and executed for the synthesis of quinolone core using batch and flow methods. Details are reported here.



Scheme 1: One-pot batch optimization reaction for quinolone synthesis

Attempts on oxidative-cleavage of indole moiety using $NaIO_4$ resulted in very good yield but it was always accompanied with significant amounts of solid byproduct, (see SI). In order to reduce the work-up after every reaction step, multistep synthesis was aimed to be carried out with minimal solvent changes (so as to achieve close to one pot synthesis). Keeping this aspect in mind, a new route, which involved ozonolysis of indole moiety and subsequent cyclization (Scheme 1) was developed using single solvent THF throughout the process with a moderate yield (47%). It is necessary to highlight that the desired compound **3** could be isolated without any chromatographic purification and all spectral data are in agreement with literature reported value.[13a]

Complete details on optimization of the synthesis protocol are provided in the supporting information (SI). As the developed protocol involves ozonolysis, eneaminone formation, aza-Michael addition-elimination and deformylation, this process can be regarded as one-pot quadruple reaction.[13] Ozonolysis is considered as an alternative to metal-based oxidants, where ozone gas is used as greener oxidizing agent and widely utilized for several functional group transformations in organic synthesis.[14] Although it is a very useful oxidation platform, its utility in large-scale synthesis is limited due to high exothermicity and the hazards associated with the ozonide intermediate. Jensen *et al*. demonstrated continuous flow ozonolysis in multichannel microreactor[15a], which is later explored by several other groups[15] for a broader range of applications.[15b, 15c] With this background we decided to translate the batch ozonolysis step into a continuous protocol.

Experiments were performed by varying flow rates, reactor volume and different reagent concentrations to arrive at the final condition (see fig. in Table 1). Initially the effect of increase in the temperature of ozonolysis reaction and reduction in the residence time was studied. For this reaction since the flow rate of the gas stream containing ozone was very high (500 mL/min with 0.0026 mole/min concentration of ozone) when compared to the substrate (1.0 mL/min), the overall residence time was very low. However, despite very low residence time, reaction was seen to get completed, which indicates ozonide **1a** formation to be a very fast reaction. After the optimization of ozonide formation step, in the next step quenching of ozonide **1a** with dimethyl sulfide (Me_2S) for the formation of β-keto ester **2** was explored (see fig. in Table 3 SI).

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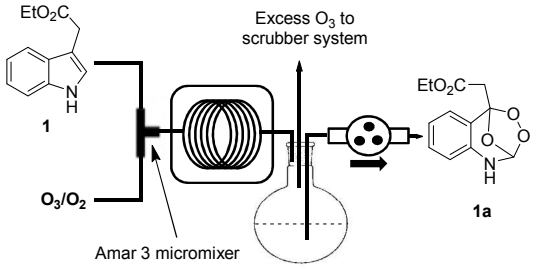
Table 1: Optimization for ozonide formation



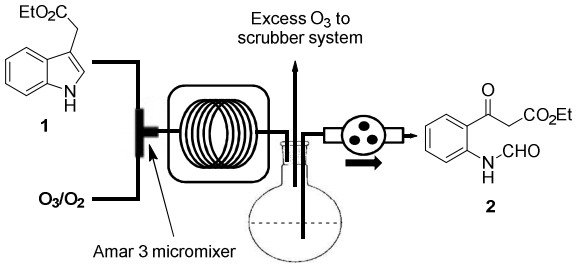
Sr.No	Comp 1 (g)	Flow rate (mL/min) Comp1	Flow rate (mL/min) O_3/O_2	RV (mL)	RT (sec)	T (°C)	Conversion
1	0.5	1.0	1000	7.5	0.4	-60	Incomplete
2	0.5	0.5	1000	7.5	0.4	-60	Incomplete
3	0.5	0.5	500	28	3.3	-60	Incomplete
4	0.5	1.0	500	28	3.3	-60	100%
5	0.5	1.5	500	28	3.3	-60	Incomplete
6	0.5	1.0	500	28	3.3	-40	100%
7	0.5	1.0	500	28	3.3	-10	100%
8	1.0	1.0	500	28	3.3	-10	100%
9	1.0	1.0	500	20	2.4	-10	100%
10	1.5	1.0	500	20	2.4	-10	Incomplete
11	1.5	0.5	500	20	2.4	-10	100%
12	1.5	0.5	500	20	2.4	-10	100%
13	2.0	0.5	500	20	2.4	-10	100%
14	2.5	0.5	500	20	2.4	-10	Incomplete

RT - Residence time; RV – Reactor volume; (a) In all cases compound 1 was dissolved in 50 ml THF; (b) Reaction was monitored by TLC for absence of starting material. For entries (1-3, 5, 10 and 14) conversion is given as 'incomplete' as quantitative off-line characterization in the presence of reactive unstable ozonoids in the solution was not sufficiently reliable. Only qualitative analysis using TLC was performed to check the presence of the limiting reactant.

Though the reaction time for quenching of ozonide **1a** was sufficiently long (12 h) in batch mode, we firmly believed that it is possible to reduce the reaction time in microreactor by enhancing the intrinsic kinetics by changing concentration and/or temperature. Initial experiments were performed using large excess of Me_2S in THF or with neat Me_2S (entry 1 to 8, Table 3 in the SI) by varying flow rate of both reactants at ambient temperature. However the concentration of Me_2S did not influence the reaction rate. The reaction progress was monitored using starch-KI strips (Sigma-Aldrich) for the completion of reaction which was confirmed by the disappearance of the blue color.[16] (***CAUTION!*** *As the most of ozonides and peroxides are potentially explosive, the reaction mass has to be subjected to further transformation/ workup only after NEGATIVE test with starch-KI or peroxide test strips*).

No significant improvement was observed by using pyridine as reducing agent before[17a] or after the ozonolysis (Table 3 SI, entry 9, 10)[17b]. This implied that the determination of kinetics was essential for this step. Accordingly batch experiments were planned at two different temperature i.e. 25°C and 30°C in a 50 ml jacketed reactor. Ozonide intermediates generated by the flow experiments were collected in the reactor at the same temperature as for the ozonolysis reaction. After collection for sufficient time, Me_2S (10 eq) was added and the reaction temperature was raised to 25°C. Once addition was over the reaction was monitored for the consumption of ozonide by using starch-KI strips after an interval of every half an

Table 2: Safe ozonolysis optimization

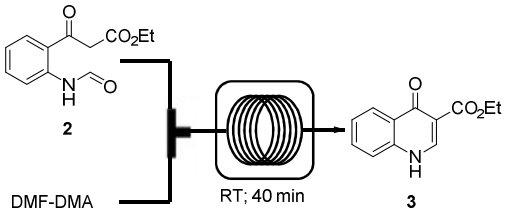


Sr. No	Comp. 1 (g)	Flow rate (mL/min) Comp. 1	RV (mL)	RT (sec)	Acetone :H_2O (2:1) (mL)	Conversion
1	1	1.5	15	1.0	60	Incomplete
2	2	1.0	15	1.0	60	100%
3	2	1.0	15	1.0	50	100%
4	2	1.5	15	1.0	50	incomplete
5	2	1.5	30	2.0	50	incomplete
6	3	1.0	30	2.0	50	100%
7	4	1.0	30	2.0	50	incomplete

RT- Residence time; RV- Reactor Volume; (a) all the reaction were run at 0 °C and flow rate for ozone (O_3/O_2) kept constant (1000 mL/min); In all cases Comp. 1 was dissolved in Acetone: water mixture. For entries (1, 4, 5 and 7) conversion is not given in terms of % (reported as incomplete) as quantitative off-line characterization in the presence of reactive unstable ozonoids in the solution was not sufficiently reliable. Only qualitative analysis using TLC was performed to check the presence of the limiting reactant.

hour. The observations indicated that the reaction took 6 hours at 25°C, which decreased to 3.5 hour upon rising temperature (30 °C) along with untraceable impurities. Experiments with higher mole ratios of Me_2S (25 eq) did not result in any significant improvement. From the findings from the batch experiments it is very clear that quenching of the ozonide is a slow reaction and for the flow reactor volumes used in this work (Table 3 SI) the flow rates have to be very low, which will result in very low throughput. For higher throughput with the required flow rate the reactor volume has to be increased significantly and is not a viable option as it will result in a very long

Table 3: Optimization for Batcho-cyclization



Sr.No	Amount DMF-DMA (mL)	Amount Comp. 2 (g)	Flow rate (mL/min) Com. 2	Flow rate (mL/min) DMF-DMA	RT (Min)	Conv. (%)
1	1.4 ml (5eq)	0.5	0.1	0.1	70	100%
2	4.2 ml (5eq)	1.5	0.1	0.1	50	100%
3	8.4 ml (5eq)	3.0	0.1	0.1	40	100%
4	2.8 ml (10eq)	0.5	0.1	0.1	60	100%
5	5.6 ml (20eq)	0.5	0.1	0.1	50	100%
6	7.0 ml (25eq)	0.5	0.15	0.15	40	100%
7[a]	7.0 ml (25eq)	0.5	0.4	0.4	40	100%

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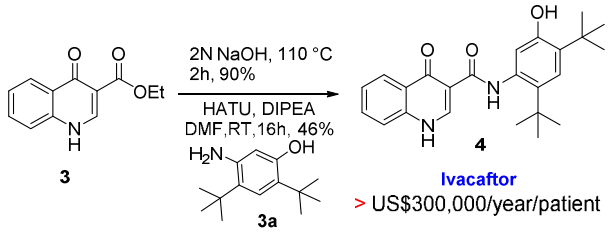
RT- Residence time; for all cases comp. 2 and DMF-DMA was dissolved in 50 mL THF except entry 7; (a) Reaction were done in Ethyl acetate instead of THF.

tubular reactor. For an inherently slow reaction, a continuous stirred tank reactor (CSTR) serves as a better alternative[18] where outlet from the ozonolysis step can be fed to a CSTR and Me_2S can be added simultaneously allowing the reduction of ozonide with sufficient residence time and product can be withdrawn continuously using a separate pump.

In view of this, an experiment was carried out in a CSTR (100 mL) for quenching of ozonide **1a** with 7 hour residence time and the product β-keto ester **2** was collected continuously at the outlet (SI Fig. 2). It is important to note that all the known continuous flow ozonolysis methods[14-15] involve ozonide intermediate, which is eventually reduced/oxidized with a variety of reagents e.g. PPh_3, $NaBH_4$, H_2O_2, $P(OEt)_3$, solid supported reagents (thiourea, phosphines, and amines). Here we have purposely avoided all these reagents for ozonide quenching which needs additional purification step after the reaction. In search of an alternative method to traditional ozonolysis we found an interesting report[19] from Dussault and co-workers which involves in-situ capturing of the carbonyl oxide intermediates followed by decomposition to desired carbonyl compound. Recently this approach has been used in similar reactions.[15i-15k] Accordingly, a solution of indole acetic acid ester **1** in acetone: water (2:1 vol. /vol.) was pumped through our continuous flow reactor set up to get oxidized compound **2** without adding any additional additive or reagents (see fig. in Table 2). The approach is found useful and we were able to make the desired β-keto ester **2** along with some unreacted starting material **1** (Table 2, entry 1). Further systematic fine-tuning of reaction conditions by changing concentration and reactor volume led us to the optimal conditions (Table 2, entry 6). Notably, this ozonolysis reaction does not go through the potentially toxic/explosive ozonide intermediate and reaction completed within 2 seconds and can give an overall throughput of 84 g/day with simple bench top flow reactor (30 mL) system.

The next step of cyclization reaction of β-keto ester **2** with DMF-DMA could be carried out successfully in a continuous flow tubular reactor where the reaction time was significantly reduced from 12 h to less than 1 h (Table 3, entry 1-3). Increase in the concentration of DMF-DMA plays a key role for altering the residence time (Table 3, entry 4 to 7).



Scheme 2: Gram-scale synthesis of ivacaftor

In general, the reaction time was seen to decrease with increase in either the concentration of substrate **2** or the amount of reagent DMF-DMA. With available solvent options THF was discarded due to its high miscibility in water and instead ethyl acetate (EA) was employed for cyclization (Table 3, entry 7). In the modified safe ozonolysis protocol water-acetone system in used where extraction of ozonized product is needed for cyclization with DMF-DMA. The suitability of EA was first verified through a batch experiment where intermediate from the first step was extracted in EA and DMF-DMA was added in the batch reactor and formation of product was confirmed. The completion of reaction confirmed the suitability of EA for further flow reaction. The complete process integration for producing quinolone core by ozonolysis of indole ester **1**, in-line extraction of compound **2** in EA, subsequent cyclization was carried out to obtain compound **3** and spectral data of synthesized compound **3** matching with literature values.[13a]

Integrated continuous experimental setup is shown in figure 2. Next, quinolone ester **3** thus obtained was subjected to ester hydrolysis to render corresponding acid,[13a] which on further coupling with required aniline **3a** using HATU as coupling reagent allowed us to access ivacaftor on a gram-scale (Scheme 2). The spectral data of the synthesized drug is in complete agreement with that of reported one.[12a,12e] It is worth highlighting that the present protocol for synthesis of quinolone ester is far more convenient than the commercial processes[12a] which involving very high temperature (>250 °C) or corrosive reagents ($PPA/POCl_3$) with high boiling solvents such as diphenyl ether or dowtherm.[12b,12c] White[20a] and Lengyel[20b] group have individually reported flow synthesis of pyrimidinone and quinolone by Gould-Jacobs approach.

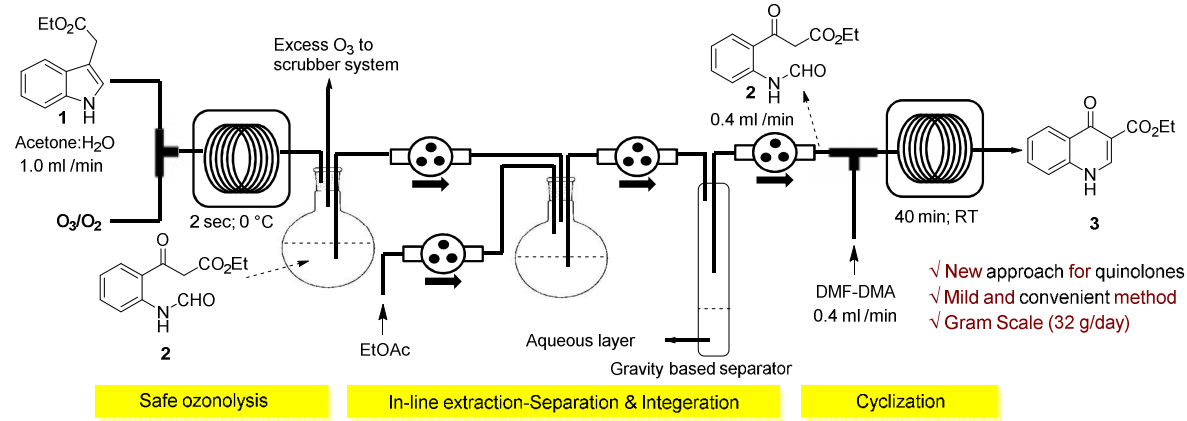


Figure 2. Integration of all steps with in-line extraction

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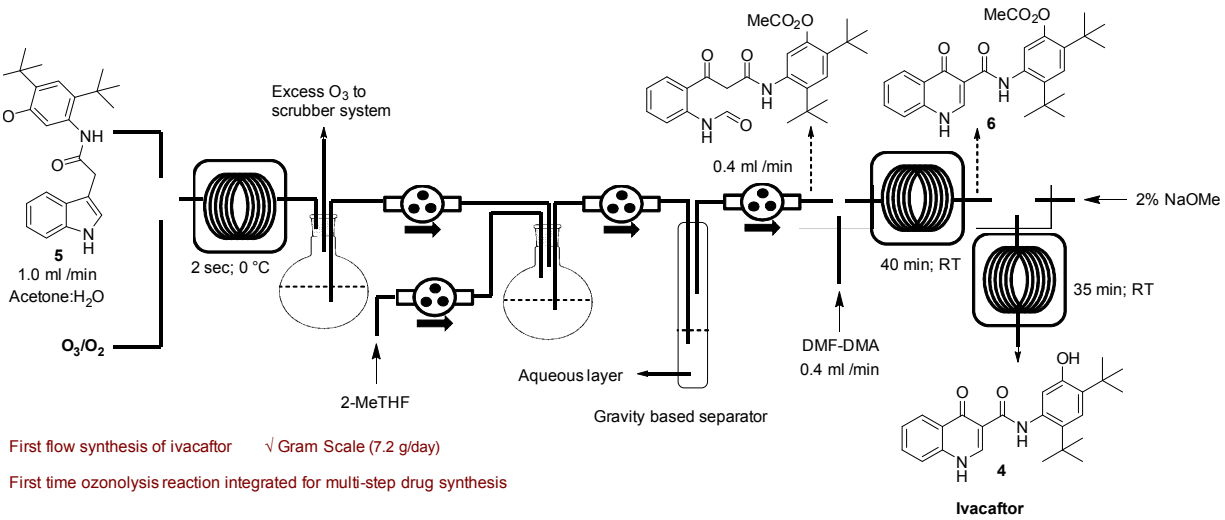

Figure 3. Continuous flow synthesis of ivacaftor

However these methods lack generality and gives poor yields. With the protocol being established independently for each step, it was followed for the flow synthesis of the desired drug. Accordingly the compound **5**, previously prepared[12f] in our laboratory was subjected to the optimized condition to get corresponding quinolone carboxylic acid amide **6**. The outlet of the set up was connected to another tubular reactor (1/8" Teflon tube of 40 ml volume) using a T-mixer (see fig. 3) for the removal of phenolic protecting group in compound **6** using sodium methoxide solution (2% in MeOH, W/V) which directly produced the desired product ivacaftor **4**.[12a, 12e] Upon complete integration of all the continuous flow steps, the set-up was operated continuously and the bench top experimental setup (photograph given in the SI) is able to produce 450 mg in 90 minutes implying that it can synthesize 7.2 g/day (60% yield over 3 steps), which is actually sufficient to treat 50 patients/day.

To the best of our knowledge, this is the first example where safe ozonolysis is integrated in multi-step continuous flow synthesis of drug ivacaftor. Several commercial processes in particular many drugs such as oxandrolone, cefaclor, ceftibuten etc[14c] involve ozonolysis reaction.[14c] However, it has been carried out in semi-batch method due to difficulties in handling large volume of highly exothermic ozonides and additional reductive/oxidative work up procedure, which sometime also involves removal of quenching reagents such as PPh_3. We strongly believe that present safe ozonolysis protocol will be useful to improve efficiency of chemical process of the APIs and biologically active compounds.

Conclusions

To summarize, here we are reporting mild and convenient method for the synthesis of quinolones via new one-pot quadruple reaction by batch as well as continuous flow process. The present method also paved the way for the two unique approaches for the synthesis of drug ivacaftor and ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate. We have successfully demonstrated that new chemistry route in combination with flow synthesis can result in significant reduction in reaction time with safe protocol. The developed synthetic route can produce 32 g/day of ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate and 7.2 g/day of drug ivacaftor using available bench-top infrastructure. The present approach is being used for similar quinolone-based drugs such as well-known fluoro quinolone carboxylic acid based antibiotics and will be reported separately.

Conflicts of interest

The authors declares no competing financial interests.

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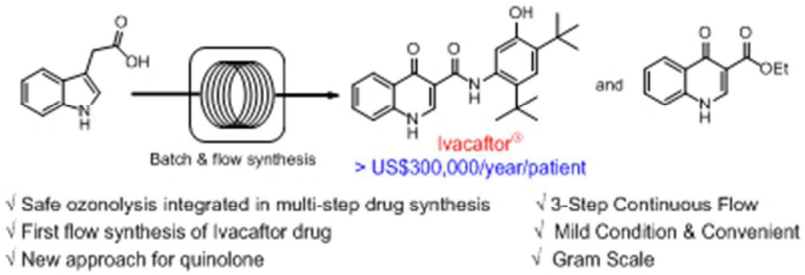

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Correction: Assessing the impact of deviations in optimized multistep flow synthesis on the scale-up

M. K. Sharma, J. Raval, Gwang-Noh Ahn, Dong-Pyo Kim* and A. A. Kulkarni*

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CORRECTION

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The authors regret an incorrect affiliation in the original article. The correct affiliation 'b' is as shown here.

The Royal Society of Chemistry apologises for these errors and any consequent inconvenience to authors and readers.

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Assessing the impact of deviations in optimized multistep flow synthesis on the scale-up

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This manuscript highlights the unavoidable connection between manual and self-optimized flow synthesis protocols for multistep flow synthesis and its scale-up. While briefly summarizing the state of the art in the self-optimization approach, a brief summary of industrially scaled-up processes is also given. We have used as a case study the flow synthesis of ivacaftor that is optimized at the laboratory scale and is subjected to specific deviations deliberately. The resulting effects are captured in terms of their effect on the scale-up approach. The analysis shows that small deviations in performance *viz.* conversion or selectivity at every reaction step would lead to significant deviation in the process and the overall capital investment. Translating "laboratory synthesis" into "commercial scale manufacturing" needs careful differentiation between an optimized reaction step and realizing a commercially feasible process. We have also highlighted the role of 3D printing in fabricating prototype and scalable flow systems.

Introduction

Automated flow synthesis has become the new and latest buzzword in the field of flow synthesis primarily aiming at interfacing artificial intelligence with synthesis platforms. This approach has eventually led to concepts like 'dial-a-molecule',[1–4] 'synthesis 4.0',[5] 'intelligent retrosynthesis',[6–8] *etc.* These approaches have facilitated the identification and rapid screening of synthesis protocols backed by a very large database of reactions, kinetics, analysis procedures, *etc.* for designing an efficient experimental setup suitable for a specific synthesis. Very often when broken down in a system's approach, the tasks are simple *viz.* synthesis, optimization of individual reaction steps, separation of reactants and products, *etc.* Advancement in reactor fabrication technologies, *e.g.* 3D printing, has made it easy to fabricate complex flow reactors as designed from CAD on the basis of a simulated flow field using flow modelling tools. And the optimum performance of the synthesis is attained by resolving the composition along the reactor length and various operating conditions. Furthermore, the system for multistep flow synthesis becomes much more complex on integrating various reaction steps/reactors. This demands a complementary system that banks on advancement of technology with experience of a process chemist/engineer to deliver a reliable and adaptable synthesis machine. While very few efforts are seen to have total reliance on automated decisions, manufacturing plants are mostly still designed and operated based on experience or a combination of experience, empiricism and heuristics. So, with the proven set of examples that clearly suggest adoption of continuous manufacturing as the best way to synthesize high value specialty chemicals,[9–15] it is especially certain that the pharma industry would make some moves to align with flow synthesis. There are many examples in the literature focusing on scale-up using flow synthesis,[16–18] inline analysis for real time monitoring,[19,20] printing of a reactor for fabricating complex reactor geometries[21,22] and very recently utilization of smart algorithms for automation. However, it is very early stage of an attempt on substantial integration of the individual system and process. Words like synthesis automation for increasing output, safety in manufacturing, spending time on important aspects of research rather than building setups and synthesis of molecules seem lucrative but demonstration of such an integration is not very common since it requires many challenges to be addressed.

Reaction optimization at the laboratory scale for single step synthesis or for individual reaction steps is now a relatively easy task using the algorithms on hand. However, as complexity increases, the task becomes more data driven, requiring more computing power and highly skilled personnel having multidisciplinary background. The situation becomes even more critical in an actual plant

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environment where the systems have several interconnecting segments and interact with other instruments thereby creating an interesting situation where the time scales of the reaction are smaller than the time lags from the interacting system. Optimizing a reaction is very much different than optimizing a process, the latter being far more complex, needing significant engineering inputs. This perspective article aims at taking a realistic view of moving from "laboratory synthesis" to "commercial scale manufacturing" for high value and small quantity chemicals in the fine and specialty chemicals sectors including pharmaceutical drugs. Here we make an attempt to explore the viability of a process for the commercial scale based on the laboratory scale optimization (equally applicable for self-optimized systems) of multistep flow synthesis.

State-of-the-art of scale-up of flow reactors/processes

In general, there are only limited cases in commercial production that have been realized from laboratory scale flow synthesis. This situation is changing as recently a large number of industries have been practicing flow synthesis at the pilot and commercial scale. It becomes evident from the total number of large-scale flow reactors that are sold by various manufacturers (*viz.* Corning Inc., Chemtrix LLC., Kobelco Ltd., Ehrfeld Mikrotechnik BTS., Amar Equipments, Himile Microrectors, AM Technologies, GMM-pfaudler, *etc.*) as otherwise they would not have sustained only based on laboratory scale flow synthesis devices. Among the very early reports of using a microreactor of a flow reactor for commercial scale production, Mehrabi and co-workers have shown a reconfigurable system for adopting various manufacturing demands.[23] Efficient heat and mass transfer in all the capillaries has helped to achieve the desired level of polymerization. However, the reactor used is a horizontal flow reactor with capillaries at different levels. This approach would not work for reaction mass of lower viscosity due to the influence of gravity on distribution. May *et al.* have reported a continuous process for a 1*H*-4-substituted imidazole intermediate in two different approaches that use optimization and scale-up rapidly in plug flow reactor (PFR) and automated sampling, process analytical technology and inline separation for screening the best possible route for synthesis and scale-up, respectively.[24] Fitzpatrick *et al.* developed a software program called Leylab for remote reaction monitoring and have demonstrated its use for reaction optimization.[25] Laue *et al.* performed the lithiation reaction of fluoro-aromatics in a microreactor under non-isothermal conditions while achieving controlled precipitation.[53] Fitzpatrick and Ley have reported successful integration of batch and flow experiments on a single platform with an automated system for synthesis of 5-methyl-4-propylthiophene-2-carboxylic acid.[26] They also incorporated automated downstream processing and solvent switching steps to free chemists from more routine laboratory tasks. A sophisticated approach that involves reaction automation, inline analysis and feedback systems to drive the reaction systems to continuously generate new insights into the reaction has also been reported.[3]

A continuous sequence for synthesis of benzoxazole building blocks involving a flow synthesis set-up, getting the heat profile of the reactors and then finally combining the batch reactor, semi batch reactors and flow reactors to get the desired production is reported in a systematic manner.[27] Continuous manufacturing of the drug prexasertib monolactate monohydrate on a 24 kg scale involving 8 unit operations has also been reported.[13] The effects of recycle in the reactor and in the crystallizer on the enhancement of the yield and selectivity using dynamic simulations and optimization in an end-to-end continuous pharma manufacturing have also been studied.[28]

Scale-up through numbering-up works exceptionally well for ultrafast reactions.[29] However, throughput limitations and complexities of flow distribution are major challenges that need case-by-case scrutiny before design. For example, Iwasaki *et al.* have demonstrated the scale-up *via* numbering-up for radical polymerization using a micro-flow system for producing methyl methacrylate up to 2.5 kg of the product per week.[17] Five parallel monolithic microreactors were used for the synthesis of an intermediate of valsartan, a therapeutic agent for hypertension and diabetes.[18] A similar approach has been used for numbering-up of gas–liquid photocatalytic reactions.[30] As another example, it was shown that the productivity can be increased by parallelizing up to 32 visible light-mediated organic photocatalytic reactions in microfluidic reactors based on luminescent solar concentrators.[31] Very recently, Jang *et al.* demonstrated ~4 g of drug production per hour. The system comprises a total of 10 photoreaction capillary reactors connected by 3D distribution modules needing a total residence time of 2.2 minutes from synthesis to product separation.[32] A similar approach has been demonstrated using an integrating flow distributor and a copper catalytic module for high productivity of 'Rufinamide'.[16]

These reports in the published literature from industry is the tip of an iceberg of the actual implementations. However, this brings out a very important question on deciding the viability of a "process for commercial scale" based on the "laboratory scale (self) optimization" of multistep flow synthesis. In general, since these two aspects are important yet unconnected, it is necessary to understand how the former can help the latter cause, which is the ultimate reason for all the efforts of process development. All the reported scale-up approaches, which involve integration of multiple steps and integration of separation and inline analysis, involve thorough investigation of various parameters of the process. Once each step or sequence of operation is optimized and integrated, they can run continuously as there is no scope for any significant change to be incorporated at the large scale. Usually, the scale-up approach is very specific to the chemistry under consideration. The general scale-up

procedure depends on the know-how available, physicochemical properties of chemicals/materials involved, specific chemistry and experience of individuals involved in the exercise. Using artificial intelligence (AI) in incorporating automation in developing methodology and devising algorithms with decision making ability will help to predict the scalability. Here, we aim to evaluate the extent of variations that can happen beyond laboratory scale experiments when one uses them directly for scale-up. Efforts in development of self-optimization platforms will reduce the time and efforts which are necessary but they need to be coupled with reliable predictive scalability. Before moving to the main contents of this article, we give a brief summary of the state of the art of efforts in self-optimization in the next section. Although this theme issue has focused articles on self-optimization platforms, below discussion will help retain a connectivity with the objective of this work.

Self-optimization tools: need, limits and scope towards predicable scalability

Continuous flow multistep synthesis coupled with online analysis can help rapidly test the effect of different reaction conditions on subsequent reactions. Self-optimising systems typically use a feedback control algorithm with automated process control. Automated systems can perform "black-box" optimization[33] wherein no prior knowledge of the reaction parameters is required provided that the desired boundary conditions are already fed to the system. In general, such an approach becomes useful even when the kinetic data are limited or not available. Automated synthesis platforms can be used to monitor reaction parameters (primarily, temperature, pressure, residence time and outlet composition). Precise control over reaction parameters can be achieved by continuous generation of data (real time analytics using Raman spectroscopy, IR spectroscopy, mass spectroscopy, nuclear magnetic resonance, UV–vis, *etc.*) and using precision sensors.[34] This would help to determine information like reaction kinetics, yield and selectivity. Resulting conditions can be used for process optimisation that can lead to integration of chemistry and engineering.

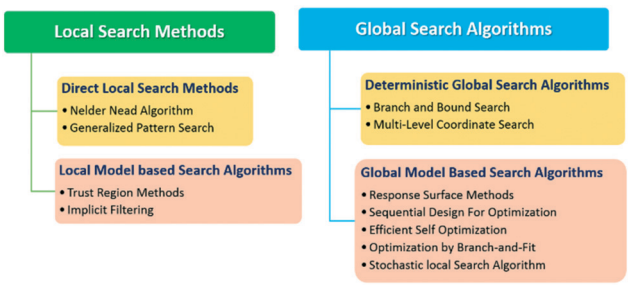

Fig. 1 Classification of different decision/search algorithms.

One of the primary requirements of a self-optimization system is an intelligent algorithm (Fig. 1). Data from every planned experiment are used as information for transforming into a knowledge base to make decisions based on heuristics and trends or imposed guidelines/constraints. In general, having rapid data acquisition is essential and can help in minimisation of time in optimising any reaction. Smart algorithms will also account for any unforeseen changes in the input variables. The basic aim of any optimisation algorithm is to reduce the number of experiments required during an optimisation process. It creates a feedback loop wherein at any given point of time the reaction mixture is analysed and a new set of conditions is generated based on the previous experimental data. As for self-optimisation, the black-box approach is generally followed; the optimisation problem becomes bound-constrained optimisation wherein only the objective function is known. The algorithms employed to solve such a problem are referred to as derivative-free algorithms (as they do not require any derivative information of the objective function). The literature on self-optimisation in microreactors generally uses the following algorithms: (i) Nelder–Mead simplex algorithm, which is the simplest direct search algorithm used for multidimensional unconstrained optimisation. As no derivative of function is required, it becomes easy to use Nelder-Simplex for noisy problems; (ii) Response Surface Methods (RSMs): this method optimises a function by examining the relationship between the response and the factors affecting the response using regression models; (iii) optimisation by branch-and-fit: the algorithm combines global and local searching by branching and local fits. It provides a fast solution for bound-constrained noisy optimisation; (iv) hit-and-run algorithms: this approach can be used for getting global optimum values in continuous optimisation problems under mild conditions. It generates an optimum value by comparing the current iterate value with a randomly generated candidate. Table 1 summarizes them and also draws a comparison so as to use the specific algorithm for a specific purpose/complexity.

While another perspective article in this theme issue covers the self-optimization systems and algorithms in detail,[35] the relevant literature will help get more details on the systems, approach (Fig. 2), objectives and development in the field. Self-optimisation has been reported in the literature since 2010. In a first attempt, Jensen *et al.* used the Nelder–Mead simplex method coupled with online HLPC analysis to maximise the yield of the Heck reaction.[20] It took 19 automated experiments to determine the optimum reaction conditions and the reaction was scaled-up to about 50 times using these conditions. Jensen *et al.* later also demonstrated using different algorithms with inline HPLC monitoring for optimising the Knoevenagel condensation reaction and oxidation of benzyl alcohol.[19] A six step system comprising three synthesis steps and three workup stages for synthesis of 2-aminoadamantane-2-carboxylic acid has been reported and studied using advanced control strategies.[36] The

Table 1 Summary of different self-optimization algorithms (in comparison with algorithm 1)

	Convergence	Optimizing the chemical system with	
		Single optimum	Multiple optimum
Nelder–Mead simplex algorithm	Fast	✓	✗
Response surface methods	Slow	✓	✓
Optimisation by branch-and-fit	Slow	✓	✓
Hit-and-run algorithms	Slow	✓	✓

applicability of a self-optimised system using supercritical CO_2 as a solvent has also been demonstrated.[37] Nanoparticle synthesis using an autonomous "black-box" system has also been reported in the literature.[38]

A parallel development of a modular, continuous, integrated, automated and remote-controlled reaction platform that sets up and performs the necessary unit tasks is also an important milestone.[39] Li *et al.* presented a method for creating complex polycyclic structures involved in biochemistry and drug design based on carbon-based small molecules through deprotection, coupling, and purification modules, as well as reaction automation techniques.[40] Jensen and Jamison groups have built and miniaturized a refrigerator-sized continuous flow system for continuous and productive drug synthesis and presented an integrated set of modules.[41] In addition, a system was proposed that can perform various chemical reactions through optimization of temperature and concentration and feedback control that can greatly affect the product yield.[42] In particular, recently, a system has been proposed for molecular synthesis led by AI, performing it through a robotic arm to greatly reduce the efforts of experts in complex organic molecular synthesis. As a result, they succeeded in applying this strategy for a total of 15 active pharmaceutical ingredients (APIs).[43] Other excellent efforts include modular robotic platforms that formulate and control the assembly of molecules, which have successfully synthesized three pharmaceutical compounds, including the paediatric anticonvulsant Rufinamide,[44] automated control systems for photochemical chemistry with constant yields under rapidly changing light conditions,[45] machine learning-based synthesis efficiency with human experimenter-led synthesis efficiency,[46] and development of systems to remotely monitor and integrate many chemical experiments on a large scale, *viz.* use of networked robots to explore azo-coupling reactions.[47] These efforts are transforming the chemical synthesis beyond imagination and are mature enough to convert synthesis into robust processes that would eventually lead to manufacturing.

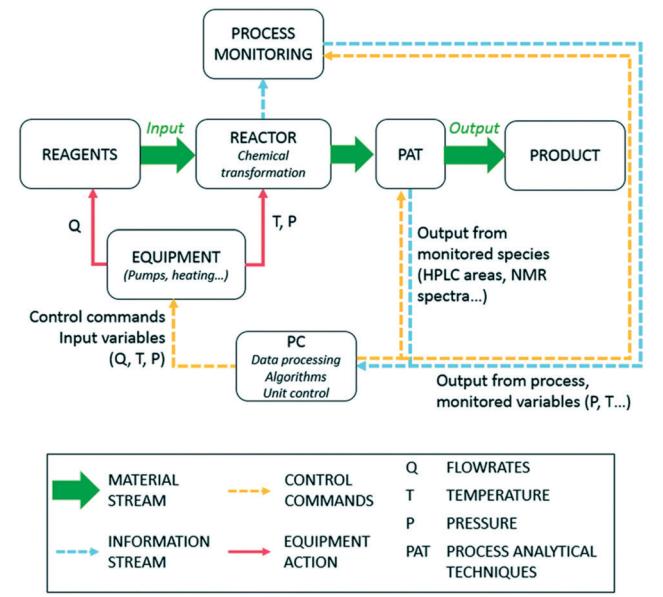

Fig. 2 Overall process of a self-optimised microreactor system.[35]

Moving multistep flow synthesis beyond the laboratory scale

Though these reports shed light on the future of manufacturing in terms of automation and machine learning, several criteria are ignored in the development of these methods or devices. Automated manufacturing involves the simultaneous monitoring and control of important process parameters with very little human interaction when the process is operating at the steady state or within the constraints. It also involves logic development and control algorithms in the case of slight disturbance in the processing parameters at any stage. In the rest of this section, we will discuss these aspects with greater detail but with more caution.

What is a real optimum?

As mentioned earlier in the Introduction, the optimization studies involve the development of the search algorithms. In process development activity, this is a very complex process and requires perfect logic coupled with necessary constraints in a highly trained algorithm. For automated feedback based optimization (*i.e.* black box approach/deterministic model/stochastic models), the optimum from individual methods may vary.[48] This becomes crucial for a multistep reaction sequence, where the need for more than one product optimization makes the approach very difficult upon integration of steps. While a well-trained algorithm can be used, collaborative human intervention by involving an experienced chemical engineer or chemist becomes very helpful in deciding the critical parameters to define the set of conditions for the optimal point.

Economic feasibility of a versatile self-optimization system

A multipurpose self-optimization platform would help perform a very rapid assessment of optimal conditions for almost every reaction. It will reduce significant process costs but at the cost of development of such a platform. It will also need a lot of data in terms of the physical properties of all the components and reaction mixtures (which are usually unavailable for complex reactions). It should also have almost every possible in-line or on-line analytical instrument attached to it to ensure that every single experiment gives the maximum information that becomes useful for optimization, scale-up, and sometimes even for formulation. When we consider the total time required by those platforms for optimization, it will significantly depend on the desired residence time and analysis time for any reaction.

Post processing of the data and sensitivity analysis

The final aim for the generated data from the optimization platform is its utilization for scale-up, which depends on many aspects *viz.* the reactor chosen for optimization, critical parameters assumed, time of analysis, method of analysis, *etc.* In the chemical engineering literature, it is well documented that scale-up is not so straightforward and involves rigorous quantitative estimations and many other engineering aspects. Hence while the objective of scale-up is to achieve the same performance as optimized by the laboratory scale system, a lot more information which was not relevant at the laboratory scale becomes important. And hence it is not necessary that the optimum at the lab scale would be optimal only in terms of the reaction performance. The usefulness of these data for predictability of the scale-up approach is going to be an important step in the decision-making process.

Process economics

The success of any process for synthesis depends on the overall process economics, which is usually not only dependent on the actual process but also on the nature and quantum of downstream processing. It is always possible that the optimum obtained in the case of lab scale studies would need specific downstream processing equipment that may not be available in higher capacities. For example, standard equipment, *viz.* a wiped film evaporator, is never seen in any published literature where solvent recovery is needed or a miniaturized cyclone separator is never used for lean suspensions before moving for the next step. The matching of time scale for downstream processing operation with the reactor conditions also becomes critical, which does not seem to be the criterion of consideration in the current scenario. Also, slight deviation from the optimized set of conditions may have a huge impact on the downstream processing which may reflect in the overall costing. This can have minor or major implications on the overall viability of the process. In the current scenario from the literature on multistep flow synthesis, development of a clear understanding of the economic viability of an optimized laboratory protocol is needed.

If the above gap in the existing literature is addressed, it would help in moving from "laboratory synthesis" to "commercial scale manufacturing" and bring out a need for a "comprehensive process evaluation cum decision making tool" having predictive scalability. Here we present a case study that would highlight such a need.

Flow synthesis of ivacaftor: sensitivity analysis

Ivacaftor is used for the treatment of cystic fibrosis and it is one of the most expensive drugs. The analogues of this drug including deuterated versions are also being explored for efficacy in treating the disease. Laboratory scale multistep flow synthesis of ivacaftor is considered[49] and a process flow diagram is built based on the optimal conditions reported in the literature (Fig. 3). The process consists of three reactors, two separators and a scrubber for the synthesis of ivacaftor (Fig. 4) and certain assumptions were made to show how an optimised process can change even with very small variations in the optimised parameters. Three different cases are considered to show how small changes in performance could affect the overall process flow. It was assumed that the optimised conditions for the process gave 1 gram of pure ivacaftor per unit time. For the initial base conditions previously reported,[49] experimentally optimized conversions were used for all three reaction steps based on which rate constants were calculated.[49] In every reaction step, since one of the reactants was always in excess all the three reactions

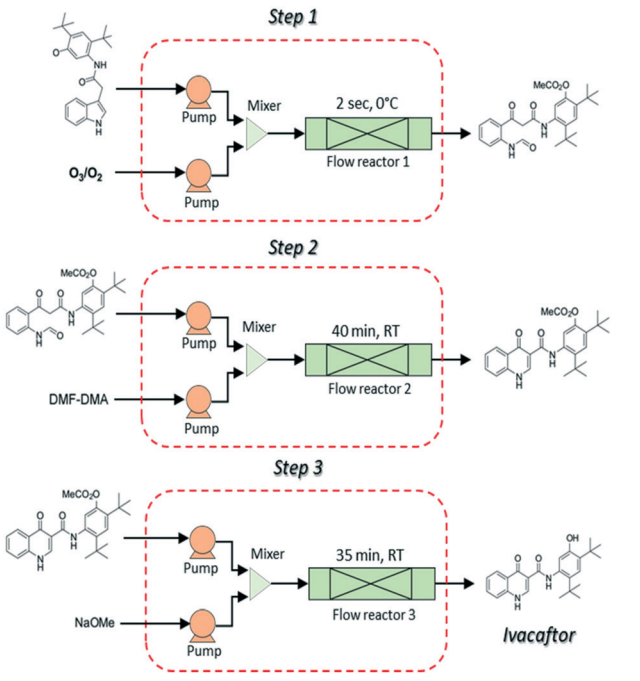

Fig. 3 Typical schematic of the experimental set-up for optimizing individual reaction steps in flow synthesis.

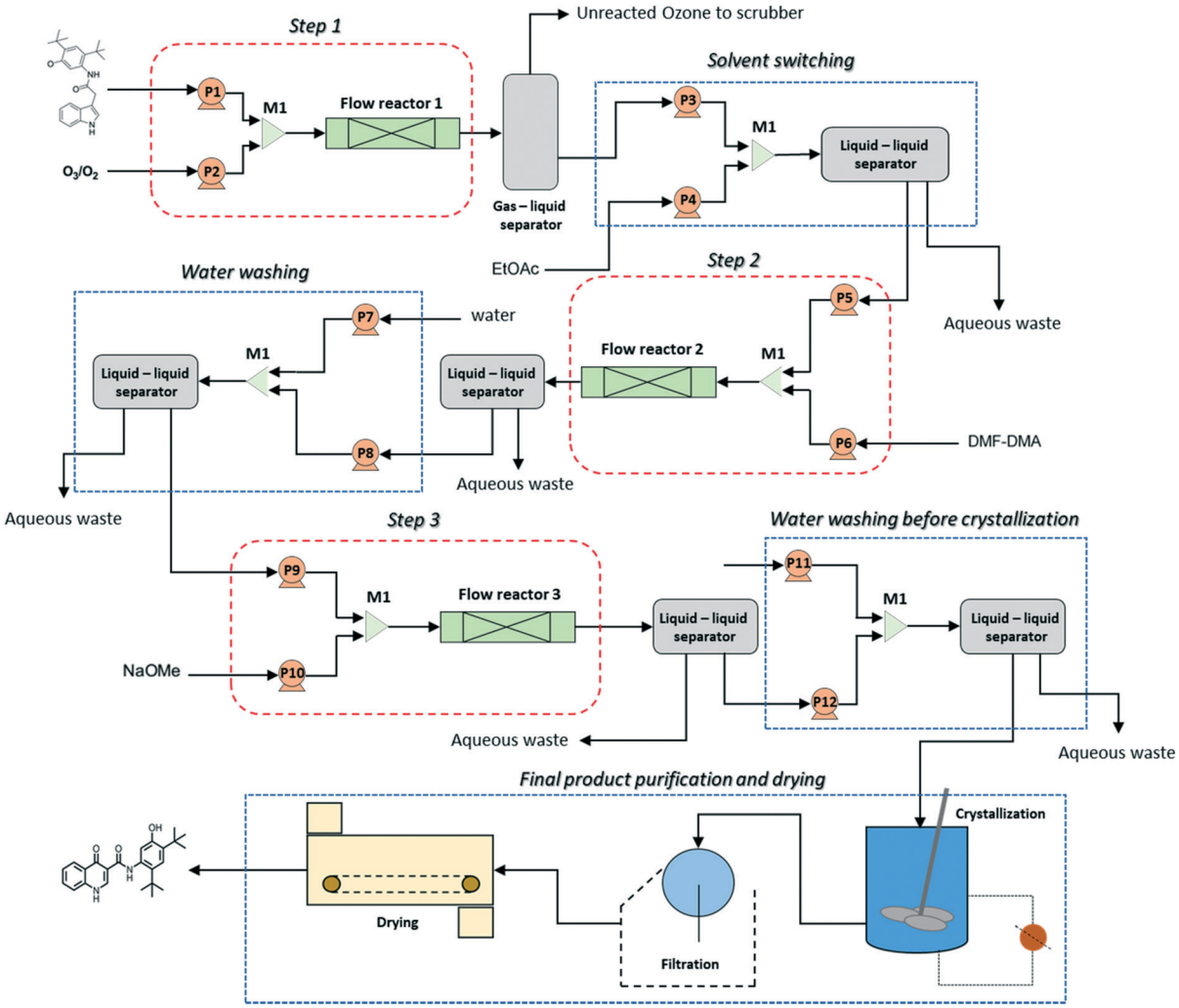

Fig. 4 A typical possible process flow diagram for flow synthesis of ivacaftor.

were considered to follow first order kinetics, based on which the rate constant k for each reaction was obtained. The volumes for the liquid–liquid separator, gas–liquid separator, and scrubber were estimated considering a residence time of 30 minutes for separating the reaction mixture when all of them are working at 100% efficiency. In order to assess the effect of temperature variation, three reaction temperatures were considered with a difference of 10 °C. It was assumed that the reaction rate doubles with every 10 °C rise in the reaction temperature. These assumptions have helped to get certain parameter values for the synthesis of 1 gram of ivacaftor. This was considered to be a model optimised table for all further calculations. It needs to be noted that the above assumption about rate doubling depends on activation energy and thus highlights the need for measurement of reaction kinetics.

Table 2 Change in reactor volume based on the effect of variation of throughput and kinetics in the synthesis of ivacaftor

Temperature (°C)	Reactor	1 g scale		1.5 g scale		2 g scale	
		RV (ml)	K	RV (ml)	K	RV (ml)	K
25	R1	30	0.153506	45	0.153506	60	0.153506
	R2	30	0.021245	45	0.021245	60	0.021245
	R3	40	0.012876	60	0.012876	80	0.012876
35	R1	15	0.307011	22.5	0.307011	30	0.307011
	R2	15	0.042489	22.5	0.042489	30	0.042489
	R3	20	0.025751	30	0.025751	40	0.025751
45	R1	10	0.460517	15	0.460517	20	0.460517
	R2	10	0.063734	15	0.063734	20	0.063734
	R3	13.3	0.038627	20	0.038627	26.67	0.038627

Based on the laboratory optimised values for 1 g of the process, the values for scaling up the process by 1.5, 2 and 10 times were obtained. A 5% change in the conversion in the individual reactors was assumed to show how the reactor volume changes drastically during scale-up with a small change in conversion while all the other parameters remain unchanged. The resulting values are given in Table 2, assuming 100% efficiency of all the separators and scrubber.

However, if the separation/purification equipment does not work at 100% efficiency, the conversion and hence the yield of the final product would be lower than expected. In order to determine the sensitivity of this effect during scale-up, a 5% variation was assumed in the efficiency of the separators and scrubber and the subsequent yield of ivacaftor was calculated. The effect of these variations on the overall process is described subsequently.

Effect of throughput variation in combination with other reaction parameters

The optimized conditions for a specific reaction step are usually valid only for a specific throughput within the desired parameter constraints. Any variation in the throughput will need a different reactor to match the desired residence time. However, there will be consequences beyond only changing the reactor volume as the heat transfer rates, mass transfer rates and mixing efficiency can change and thus would need a new set of optimal conditions, which can be different than those of the initial one and can be different from the real optimum with the available reactor volumes. One of the ways to compensate for such variations can be through changing the temperature, provided that the reaction kinetics are known or by ensuring certain values of transport coefficients. It also puts an important constraint of retaining a fixed outlet composition as the downstream unit operations including subsequent reactions are designed for a specific inlet composition.

Conventionally, a multistep flow synthesis goes through an individual step optimization followed by integration of the separation stages. In the presented exercise, the experimentally measured reaction kinetics for each step were used for estimating the reactor volume for each step, and the corresponding temperature in each reactor for the final desired output of ivacaftor (Table 2). The best-case scenario is the optimum obtained from the literature[49] and reaction rates were varied for 3 different temperatures which will enhance the reaction rate and reduce the reactor volume. For an expected output of 1 g min^{-1}, there are 3 sets of reactor combinations for all the three reactions. Thus, if the self-optimization platform consists of reactors of volumes 10 ml, 10 ml and 13 ml, each for the first, second and the third reaction step, respectively, then, for an expected throughput of 1 g, the stoichiometry and inlet concentration would result in specific flow rates at 45 °C.

Enhancing the production rate beyond 1 g would need a larger reactor volume. However, for the same production rate, if we choose the lowest temperature and the highest reactor volume, (*i.e.* 30 ml, 30 ml, 40 ml) the same reactor combinations can achieve 2 g output at higher temperature and increased flow rates. However it would still be oversized by 25% in each step and can actually achieve the design specific production capacity only under another set of conditions. This would lead to an unending loop where the change in one parameter would lead to the change in the optimal conditions only within a small range. Such a situation leading to *on-site optimization* can be avoided through a detailed modelling exercise involving intrinsic kinetics, transport coefficients, and the extent of dispersion for a specific throughput.

Optimization at a large scale based on optimized conditions

Enhancing the production capacity from a flow reactor (*i.e.* scale-up) can be achieved either by numbering up (where a number of geometrically and dimensionally similar units are run in parallel under identical conditions) or through conventional scale-up by changing the reactor dimensions. If the production capacity in the present case is to be enhanced by 10 times, the required reactor volumes would be 300 ml, 300 ml and 400 ml. The numbering up approach would need 10 reactors of the same dimensions running in parallel, while the second approach would demand identical rates of heat transfer and mixing at a smaller scale. Any deviations from the desired hydrodynamics would reduce the conversion at the outlet of the specific reactor.

In order to quantitatively evaluate this effect, from the known kinetic data we identified the conditions that would result in lower conversion in each reaction step by 5% individually as well as an overall 5% lower productivity at the outlet of the sequence of reactors. A quantitative analysis of the final yield is given in Table 3, where the change in volume required for a change in the conversion in the individual reactor as well as for their combinations is given. If any of the reactors underperforms then to meet the overall throughput the new reactor has to be of higher capacity to get

Table 3 Change in reactor volume based on the effect of variation of conversion on the scale-up process compared to the initial laboratory scale optimized conditions to obtain 10 g yield of ivacaftor

Temperature (°C)	Reactor for a specific reaction step	Rate constant *K*	Reactor volume for 10 g production scale: Optimal condition (ml)	Reactor volume for 10 g production scale: 5% reduction in the conversion in all the reactors (ml)
25	R1	0.153506	300	390.31
	R2	0.021245	300	341.6
	R3	0.012876	400	455.5
35	R1	0.307011	150	195.2
	R2	0.042489	150	170.8
	R3	0.025751	200	227.72
45	R1	0.460517	100	130.3
	R2	0.063734	100	113.9
	R3	0.038627	133.33	151.8

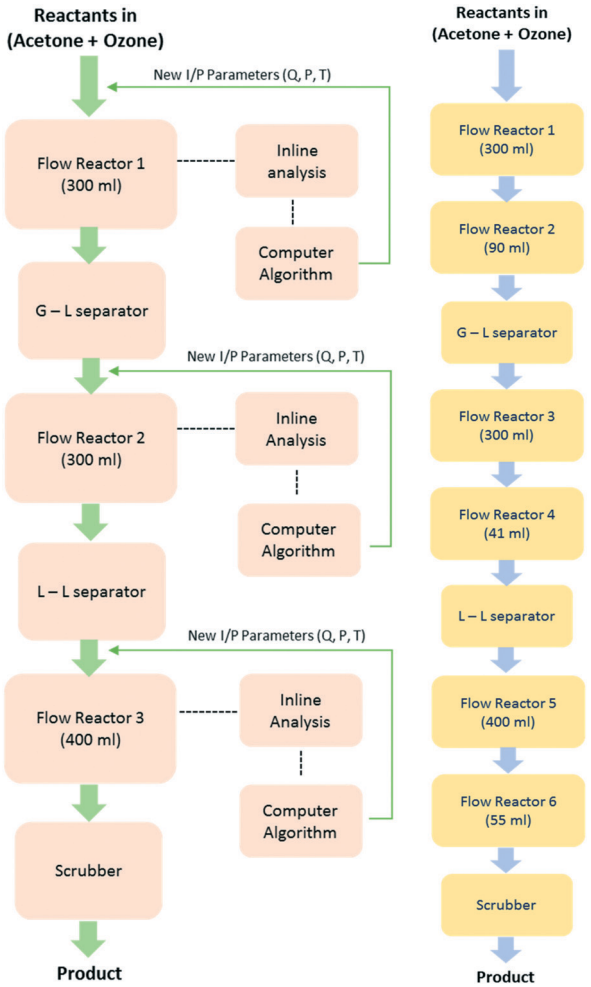

Fig. 5 Comparison of the process block diagram for optimal and sub-optical conditions.

the required input for the feed at the next stage, which is very much expected. In all these cases, the overall volume was found to increase by almost 18%, which will also add to the capital cost and also slightly to the operational costs (Fig. 5).

Design of separation stages/change in operating conditions of the separation stages

As discussed earlier usually laboratory scale process development does not include the design of a continuous separation stage as the type of separation depends on the reaction. In general, recently a lot of examples have been reported, where liquid–liquid separation is demonstrated using a membrane separator or using simple gravity-based layer separation. Using a membrane separator demands the solutions to be completely homogeneous in terms of dissolved solids. This also implies that using an excess of solvent might be needed to facilitate easy separation of two immiscible phases. However, when going for the scale-up, the separation strategy needs to be carefully designed to match the desired output for the input of the subsequent step. In general, while one can still accept slight variations in the residence time in the reactor, variation in the residence time in a continuous separator may or may not be acceptable due to specific time scales relevant to the mechanism of separation. In general, no literature reports any deviation from the optimal performance that would add more process equipment to the plant adding to higher capital cost, higher operational cost and operational issues, in spite of the fact that they hold a key to the plant design and process realization. In cases where reactors are already designed for a specific production capacity, if they underperform for the parameters obtained from optimized conditions the separation approach would change completely as one has to then even plan to separate unreacted reactants from the product, both probably in the same phase. The situation completely rests on the design of the separation stages to incorporate the feed composition change for certain capacity, which is not an easy task. For the separations involving distillation, the change in the feed composition can be handled using the change in column operating conditions but for the separation involving liquid–liquid extraction the change in the feed composition can completely change the separation dynamics which may result in one phase being contaminated by the other. It might also need a second level of separation to take care of such issues. In order to observe such an effect, *i.e.* change in separation efficiency affecting the complete plant design, we have varied the separation efficiency at each stage by 5% and the observations are shown in Table 4. Deviations beyond this would have significant effects on the overall process economics.

It can be seen that every separation step must work close to the desired efficiency as else it can affect the performance drastically, although all reactors would work under optimal conditions. In such situations, having access to rapid prototyping and fabrication of additional components using 3D printing would save time in process realization. While here we do not want to have an elaborate discussion on 3D printing of process equipment, it is necessary to touch upon this aspect as for any on-site optimization of a flow process, 3D printing is going to be a viable option.

Fabrication of flow systems using 3D printing

The automated synthesis platforms in prototype or scalable flow must be elaborately tailored with precise monitoring and control functions for specific chemical processes. It requires conceiving a flexible set-up, showing the readiness of the system to perform a varied array of reactions without complex redesign or reoptimization. For these advantages, it is worth looking into recent advances of microreactor systems, which are fabricated by various 3D printing techniques. The 3D printing technique as an additive manufacturing technology has drawn much attention due to its relatively facile way of fabricating monolithic bodies even with several centimeters in size. Implementation of changes in the design in a rapid manner helps in real time prototype design and its use. It

Table 4 Effect of yield variation due to lower efficiency of separation and purification equipment on the plant footprint

Conditions with relevance to the optimal	Yield (g)	Additional process equipment to meet the desired production capacity
Under optimum conditions	10	—
5% reduction in the GLS efficiency	9.03	1
5% reduction in the LLS efficiency	9.5	1
5% reduction in the scrubber efficiency	9.5	1
5% reduction in the efficiencies (all three)	8.14	3

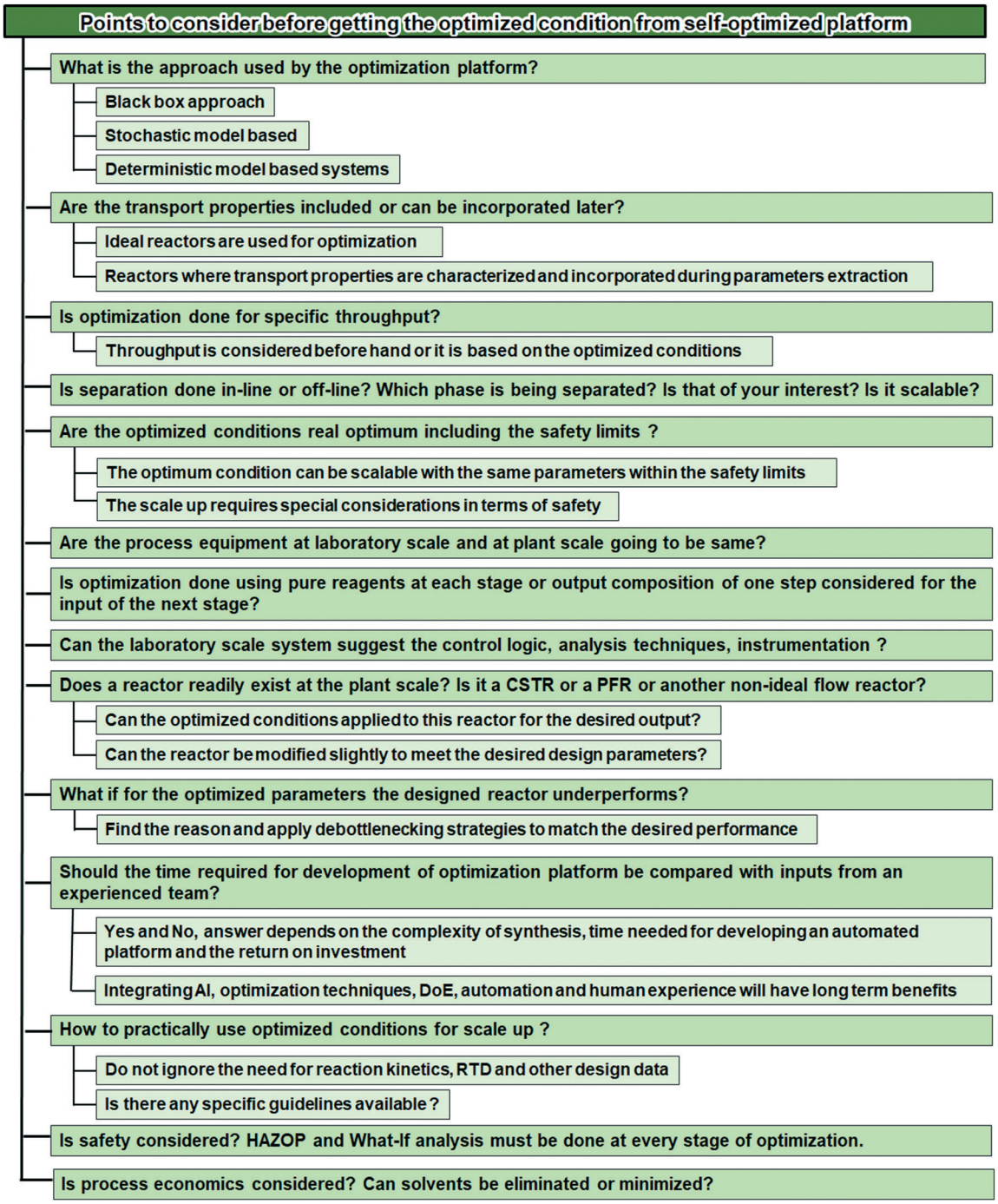

Fig. 6 A model questionnaire *cum* flow chart for moving from a (self) optimized system predicting synthesis conditions to a scalable manufacturing scale process involving multistep flow synthesis.

would help for real time scalable manufacturing by simply numbering-up microreactor units in parallel for increasing throughput. Glass, metals, and ceramics are promising materials for 3D printers to fabricate diverse types of flow reactors for various applications[21] including continuous flow electrochemistry,[50] fast difluoro methylation reaction with *n*BuLi,[22] bio-diesel production[51] and multistage glyco-oxidation reactions.[52]

The approach involves several points to be addressed and evaluate the effect of a decision on the entire process. We have given one such set of questionnaires that would help anyone who wants to assess the efficacy of an optimized synthesis protocol towards its realization into a commercially viable process (Fig. 6). More work on developing a soft tool that uses the optimized data for a variety of reactions to develop predictability is in progress and will be reported separately.

Conclusions and recommendations

In summary, it is well understood that utilization of advanced algorithms and self-optimization platforms is a critical requirement of future chemical synthesis plants at the laboratory scale and production scale. However, significant input in terms of development and assessment of critical parameters for each individual synthesis step or the complete process for chemical synthesis is necessary. Every chemical synthesis step cannot be generalized but can be incorporated in specifically designed algorithms with advanced processing techniques with the help of experienced professionals in the field or through the incorporation of AI tools. It is also shown that having assessed the parameters at the laboratory scale for any synthesis is just the first step in overall plant design in terms of anticipating and preparing for the probable deviations during scale-up which does not avoid the knowledge of experienced personnel (chemists/chemical engineers) in the field.

We have shown that as small as 5% change in conversion or change in performance of separation stages may result in 18% change in throughput which results in manipulation of other parameters or utilization of additional equipment to meet the quality criteria. Also, using laboratory scale optimization, it is shown that the throughput and available reactor size put constraints on the optimized parameters which can change if different reactors are available as options. Upon reaching the plant scale, it is almost impossible to accept any deviations in any parameters (conversion, temperature variation, efficiency of separation stages, *etc.*) which may change the process flow diagram and add additional burden to the capital investment.

It is envisaged that for any manufacturing, advanced algorithms and knowledge of experienced personnel will go hand in hand to design better plants and efficient manufacturing techniques by adopting newly emerging techniques such as the 3D printing method. Realizing self-optimization and automation in laboratory synthesis will require many challenges to be addressed (apart from the technical issues mentioned here) in terms of result interpretation, decision on final optimum parameters, troubleshooting, generating know-how to develop and utilize advance synthesis platforms, utilization of new information for the modification or incorporation in the existing process, *etc.*, all of which require significant human intervention. Addressing all the above challenges would help in successful translation of "laboratory synthesis" into "commercial scale manufacturing".

A large body of the organic synthesis and reaction engineering community is working on automation of synthesis, optimization, data analysis, integration of PAT tools in the system, *etc.*, primarily for medicinal chemistry. In such a situation it might be useful to look at the state of the art of automation in petrochemical refineries, bulk chemicals and polymers as a few decades ago these industries have made revolutionary changes in manufacturing involving flammable products. Maybe, it will help the community to save time in re-inventing some parts of the wheel.

Another important point that needs to be addressed in the entire endeavour is planning for imparting multiple complementary skills to the next generation, which significantly deviates from the erstwhile generation of chemists and engineers. Including AI for property estimation, python-based programming, making chemists use self-optimization tools, *etc.* will bring the community closer than before. This will definitely make everyone work on more challenging and more relevant problems of sustainability.

Conflicts of interest

Patents have been filed for the batch and continuous flow synthesis of ivacaftor by CSIR-National Chemical Laboratory (Pune, India) and the process is under evaluation for industrial implementation. POSTECH (Korea) does not have any rights on the work on ivacaftor reported in this manuscript.

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