CHAPTER 1

Literature Survey

1.1 Introduction

Aliphatic polyesters based on lactic and glycolic acid are among the most widely used biodegradable polymers for a broad variety of biomedical applications like surgical sutures, prosthetics, dental implants, pins, bone screws and plates for temporary internal fracture fixation (Albertsson, 2001). In the 1960s poly (L-lactide), PLLA, was proposed as a biocompatible, biodegradable, and bioresorbable material. (Vert, 1992). Aliphatic polyesters have been known to have excellent physical properties (Sorenson, 1961), and find applications as absorbable sutures and prosthetic devices (Frazza, 1971). Polyesters of glycolic and lactic acids biodegrade via simple, non enzymatic hydrolysis of the polyester bond (Kulkarni, 1971). Hydrolysis continues to break the polyester bonds at random sites along the polymer chains until, the degradation products like lactic and glycolic acids, carbon dioxide and water are generated. These acids occur naturally in the human body and and are processed through normal metabolic pathways. Elimination from the body is ultimately achieved through the respiratory system as carbon dioxide.The degradation time of these polymers is of the order of two to six months, depending upon environment, chemical composition, and geometry of the polymer devices (Sinclair, 1973).

Lactic acid can not form a lactone as other hydroxy acids do because the hydroxy group is too close to the carboxylic group. Instead, lactic acid first forms a dimer, which is similar to 5-hydroxyacid. The dimer contains a hydroxy group at a convenient distance from the carboxylic group for the formation of a lactone. Indeed, the dimer readily forms a six-membered cyclic diester known as lactide. Dilactide (3, 6-dimethyl-1, 4-dioxan-2, 5-Dione) contains two asymmetric centers and therefore exists as L -lactide, D-lactide and *meso*-lactide. The racemic 1:1 mixture of L and D is generally called D, L-lactide (Bendix, 1998).

Thus, lactide is the cyclic diester of lactic acid. It can be polymerized to polylactide using suitable catalysts, with either syndiotactic or a heterotactic stereocontrol, to yield materials with many useful properties.

1.2 Lactide Polymerization

Poly lactide, a semi crystalline polymer, is a white fibrous material with T_g of 61 °C and T_m of 174 °C (Vert, 1984). Polylactide (PLLA) is produced from lactic acid, either by direct polycondensation of lactic acid or via ring opening polymerization of lactide. It is reported that the most effective way to prepare polylactide is the ring opening polymerization (ROP) by anionic, cationic and coordination initiators (Dechy-Cabaret 2004). A number of different initiators and catalysts like aluminium (Dubois, 1991; Kricheldorf, 1988), lead (Kricheldorf, 1985), tin (Nijenhuis, 1992; Leenslang, 1987), zinc (Bero, 1990; Chabot, 1983) and bismuth (Kricheldorf, 1985) have been used in the ROP reactions. The catalytically active metal is covalently bound to the polymer chains as a result of polymerization mechanism and is in most cases difficult to remove completely from the polymer. This affects the degradation environment and even results in accumulation. This is particularly undesirable in medial applications, where both the polymer and the degradation products, including residues of the initiator should be non toxic and resorbable. For this reason, salts and complexes of metals such as Al, Bi, Cd, Pb, Y and Sn compounds should be avoided.

On the other hand, a number of iron compounds occur in living organisms and in nature which are less harmful than other metal compounds. The use of iron compounds has been described only to some extent. Iron oxide was used as a catalyst in melt polymerization of lactide (Kricheldorf, 1985). These polymerization experiments were performed at various temperatures, but the catalyst proved to be useful only at the highest polymerization temperature (180^0C). Polyester from L-lactide and sorbitol was prepared using $FeCl_3$ (Arvanitoyannis, 1996). Other iron compounds like iron acetate, iron trifluoroacetate and iron isobutyrate were used for synthesis of homopolymers of lactide (Stolt, 1999). But yet iron compounds are not reported for copolymerization reactions of lactide.

To avoid the difficulties of metal catalyzed polymerization, enzymatic polymerization may be one of the possible options. Porcine pancreatine lipase and

lipase from Candida cylindracea were used for bulk homopolymerization of lactide for seven days (Matsumura, 1997). But the polymerization yields were low.

1.3 Lactide-Glycolide Copolymers (PLGA)

PLLA is less crystalline and more hydrophobic than PGA and therefore degrades at a slower rate. The major degradation mechanism is simple hydrolysis, but there is a small but nonetheless significant contribution from *in vivo* enzymatic degradation.The lower degradation rate of PLLA as compared to PGA, is due to the presence of the methyl groups, which gives PLLA its hydrophobic character and sterically hinders ester bond cleavage. PLLA is one of the strongest known biodegradable polymers and has therefore found many applications in areas, such as orthopedics, where structural stength is an important criterion (Engelberg, 1990).The mechanical strength of PLLA allows its use as a scaffold material for both soft tissues, as liver and hard, load bearing tissues such as cartilage and bone. A porous form of PLLA has been used as a scaffold for both chondrocyte and hepatocyte transplantation in the regeneration of cartilage and liver respectively. The surface chemistry and the pore morphology of this material are such that they provide an environment for cell attachment, growth and differentiation. In addition, FDA approval for other biomedical applications and proven ability to act as suitable substrates for several cell types has made these polymers attactive choice as scaffold materials to engineer many tissues (Thomson, 1995) .

PLGA copolymers, with glycolic acid contents between 25 to 70 % are amorphous and are therefore not as strong as partially crystalline PLLA.The range of physical properties and degradation rates which may be achieved using PLLA, PLGA polymers and PGA makes these synthetic degradable polymers extremely versatile as scaffold materials.

1.3.1 PLGA Applications

Homopolymers and copolymers of lactide and glycolide (PLGA) polymers have a long and successful history of medical and pharmaceutical use in fields as diverse as sutures, bone fixatives, artificial skins and cartilages, dental materials, body implants, materials for bone regeneration, drug delivery and many others (Grijpma, 1994; Holland, 1986; Lewis, 1990, Ueda, 2003). The lactide and glycolide polymers are among the few biodegradable polymers approved by US Food and Drug Administration for human clinical use (Davis, 1996). One example is PLGA containing leuprorelin acetate (LH-RH agonist) for the treatment of endometriosis and prostate cancer. These polymers are also being explored for long-term delivery of antimalarial drugs, contraceptives, ophthalmic drugs. The major application areas of these aliphatic polyesters are thus in the form of pharmaceutical excipients in formulation design. (Ikada, 2000).

Aliphatic polyesters such as poly (D, L-lactide) and its copolymers with glycolic acid have received considerable attention for the preparation of sustained release drug delivery systems (Toguchi, 1995; Bala, 2004; Matsumoto, 2005), in the medical field as substrates for tissue engineering (Lu, 2001) as well as osteofixation devices in cranio maxillofacial surgery (Ashammakhi, 2001). The different uses of these polymers in pharmaceutical and biomedical fields are based on their biocompatible and biodegradable characteristics.

The degradation characteristics of these polymers are very important for their pharmaceutical and biomedical applications (Blanco, 2006). The rate of degradation is known to be affected by the method of preparation, (Lemoine, 1996; Cai, 2003) by polymer properties such as initial molecular weight, morphology of the devices and lactide/glycolide ratio of the copolymers (Li, 1990a, 1990b, 1990c), as well as by physical and chemical parameters such as temperature and pH of the external medium (Li, 1999). Studies have been also carried out to evaluate the effect of the particle size (Lemoine, 1996; Dunne, 2000), the number of carboxylic end groups in the device (Schliecker, 2003) or the presence of enzymes in the external medium (Cai, 2003) on the degradation behavior of poly (α-hydroxy acids). The release of drugs from microparticulate delivery systems prepared with poly (D, L lactide) and poly (lactide-co- glycolide) is controlled by diffusion and / or erosion mechanisms

(Batycky, 1997; Wong, 2001; Lemaire, 2003). The erosion of microparticles depends on the polymer, the size of the system and the process used to obtain the particles (Dunne, 2000).

1.3.2 PLGA - Biodegradable Polymers

For PLGA, the term biodegradable refers to a non enzymatic, hydrolytic cleavage upon contact of any PLGA device with artificial or biological fluids (Tamber, 2005). Polymers and copolymers of lactic and glycolic acids, also known as poly (α-hydroxy acids), are the best known representatives of this class of materials (Dunn, 1991; Dunn, 1995; Aguado, 1992; Spenlehauer, 1989; Cohen, 1991). PLGA copolymers degrade via hydrolytic cleavage of their backbone by hydrolysis to lactic and glycolic acids through Krebs cycle to produce CO_2 and water which are normal metabolic compounds (Aguado, 1992; Vert, 1991; Wang, 1990; Lewis, 1990; Li, 1990). One of the most important advantages of these macromolecules is that by varying the lactide / glycolide ratio in copolymers or by altering the molecular mass of the polymer, the degradation rate and mechanical properties of these materials can be accurately controlled (Andrianov, 1998). Commercial availability of these polymers and biocompatibility also contribute to the popularity of these macromolecular systems in the development of drug delivery systems. A number of different antigens and vaccines including diphtheria toxoid, tetanus toxoid, malaria vaccine, staphylococcal enterotoxin B toxoid and contraceptive vaccines have been incorporated into lactide / glycolide copolymers (Dunn, 1995). However, recent studies have shown that the use of poly (lactide / glycolide) (PLGA) copolymers for protein drug delivery also entails some problems. Among them is the loss of biological activity of the encapsulated protein possibly due to polymer matrix hydrophobicity and acidity (Sluzky, 1991; Li, 1997; Hanes, 1995) In order to stabilize proteins in poly(lactic-co-glycolic acid) (PLGA) matrices, an attempt to first encapsulate the protein drug in gelatin nanoparticles prior to encapsulation in PLGA, was reported (Li, 1997).

When used as matrix material for microspheres, PLGA degradation proceeds in two stages (Göpferich, 1996).The first involves the hydrolytic scission of the ester bonds (degradation), generating oligomers and monomers and general decrease in the polymer molecular weight. In the second stage (erosion), the microspheres lose mass and the rate of polymer chain scission increases due to autocatalysis in the presence of acidic degradation products (Pitt, 1981) and (Fu, 2000).

In recent years, environmental concerns have led to renewed interest in biodegradable polyesters as an alternative to commodity plastics (Vert, 1995; Mayer, 1994).

1.4 Biodegradable Polymers

The use of synthetic biodegradable polymers as carriers to deliver drugs and antigens has increased dramatically in recent years (Chasin, 1995; Park, 1993). Biodegradable polymers are generally defined as macromolecular materials capable of conversion into less complex products through chemical reactions, such as simple or enzyme catalyzed hydrolysis over a reasonable period of time (Wang, 1990; Park, 1993). Such chemical changes usually result in the dissolution of the previously insoluble material and involve either alterations in polymer side groups or destruction of the macromolecular backbone into shorter chain segments and low-molecular-mass products. The most desirable biodegradable system is a completely degradable system, which leaves no residual polymer following the release of the drug in a reasonable period of time. However, bioerodible materials are also widely employed in drug delivery (Park, 1993). In these systems the release of the drug is accomplished through a decrease in the integrity and a subsequent dissolution of the polymeric matrix, but not necessarily chemical degradation.

A great deal of attention and research effort is being concentrated on biodegradable polymers as these materials degrade within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable,

and progressively smaller, compounds. Degradation may take place through bulk hydrolysis, in which the polymer degrades in a fairly uniform manner throughout the matrix, as shown schematically in **Figure 1 a**. For some degradable polymers, most notably the poly anhydrides and poly ortho esters, the degradation occurs only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system, as shown in **Figure 1 b**.

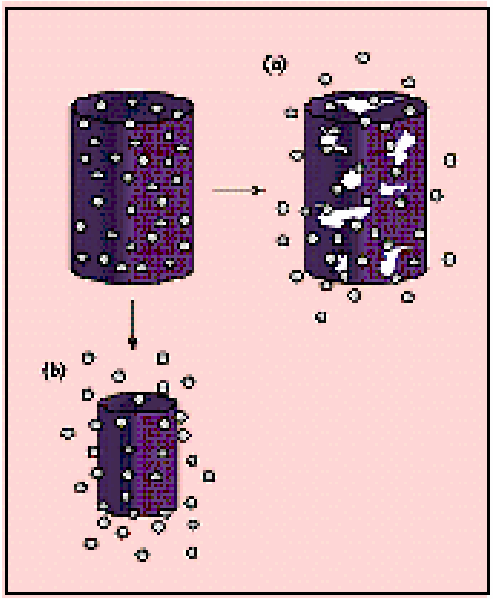


Figure 1:

Drug Delivery from (a) Bulk-eroding and (b) Surface-eroding Biodegradable Systems

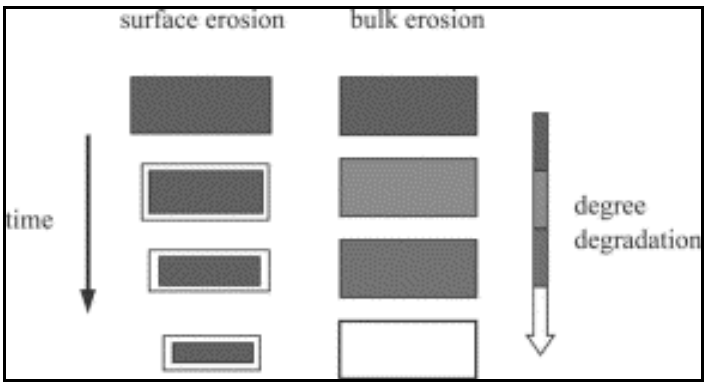


Figure 2 Schematic Illustrations of Surface and Bulk Erosion (Winzenburg, 2004)

1.4.1 Factors Affecting Biodegradation

The biodegradation of polymers proceeds via hydrolysis and oxidation. Most of the biodegradable synthetic polymers and biopolymers contain hydrolysable groups along the main chains. Initial studies of biodegradation mechanisms were motivated by biomedical applications of biodegradable polymers. There are many factors which contribute to biodegradability of polymers.

Key factors elucidated by Huang and co- workers (Huang, 1986) include segmental mobility, surface area, morphology, molecular weight, hydrophilic / hydrophobic interactions and the availability of hydrolysable links. It was also learnt that functional group recognition by specific enzyme enhances degradability. There are many factors which influence rate and extent of biodegradation of polymers. **Figure 3** highlights factors affecting rate of biodegradation.

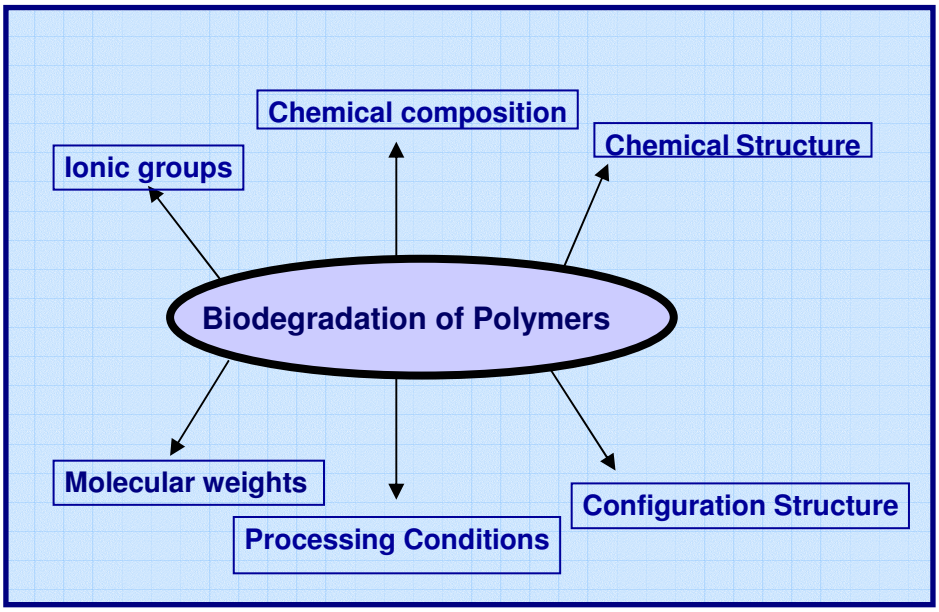


Figure 3 Factors Affecting Biodegradation of Polymers

1.4.2 Criteria for Marketable Polymers

All the polymers of aliphatic polyester group have been investigated for therapeutic applications during last 20 years and only a few are now on the market. Still there is a huge gap between materials investigated in the laboratory and those which have been commercially successful. Many prerequisites must be fulfilled if one really wants to reach the stage of clinical applications.

1. Biocompatibility
2. Biofunctionality
3. Stability
4. Bioresorbability

Depending on the biodegradation criteria, the lactide polymers have been explored as excipients in parenteral drug delivery applications. There is a need for modification in lactide polymer structure in order to tailor it for oral application.

1.5 Drug Design

Drugs, whether they are obtained from plant, animal or mineral sources or synthesized chemically, are rarely administered in their pure chemical form. Often they are combined with a number of inert substances and transformed into a convenient dosage form that can be administered by a suitable route. Earlier it was believed that the intrinsic response of the drug is an attribute of its pharmacological activity. But now it is realized that the dose-response relationship obtained after drug administration by different routes – for example oral and parenteral are not same. Variations are also observed when the same drug is administered as different dosage forms or similar dosage forms are produced by different manufacturer, which in turn depends upon the physicochemical properties of the drug, the excipients present in the dosage form, the method of formulation, and the manner of administration. A new and separate discipline called biopharmaceutics has therefore been developed to account for all such factors that influence the therapeutic effectiveness of drug.

1.5.1 Drugs and Biopharmaceutics

Biopharmaceutics is the study of the factors influencing the rate and amount of drug that reaches the systemic circulation and the use of this information to optimize the therapeutic efficacy of the drug products.

To achieve optimal results with the drug, the dosage form must be designed to deliver the active principle at optimal rate and amount, depending upon patient's needs. Knowledge of factors affecting the bioavailability of the drugs helps in designing such an optimum formulation.

On the other hand, rational use of the drug or the therapeutic objective can only be achieved through a better understanding of pharmacokinetics, which helps in designing proper dosage regimen. Majority of drugs are administered extravascularly, generally orally. If intended to act systemically, such drugs can exert their pharmacologic actions only when they enter blood circulation from their

site of application, and for this, absorption is an important prerequisite step. By proper biopharmaceutical design, the rate and extent of drug absorption (also called bioavailability) or the systemic delivery of drugs to the body can be varied from rapid and complete absorption to slow and sustained absorption depending upon desired therapeutic objective.

1.5.2 Pharmacokinetics and Pharmacodynamics

Absorption of drugs is responsible for therapeutic effectiveness of drugs. Absorption is the process of movement of drug from its site of administration to systemic circulation. The concentration of the drug in plasma and the onset of action, the intensity and duration of response depend upon bioavailability of drug from its dosage form. The knowledge and concepts of biopharmaceutics and pharmacokinetics play an integral role in the design and development of dosage forms and improvement of therapeutic efficacy of the drugs.

Drug administration and therapy can be divided into four processes.

1. Pharmaceutics process- It is concerned with the formulation of an effective dosage form of the drug for administration by a suitable route.
2. The pharmacokinetic process- It is concerned with absorption, distribution, metabolism and elimination (ADME) of drugs as elicited by the plasma-drug concentration-time profile and its relationship with the dose, dosage form, frequency, and route of administration. In short, it is the sum of all the processes inflicted by the body on the drug.
3. The pharmacodynamic process - It is concerned with the biochemical and physiologic effects of the drug and its mechanism of action. It is characterized by the concentration of the drug at the site of action and its relation to the magnitude of effects observed. Thus pharmacodynamics deals with what the drug does to the body in contrast to pharmacokinetics which is a study of what the body does to the drug.
4. The therapeutic process- It is concerned with the translation of pharmacologic effect into clinical benefit.

1.5.3 New Drug Delivery Systems (NDDS)

New drug delivery systems have been successfully introduced throughout the 1980s and 1990s, mainly through the development of sustained-release (controlled-release) oral delivery forms or transdermal patches. These new dosage forms were mainly applied in the therapeutic areas of hypertension, angina, arthritis, smoking cessation, and hormone replacement therapy i.e. chronic diseases or conditions that require continuous drug therapy for long (even life-long) periods of time (Seager, 1998). An additional advantage of advanced controlled-release formulations of drugs such as verapamil, nifedipine, metoprolol, nitroglycerine, morphine, fentanyl, and estrogens is added economic value due to simplified administration regimens (resulting in enhanced compliance) and controlled drug input that prevents super- or subtherapeutic plasma drug concentrations (Cramer, 1994). The multiple benefits of employing new drug delivery systems and innovative drug formulations are being increasingly recognized and are now better understood (Frijlink, 2003). Studies have shown that innovative drug delivery systems can improve drug therapy in several different ways, such as

- Enabling targeting of drugs to the site of action.
- Enabling usage of drug therapy that would otherwise be impossible.
- Allowing usage of new, more convenient/comfortable routes of administration.
- Enabling a drug's release at the time when pharmacological action is indicated / needed.
- Improving patient compliance with medication.
- Increasing comfort to the patient and improving health-related quality of life.

To achieve optimal therapy with a drug, the drug product must be designed to deliver the active principle at an optimal rate and amount, depending upon patient's needs. On the other hand, rational use of the drug or the therapeutic objective can only be achieved through a better understanding of pharmacokinetics in addition to pharmacodynamics of the drug, which helps in designing a proper dosage regimen.

1.5.4 Routes of Drug Delivery

For most drugs, there is a direct relationship between pharmacological response and concentration at the receptor. Thus to be biologically active, the drug must gain access to the systemic circulation. Plasma drug concentration depends on both drug kinetics and the design of the drug delivery system. Not only the magnitude of drug that comes into the systemic circulation but also the rate at which it is absorbed is important.

A drug that is completely but slowly absorbed may fail to show therapeutic response as the plasma concentration for desired effect is never achieved. On the contrary, a rapidly absorbed drug attains the therapeutic level easily to elicit pharmacologic effect. Thus both the rate and the extent of absorption are important.

Drugs that have to enter the systemic circulation to exert their effect can be administered by three major routes:

1. The Enteral Route: Includes *per oral* i. e. gastrointestinal, sublingual / buccal and rectal routes. The GI route is the most common for administration of majority of drugs.

2. The Parenteral Route: Includes all routes of administration through or under one or more layers of skin. While no absorption is required when the drug is administered i. v., it is necessary for extravascular perenteral routes like the subcutaneous and the intramuscular routes.

3. The Topical Route: Includes skin, eyes or other specific membranes. The intranasal, inhalation, intravaginal and transdermal routes may be considered.

The average development cost of a new chemical entity (NCE) is approximately $ 600–850 million. It often costs substantially less to develop new methods of administration for an existing drug, which results in improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. Therefore, pharmaceutical companies are under constant pressure to maximize the full potential of a drug candidate at an early stage of its life cycle. This objective can be accomplished by incorporating the drug into various drug delivery systems. This exercise can lead to extended patent life and convenient dosage forms that overcome

previously presented administration problems. For the last two decades, there has been enhanced demand for more patient compliant dosage forms. Novel technologies with improved performance, patient compliance and enhanced quality have emerged in the recent past (Venkateswara**,** 2000). Electrostatic drug deposition and coating, and computer-assisted three-dimensional printing (3DP) tablet manufacture have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance for oral delivery of drugs.

1.6 Oral Route of Administration

Of the many routes of novel drug delivery, the oral administration has been considered to be the most convenient means to introduce drugs into the systemic circulation. Drug delivery technologies are therefore aimed to develop novel, innovative drug delivery systems and dosage forms that will be more user-friendly as well as more efficient in maximizing the therapeutic potential of the active compounds. The availability of novel, sophisticated drug delivery systems and formulations offers a range of benefits to patients, in terms of maximizing the pharmacological potential of drugs, as well as optimizing acceptability to the patient (Gohel, 2002). These innovative approaches are of particular importance in the treatment of chronic diseases that need regular pharmacotherapy but are often associated with suboptimal compliance and poor outcomes resulting from it. The availability of drug delivery systems that will facilitate regular drug intake in a patient-friendly manner has a major impact on quality of health care provided to patients, as well as on health-related quality of life, and may ultimately lead to improved overall outcomes in an array of serious, chronic illnesses. Better patient compliance and large surface area in the gastrointestinal tract are the two most important advantages of oral drug delivery systems. Zero-order drug delivery systems are designed by researchers assuming that physiological processes and biological functions display constancy over time. Therefore, many efforts have been

devoted in the past in developing the drug delivery systems that maintain a flatter plasma level for an extended time period.

1.6.1 GIT Anatomical Considerations

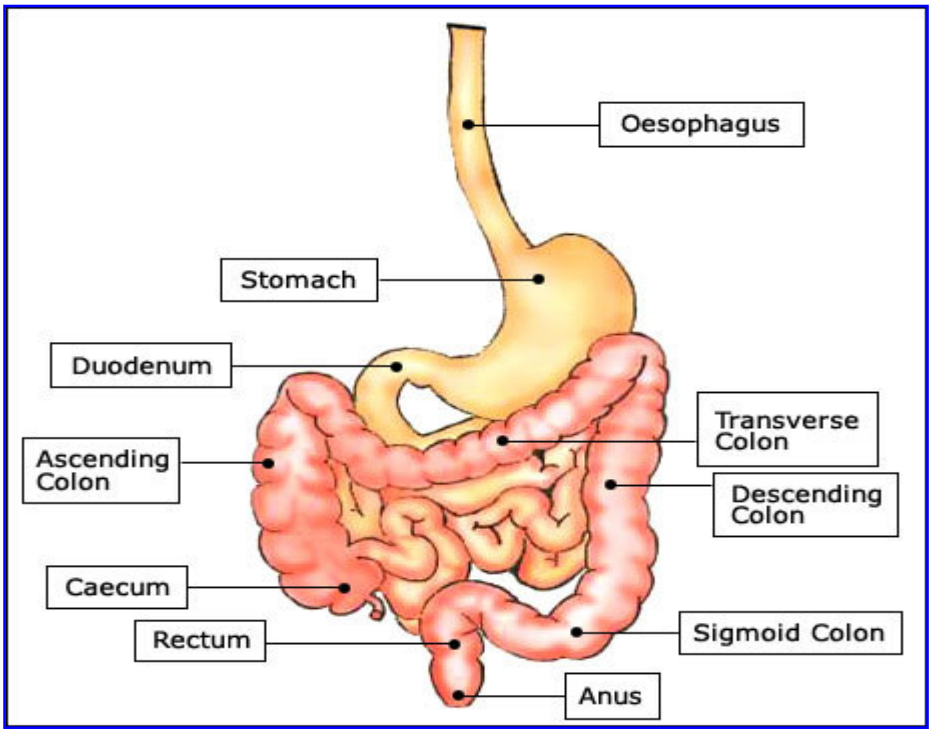


Figure 4 A Schematic Representation of the Gastrointestinal Tract

Oral administration commences with ingestion of the dosage form through the mouth. The stomach normally functions as storage and grinding organ, also some drugs are absorbed through the stomach. Acid is produced by the parietal and oxyntic cells in the stomach and pH of the stomach under fed state is 2 to 6.The stomach does contain gastric pits, which increase surface area to a limited extent. The entry of materials into the small intestine is controlled by co-ordination of gastro duodenal junction and the proximal duodenum. pH of the small intestine ranges from 6 to 7.5. By virtue of its large surface area, the small intestine is primary site of drug absorption. Theoretically, drug absorption can occur along the entire GI tract, but most drugs are absorbed in the duodenum and small intestine.

1.6.2 Types of Oral Dosage Form

The most commonly used delivery systems involve absorption of drug from the gastrointestinal tract following buccal, sublingual, rectal or most often, oral administration. Commonly encountered oral forms can be broadly categorized as Solids and liquids.

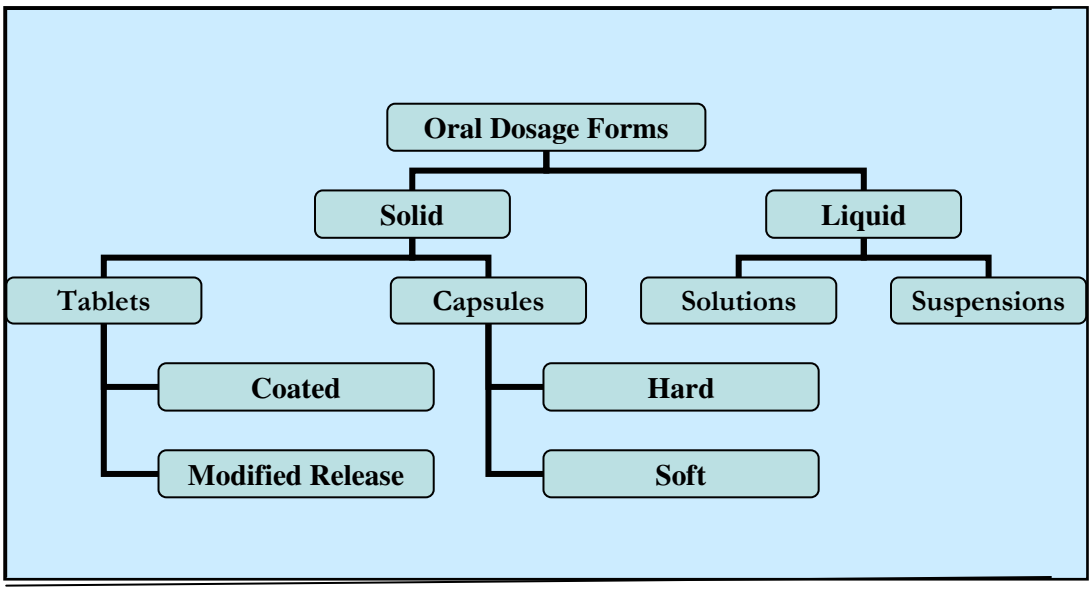


Figure 5 Oral Dosage Forms at a Glance

Tablet is the most common delivery system. It has advantages of convenience and accuracy of dose. It is possible to alter the delivery and apparent kinetics of drug absorption and metabolism by changing the dissolution characteristics of tablets. Thus, a tablet may be enteric-coated to prevent breakdown in the stomach, ensuring that it remains intact until it reaches the small intestine. This approach is commonly used to protect drugs that are destroyed by gastric acid (e.g. omeprazole).

The tablet excipients may be modified to improve drug delivery by controlling the rate, amount and duration of drug release over a 24-hour period. This approach is

used for drugs with short half life (t ½), which require frequent dosing to maintain therapeutic levels (e.g. theophylline, verapamil, nifedipine).

Conventional oral drug administration does not usually provide rate-controlled release or target specificity. In many cases, conventional drug delivery provides sharp increases in drug concentration at potentially toxic levels. Following a relatively short period at the therapeutic level, drug concentration eventually drops off until re-administration. Today new methods of drug delivery are possible which can attain constant drug levels by tailoring desired drug release though rate-controlling membranes or by implanted biodegradable polymers containing dispersed medication.

1.6.3 Oral Controlled Release Systems

Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design (possible because of versatility of GI anatomy and physiology) and ease of production and low cost.

Ideally drug release should match patient's physiological needs in terms of time and / or site of release. This is why there is a great interest in the development of controlled delivery systems (Qiu, 2001). Drug delivery technology has been brought to an advanced level by fabrication of smart materials into a single assembled device that is responsive to the individual patient's therapeutic requirements and delivers desired amount of drug in response to a biological state. Such smart therapeutics should possess one or more properties such as proper drug protection, local targeting, precisely controlled release, self-regulated therapeutic action, permeation enhancing, enzyme inhibiting, imaging and reporting. This is clearly highly challenging task and it is difficult to add all of these functionalities in a single device.

Current understanding of the mechanisms of drug absorption, GI transit, and the microenvironment of the GI tract under normal and pathological conditions is still incomplete. Design of the controlled release products is usually empirically based,

relying on gross characteristics of the GI tract, e.g. pH and transit, rather than the preferred cellular and molecular information.

1.6.3.1 Prerequisites of Oral Controlled Release Systems

The performance of oral controlled release dosage form is usually determined by the interplay of following three major variables:

a. Physicochemical properties of the drug

b. Composition and characteristics of the dosage form

c. Anatomical and physiological constraints

The task of pharmaceutical scientists is to optimize factors (a) and (b) within the inherent constraints of (c) which encompasses factors such as chemical and enzymatic degradations in the stomach and small intestine, gastric emptying, intestinal motility, mucosal barriers as well as metabolic degradation during passage through mucosa and subsequently the liver.

However with exception of prodrugs, all oral controlled release systems can only exercise control over the release rate of the drug from the dosage form, and perhaps the residence time in GI tract. They have virtually no control over the fate of the drug once it is absorbed into systemic blood circulation. Other factors such as the presence of enzymes, influence the performance of the drug and the drug delivery system in the GI tract. These factors are in turn influenced by factors such as age, circadian rhythm and diseases as well as intra and inter subject variations.

The factors which influence performance of oral controlled release products are

1. GI motility and transit time
2. pH of the GI tract
3. GI secretions
4. Blood flow
5. Luminal contents
6. Luminal metabolism: Gut wall and bacterial
7. Membrane motility
8. Site specific absorption.

1.6.3.2 Classification of Oral Controlled Release Forms

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon manner of drug release, these systems are classified as follows:

A. Sustained Release Systems

These systems release the drugs along the entire length of GIT (especially upto the terminal region of small intestine) with normal transit of the dosage form. The various systems under this category are:

1. Dissolution controlled release systems
2. Diffusion controlled release systems
3. Dissolution and diffusion controlled release systems
4. Ion exchange resin drug complexes
5. Slow dissolving salts and complexes
6. pH dependent formulations
7. Osmotic pressure controlled systems
8. Hydrodynamic pressure controlled systems

B. Delayed Transit and Continuous Release System

These systems are designed to prolong their residence in the GIT along with their release.

Often, the dosage form is fabricated to detain in the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are…

1. Altered density systems
2. Muco adhesive systems
3. Size based systems

C. Delayed Release Systems

The design of such systems involves release of drug only at a specific site in the GIT. The drugs contained in such a system are those that are:

a. Destroyed in the stomach or by intestinal enzymes

b. Known to cause gastric distress

c. Absorbed from a specific intestinal site, or

d. Meant to exert local effect at a specific GI site

The two sites for delayed release

1. Intestinal release systems

2. Colonic release systems

1.6.3.3 Drug Release Patterns

Depending on the pattern of drug release, the dosage forms can be divided into three categories

1. Delayed release-Release of drug from dosage form immediately after reaching the intestine

2. Extended release-Release of drug from dosage form at a slow rate after reaching intestine

3. Immediate Release- Release of drug immediately after reaching the stomach.

Release of the drug from dosage form can be studied in vitro using dissolution apparatus. Dissolution of most of the drugs has greatest influence on its absorption. The best way to assess therapeutic efficacy of drugs with a slow dissolution rate is *in vivo* determination of bioavailability which has to be done whenever a new formulation is to be introduced into a market. However, monitoring batch to batch consistency through use of such *in vivo* tests is extremely costly, tedious and time consuming besides exposing the healthy individuals to hazards of the drug. The *in vivo* bioavailability tests are later substituted by inexpensive *in vitro* methods. The best tool available today which can at least quantitatively assure about the biologic availability of a drug from its formulation is its in vitro dissolution test.

1.6.3.4 Dissolution of the Dosage Form

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two steps, *in vitro* dissolution is relevant to the prediction of *in vivo* performance. Based on this general consideration, *in vitro* dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules, are used to (1) assess the lot-to-lot variation in the quality of the drug product; (2) guide development of new formulations; and (3) ensure continuing product quality and performance after changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process.

There are two principal types of dissolution apparatus depending on presence or absence of sink conditions.

1. Closed compartment apparatus- Limited volume apparatus operating under non sink conditions. The dissolution fluid is restrained to the size of the container e. g. beaker type apparatus

2. Open compartment apparatus: It is the one in which the dosage form is contained in a column which is brought in continuous contact with fresh, flowing dissolution medium (perfect sink conditions).

In light of the FDA's recent guidance regarding oral modified release dosage forms, there is an increased awareness of the potential relevance of dissolution tests. Previously this test was used to as a quality control tool, but now it is developing into a tool for predicting bioavailability, and in some cases, replaces clinical studies to determine bioequivalence. The biopharmaceutical relevance of dissolution testing has certainly increased. The FDA provides guidelines for dissolution tests for oral modified release dosage forms, but also realizes the need for individualizing the method on a case by case basis leaving the justification of a given methodology up to the scientist. Therefore, the individual scientist is challenged to design an appropriate test based on the objectives to be accomplished, e.g., quality control, *in*

vitro-in vivo correlations, showing bioequivalence, etc. The physical chemical parameters and physiological conditions need to be considered when designing a dissolution test for modified release delivery systems.

While considering any oral dosage form, laboratory study for in vitro drug release needs to be performed according to official pharmacopoeial standards. Special equipment called as dissolution apparatus is used for this purpose. Comparative release study of drug release from dosage forms can be performed under sink conditions. Appropriate dissolution medium of constant volume is added in all dissolution tubs and physiological temperature is maintained throughout the release study. Samples are withdrawn at regular time intervals depending on type of dosage form and medium is replaced with same amount of fresh medium.

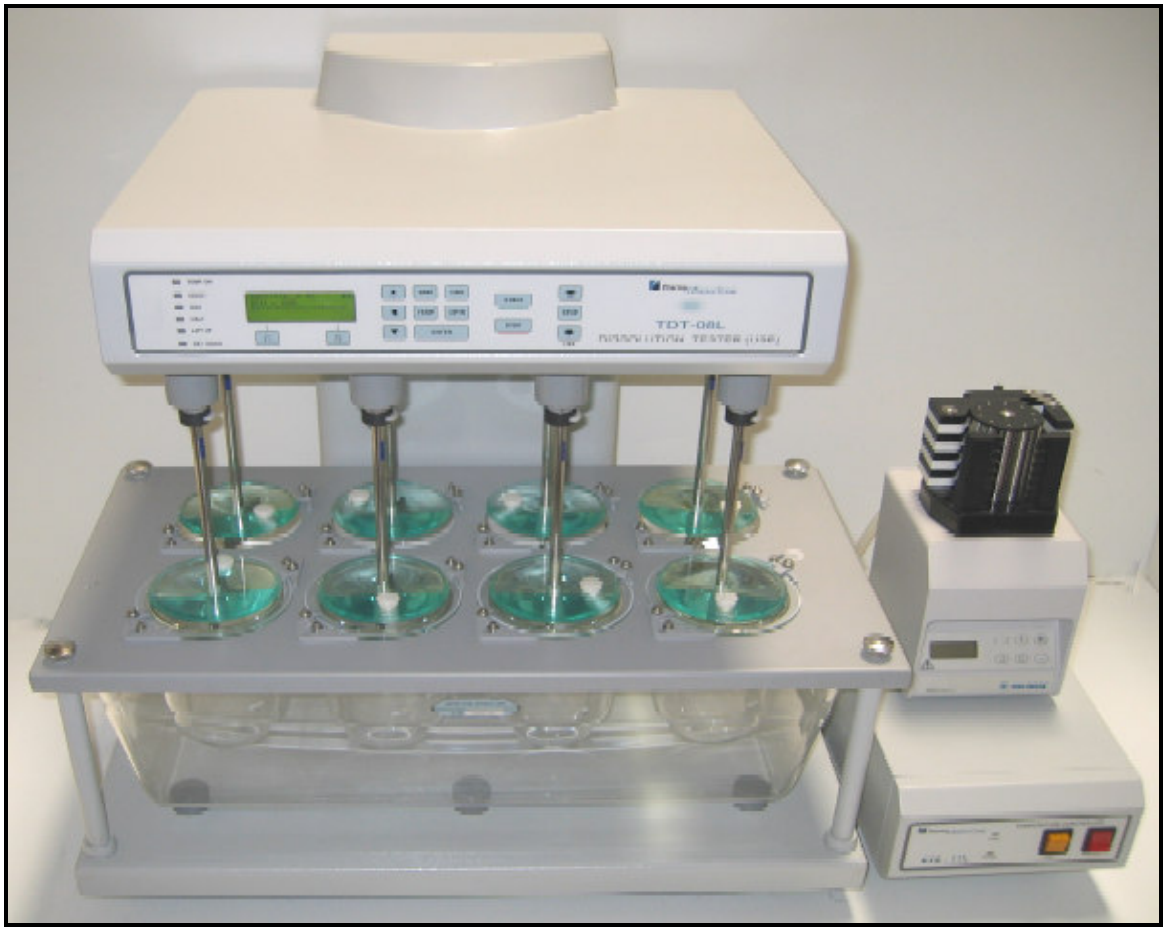


Figure 6 Dissolution Apparatus

Current knowledge about the solubility, permeability, dissolution, and pharmacokinetics of a drug product should be considered in defining dissolution test specifications for the drug approval process. This knowledge should also be used to ensure continued equivalence of the product under certain scale-up and post approval changes.

When considering oral administration, a more or less significant loss in drug activity is frequently observed (Duchêne, 1999). In fact, this is the consequence of, either partial destruction of the drug through the gastrointestinal tract due to pH or enzymatic degradation, or partial absorption because of narrow absorption window. Hence these physiological constraints and physicochemical characteristics should be considered for design of modified drug delivery systems.

1.7 Modified Oral Dosage Forms

1.7.1 Site Specific Drug Delivery through GIT

Among modified release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsatile) and site specific delivery of drugs. Site specific drug delivery can be defined as delivery from a specific site (i.e. the route of administration) as well as delivery to a specific site (i.e. the site of action).Hence here it can be specified as oral drug delivery to specific site in GIT. This site can be stomach, small intestine or colon, depending on type of drug and its site of action. Low pH and the presence of proteolytic enzymes of the stomach present a very harsh environment for many drugs. Therefore, the need to by-pass the stomach has been shown to be important for a wide range of drugs. For instance, in order to apply acid-unstable antibiotics (Erah, 1997) or peptide drugs that are degraded by gastric enzymes (Bernkop-Schnürch, 1999), a protective effect is required. Also, direct targeting to the small intestine appears essential for successful immunization with orally administered antigens (Haneberg, 1994). Furthermore, drugs such as salicylates are irritating to the stomach (Carter, 1980) or even cause critical gastric damage leading to an obstruction of digestion in

case of tannins (Murakami, 1992). All these examples demonstrate the need for an acid stable delivery system preventing the release of the drug during gastric passage. Traditionally, the stomach is by-passed by a pH-sensitive coating of the drug carrier matrix. Methacrylic acid–methyl methacrylate copolymers registered as Eudragit, hydroxypropyl methylcellulose or cellulose acetate phthalate are currently used to form coatings, depositing the dose at the site where the coating dissolves (Odegardstuen, 1991; Kokubo, 1997; Lin, 1987). However, an additional production step is needed for the coating. A new way to overcome the passage through the stomach would be to develop a directly compressible excipient showing stability at the low pH of the stomach and drug release at the higher pH of the intestine or colon. A preferred formulation would consist of a single compound which is cheap and consists of commonly used biocompatible pharmaceutical excipients. Previous studies introduced systems with low cohesiveness (Carelli, 2000) which had to be hardened by an additional production step. This demonstrates that the aim of a single, easily compressible compound showing controlled pH-sensitive disintegration behavior has not yet been attained. The efforts were taken to generate a directly compressible tablet containing poly methacrylic acid and starch. The dissolution and disintegration behavior of matrix tablet was studied (Clausen, 2001). In particular, systems for delayed release are meant to deliver the active principle after a programmed time period following administration. These systems constitute relatively new class of delivery systems in accordance with the chronopharmacology of the drug. It is by now well-known that the symptomatology of a large number of pathologies as well as the pharmacokinetics and pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations (Lemmer, 1991). Therefore, the possibility of exploiting delayed release to achieve chronotherapeutic delivery is quite appealing for those diseases, the symptoms of which recur mainly at night time or in the early morning, such as bronchial asthma, angina pectoris and rheumatoid arthritis. The delay in the onset of release has so far mainly been achieved through osmotic mechanisms, hydrophilic or hydrophobic layers coating a drug-loaded core and swellable or erodible plugs sealing a drug-containing insoluble capsule body (Gupta, 1996;

Maffione, 1993; Gazzaniga, 1994; Pozzi, 1994; McNeil, 1994; Kroegel, 1998; Ross, 2000).

Time and / or site specific drug delivery can be advantageous in the treatment of certain diseases. The symptoms of bronchial asthma and rheumatoid arthritis, for example, follow circadian rhythms, recurring primarily at night or in the early morning. A delayed release formulation that can be taken before bedtime is advantageous in these cases. Delayed release is typically achieved through osmotic mechanisms, with tablets that contain a drug-loaded core which is surrounded by outer layers that slowly erode and then release the core. Alternatively, site-specific release is often used as a method to achieve drug delivery into specific regions of the gastrointestinal (GI) tract. In this regard, colon-specific release has advantages as a strategy for improvement of the oral bioavailability of peptide drugs. The local concentration of peptidases is lower in the colon than in the small intestine. Although physiologically it is not the ideal site for absorption when compared to the small intestine, the colon is the site of significant absorption, and some of the disadvantages are offset by the long residence time. In addition, colon specific delivery of drugs represents an advantageous approach for the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease (Weidner, 2001).

On the other hand, site specific release following oral administration is intended as drug delivery into specific regions of the gastrointestinal tract. In this respect, colon-specific release is particularly interesting as a potential strategy for the improvement of the oral bioavailability of peptidic drugs. In fact, it is known that the local peptidases concentration in colon is lower than that in the small intestine (Friend, 1991). Moreover, it has been proved that, although the colon is not inherently the ideal site in view of its anatomical and physiological features, it is the site of a significant absorption; it seems that these can be partially offset by the long residence time (Mrsny, 1992). In addition, targeted delivery to the colon represents an advantageous approach for the treatment of widespread inflammatory bowel disease (IBD) including ulcerative colitis and Crohn’s disease, as well as of tumoral, infective or neurovegetative colonic pathologies (Gazzaniga, 1994). Until now,

different strategies have been followed to achieve colon-specific delivery, based on the use of prodrugs or polymers selectively degraded by the local microflora (chemical / microbiological approach), on the exploitation of the pH variation along the gastrointestinal tract or of the relative reproducibility of small intestinal transit time (SITT) (technological / physiological approaches (Leopold, 1999).

In the last decade numerous animal as well as clinical studies have provided convincing evidence, that the pharmacokinetics and / or the side effects of the drug can be modified by the circadian time and / or the timing of drug application within 24 h of a day (Lemmer, 1991; Bjarnason, 2001; Bjorn, 1996). As a result of this, colon-specific drug delivery systems (CDDS) have been developed as one of the site-specific drug delivery systems (Mastiholimath, 2007). Along with many applications in local and systemic delivery of drugs, the CDDS would also be advantageous when delay in absorption is desirable from therapeutic point of view as for the treatment of diseases that exhibit peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis. (Bi-Botti, 2004; Sarasija, 2005). So by developing the pulsatile device for specific colonic delivery, plasma peak is obtained at an optimal time, number of doses per day can be reduced; saturable first pass metabolism and tolerance development can also be avoided (Morta., 1998; Richard, 1998; Gwen, 2002). There are few strategies to achieve colonic specificity such as bacterially triggered, pressure controlled, pH dependent and time dependent CDDS (Libo, 2002; Abdul, 2003 ; Chourasia, 2003).

Oral modified release systems are popular and can be formulated as single or multiple unit dosage forms. The relative merits of multiple unit dosage forms (e.g., in terms of bioavailability, more consistent blood levels, predictable gastrointestinal transit time, less localized gastrointestinal disturbances and greater product safety) over single unit products are well established (Marvola,1999; Davis, 1984; Hardy, 1985).

In modified release systems the design of the dosage form allows for a specific drug delivery pattern so that the release rate becomes the rate-limiting step (Pillay, 1999). This should be viewed in the context of other existing parameters within the

gastrointestinal tract. For example, the two major rate limiting factors which limit drug absorption are gastrointestinal environment (e.g., pH, site and efficiency of absorption, gut metabolism, gastrointestinal content) and transit rate of the dosage form (Sangalli, 2001). From a manufacturing point of view, irrespective of the types of the dosage form (single or multiple unit), currently the utilization of hydrophilic swellable ingredients in the design of modified release systems are common and offer significant flexibility in pharmaceutical technology (Singh, 1993; Ostberg, 1994; Monshipouri,1995; Garcia, 1996; Kim, 1997; Yang, 1997). In view of the benefits offered by multiple unit dosage forms, it is speculated that such systems are particularly useful: (i) for delivering highly-irritant drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) (Heinamaki, 1998; Lin, 1993); (ii) for site-specific targeting to the gastrointestinal tract (Ritschel, 1991); and (iii) for delivery of enzymes, peptides / proteins and vaccines (Chen, 1997; Desai, 1997)

1.7.2 Taste Masking

Taste masking is another type of modification in formulation which is used to increase patient compliance. Many pharmaceutical drugs have an unpleasant and very bitter taste. The major consequence of the bitter taste is to restrict greatly the further development of oral preparations and clinical applications of these drugs. Accordingly, it is important to mask the unpalatable taste of a drug in order to improve the product quality. This will also increase the value of the finished product as well as patient compliance, especially where infants, children and elderly are concerned.

1.7.2.1 Compliance

If a drug is to achieve the desired therapeutic effect, it is necessary for the patient to be compliant (concordant) with medical therapy (Dimou, 2000). Compliance with therapy is defined as the extent to which patients follow the course of treatment. Factors believed to be important in ensuring patient compliance include the

complexity of the therapeutic regimen and patients' understanding of their disease and the need for and benefits of treatment (Bateman, 2003).

Noncompliance (NC) has been reported as a problem for wide range of diseases, both acute and chronic, including diseases that are life-threatening. Specific diseases or conditions for which noncompliance has been a significant problem include hypertension, epilepsy, diabetes mellitus, asthma, psychiatric disorders, peptic ulcers, rheumatoid arthritis, tuberculosis, hyperlipidemia, cancer, congestive heart failure and human immunodeficiency virus (HIV) infection. Thus, noncompliance is a serious and a widespread problem for a wide range of diseases, resulting in adverse health and economic consequences.

A special type of NC is inappropriate technique of self-administration of drugs using sophisticated delivery systems, such as administration of inhalation therapy for respiratory diseases. Failure of a patient to use a correct technique to administer a drug will lead to suboptimal dosing and poor therapeutic outcome. To improve drug delivery and compliance management in chronic diseases such as asthma, several microprocessor-assisted systems have been developed to help patients to improve the use of inhalers (Gonda, 1998)

NC is recognized as an important issue in both clinical practice and research. It is especially harmful when NC is present simultaneously at the interface between clinical practice and research namely, in patients enrolled in clinical trials (Serebruany, 2005). NC with prescribed medication regimens not only undermines the success of the therapy, but also represents a tremendous burden to the health care system. Rates of NC vary depending on a wide range of factors, including the socio demographic profile of the study population, (Wang, 2003) and (Worcester, 2003) the type of intervention (Carder, 2003; Cork, 2003) the duration and complexity of treatment, (Botelho, 1992) the perceived effectiveness of the drug therapy, and the occurrence of real or perceived adverse effects of the prescribed therapy (Bruckert, 1999). The more intensive the medication schedule (i. e, more doses per day) (Botelho, 1992) and the more severe the side effects, (Bruckert, 1999) the higher the rate of NC.

1.7.2.2 Methods for Taste Masking

In order to achieve more pleasant dosage forms, various masking techniques have been described in the literature (Zhang, 2003). The simplest method is to add flavors or sweeteners (Hussein, 1991; Eby, 1992). However, in most cases, these are rather limited and may not be effective enough to mask the unpleasant taste of some drugs. A number of more useful approaches have been tried, including capsule formulations, coating with lipids (Cherukuri, 1991; Shiozawa, 1993; Katsuragi, 1993), hydrophilic materials (Wheatley, 1992 ; Roche, 1994), water insoluble polymers or pH dependent water-soluble polymers (Yajima , 1996). Microencapsulation with various polymers (Sjoqvist, 1993; Gouin, 2004; Nii, 2005),complexation with ion exchange resin (Jaskari, 2001; Vuorio, 2003; Lu, 1991), inclusion complexes with cyclodextrins (Duchene, 1999; Loftsson, 2001) and viscosity modification (Blase, 1993) are other taste masking approaches described in the literature. In addition, chemical methods such as altering the chemical structure of the drug itself to remove the bitter taste have been used (Gregory, 1990; Asaka, 1994). In chemical taste masking, a lot of attention must be paid to prevent any loss of bioavailability after modification. In various methods taste masking is achieved in three steps. The first is to mask the distasteful sensation by the addition of flavors and sweeteners. The second is to avoid the bitter drugs coming into direct contact with patients' taste buds and the third is to reversibly anaesthetize patients' taste buds temporarily.

Microencapsulation techniques have become more and more popular in the last few decades because they offer significant advantages as far as taste masking of solid formulations is concerned (Gao, 2006). Furthermore, the materials used to coat the drug particles create a physical barrier and thereby enhance the stability of the particles.

1.7.2.3 Taste Masking of Oral Liquids

In case of infants and young children, many drugs are presented as liquid formulations, due to difficulties associated with conventional solid dosage forms like the need for fractional doses and the difficulty in swallowing relatively large, solid objects (Robson, 1999). The medication which imparts an unpleasant taste is likely to result in poor compliance to a drug regimen in case of such patients (Aronson, 1992). To overcome this problem, a number of taste-masking approaches have been described in the literature as cited above. In all cases it is essential for the liquid formulation to mask the taste of the drug in the vicinity of the taste buds while allowing favorable release in the lower gastrointestinal tract. These dual requirements have led to the development of suitable taste-masking formulations remaining a particular difficulty.

Taste masking is more important in case of some bitter antibiotics which are prescribed as full 3 to 5 day course to take care of wide spectrum infective organisms. Bitter taste of such antibiotics may lead to non compliance which generates drug resistant micro-organisms, further complicating the treatment. Classic example of such extremely bitter drug is cefuroxime axetil, an orally active pro- drug of second generation cephalosporin antibiotic cefuroxime. Cefuroxime axetil (CA) is prescribed for the treatment of a variety of complaints such as bacterial infection of skin and soft tissue, uncomplicated gonococcal infections, and lower respiratory tract and urinary tract infections (Gooch, 1987; Baddour, 1989).

Previously cefuroxime was marketed as a parenteral product (Zinacef™). On introduction the drug was reported to be active against a wide spectrum of bacteria, attributed to its stability towards β-lactamase-producing organisms (Ryan, 1976). However, as absorption via the oral route was minimal, (Foord, 1976) an orally active pro-drug was developed by substituting a 1-acetyloxyethyl ester group for sodium on the parent molecule. This substitution enhanced the lipid solubility and gastric stability of the molecule, thereby facilitating its oral absorption. Cefuroxime axetil itself has no antimicrobial activity. After oral administration, the ester is absorbed intact then rapidly hydrolysed by non-specific esterases in the internal

mucosa and portal blood to produce cefuroxime which is then absorbed into the blood stream (Harding, 1984).

However, administration of cefuroxime axetil to babies and young children was restricted since only a tablet form was available and it was sometimes necessary to administer crushed tablets mixed with a suitable beverage (Ginsburg, 1985). Studies by St. Claire, (1989) showed crushed cefuroxime axetil tablets to be stable for at least 2 hours when dispersed in several brands of fruit juice and chocolate milk then left at room temperature. This practice overcame some of the administration difficulties but a second problem became apparent. The unpleasant taste of Cefuroxime axetil was exacerbated when the tablets were administered as a temporary suspension. There was, therefore, a need to develop a liquid form of the drug which masked its unpleasant taste.

Several efforts were made in order to improve the palatability of the suspension. In one of the work, cefuroxime axetil was coated with stearic acid. This stearic acid-coated cefuroxime axetil was formulated in the form of solid droplets of stearic acid which contain the drug. These microspheres are granulated with sucrose prior to the addition of flavor to produce the final product which, when reconstituted with water, provides a sweetened and flavored aqueous suspension of the drug which retains the drug until after ingestion. Trials of the suspension in children have shown a good tolerance of the medication, indicating that the unpleasant taste of the drug has been successfully masked (Powell, 1991). Thus encapsulation of the drug inside polymeric materials has been successfully used for taste masking of the drugs.

1.7.3 Encapsulation of Drugs (Nanoparticles and Microspheres)

Nanoparticles and microspheres have become an important area of research in the field of drug delivery because they have the ability to deliver a wide range of drugs to varying areas of the body for sustained periods of time. Natural polymers (proteins or polysaccharides) have not been widely used for this purpose since they vary in purity, and often require crosslinking that could denature the embedded drug. Consequently, synthetic polymers have received significantly more attention

in this area. The most widely used polymers for encapsulation have been poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and their copolymers, poly (lactide-co-glycolide) (PLGA) (Rieux, 2006). These polymers are known for both their biocompatibility and resorbability through natural pathways.

During the 1980s and 1990s several microparticulate drug delivery systems were developed to improve the efficiency of drugs and minimize toxic side effects. The early nanoparticles and microparticles were mainly formulated from poly (alkyl cyano acrylate). Initial promise for microparticles was dampened by the fact that there was a size limit for the particles to cross the intestinal lumen into the lymphatic system following oral delivery. Likewise, the therapeutic effect of drug-loaded nanoparticles was relatively poor due rapid clearance of the particles by phagocytosis post intravenous administration. In recent years this problem has been solved by the addition of surface modifications of nanoparticles (Hans, 2002).

Particles with sizes ranging from submicron to several hundred microns have been made from various degradable polymeric materials. These biodegradable polymers have several advantages. First, they have demonstrated biocompatibility, and have been used in pharmaceutical and medical applications for many years. Second, biodegradation of the polymers results in release of encapsulated drugs over time, which enables the particles to serve as depots for controlled drug delivery. Over the past 25 years research has also been focused on degradable polymer microspheres for drug delivery. Examples of biodegradable polymers that have been explored for potential oral drug delivery include poly (lactide-co-glycolide) (PLGA), polyanhydrides, poly (methyl methacrylate), and poly alkyl cyanoacrylates (Challacombe, 1997; Kreuter, 1991; Kreuter, 1995; Mathiowitz, 1997). Among them, the PLGA polymer has been extensively studied. In most cases, drugs are encapsulated in these particles using the solvent evaporation technique (Mathiowitz, 1997). Release of drugs from the particles is controlled by the particle degradation rate, which is in turn determined by the polymer composition and its molecular weight (Chen, 1998). Administration of medication via such systems is advantageous because microspheres can be ingested or injected; they can be tailored for desired release profiles and in some cases can even provide organ-targeted

release (Jalil, 1990; Kawaguchi, 2000; Mueller, 2001; Edlund, 2002 ; Vasir, 2003).

1.7.3.1 Methods of Microencapsulation

Biodegradable and biocompatible microspheres of PCL, PLA, PGA and blends thereof have currently been prepared by different methods, such as emulsion/ evaporation, precipitation processes and dispersion polymerization and have found applications as carriers for sustaining the release of bioactive moleculaes.

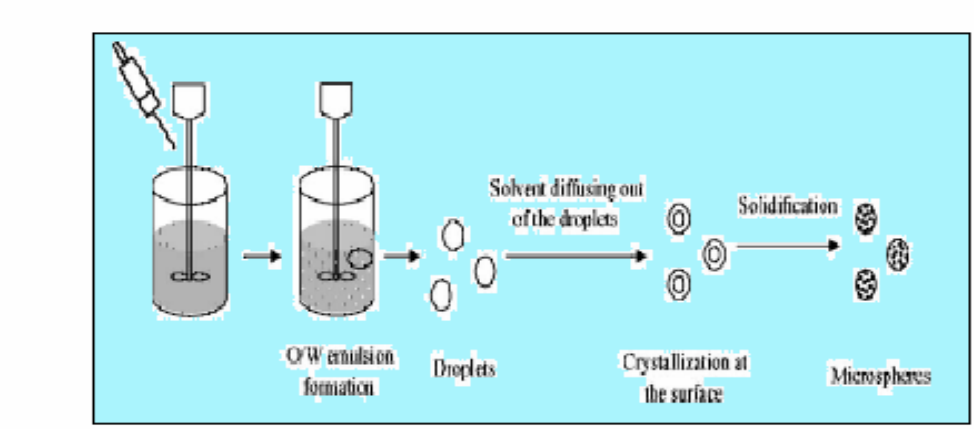


Figure 7 Encapsulation by Emulsion Solvent Evaporation Method (Gao, 2006)

The idea of polymeric microcapsules as delivery systems was reported as early as the 1960s (Chang, 1964). Recent literature shows that suspensions of degradable microspheres can be employed for sustained drug release at desirable doses and by implantation without surgical procedures. Biocompatibility can be achieved by the use of natural polymers such as cellulose, chitin, and chitosan or the polymers made from naturally occurring monomers such as lactic and glycolic acids. Polymers derived from synthetic monomers also show excellent delivery properties. However, their toxicity effects may require further evaluation.

The factors affecting drug release from microspheres are controllable; they are attributed to properties such as polymer molecular weight, as well as microsphere size, distribution, morphology and make-up. Although most microspheres employed

for drug delivery are prepared from linear polymers, the preparation of microspheres from monomers is still of relevance. Methods used for such synthesis are emulsion, suspension, and dispersion techniques (Piirma, 1985). Some other commonly employed methods for microsphere preparation are the solvent evaporation technique (or the double emulsion technique) and spray drying (Vasir, 2003; Masters, 1985; Berkland, 2001). Spray drying technique (Blanco, 2007) was explored for the formation of very monodisperse spheres and this method was tried for use with PLGA (Pavanetto, 1993; Witchi, 1998, Blanco, 2003; Blanco, 2004; Pamujula, 2004).

Microspheres can be used to overcome many of the shortcomings of conventional drug delivery routes. To date a limited number of companies provide commercially available microspheres and / or have active product development programs in the field. For market applications, microsphere systems are expected to undergo phase and clinical testing just as non-encapsulated drug systems. However, the use of materials already approved for in vivo degradation, such as PLGA may increase their likelihood and speed of acceptance for conventional and controlled release of drugs.

1.7.3.2 Controlled Release from Microspheres

The controlled release of drugs from polymer microspheres is achievable by manipulating the physical and chemical properties of the polymer as well as those of the microspheres. Issues such as polymer molecular weight, blend composition, polymer and drug crystallinity, drug distribution, sphere porosity, and sphere size all influence the release profile and can be tailored to fit a desired release. Extra control over microsphere release can be obtained by the addition of a pH-sensitive outer core, and / or by the employment of a pH-sensitive inner shell. Microspheres provide sustained release in localized areas and can be employed to reduce medication doses and its frequency of use.

The utility and potential of microsphere drug delivery systems have been demonstrated and it has been shown that tailored delivery is possible (Freiberg,

2004). Site specific applications would normally imply site injection. Oral delivery is also desirable for medications that are effective upon intestinal absorption and can be administered with microspheres that are unaffected by the stomach followed by adherence and degradation at the colon wall. Such formulation can be designed by careful choice of polymeric excipients. pH sensitive polymers will be useful excipients to deliver the drug at specific sites in GIT depending on varying pH conditions of the surroundings.

1.8 Applications of Polymeric Excipients in Drug Delivery Systems

1.8.1 Smart Polymers

Stimuli-responsive polymers show a sharp change in properties upon a small or modest change in environmental condition, e.g. temperature, light, salt concentration or pH. This behavior can be utilized for the preparation of so called 'smart' drug delivery systems, which mimic biological response behavior to certain extent. The possible environmental conditions for this purpose are limited due to the bio-medical setting of drug delivery as application. Different organs, tissues and cellular compartments may have large differences in pH, which makes the pH a suitable stimulus.

Stimuli-responsive polymers offer great advantages in drug delivery. Instead of acting passively as pure drug carriers, they will interact and respond to the environmental setting. This allows us to aim further for tailor made drug delivery with superior pharmacokinetics while having all safety questions addressed.

There is an extensive list of criteria a polymer has to fulfill, in order to be applied safely as polymer therapeutics or as an agent in tissue regeneration and repair. If the polymer is not a drug itself, it often provides a passive function as a drug carrier, reducing immunogenicity, toxicity or degradation, whilst improving circulation time and potentially a passive targeting function. In this case the polymer has to be water-soluble, non-toxic, non-immunogenic and it need to be safe at all stages of the drug delivery process (e.g. before and after the drug has been released) including a safe excretion. If the polymer is non-degradable (e.g. poly (meth) acrylate), the size

needs to be below the renal threshold ensuring that it is not accumulated in the body. If the polymer is degradable (e.g. polyesters), the toxicity and / or immune response of the degradation products have to be considered as well.

Besides its application in a passive fashion, synthetic polymers often adopt more active role such as releasing a drug molecule, peptide or oligo / poly (nucleic acid) upon an external stimulus. Stimuli-responsive polymers mimic biological systems in a crude way where an external stimulus (e.g. change in pH or temperature) results in a change in properties. This can be a change in conformation, change in solubility, alteration of the hydrophilic/hydrophobic balance or release of a bioactive molecule (e.g. drug molecule). This also includes a combination of several responses at the same time.

1.8.2 pH Sensitive Polymers

The most common smart polymers generally undergo conformational or phase changes in response to the variations in temperature and / or pH. Smart polymers have been developed and widely used in a range of applications such as microfluidic devices, pulsatile drug release systems, bioadhesive mediators and nanoscale technologies. Other examples of smart polymers include poly (N-isopropyl acrylamide), poly (N-vinyl caprolactam), poly (acrylic acid) and poly (methacrylic acid). Swelling and shrinking of the structure of smart polymers can be applied to pharmaceutical formulations to control the release of bioactive agents by subjecting the polymers to external stimuli such as pH or temperature. When a smart polymer is integrated as a coating agent or microcapsule wall, the conformational transition of a polymer structure can be utilized to allow drug release from the microcapsule (Tandya, 2006). pH responsive polymeric networks have been extensively studied due to large variation in physiological pH at various body sites (Gupta, 2002; Risbud, 2000).

The pH is an important signal, which can be addressed through pH-responsive materials.

Ionizable polymers with pK_a value between 3 and 10 are candidates for pH responsive systems (Siegel, 1993). Weak acids and bases like carboxylic acids,

phosphoric acid and amines, respectively, exhibit a change in the ionization state upon variation of the pH. This leads to a conformational change for the soluble polymers and a change in the swelling behavior of the hydrogels when these ionizable groups are linked to the polymer structure (Schmaljohann, 2006). The pH-responsive swelling and collapsing behavior has been used to induce controlled release of model compounds like caffeine (Nakamae, 1997), drugs like indomethacin (Dong, 1991) or cationic proteins like lysozome (Nakamae,1996)

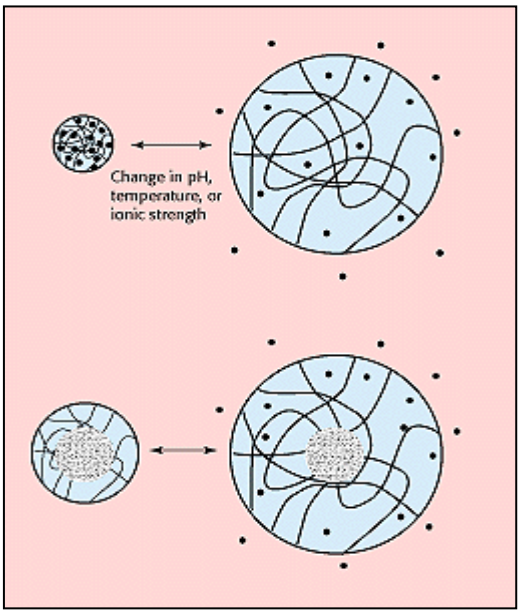


Figure 8 Drug Delivery from Environmentally Sensitive Release Systems

1.8.3 pH Sensitive Polymeric Coating Excipients

Typically pH-sensitive materials have been used as coatings to protect drugs or to encapsulate irritating drugs during transit through the stomach, and then release it shortly after entering the small intestine. Most commonly used pH-dependent coating polymers are methacrylic acid copolymers – Eudragit® L100-55, Eudragit® L100 and Eudragit® S100 which dissolve at pH 5.5, 6.0 and 7.0 respectively and hence, none of these polymers are suitable to be used alone for coating of dosage forms that would start releasing the drug at pH 6.5 (Khan, 1999).

pH sensitive polymers have been used in different forms such as encapsulation materials for colon delivery (Davis, 1990), coating excipient for a controlled release tablet formulation which is water soluble at pH>5.0 (Curatolo, 2000) and in pH dependent or pH regulated controlled release of drugs (Urtti, 1997). A dual mechanism polymer mixture composed of pH-sensitive enteric materials and film-forming plasticizers capable of conferring permeability to the enteric material was evaluated for use in drug-delivery systems. The matrix pellet was designed for release of acid-soluble drugs by diffusion in acid pH and by disintegration at pH levels of nominally about 5.0 or higher (Goldman, 1992). pH sensitive terpolymers were explored as carriers for conducting the drug through the gastric juices of the stomach in a protected form. The terpolymers swell at the higher physiologic pH of the intestinal tract causing release of the drug into intestine (Bae, 1996). Thus the terpolymer functions as a protective carrier in the acidic environment of the stomach and also protects the drugs from digestive enzymes until it is released in the intestinal tract. pH sensitive polymers containing sulfonamide groups showing changes in swellability and solubility, depending on pH were explored in drug-delivery system, bio-material and sensor (Bae, 2000). These pH-sensitive polymers may have a structure of linear polymer, grafted copolymer, hydrogel or interpenetrating network polymer (Shefer, 2004).

1.8.4 Tablet Coating

Coatings play a passive role in the behavior of the drug product, serving as protective layers, cosmetic and product branding devices, and aids to ingestion. However, active and functional coatings are becoming more commonplace. Mostly pharmaceutical tablet formulations are in coated form. For example, enteric coatings determine the location of drug release, and many controlled release products deliver an immediate dose via a quickly dissolving coating over a delayed release core. Common coating operations are inherently variable, relying on the statistical likelihood that each tablet will be exposed to the same distribution of the coating formulation to produce a uniformly coated tablet batch. Finally, the coating process

occurs near the end of the value chain, and therefore variability or operational errors at this stage in the manufacturing process can have a relatively large financial penalty.

1.8.4.1 Types of Tablet Coatings

Tablet coatings are the functional membranes which surround tablets uniformly and serve many purposes from conferring elegancy to the product to deciding fate and drug release from the formulation. Coatings offer many advantages to the tablet dosage form which can be enumerated as follows:

1. Protection against deterioration by environmental factors like sunlight, temperature variations, moisture, environmental gases etc
2. Impart ease for swallowing
3. Taste and odor masking
4. Enhancement of aesthetic appeal and brand image
5. Increase in shelf-life
6. A means of product identification during manufacture and prevent wastage during packing and handling
7. Confer immediate release, specific release, sustained release, controlled release and targeted drug delivery properties
8. Impart enteric release properties for release in the intestinal tract
9. Ease in identification of oncological drugs

There are different types of tablet coatings in the pharmaceutical field. These are film coating, sugar coating (Bauer, 1998), spray coating and compression coating. Both pharmaceutical and nutritional solid dosage forms commonly use film coatings. Film coated tablets have excellent properties such as masking of bitter taste, slight size increase, low calorie due to a polymer, and low moisture content (Saly, 2005). However, film-coated tablets are inferior to sugar-coated tablets in terms of easiness of swallowing, elegant appearance and masking of unpleasant odor (Ohmori, 2004). However, sugar-coated tablets still have problems of

remarkable size increase, high calorie due to sucrose, and relatively high moisture content.

If the active ingredient of a tablet is sensitive to acid, or is irritant to the stomach lining, an enteric coating can be used, which is resistant to stomach acid and dissolves in the high pH of the intestine. Enteric coatings are also used for medicines that can be negatively affected by taking a long time to reach the small intestine where they are absorbed. Coatings are often chosen to control the rate of dissolution of the drug in the gastro-intestinal tract. Some drugs are absorbed better at different points in the digestive system. If maximum absorption of a drug takes place in the stomach, a coating that dissolves quickly and easily in acid is selected. If the rate of absoprtion is high in the large intestine or colon, then a coating that is acid resistent and dissolves slowly is used to ensure it reached that point before dispersing. The area of the Gastro-intestinal tract where the absorption of drug is maximum is usually determined by clinical trials.

On the laboratory scale, enteric polymers can be applied to tablet formulation by ladling method. This consists of dipping the tablet in coating solution in order to apply a uniform, thin coat on the formulation and drying out the tablet (Alvarez, 2004).

The majority of coatings applied to tablets are polymers and their performance is based on the characteristics of the polymer, the solvent system from which they are applied and the conditions under which they are applied. Successful coating requires that the polymer solution or dispersion is applied to the surface and the fluid carrier is removed by the application of heat. In the case of the polymer dispersions, film formation depends on the dispersed polymer fusing to form a continuous film. The variation in mechanical properties of the films as a function of temperature would be a useful parameter to evaluate the performance of a film forming formulation (Lafferty, 2002).

1.8.4.2 Coating Technology

During the last two decades, pharmaceutical coating technology has been shifting from organic solvent-based systems to aqueous systems, which are advantageous from the view points of environmental pollution, safety and cost (Nakagami, 1991; Ebey, 1987; Porter, 1979). Water-soluble materials, such as hydroxypropyl methylcellulose, are now widely used for aqueous film coating of pharmaceutical solid dosage forms (Porter, 1979). Aqueous coating systems using water-insoluble materials, such as enteric coating polymers, have also been developed, and aqueous polymeric dispersions of acrylic resins, a vinyl polymer and cellulosic polymers are commercially available for this purpose (Chang, 1987; Banker, 1981; McGinity, 1990). However, aqueous coating systems are not always applicable, for example if the active ingredient is sensitive to water. From the view point of cost, usage of water in place of organic solvent is highly beneficial. However, reduction of processing time and coating level are also important. A simple way to shorten coating time is to use a coating solution or dispersion of higher concentration, but this approach is limited by the viscosity increase of the solution or blocking of the spray nozzle (Obara, 1999). Polymeric coating techniques using fluid-bed or pan coater have been widely recognized in the pharmaceutical industry for many reasons such as taste masking, protective barrier, stability improvement, but mostly controlled release of drugs (McGinity, 1989). In general, coating dispersions are applied on various drug-loaded cores such as nonpareil seed, pellet, bead, granule or tablet. However, it is interesting to prepare coated HPMC matrix tablets using drug-containing polymeric coating dispersions because conventionally, no drug is included in coating dispersions (Lee, 1999).

1.8.4.3 Coating Materials

Modern tablet coatings are polymer and polysaccharide based, with plasticizers and pigments included. Tablet coatings must be stable and strong enough to survive the handling of the tablet, must not make tablets stick together during the coating

process, and must follow the fine contours of embossed characters or logos on tablets. Coatings can also facilitate printing on tablets, if required. Opaque materials like titanium dioxide can protect light-sensitive actives from photodegradation. Special coatings (for example with pearlescent effects) can enhance brand recognition. Cellulose ethers form strong films with good adhesion and taste masking properties. Films of METHOCEL cellulose ethers make clear, sharp coatings that are nonionic and compatible with FD&C dyes, lakes, and pigments. They are excellent surfaces for printing, while enhancing and displaying scoring, logos, and other distinguishing features of a tablet's surface. Cellulose ethers also permit coatings to be applied in one pan, shorten coating time, reduce skilled operator requirements, and permit the use of automated coating systems.

Sugar was popularly used as a coating material for taste masking in 1890 as sugar coating gave very good appearance to tablets. But the technique was time consuming, it needed a lot of space and labor along with special equipment. Hence trials were taken to replace sugar coating with polymer coatings using organic solvents in 1970. Then it was in the form of film coatings using polymers such as cellulose ethers like ethyl cellulose, methyl cellulose, hydroxy propyl methyl cellulose (HPMC) and hydroxy propyl cellulose. Another polymer tried was aqueous shellac which had additional advantages like lower viscosity, better barrier properties and resistance to discoloration. With further development, polymers like HPMC, PVP (poly vinyl pyrrolidone), PVA (poly vinyl alcohol), poly (vinyl pyrrolidone - vinyl acetate) copolymer, poly vinyl alcohol polyethylene glycol copolymer were tried in aqueous solvents. This technique was found to be beneficial in terms of barrier property, adhesion, gloss and flexibility. The polymeric materials like PVP and PVA which are used for tablet coating, at the same time these can be useful in synthesis of hydrogels and find applications in drug delivery systems and other biomedical fields.

1.9 Polymer Systems

Based on the type of monomers, different polymer systems like water soluble polymers, hydrogels and graft polymers are synthesized and explored in different pharmaceutical applications.

1.9.1 Water Soluble Polymers

Polyethylene glycol, polyethylene imine and poly acrylic acid are polymers which can be solubilized in body fluids without any chemical degradation. Water-soluble polymers may undergo simple hydration, ionization or protonation and dissolve in the biological environment. Gelatin, starch and dextran are other examples of water-soluble polymers which are suitable for short-term (several hours to days) drug delivery due to their rapid dissolution in the biological fluids.

1.9.2 Hydrogels

Hydrogel is a three dimensional polymeric network that is insoluble in water at physiological pH, temperature and ionic strength. The existence of hydrogel dates back to 1960, when, Wichterle and Lim first proposed the use of hydrophilic networks of (2-hydroxyethyl methacrylate) [PHEMA] in contact lens applications (Wichterle, 1960). Since then, the use of hydrogels has been extended to various biomedical and pharmaceutical applications (Hoffman, 2002). Hydrogels resemble living tissues very closely in their physical properties because of their relatively high water content and soft and rubbery nature. A large number of natural and man-made hydrogels are well known. For example, the vitreous humor that fills the interior of the eye and the synovial fluid that lubricates the joints of the skeleton are natural gels. These hydrogels consist of two components, a polymer network and a liquid. The network provides the structural framework and holds the liquid in space. Depending on the chemical composition and various other factors, hydrogels vary in consistency from viscous fluid to fairly rigid solids, but typically, they are soft and

resilient, like jelly. They are viscoelastic in nature i.e. they have properties of a viscous solution and of an elastic solid. Routinely, the terms 'gel' and 'hydrogel' are used interchangeably. This could be a misinterpretation because although, as polymer networks, both gels and hydrogels might be similar chemically, but they are physically distinct. Hydrogels are generally described as gels swollen in water. Whereas, gel need not contain any solvent and could be a flexible / hard matter, for example, rubbery silicon gel or polystyrene gel, etc.

1.9.3 Classification of Hydrogels

There are two types of hydrogels- Naturally occurring hydrogels and Synthetic hydrogels

1.9.3.1 Naturally Occurring Hydrogels

These are polysaccharides, carrageenans, gum arabic, agarose, cuprophan, dextran, collagens, etc. They have applications in pulp and paper production, artificial silk and cellulosic membrane production. However, they have limitations due to their poor mechanical properties, low temperature tolerance and poor resistance to microbial attack.

1.9.3.2 Synthetic Hydrogels

Synthetic hydrogels have mostly been prepared from monomers and polymers such as hydroxyethyl methacrylate (HEMA), polyethyleneglycol methacrylate (PEGMA), acrylamide (AAm), methoxy-terminated PEG derivative (MPEGMA), N-vinyl pyrrolidone (NVP), polyethylene oxide (PEO), acrylic acid (AA), poly(vinyl alcohol) etc. These gels have been prepared mostly in the form of membranes, beads, rods, strips, etc. Synthetic hydrogels demonstrate better mechanical properties, good temperature tolerance and resistance to microbial attack. Some of these hydrogels do not exhibit significant sensitivity to the external

changes and termed as conventional hydrogels. Others show varying degree of responses to different stimuli such as temperature, pH, and electric field and are popularly known as “stimuli-responsive” hydrogels (Hoffman, 2002; Qiu, 2001).

Hydrogels which exhibit swelling and stimuli dependent drug release, have been used in controlled drug delivery systems. The ideal drug-delivery system should have capacity to sense the changes and alter the drug release accordingly by releasing the drug in response to physiological requirements. The controlled drug release as a function of temperature have been evaluated by using thermoresponsive networks (Okano, 1990; Bae, 1987) demonstrated the pulsatile drug release pattern through crosslinked Poly(N-isoproyl acrylamide-co-butyl methacrylate) system regulated by temperature changes due to thermosensitive swelling-deswelling behavior of polymer.

Table 1: Stimuli Sensitive Hydrogels

Stimulus	Hydrogel	Mechanism
pH	Acidic or basic hydrogel	Change in pH — swelling — release of drug
Ionic strength	Ionic hydrogel	Change in ionic strength — change in concentration of ions inside gel — change in swelling — release of drug
Chemical species	Hydrogel containing electron-accepting groups	Electron-donating compounds — formation of charge/transfer complex — change in swelling — release of drug
Enzyme-substrate	Hydrogel containing immobilized enzymes	Substrate present — enzymatic conversion — product changes swelling of gel — release of drug
Magnetic	Magnetic particles dispersed in alginate microshperes	Applied magnetic field — change in pores in gel — change in swelling — release of drug
Thermal	Thermoresponsive hrydrogel poly(N-isopro-pylacrylamide)	Change in temperature — change in polymer-polymer and water-polymer interactions — change in swelling — release of drug
Electrical	Polyelectrolyte hydrogel	Applied electric field — membrane charging — electrophoresis of charged drug — change in swelling — release of drug
Ultrasound irradiation	Ethylene-vinyl alcohol hydrogel	Ultrasound irradiation — temperature increase — release of drug

Table 2: Factors Influencing Swelling of Hydrogels

Favorable to Swelling	Inhibit Swelling
• Osmotic pressure • Strong interactions (H-bonding) with water • High free volume • Chain flexibility • Low crosslinking density	• Weak interactions with water • Low free volume • Low chain flexibility • High crosslinking density

Like hydrogels, a graft polymer is another polymeric system which is being used in variety of applications depending on type of graft.

1.9.4 Graft Copolymers

Arrangement of monomers in a polymer gives rise to different structures like block, random, alternative or graft polymers (Neeraj, 2001). Graft Copolymers are defined as

copolymers composed of several different monomer units arranged to give a comb type structure as shown in **Figure 9**. In grafting method the monomers are introduced laterally on to the polymer chain with the help of covalent C–C bonds. By varying the molecular weight of main chain and / or graft chain and the number of graft chains, graft copolymers of different architecture with tailored degradation properties can be synthesized (Breitenbach, 2000).

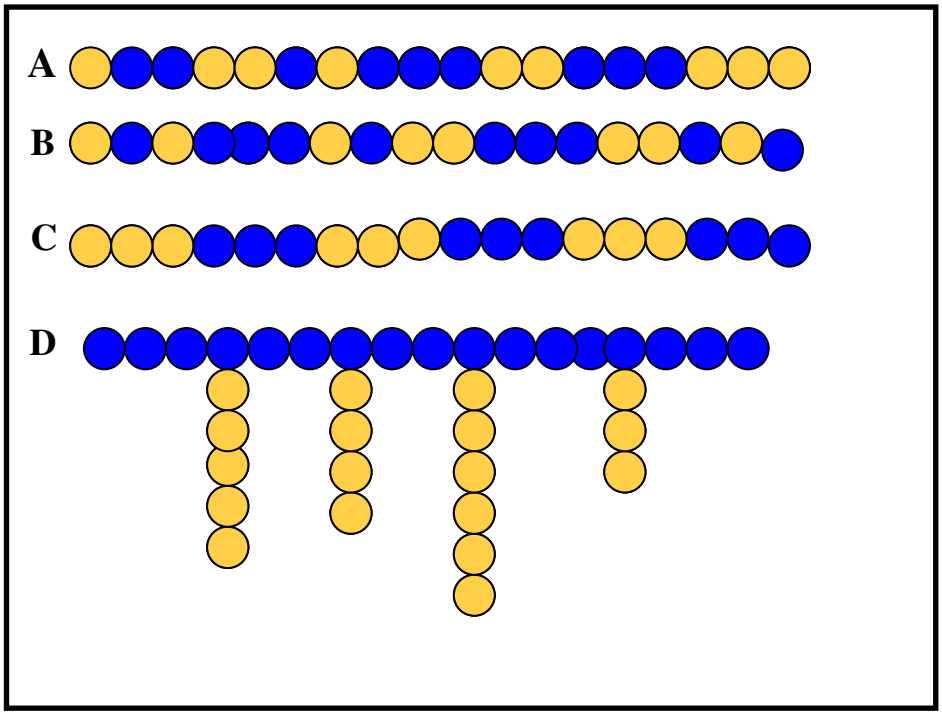


Figure 9 Different Arrangements of Comonomers

A-Random, B –Alternate, C- Block, D-Graft Copolymers

Along with graft copolymers and hydrogels, macromonomers and telechelic polymers are other concepts to tailor made the polymers and introduce desirable properties.

1.9.5 Macromonomer

The macromonomer method has recently been used to prepare tailor made graft copolymers (Yamashita, 1981; Rempp, 1984; Lutz, 1984; Asami, 1985)

The term macromonomer is abbreviated from macromolecular monomer and defined as a polymer or oligomer having a polymerizable group at a chain end.The polymerizable

group may be an unsaturation (vinylic and acrylic group), a heterocycle for ring opening polymerization and also a dicarboxyl or dihydroxyl groups for step growth polymerization. By using the macromonomer rmethod, it is easy to control the number and length of branches and to combine variable backbones and branches in the graft polymers.Thus, in the last decade, the macromonomer method has been one of the most promising concept in the field of polymer synthesis. In the 1970's Milkovich and co-workers developed a new method for preparing tailor made graft polymers by using oligomers with a polymerizable group at one end.They have named these polymers as "Macromer." (Milkovich, 1980; Milkovich patents, 1974; Schulz, 1982)

The molecular weight and the molecular weight distribution and the functionality of macromonomers are important in controlling the length and the number of branches, respectively of the resulting graft copolymers.The macromonomer method is useful for the molecular design of graft polymers.Therefore macromonomer method can contribute toward most of the applications of graft copolymers.

1.9.6 Telechelic Polymers

The term **t**elechelic polymers was proposed in 1960 by Uraneck to designate relatively low molecular weight macromolecules possessing two reactive functional groups situated at both ends. (Uraneck, 1960). By means of ring opening polymerization, it is possible to prepare an extremely wide variety of polymers containing various kinds of functional groups in the chain and showing a wide array of physical properties.The synthesis of telechelics based on this chemistry has attracted great interest because of potential uses of such compounds (Goethals, 1989).

1.9.7 Modifications in Lactide Structure

Aliphatic polyesters like PLGA are an attractive class of polymer that can be used in biomedical and pharmaceutical applications. One reason for growing interest in this type of degradable polymer is that their physical and chemical properties can be varied over a wide range by copolymerization with other monomers and building new macromolecular architecture. The copolymerization of hydrophobic lactide molecules with hydrophilic units like glycolide is explored for variety of applications. The synthesis of novel polymer structures through ring opening polymerization has been studied for a number of years (Yui, 1990; John, 1997). The development of macromolecules with strictly defined structures and properties, aimed at biomedical applications, leads to complex and advanced architecture and diversification of the hydrolyzable polymers. Degradable materials having new mechanical properties and modified degradation profiles have been produced and characterized. The increasing demands of a larger number of biomedical applications have resulted in an increasing interest in producing macromolecules through controlled polymerization (Ohya, 1998).

Although lactide has good biodegradability, good biocompatibility, high mechanical strength and excellent shaping and molding properties, it suffers from difficulty of controlled degradation because of its high crystallinity. Possible promising approaches to overcome these problems are the introduction of hydrophilic units to control the biodegradability and branching to decrease crystallinity of PLA. Generally it is well known that a branched polymer has different physicochemical properties compared with its linear counterpart. A comb type biodegradable PLA, having both hydrophilic units and branched structure was synthesized by graft copolymerization of lactide onto depsipeptide-lactide copolymer containing serine residues. The obtained comb type PLA showed decrease of crystallinity and an increase of biodegradability compared with linear PLA. The degradation rate of the resulting material could be controlled by varying the molecular architecture (Tasaka, 2001).

The advantages offered by new molecular architecture available from this macromolecular engineering of aliphatic polyesters can be applied in the form of use of materials as micro or nano carriers for drug substances (Slomkowski, 1997).

1.10 Concluding Remarks

The introductory chapter reviews various aspects of biodegradable polymers and lactide polymers along with discussion on degradation mechanism of lactide polymers and their applications as reported in the literature. The pharmacokinetics and pharmacodynamics of the drug and design of drug therapy has been discussed next with special stress on biopharmaceutical considerations of dosage forms. The literature search covered types of dosage forms and then reviewed aspects of controlled release technology. Modifications in the design of oral formulations with special highlight on site specific dosage forms and taste masking technology have been described. Microencapsulation as one of the ways for taste masking along with encapsulation methods (reported in the literature) and pharmaceutical applications constituted next part of the discussion.

Role of polymeric excipients in design of formulations has been described at length with special stress on stimuli sensitive polymers and role of pH sensitive monomers as coating excipients. In this context coating technology with special stress on tablet coating has been explained to the great extent. Different polymer systems such as water soluble polymers, hydrogels and graft polymers which are explored as excipients in biomedical applications have been described.

Macromonomers have attracted lot of attention as functional moieties useful in tailoring of polymers to result in modified architectures with desirable properties. These have been described along with telechelic polymers as another tool for structural polymer design. These concepts of polymer modifications have been then related to lactide polymers for drug delivery applications. Furthermore, various methods of lactide modification used so far in literature have been elaborated in this chapter.

In conclusion, modified lactide polymers are active areas of research in polymer science and pharmaceutical technology as evidenced by large number of publications in the literature. Although there are numerous developments which have taken place in this area leading to marketing of parenteral preparations containing lactide polymers, there is tremendous scope to design low molecular weight smart lactide excipients having desirable properties. The modified lactide polymers with tailored crystallinity, molecular weight and degradation profile can work as excellent polymeric excipients for oral drug delivery.

1.11 References

Aguado M. T., Lambert P. H. Immunobiology **1192**, *184*, 113

Albertsson A.C., Varma I. K. Advances in Polymer Science **2001**, *157*, 1436

Alexander K. A., Lendon G. P. Advanced Drug Delivery Reviews **1998**, *34*, 155

Alvarez-Fuentes, Ferna Ndez-Arevalo M., Gonzalez-Rodri´Guez M.L., Cirri M. , Mura P. Journal of Drug Targeting **2004,** *12,* 607

Anne des, Virginie Fievez, Marie Garinot, Yves-Jacques Schneider, Véronique Préat JCR **2006,** ***116*****,** 1

Aronson J. K., Hardman M. Br. Med. J. **1992**, *305*, 1009

Arvanitoyannis I., Nakayama A., Psomidou E., Kawasaki N., Yamamoto N. Polymer, **1996**, *37*, 651

Asaka, T., Misawa, Y., Kashimura, M., Morimoto, S., Watanabe, Y., Hatayama, K., 2′-Modified erythromycin or derivative thereof. EP application no. 0 553 353 A1 **(1994)**

Asami, R. , Takaki, M. Macromol.Chem., **1985,** *12* ,163

Baddour L. M., Gibbs R. S., Mertz G., Cocchetto D. M., Noble R. C. Antimicrob. Agents Chemother. **1989**, *33*, 801

Bae Y. H.; Okano, T.; Hsu, E.; Kim, S. W. Macromol. Chem. Rapid Commun. **1987**, *8*, 481.

Bae Y. H. pH and temperature sensitive terpolymers for oral drug delivery U.S. Pat. No. 5, 484, 610 **(1996)**

Bae Y. H. PH-sensitive polymer containing sulfonamide and its synthesis method , U.S. Pat. No. 6,103,865 **(2000)**

Banker G.S., Peck G.E., Pharm. Technol. **1981**, *5,* 55

Bateman D. N., McLay J. S. Surgery (Oxford) **2003**, *9*, 2

Batycky R. P., Hanes J., Langer R., Edwards D. A., J. Pharm. Sci. **1997**, *86*, 1464

Bernkop-Schnürch A., Kirchmayer R., Kratzel M., J. Drug Target **1999,** *7,* 55

Bendix D., Polymer degradation and stability, **1998,** *59*, 129

Bero M., Kasperczyk J., Jedlinski Z. J. Macromol. Chem. **1990**, *191*, 2287

Bjarnason G.A., Jordon R.C.K., Wood P. A., Li Q., Lincoln D. W., Sothern R. B., Yaacov B. Hrushesky W. J. M. , American J. of Pathology **2001,** *158*, 1793

Blanco, M.D., Sastre, R.L., Teij´on, C., Olmo, R., Teij´on, J.M., International Journal of Pharmaceutics **2006**, *326*, 139

Blase C.M., Shaw, M.N,. Aqueous pharmaceutical suspension for pharmaceutical actives. EP application no. 0 556 057 B1 **(1993)**

Breitenbach A., Pistel K. F., Kissel T. Polymer **2000**, *41,* 4781

Bjorn L. Pharmacological Res. **1996**, *33*, 107

Botelho R. J., Dudrak R. J. Fam. Pract. **1992**, *35*, 61

Bruckert E., Simonetta C., Giral P. J. Clin. Epidemiol. **1999**, *52*, 589

Carder P. C., Vuckovic N., Green C. A. J. Clin. Pharm. Ther. **2003**, *28*, 409

Carter G.W., Young P.R., Swett L.R., Paris G.Y., Agents Actions **1980,** *10*, 240

Chabot F., Vert M., Chapelle S, Granger, P. Polymer **1983**, *24*, 53

Chang R.K., Hsiao C.H., Robinson J.R., Pharm. Technol. **1987,** *11,* 56

Carelli V., Di Colo G., Nannipieri E., Poli B., Serafini M.F., Int. J. Pharm **2000,** *20*, 103

Chasin M. in "Biodegradable polymers for controlled drug delivery", Editors: J.O. Hollinger, Biomedical Applications of Synthetic Biodegradable Polymers, CRC Press, Boca Raton, FL, New York, 1995

Challacombe S.J., Rahman D., O'Hagan D.T, Vaccine **1997,** *15*, 169

Chen H., Langer R. Pharm. Res. **1997**, *14*, 537

Chen H.' Langer R. Advanced Drug Delivery Reviews **1998,** *34,* 339

Cherukuri, S.R., Chau, T.L, Delivery system for cyclic amino acids with improved taste, texture and compressibility. EP application no. 0 458 751 A1 **(1991)**

Clausen A.E. , Bernkop-Schnürch A., Journal of Controlled Release **2001**, 7*5,* 93

Cleland J., Design and production of single-immunization vaccines using polylactide polyglycolide microsphere systems, in: M.F. Powell, M.J. Newman (Eds.), Vaccine Design: The Subunit and Adjuvant Approach, Plenum Press, New York, **1995**, pp. 439–462.

Cohen S., Yoshioka T., Lucarelli M., Hwang L. H., Langer R. Pharm. Res. **1991**, *8*, 713 Cork M. J., Britton J., Butler L. Br. J. Dermatol. **2003,** *149*, 582

Cramer M. P., Saks S. R. Pharmacoeconomics **1994**, *5*, 482

Curatolo W. J., Friedman H. L., Korsmeyer R.W., LeMott S. R. Controlled-release dosage forms of Azithromycin U.S. Pat. No. 6,068,859 **(2000)**

Davis J. D., Touitou E., Rubinstein A. Targeted enternal delivery system U.S. Pat. No. 4,910,021 **(1990)**

Davis S., Hardy J., Taylor M., Whalley D., Wilson C. Int. J. Pharm. **1984**, *21*, 167

Davis S., Illum L., Stolnik S. Curr. Opin. Colloid Interface Sci. **1996**, *1*, 660

Dechy-Cabaret O., Martin-Vaca B., Bourissou D. Chem. Rev. **2004**, *104,* 6147

Desai M. P., Labhasetwar V., Walter E., Levy R. J., Amidon G. L., Pharm. Res. **1997**, *14*, 1568

Dimou C. Disease-a-Month **2000**, *46,* 811

Dong L.C., Hoffman A.S., J. Control. Release **1991,** *15*, 141

Dubois P., Jerome R., Teyssie P. Macromol. Chem. Macromol. Symp.**1991**, *42/43*,103

Duchêne D., Ponchel, G., Wouessidjewe D. Advanced Drug Delivery Reviews **1999**, *36*, 29

Duchene D., Wouessidjewe D., Ponchel G., J. Contr. Release **1999,***62*, 263

Dunn R.L., in "Polymeric matrices", Editors: R.L. Dunn, R.M. Ottenbrite , Polymeric Drugs and Drug Delivery Systems, American Chemical Society, Washington, DC, **1991**, pp. 11–23

Dunn R. L. in "Clinical applications and update on the poly(α-hydroxy acids)", Editors: J.O. Hollinger (Ed.), Biomedical Applications of Synthetic Biodegradable Polymers, CRC Press, Boca Raton, FL, **1995**

Dunne M., Corrigan O. J., Ramtoola, Z. Biomaterials **2000**, *21*, 1659

Ebey G.C., Pharm. Technol. **1987,** *11*, 41

Eby, G.A. Flavour stable zinc acetate compositions for oral absorption.
US Patent 5,095,035 **(1992)**

Engelberg I., Kohn J., Biomaterials **1990**, *12*, 292

Erah P.O., Goddard A.F., Barrett D.A., Shaw P.N., Spiller R.C., J. Antimicrob. Chemother. **1997**, ***39,*** 5

Foord, R. D., Antimicrob. Agents Chemother. **1976**, *9*, 741

Frazza E. J., Schmitt E. E. J. Biomed. Mater. Res. Symp. 1971, *1***,** 43

Freiberg S., Zhu X. X. International Journal of Pharmaceutics **2004**, *282,* 1

Friend D. R. Advanced Drug Delivery Reviews **1991**, *7*, 149

Frijlink, H. W. European Neuropsychopharmacology **2003**, *13*, 77

Fu K., Pack D. W., Klibanov A. M., Langer R. Pharm. Res. **2000**, *17*, 100

Gao Y., Cui F. , Guan Y., Yang L., Wang Y., Zhang L. International Journal of Pharmaceutics **2006,** *318*, 62

Garcia A. M., Ghaly E. S. J. Control. Release **1996**, *40*, 179

Gazzaniga A., Sangalli M. E., Giordano F. Eur. J. Pharm. Biopharm. **1994**, *40*, 246

Gazzaniga A., Sangalli M. E., Giordano F., Zema L., STP Pharma Prat. **1994,** ***4***, 336

Ginsburg C. M., McCracken G. H., Petruska M., Olson K. Antimicrob. Agents Chemother. **1985**, *28*, 504

Goethals E. J., Telechelic polymers:Synthesis and Applications, CRC press Boca Raton, Florida, **1989**

Gohel M. C.; Manhapra S. G. J. Control. Release **2002**, *79*,157

Goldman R., Dual mechanism controlled release system for drug dosage forms, U.S. Pat. No. 5,175,003, **(1992)**

Gonda I., Schuster J. A., Rubsamen R. M., Lloyd P., Cipolla D., Farr S. J. J. Control. Release **1998**, *53*, 269

Gooch W. M., Swenson E., Higbee M. D., Cocchetto D. M., Evans, E. C. Clin. Ther. **1987**, *9*, 670

Göpferich A. Biomaterials **1996**, *17*, 103

Gouin S., Trends Food Sci. Technol. **2004,** *15*, 330

Gregory S. P., Jozsa A. J., Kaldawi, R. E. Non-effervescent ibuprofen compositions. EP application no. 0 418 043 A1 **(1990)**

Grijpma D. W., Pennings A. J. Macromol. Chem. Phys. **1994**, *195*, 1633

Gupta P.; Varmani, K.; Garg, S. Drug Discovery Today **2002**, *7*, 569Loftsson T., Masson M., Int. J. Pharm. **2001,** *225*, 15

Gupta S. K., Atkinson L., Theeuwes F., Wong P., Gilbert P. J., Longstreth J. Eur. J. Pharm. Biopharm. **1996**, *42*, 74

Haneberg B., Kendall D., Amerongen H.M., Apter F.M., Kraehenbuhl J.P. , Neutra M.R., Infect. Immun. **1994,** *62,* 15

Hanes J., Chiba M., Langer R., in "Polymer microspheres for vaccine delivery", Editors: M.F. Powell, M.J. Newman, Vaccine Design, Plenum Press, New York, 1995

Hans M. L. , Lowman A. M. ,Current Opinion in Solid State and Materials Science **2002**, *6,* 319

Harding S. M., Williams P. E. O., Ayrton J., Antimicrob. Agents Chemother. **1984**, *25*, 78

Hardy J., Wilson C., Wood E. J. Pharm. Pharmacol. **1985**, *37*, 874

Harjit T., Pål J., Hans P. M., Bruno G. Advanced Drug Delivery Reviews **2005**, *57*, 357

Heinamaki J., Marvola M., Happonen I., Westermarck E. Int. J. Pharm. **1988**, *42*,105

Hoffman A. S., in "Polymer Gels", Editors: DeRossi, D.; Kajiwara, K.; Osada, Y, Yamauchi A., Plenum Press, New York, **1991**

Hoffman A.S., J. Biomater. Sci., Polym. Ed **1997**, *9,* 43

Hoffman A.S. Advanced Drug Delivery Reviews **2002**, *54*, 3.

Holland S. J., Tighe B., Gould P. L. J. Controlled Release **1986**, *4*, 155

Huang S. J., Roby M. S. J. Bioact. Compat. Polym, **1986**, *1*, 61

Hussein, M.M., Barcelon, S.A, Flavor enhancing and medicinal taste masking agent. USP no. 4 983 394 (**1991)**

Ikada Y., Tsuji H. Macromol. Rapid Commun. **2000**, *2*, 117

Jaskari T., Vuorio M., Kontturi K., Manzanares J. A., Hirvonen J. J. Control. Release **2001**, *70*, 219

John G., Tsuda, S. Morita, M., J. Polym. Sci Part A: Polym. Chem. **1997**, *35*, 1901

Kreuter J., Adv. Drug Delivery Rev. **1991, *7***, 71

Kreuter J., "Nanoparticles as adjuvants for vaccines", in: M.F. Powell, M.J. Newman (Eds.), Vaccine Design. The Subunit and Adjuvant Approach, Plenum Press, New York, 1995.

Katsuragi Y., Kurihara, K. Nature **1993**, *365*, 213

Khan M. Z. I., Prebeg Z. and Kurjakovic N. Journal of Controlled Release 1999**,** *58*, 215

Kim H., Fassihi R. J. Pharm. Sci. **1997**, *86*, 316

Kricheldorf H.R., Berl M., Scharnagl N. Macromolecules **1988**, *21*, 286

Kricheldorf H.R., Serra A. Polym. Bull. **1985**, *14*, 497

Kroegel I., Bodmeier R. Pharm. Res. **1998**, *15*, 474

Kulkarni R. K., Moore E. G., Hegyeli A. F., Leonard F. J . Biomed. Mater. Res. **1971**, *5***,** 169

Kumar N., Ravikumar M. N. V., Domb A. J. Advanced Drug Delivery Reviews 2001*, 53,* 23

Kokubo H., Obara S., Minemura K., Tanaka T., Chem. Pharm. Bull. **1997,** *45,* 1350

Lafferty S. V., Newton J. M. , Podczeck F. International Journal of Pharmaceutics **2002**, *239,* 143

Lewis D. H. In "Biodegradable polymers as drug delivery systems" Editors: Chasin M, Langer R, Marcel Dekker, New York, **1990**

Lemaire V., Belair J., Hildgen P. Int. J. Pharm. **2003**, *258*, 95

Lemoine D., Francois C., Kedzierewicz F., Preat V., Hoffman M., Maincent P. Biomaterials **1996**, *17*, 2191

Lemmer B. J. Contr. Rel. **1991**, *16*, 63

Lee B., Ryu S., Cui J., International Journal of Pharmaceutics **1999**, *188,* 71

Leopold C. S. Pharm. Sci. Technol. Today **1999**, *2*, 197

Lewis D. H. in "Controlled release of bioactive agents from lactide/glycolide polymers" Editors: M. Chasin and R. Langer, Biodegradable Polymers as Drug Delivery Systems, Marcel Dekker, New York , **1990**

Lin S.Y., Kawashima Y., Pharm. Res. **1987,** *4,* 70

Leenslag J. W., Pennings A. J. Makromol. Chem. **1987**, *188*, 1809

Li J. K., Wang N., Wu X. S. Polymer Preprints **1997**, *38*, 604

Li S. M., Garreau H., Vert M. J. Mater. Sci. Mater. Med. **1990**, *1*, 131

Li, S. M., Garreau, H., Vert, M. J. Mater. Sci. Mater. Med. **1990**, *1*, 23

Li S. M., Garreau H., Vert M. J. Mater. Sci. Mater. Med. **1990**, *1*, 131

Li S. M., Garreau H., Vert M. J. Mater. Sci. Mater. Med. **1990**, *1*, 23

Li S. M., Biomaterials **1999**, *20*, 35

Lin S.-Y. J. Microencapsulation **1993**, *10*, 319

Lu L., Yaszemski M. J., Mikos A. G. Biomaterials **2001**, *22*, 3345

Lu M. Y. F., Borodkin S., Woodward L., Li P., Diesner C., Hernandez L., Vadnere M. Pharm. Res. **1991**, *8*, 706

Marvola M., Nykänen P., Rautio S., Isonen N., Autere A. -M. European Journal of Pharmaceutical Sciences **1999**, *7, 259*

Mastiholimath V.S., Dandagi P.M., Jain S. S., Gadad A.P. ,Kulkarni A.R., International Journal of Pharmaceutics **2007**, *328*, 49

Matsumoto A., Matsukawa Y., Suzuki T., Yoshino H. J. Controlled Release **2005**, *106*, 172

Matsumura S., Mabuchi K., Toshima K. Macromol. Rapid Commun. **1997**, *18*, 477

Mathiowitz E., Jacob J.S., Jong Y.S., Carino G.P., Chickering, D. Charturved P., Santos C.A., Vijayaraghavan K., Montogomery S., Bassett M., Morrell C., Nature **1997,** *386*, 410

Mayer J. M., Kaplan D. L. Trends Polym. Sci. **1994**, *2*, 227 Maffione G., Iamartino P., Guglielmini G., Gazzaniga A. Drug Dev. Ind. Pharm. **1993**, *19*, 2043

McGinity J.W, Proceedings of Pre-World Congress Particle Technology, Gifu, Japan, September 17–18, **1990**.

McNeil M. E., Rashid A., Stevens H.N.E. Drug dispensing device, US Patent 5,342,624 (1994)

Milkovich, R., Am.Chem.Soc.Polym.Prepr. **1980,** *21*, 40

Milkovich R., Chiang M.T.,

U.S. Patent Nos, 3,786,116, 3,842,050, 3,842,057, 3,842,058, 3,842,059 **(1974)**

Monshipouri M., Rudolph, A. S. J. Microencapsulation **1995**, *12*, 117

Mrsny R. J. J. Control. Release **1992,** *22*, 15

Nakagami H., Keshikawa T., Matsumura M. Tsukamoto H., Chem. Pharm. Bull. **1991,** *39,* 1837

Nakamae K., Nizuka T., Miyata T., Furukawa M., Nishino T., Kato K., Inoue T. , Murakami S., Muramatsu M., Otomo S., J. *Nat. Prod.* **1992,** *55*, 513

Nakamae K., Nizuka T., Miyata T., Uragami T., Hoffman A.S. , Kanzaki Y. in: "Advanced Biomaterials in Biomedical Engineering and Drug Delivery System" ,Editors: N. Ogata, S.W. Kim, J. Feijen and T. Okano, , Springer-Verlag, Tokyo, **1996**

Nii T., Ishii F., Int. J. Pharm. **2005,** *298*, 198

Nijenhuis A. J., Grijpma D. W., Pennings A. J. Macromolecules **1992**, *25*, 6419

Obara S., Maruyama N., Nishiyama Y., Kokubo H. European Journal of Pharmaceutics and Biopharmaceutics **1999**, *47,* 51

Ohmori S, OhnoY, Makino T., Kashihara T., International Journal of Pharmaceutics **2004***, 278,* 459

Ohya, Y., Maruhashi, S.; Ouchi, T. Macromol. Chem.Phys. **1998**,*199,* 2017

Okada H., Toguchi H. Crit. Rev. Ther. Drug Carr. Syst. **1995**, *12*, 1

Okano T.; Bae, Y. H.; Jacobs, H.; Kim, S. W. J. Controlled Release **1990**, *11*, 255.

Odegardstuen L.I., Bjerknes K., Sande S.A. , Waaler T., Acta Pharm. Nord **1991, *3,*** 163

Ostberg T., Lund E. M., Graffner C. Int. J. Pharm. **1994**, *112*, 241

Park K., Shalaby W. S. W., Park H. "Biodegradable Hydrogels for Drug Delivery", Technomic Publishing, Lancaster-Basel, **1993**

Peltonen S. H., Paronen; Timo P., Nakari J., Vuorenpaa J., Urtti A. O. Composition for pH dependent controlled release of active ingredients and methods for producing it U.S. Pat. No. 5,656,292, **(1997)**

Pillay V., Fassihi R. Journal of Control. Release **1999**, *59,* 229

Pitt C. G., Gratzel M. M., Kimmel G. L., Surles J., Schindler A. Biomaterials **1981**, *2*, 215

Porter S.C., Pharm. Technol. **1979***, 3,* 55

Powell D. A., Nahata M. C., Powell N. E., Ossi M. J. Ann. Pharmacother. **1991**, *25*, 1236

Pozzi F., Furlani P., Gazzaniga A., Davis S. S., Wilding I. R. J. Control. Release **1994**, *31*, 99

Qiu Y.; Park, K. Advanced Drug Delivery Reviews **2001**, *53,* 321

Ratner B. D., Hoffman A. S. in "Hydrogels for Medical and Related Applications" Editor: J. D. Andrade, ACS symposium series, American chemical society, Washington, D. C. **1976**

Rempp P.F., Franta, E. Adv.Polym.Sci. **1984,** *58*, 1

Rempp P.F., Lutz, P., Masson, P. Franta, E. Makromol.Chem., **1984**, *8*, 3

Risbud M.V.; Hardikar, A. A.; Bhat, S.V.; Bhonde, R. R. J. Controlled Release **2000**, *68*, 23

Ritschel W. A. Methods Find. Exp. Clin. Pharmacol. **1991**, *13*, 313

Roche E. J., Reo J. P, Rotogranulations and taste masking coatings for preparation of chewable pharmaceutical tablets. EP application no. 0 411 952 A2 **(1994)**

Robson H. J., Craig D. Q. M., Deutsch D. International J. of Pharmaceutics **1999**, *190*, 183

Ross A.C., Macrae R. J., Walther M., Stevens H. N. E. J. Pharm. Pharmacol. **2000**, *52*, 903

Ryan D. M., O'Callaghan C. H., Muggleton P. W., Antimicrob. Agents Chemother. **1976**, *9*, 520

Saly R., José D. P., Kenneth R. M., Grant E. R. Journal of Pharmaceutical and Biomedical Analysis **2005**, *38,* 270

Sangalli M. E., Maroni A., Zema L., Busetti C., Giordano F., Gazzaniga A. Journal of Controlled Release **2001**, *73*, 103

Schliecker G., Schmidt C., Fuchs S., Wombacher R., Kissel T. Int. J. Pharm. **2003**, *266*, 39

Schmaljohann D., Advanced Drug Delivery Reviews **2006,** *58*, 1655

Schulz G.O. ,Milkovich R., J.Appl.Polym.Sci. **1982,** *27*, 4773

Schulz G.O. , Milkovich R. J. Polym.Sci.Polym.Chem.Ed. **1984,** *22*,1633

Seager H. J. Pharm. Pharmacol. **1998**, *50*, 375

Shefer, A Surface dissolution and/or bulk erosion controlled release compositions and devices 20040062778, **2004**

Shiozawa, H., Sugao, H., Yamazaki, S., Yano, K,. Quick release coated preparation. EP application no. 0 559 897 A1 **(1993)**

Siegel R.A., Adv. Polym. Sci. **1993**, ***109,*** 233

Sinclair R.G. Environmental Science and Technol. **1973**, *7*, 955

Singh R., Awasthi S., Vyas S. P. Die Pharm. **1993**, *48*, 728

Sjoqvist R., Graffeer C., J. Ekman, Pharm. Res. **1993,** *10,* 1020

Sluzky V., Tamada J. A., Klibanov A. M., Langer R. Proc. Natl. Acad. Sci USA **1991**, *88*, 9377

Slomkowski S., Sosnowski S., Gadzinowski M., Macromol.Symp. **1997**, *123*, 45

Sorenson, W. R., Campbell, T. W., "Preparative Methods of Polymer Chemistry," Interscience, New York, K.Y., **1961**

Spenlehauer G., Vert M., Benoit J. P., Boddaert A. Biomaterials **1989**, *10*, 557

Stolt M., Sodergard A. Macromolecules, **1999**, *32*, 6412

St. Claire R.L., Caudill, W. L. Am. J. Hosp. Pharm. **1989**, *46*, 256

Tandya, A., Mammucari, R., Dehghani, F., Foster, N.R., International Journal of Pharmaceutics **2007,** *328*, 1

Tasaka F., Ohya Y., Ouchi T., Macromolecules Vol. **2001**, *34*, 5494

Törmälä, P., Waris, T., Plast. Reconstr. Surg. **2001**, *108*, 167

Thomson R. C., Wake M. C. , Yaszemski M. J. and Mikos A. G. In "Biodegradable polymer scaffolds to regenerate organs" Editors: Peppas N. A., Langer R. S. Advances in Polymer Science-Vol.122 Biopolymers-II, Springer Berlin / Heidelberg **1995**

Ueda H., Tabata Y. Adv. Drug Deliv. Rev. **2003**, *55*, 501

Ueda H., Tabata Y. Adv. Drug Deliv. Rev. **2003**, *55*, 501

Uraneck C.A.,Hsieh H.L., Buck, O.G., J. Polym.Sci. **1960**, *46*, 535

Venkateswara S., Nyshadham J. R., Fix J. A. Pharmaceutical Sci. and Techn. Today **2000**, *3*, 138

Vert M. Angew Makromol. Chem. **1984**, *166/167*, 155

Vert M., Li S. M., Spenlehaur G., Guerin P. J. Mater. Sci. Mater. Med. **1992**, *3*, 432

Vert M., Schwarch G., Coudane J. J. Macromol. Sci. Pure Appl. Chem. A **1995**, *32*, 787

Vert M., Li S., Garreau H. J. Control. Release **1991,** *16*, 15

Victor L., Serebruany B. R. Oshrine, A.I. Malinin, D. A., Alan D. M., James J. F., American Heart J. **2005**, *5*, 882

Vuorio M, Manzanares J.A., Murtomaki L., Hirvonen J., Kankkunen T., Kontturi K., J. Contr. Release **2003,** *91,* 439

Wang H. T., Palmer H., Linhardt R. J., Flanagan D. R., Schmitt E. Biomaterials **1990,** *11*, 679

Wang N. E., Gisondi M. A., Golzari M. Acad. Emerg. Med. **2003**, *10*, 1278

Weidner J., Drug Discovery Today **2001,** *6,* 1028

Winzenburg G., Schmidt C., Fuchs S., Kissel T. Advanced Drug Delivery Reviews **2004**, *56*, 1453

Wong H. M., Wang J. J., Wang C. H. Ind. Eng. Chem. Res. **2001**, *40*, 933

Wichterle O., Lim D. Nature **1960**, *185*, 117

Worcester M. U., Stojcevski Z., Murphy B. Eur. J. Cardiovasc. Nurs. **2003**, *2*, 151

Yang L., Fassihi R. J. Control. Release **1997**, *44*, 135

Yajima T., Nogata A., Demachi M., Umeke N Itai., S., Yunoki N., Nemoto M. Chem. Pharm. Bull. **1996**, *44*, 187

Yamashita Y., J .Appl.Polym.Sci. Appl.Polym.Symp. **1981**, *36*, 193

Yui N., Dijkstra,P.J.;J. Macromol. Chem. **1990**, *191*, 481

Zhang X. B., Hou X. P. Chin. Hosp. Pharm. J. **2003**, *23*, 43

CHAPTER 2

Objectives and Scope of the Work

2.1 Objectives and Scope of the Work

The objective of this work is to synthesize, characterize and evaluate modified lactide copolymers for oral drug delivery. Lactide polymers are being explored for variety of biomedical and drug delivery applications. Because of their highly hydrophobic and crystalline nature, lactide polymers take long time for degradation ranging from several days to months. Hence these are not suitable for oral drug delivery applications. Since lactide polymers are FDA approved, safe and are already used in marketed formulations for parenteral drug delivery, regulatory approvals for oral drug delivery applications, will be relatively easy if the drug release could be achieved in time spans relevant to oral drug delivery. This could be achieved by suitable modifications to bring down crystallinity and enhance degradation rates or achieving drug release by mechanisms other than degradation, such as dissolution.

In this work, low molecular weight lactide polymers were tailor made to suit prerequisites of oral drug delivery and formulated according to dissolution patterns. Drug release from these formulations under simulated conditions was studied.

The investigation has been undertaken with following objectives.

1. To synthesize and characterize homopolymers, copolymers and macromonomers of lactide using iron and lipase catalysts. Efficiency of catalysts will be compared and the most suitable of these will be selected for further polymerization reactions. Two approaches will be tried for lowering crystallinity of lactide. According to first approach, lactide will be directly copolymerized with amino acid depsipeptide to check effect of copolymerization with hydrophilic monomer on crystallinity of polymers. Another approach will involve incorporation of structural changes in lactide molecule after ring opening polymerization and subsequent copolymerization with acidic, basic and hydrophilic monomers. Low molecular weight telechelic lactide diol of varying molecular weight will be synthesized using 1, 4 butanediol in different ratios. Lactide diol will be converted to lactide macromer, which will have one functional end. This macromer will be used for further copolymerization reactions.

2. To synthesize lactide copolymers by copolymerization of lactide macromers with VP by free radical polymerization technique and study dissolution pattern at different pH. Lactide macromers of desired molecular weight range would be selected from preliminary experiments and copolymerized by varying mole ratio of comonomer in feed. Effect of VP content and macromer molecular weight on dissolution time of these copolymers will be studied in aqueous buffers. Film forming property of the copolymers will be checked. Design of formulation based on dissolution profile and film forming property of these copolymers will be the next step in study. Drugs will be encapsulated in lactide-VP copolymers in the form of microspheres. These will be characterized for surface morphology and particle size. Drug release from this formulation will be studied in simulated gastric fluid.

3. To study effect of copolymerization with another basic monomer DMAEMA, Lactide macromonomers will be copolymerized by free radical polymerization with DMAEMA in different mole ratio. Dissolution profile of copolymers in various buffers will be studied and effect of DMAEMA content and molecular weight of copolymer on dissolution time will be monitored. Polymer compatibility with drug will be checked to determine suitability for formulation. Type of formulation will be decided after checking film-forming property of the copolymers. Solid dosage form will be fabricated using the polymer and drug along with other excipients. Taste masking efficiency will be checked if the polymer is found compatible with bitter drugs. Drug release from the formulation will be studied in simulated gastric fluid.

4. To synthesize lactide copolymers with acidic monomers like AA and MAA and study effect of acidic monomer content and copolymer molecular weight on dissolution time of copolymer in various buffers. Film forming property of lactide copolymers will be checked. Copolymer compositions exhibiting desirable dissolution profiles will be selected for formulation in dosage forms such as tablets. In this study effect of varied dissolution time of copolymer on drug release pattern will be of prime concern. Effect of hydrophobic lactide macromer copolymerization with hydrophilic acidic monomer and corresponding changes in properties of lactide will be the critical aspect of this experimental plan.

5. To study effect of lactide copolymerization with hydrophilic monomer like NVP. Dissolution of copolymers in various buffers will be studied and effect of monomer content and pH of medium on dissolution will be evaluated. Film forming property of the copolymers will be checked and accordingly polymers will be formulated using a drug. Polymers exhibiting desirable dissolution profiles will be selected for formulation. Drug will be encapsulated in polymer matrix and release in simulated physiological fluids will be monitored. Use of lactide copolymers for immediate or extended drug delivery will be demonstrated in this study. Thus effect of hydrophilic monomer on lactide copolymerization will be explored and the performance of copolymers evaluated for oral drug release.

In summary, functionalized lactide macromer will be co polymerized with acidic, basic and hydrophilic monomers and effect of copolymerization on dissolution properties of the copolymer will be studied for all systems. Modification of dissolution properties of the co polymer containing hydrophobic lactide macromer in aqueous buffers will guide formulation development using these copolymer systems. Drug release from the copolymer systems will lay the foundation for applications of tailored lactide copolymers in the field of oral drug delivery.

CHAPTER 3

Synthesis and Characterization of Modified Lactide Polymers and Macromer Using Iron Catalysts

3.1 Introduction

Lactic and glycolic acid polymers are being explored in a variety of applications ranging from degradable surgical sutures (Frazza, 1971), joints (Kobayashi, 1991) and implants for internal bone fixation (Shalaby, 1994) for a long time. Applications of lactide polymers in drug delivery systems has become area of interest because of polymer characteristics such as biocompatibility, controllable degradation kinetics, ease of fabrication and established regulatory approval for human applications (Bosewell, 1973). These applications are based on degradation of the polymer. Degradation products such as lactic acid and glycolic acid are biocompatible and non-toxic (Okada, 1991). Controlled release delivery systems for narcotic antagonists, contraceptive hormones (Kricheldorf, 1987), conventional drugs and antibiotics have been developed.

PLGA polymers have been used to prepare several commercially available controlled-release drug delivery systems, including Zoladex™ (Zeneca), Decapeptyl™ (Ipsen biotech) and Prostap SR™ (Lederle), which are licensed for use in humans in Europe and USA. Leupron depot (Takeda Pharma) is another controlled release preparation, which is used for sustained release of Leuprolide acetate over a period of one to six months. Safety of these polymers for medical use has been demonstrated through the development of several products for the controlled release of drugs.

Oral route of drug delivery is very popular because of ease of administration and better patient compliance. Lactic acid polymers are not yet explored for oral drug delivery because of their high molecular weight, hydrophobicity and crystallinity (Tasaka, 1999). Due to these reasons it becomes difficult to manipulate rate of degradation of lactide polymers over the time period relevant to oral delivery. Hence there is a need to modify these polymers, which will allow use in oral drug delivery applications. Modification in lactide polymers could be mainly achieved by copolymerization with hydrophilic monomers. Many researchers have investigated such methods in the past. For example, lactide-glycolide copolymer (Kricheldorf, 1987), lactide-ε–caprolactone copolymer (Song, 1983) and lactide-poly (ethylene

oxide) (Kimura, 1989) have been previously synthesized as biocompatible and biodegradable polymers. Also novel biodegradable copolymers of α-amino acids and α-hydroxy acids were synthesized by ring opening polymerization using stannous octoate catalyst (Ouchi, 1997).

Lactide polymers are commonly prepared by ring opening polymerization of lactide catalyzed by organometallic compounds like tin (Kricheldorf, 1988), aluminium, lead and zinc. The deleterious effects of these catalysts can be avoided by using iron compounds (Stolt, 1999). Iron compounds are biocompatible and polymerization products using iron catalysts are safe even if catalyst is covalently linked with polymer chain after polymerization.

In this work we co-polymerized lactide with amino acid depsipeptide by ring opening melt polymerization using iron catalysts synthesized in the lab and subsequently modified these copolymers with fatty alcohol. These copolymers were characterized by NMR, VPO and DSC. These preliminary efforts indicated the possibility of lowering crystallinity of lactide polymers by converting them into an amorphous form. This work further led to modification of lactide polymers by introducing functional groups, which can be tailored to achieve desired dissolution profiles. We synthesized lactide polymers with end hydroxyl groups, which could be converted to unsaturation. During this experimental scheme, we were successful in lowering down crystallinity of lactide polymers. We could synthesize low molecular weight lactide macromer (lactide acrylate / lactide methacrylate), which had one unsaturation at the end, which could be used for copolymerization with other monomers to introduce desirable dissolution or degradation property in lactide polymer in subsequent work. All our efforts were synchronized with an aim to design polymeric lactide excipients suitable for oral drug delivery.

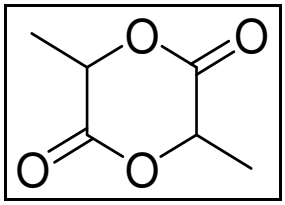
3.2 Experimental Part

3.2.1 Materials

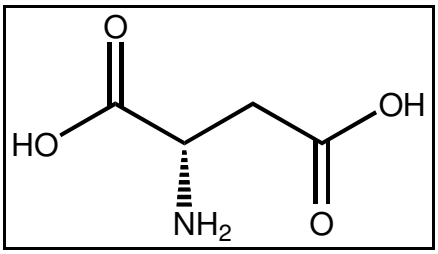
L-lactide (3S-cis-3,6-Dimethyl-1,4-dioxane-2,5-dione 98%), L-Aspartic acid, 1,4 Butanediol , and Iron acetate (99.995%) were procured from Aldrich Chemicals , USA and used without further purification. Azobis iso butyronitrile (AIBN) was purchased from SAS Chemicals Company, Mumbai. Structures of monomers and initiator are presented in **Figure 3.1**.

Porcine Pancreatic lipase and Candida Rugosa lipase were purchased from Sigma Chemicals, USA. Acetic acid, isobutyric acid and trifluoroacetic acid were purchased from Spectrochem Chemicals, India. Iron powder, dicyclohexyl carbodi-imide (DCC), dimethyl amino pyridine (DMAP), triethyl amine (TEA) and benzyl alcohol were obtained from S, D fine Chemicals, India.

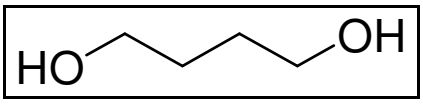
Benzoyl chloride and hydroquinone were purchased from Merck Ltd and Qualigen Chemicals, Mumbai respectively. Solvents like tetrahydrofuran, N, N dimethyl formamide, chloroform and diethyl ether were procured from S, D fine Chemicals, India.



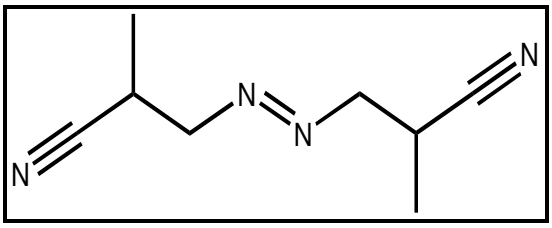
L-lactide



L-Aspartic acid



1,4 Butanediol



AIBN

Figure 3.1 Structures of Monomers and Initiator Used in the Work

3.2.2 Synthesis of Iron Catalysts

Two iron catalysts (Iron isobutyrate and Iron trifluoroacetate) were synthesized using iron metal powder and corresponding anhydrous acid i.e. isobutyric acid and trifluoroacetic acid respectively. The assembly used in the synthesis is shown schematically in **Figure 3.2**. Apparatus consisted of three main parts- A, B and C. It was assembled to vaporize acid from reservoir A through B to the condenser C, condensing the vapor as a hot condensate, passing through a bed of iron powder, thereby forming ferrous acid , and returning to the condensate together with dissolved acid of the iron back to A (Welsh, 1972).

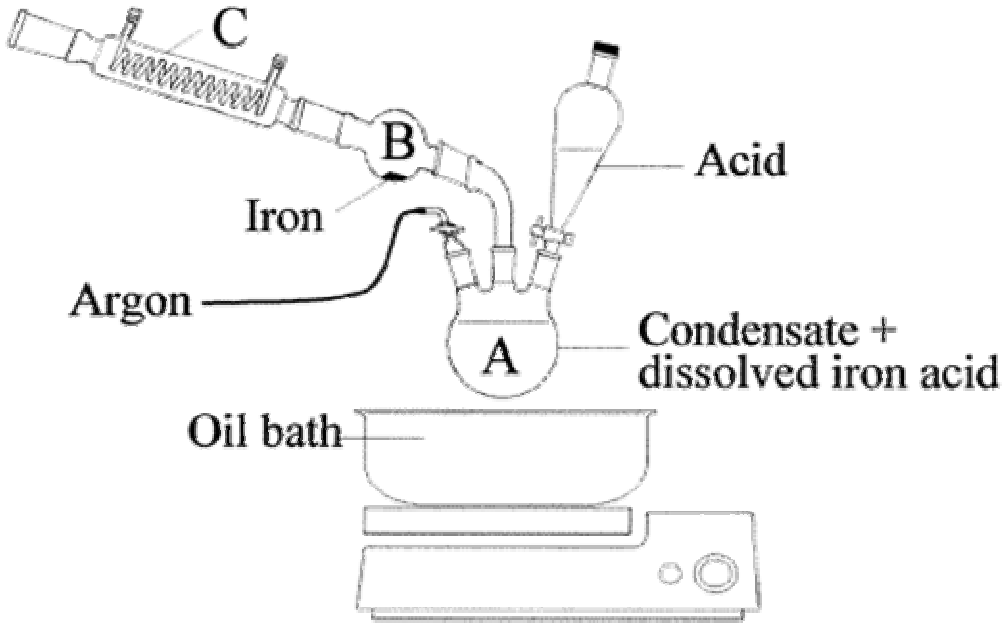


Figure 3.2 The Apparatus for Synthesis of Iron Catalysts (Stolt, 1999)

The reaction was performed under inert atmosphere. After the desired reaction time the unreacted acid was removed, leaving a solid product, which was stored in a desiccator until used in polymerization reactions.

3.2.2.1 Synthesis of Iron Isobutyrate

Dry isobutyric acid was reacted with iron metal powder at 175^0C for 24 hours under nitrogen atmosphere using experimental assembly shown in **Figure 3.2**. Part A was in contact with oil bath maintained at desired reaction temperature. After the reaction was over, unreacted acid was distilled off taking all care to avoid air exposure, when dark green powder was left. Traces of acid remaining were removed by exposing flask to high vacuum for long time.

3.2.2.2 Synthesis of Iron Trifluoroacetate

Synthesis of iron trifluoroacetate was carried out using the same assembly as described above but under different reaction conditions. Trifluoroacetic acid was reacted with iron metal powder at 85^0C for 24 hours under nitrogen atmosphere. White product was deposited along edges of flask during the reaction. Unreacted acid was distilled off under nitrogen atmosphere. After this, traces of trifluoroacetic acid were removed by applying high vacuum. Iron trifluoroacetate was stored in desiccator under vacuum.

3.2.3 Synthesis of Lactide Homopolymers

Homopolymerization of lactide was carried out by ring opening melt polymerization method. Iron acetate, iron isobutyrate and iron trifluoroacetate were used as catalyst. L-lactide and catalyst were thoroughly mixed and put in a glass ampoule. The ampoule was evacuated and sealed under vacuum. Amount of catalyst varied from iron acetate (Monomer to initiator (M/I) ratio 50 to 2000) to iron isobutyrate and iron trifluoroacetate (0.12 % w/w). The polymerization reactions were performed in a sand bath (Techne Fluidized Sand Bath, SBL-1) at specific reaction temperatures. After desired time, the polymerization was discontinued by taking out the ampoules from sand bath and cooling the reaction contents to room temperature. The polymerization products were dissolved in chloroform filtered to remove unreacted catalyst and precipitated using diethyl ether as a nonsolvent and dried in a desiccator to recover lactide homopolymers.

Two types of lipases i.e. Lipase CR (Candida rugosa) and Lipase PPL (Porcine pancreatic) were also used as catalyst for synthesis of lactide homopolymers.

L-lactide was mixed with 3% w/w of lipase under dry conditions and sealed under vacuum. This ampoule was heated in oil bath at 160^0C for 7 days. After reaction was complete, contents were dissolved in chloroform and precipitated using hexane.

Reaction conditions, monomer to initiator ratios and corresponding characterization using different types of iron and lipase catalysts is described in **Table 3.1**.

3.2.4 Synthesis of Aspartic acid Depsipeptide

Aspartic acid depsipeptide was synthesized from L-aspartic acid according to scheme shown in **Figure 3.2**. L-aspartic acid was used as starting material and depsipeptide was synthesized in three steps as described below.

3.2.4.1 Synthesis of L-Aspartic Acid-β-Benzyl Ester (β-Benzyl-L-Aspartate)

Aspartic acid (13.4 g) was added in small portions to mixture of benzyl alcohol and sulphuric acid. The resulting solution was diluted with 95 % ethanol and neutralized by the drop wise addition of pyridine. The mixture was stored in refrigerator overnight. The crystalline product was thoroughly washed by triturating on the filter with ether. The ester was recrystalized from hot water to recover β-benzyl-L-aspartate.

3.2.4.2 Synthesis of Condensed Product

Cold suspension of β-benzyl-L-aspartate was reacted with triethanolamine. p-dioxane solution containing bromoacetyl bromide was added to the resulting solution in portions. The mixture was extracted with diethyl ether. The combined organic layer was washed with water, dried with Magnesium sulphate and concentrated in vacuum. The resulting bromoacetyl-asp-O-benzyl in the form of brown oil was used in next step without further purification

3.2.4.3 Cyclization

A solution of bromoacetyl-asp-O-benzyl was added drop wise to a mixture of sodium bicarbonate in dimethyl formamide solvent with vigorous stirring. After removal of the solvent under vacuum, the residue was partitioned between ethyl acetate and water. The organic layer was separated and subsequently extracted with

water and dried with magnesium sulphate, then concentrated under vacuum to yield brown oil. Purification of this compound was carried out by column chromatography on silica gel using ethyl acetate as the eluent followed by recrystalization from ethyl acetate and hexane.

3.2.5 Synthesis of Lactide Copolymers

Lactide copolymers with Aspartic acid depsipeptide were synthesized using iron and lipase catalysts under specific reaction conditions.

3.2.5.1 Copolymerization of Lactide using Iron Catalyst

L-lactide (M1) and aspartic acid depsipeptide (M2) were added in a glass ampoule in various mole proportions (M1: M2) *viz.* 90:10, 80:20, 75:25, 65:35 and 60:40. Iron initiators were added in appropriate amount. Melt polymerization under vacuum was carried out in sand bath. After reaction time was over, the product was recovered by precipitation and dried under vacuum.

3.2.5.2 Copolymerization of L-lactide using Lipase PPL

Lactide and aspartic acid depsipeptide were mixed in an ampoule along with lipase catalyst. The reaction was carried out in sand bath and after stipulated reaction time ampoule contents were dissolved in chloroform, precipitated in hexane and washed with diethyl ether to get lactide copolymer.

3.2.6 Deprotection of Lactide Copolymers

Lactide copolymer (100 mg) was treated with 1.3 ml of 1 M tri fluoro methane sulphonic acid (TFMSA) -thioanisole / tri fluoro acetic acid (TFA) at 0-5^{0}C for 60 minutes and at room temperature for 30 minutes (Ouchi, 2002). The reaction

mixture was poured into a large amount of diethyl ether to precipitate deprotected lactide copolymer as a light brown solid.

3.2.7 Modification of Lactide Copolymers

Deprotected aspartic acid copolymer was modified with cetyl alcohol using DCC as coupling agent and DMAP as catalyst. Chloroform was used as solvent. 30 mg of deprotected copolymer and 0.0121 g of cetyl alcohol were dissolved along with DCC and DMAP in chloroform. Reaction was carried out at 0^0C for 2 hours followed by overnight stirring at room temperature. Salt was filtered out and mixture was concentrated to get the modified product.

3.2.8 Synthesis of Lactide Macromonomer

3.2.8.1 Synthesis of Oligo (Lactide) Diol OR Lactide Diol

L-lactide was polymerized with 1, 4 Butanediol (Haris, 2005) using iron acetate as the catalyst. Lactide and 1, 4 Butanediol were mixed in different mole ratios from 50:1 to 50:12 and ring opening melt polymerization reactions were carried under vacuum using a sand bath. The molten polymer was poured into petridish and dried in desiccator to get oligo (lactide) diol.

3.2.8.2 Synthesis of Oligo (Lactide) Acrylate / Oligo (Lactide) Methacrylate OR Lactide Acrylate / Lactide Methacrylate (LAc/ LMAc)

Oligo (lactide) diol was condensed with acryloyl chloride or methacryloyl chloride to get oligo (lactide) acrylate or oligo (lactide) methacrylate respectively. Dry THF was used as reaction medium and triethylamine was used as a base. Reaction mixture was cooled using ice bath and then acryloyl or methacryloyl chloride solution in THF was added drop by drop with the help of addition funnel over a period of 6 to 8 hours. The mixture was stirred further for next 14 to 16 hours at

room temperature. After the reaction was over, contents were filtered to remove chloride salt and filtrate was concentrated. This was precipitated in hexane to recover oligo (lactide) acrylate / oligo (lactide) methacrylate.

Acryloyl chloride and methacryloyl chloride were synthesized from acrylic acid or methacrylic acid and Benzoyl chloride by distillation. The reaction mixture was first refluxed for an hour using hydroquinone and then distilled out at around 70^0C. This was stored in cold in the refrigerator and was used for condensation with oligo (lactide) diol to get oligo (lactide) acrylate or methacrylate.

3.3 Characterization

3.3.1 Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectra of lactide homopolymers, modified lactide copolymers and macromonomer were recorded on Bruker DRX –500 spectrometer operating at a proton frequency of 125.4 MHz using $CDCl_3$ as a solvent.

3.3.2 Fourier Transform Infra Red (FTIR) Spectroscopy

For FTIR analysis, 5 % (w/v) solution of lactide polymers and macromer was prepared in chloroform (Spectroscopic grade) and was put on KBR pellet for analysis. Fourier transform infrared analysis was carried out using a Shimadzu FT-IR-8300 spectrometer at resolution of 4 cm^{-1}.

3.3.3 Vapour Pressure Osmometer (VPO)

Molecular weight of lactide copolymers and macromer was determined using Knauer Vapour Pressure Osmometer K-7000. Stock solution of lactide polymer (10 mg/ml) was prepared in Chloroform (Spectroscopy grade) and successive dilutions of polymer were analyzed at selected constant temperature (37^0C). Benzil was used as standard for calibration of instrument. Molecular mass of sample could be determined with known concentration of the substance using calibration value.

3.3.4 Gel Permeation Chromatography (GPC)

Waters Model 590 (Millipore) was used to determine molecular weight of lactide homopolymers using THF as solvent. 3 mg of polymer was dissolved in 1 ml THF and analyzed for molecular weight.

3.3.5 Differential Scanning Calorimetry (DSC)

A Perkin Elmer DSC-2 was used for studying the melting and crystallization behavior of lactide polymers. The temperature and energy scales were calibrated with the standard procedures. The melting studies were performed in the temperature range -50 to 240 °C with the help of intracoolers arrangement at the heating rate of 10 °C/min in the N_2 atmosphere.

3.3.6 Elemental Analysis

Elemental content of iron catalysts was found using elemental analysis technique on instrument Dionex-DX500 Ion Chromatograph.

3.3.7 Melting Point

Melting point of intermediate compounds during synthesis of aspartic acid depsipeptide was determined using model Mel-Temp (Electro thermal).

3.4 Results and Discussion

3.4.1 Synthesis of Iron Catalysts

The hot vapors of anhydrous acid in round bottom flask entered the condenser and acid condensate then passed over the bed of iron metal where reaction took place in

acid and metal to give acid salt. This salt then returned to flask as condensate and thus the flask contained unreacted acid and deposited salt. Acids could be evaporated to give desired product. The assembly was used as to avoid the contact of salt with air as to avoid the hydrolysis of iron compound.

3.4.2 Synthesis of Lactide Homopolymers

Lactide homopolymers prepared by ring opening melt polymerization were white and solid in nature. Molecular weight of these homopolymer was dependent on amount of catalyst used for polymerization. Increasing catalyst loading per unit weight of the monomer led to lower molecular weight of the resulting polymer. Polydispersity of all these homopolymers as observed from GPC results was below 1.5. Iron catalysts produced lactide homopolymers with higher molecular weights as compared to lipase catalysts. It was clearly observed from **Table 3.1** that iron catalyst was more efficient as compared to lipase catalyst with respect to yield, development of molecular weight and polydispersity of lactide homopolymers. Lipase catalysts also required longer reaction times for homopolymerization of lactide as compared to iron catalyst. Hence it was decided to use iron catalysts instead of lipase catalysts in further work.

It was evident from **Table 3.1** that amongst iron catalysts, iron acetate was more efficient than iron isobutyrate and iron trifluoroacetate with respect to yield and polydispersity index.

Table 3.1 Homopolymerization of Lactide using Iron and Lipase Catalysts

Initiator	M/C Ratio (moles)	Mol. Wt.	P.D.	Yield (%)
IA	50	3575	1.3	88
IA	100	6240	1.3	90
IA	200	5984	1.4	85
IA	300	9000	1.4	92
IA	400	17308	1.3	86
IA	500	16566	1.3	90
IA	750	33000	1.3	72
IA	1000	48000	1.2	84
IA	2000	40000	1.4	80
IIB	0.12 % w/w	45403	1.6	85
ITFA	0.12% w/w	50970	1.7	88
Lipase CR	3% w/w	12000	1.9	21
Lipase PPL	3% w/w	15000	2.1	22

P.D. = polydispersity IA= iron acetate IIB= iron isobutyrate
ITFA= iron trifluoroacetate M/C ratio = monomer to catalyst ratio
Reaction Temperature 210 ^{0}C, Time 2 hrs

Iron catalysts needed higher reaction temperatures as compared to lipase catalysts. **Figure 3.3** indicated that Iron catalyst has to be activated at higher temperatures at the beginning of polymerization and was inactive below 190 ^{0}C.

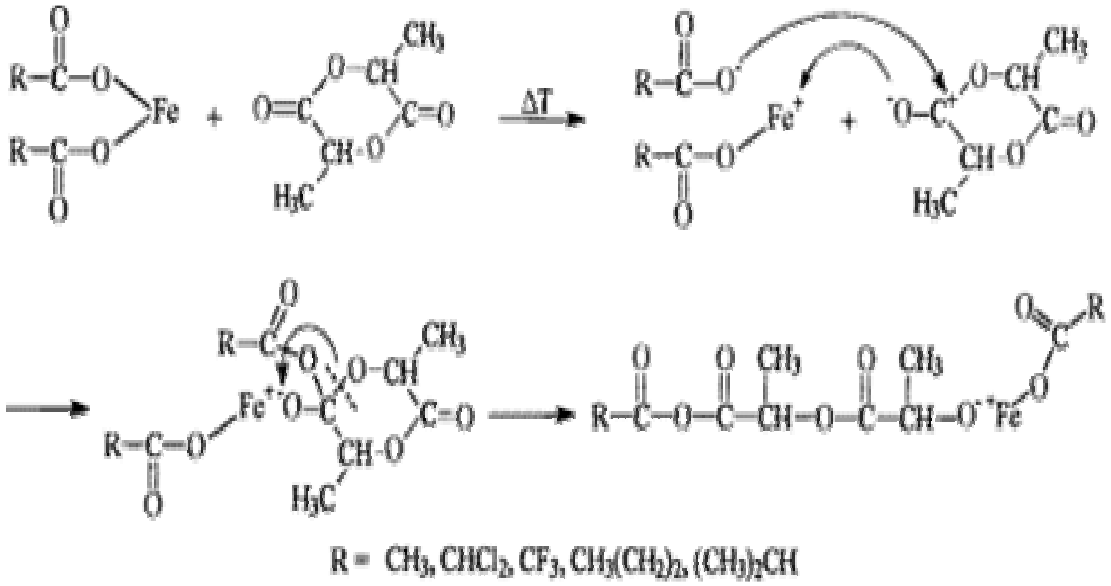


Figure 3.3 Role of Iron Initiators in Lactide Polymerization

According to **Figure 3.3**, thermal activation of the catalyst could result in an anion of the acetate, which was able to initiate the polymerization in a purely anionic manner. Some of iron was chemically bound to the polymer chain, which could not be explained with a pure anionic mechanism, as no iron was supposed to be attached to the polymers in anionic polymerization. A pure anionic mechanism would furthermore not yield methyl end groups, which were found for the PLLA prepared by using iron acetate (Stolt, 1999). The acetate anion, as well as the iron partly, was chemically attached to the polymer chain, and the proposed polymerization mechanism was an anionic type of coordination insertion as shown in **Figure 3.3**.

3.4.3 Lactide Copolymers

3.4.3.1 Aspartic Acid Depsipeptide

Aspartic acid depsipeptide was a cyclic molecule synthesized from L-lactide and L-aspartic acid in three steps. As shown in **Figure 3.4**, cyclic compound was obtained

by the intramolecular reaction of N-bromoacetyl-protected aspartic acid with sodium bicarbonate in a large amount of dimethyl formamide solvent. Melting point of benzyl protected amino acid (β-benzyl-L-aspartate) synthesized in step 1 was found to be 218-220^{o}C. Bromoacetyl-asp-O-benzyl synthesized in step 2 using bromoacetyl bromide and triethanolamine in dioxane was oily brown substance. It was then treated with sodium bi carbonate to yield cyclic aspartic acid depsipeptide monomer as shown in **Figure 3.4**.

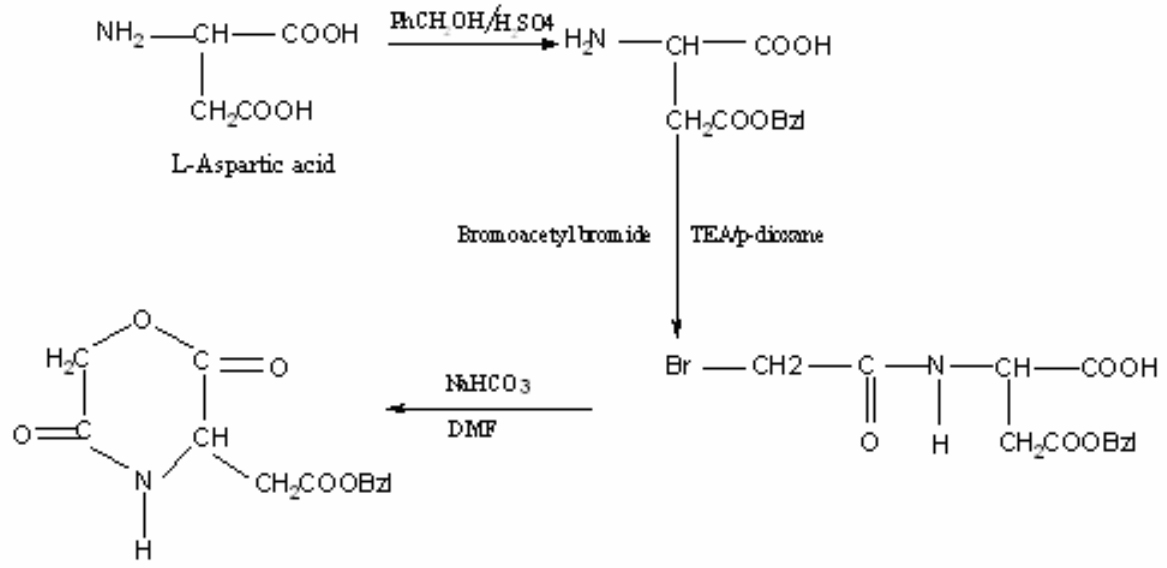


Figure 3.4 Schematic Presentation of Aspartic Acid Depsipeptide Synthesis

Aspartic depsipeptide was a light yellow solid product. Yield of the synthesis was 20%. Melting point of the monomer was 240^{0}C.

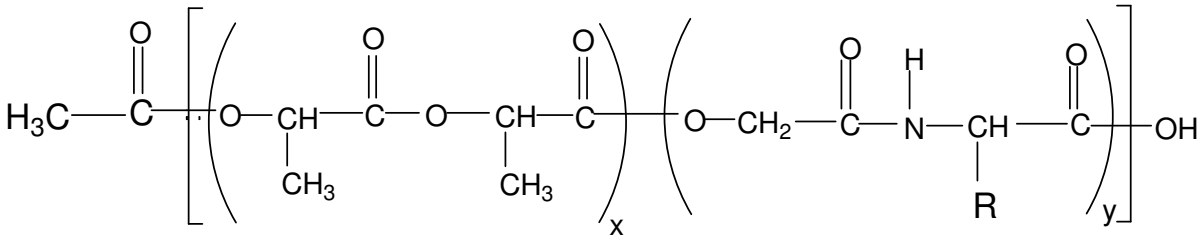
3.4.3.2 Copolymerization of Lactide with Aspartic Acid Depsipeptide

Lactide monomer was copolymerized with aspartic acid depsipeptide by melt ring opening polymerization under vacuum. Reaction conditions, monomer to catalyst ratio, composition by NMR and yield of copolymerization reaction were recorded in **Table 3.2**.

It was readily observed from **Table 3.2** that iron catalysts were more effective than lipase catalysts with respect to yield, duration of reaction and molecular weight of the copolymers.

Table 3.2 Lactide-Aspartic Acid Depsipeptide Copolymerization

Catalyst	Reaction temp(^{0}C)	Reaction time	M/C ratio (moles)	mol. wt.	Composition		Yield (%)
					In feed	By NMR	
IA	210	2 hr	1000	14000	90:10	91:09	80
IA	210	2 hr	1000	10000	80:20	78:22	85
IA	210	2 hr	1000	3000	75:25	71:29	78
IA	210	2 hr	1000	1665	65:35	62:38	72
IA	210	2 hr	1000	666	60:40	67:33	75
IIB	200	2 hr	850	1115	90:10	90:10	80
IIB	200	2 hr	850	866	75:25	80:20	83
IIB	200	2 hr	850	597	60:40	68:32	56
ITFA	190	4 hr	980	9203	90:10	98:02	73
ITFA	190	4 hr	980	3177	75:25	72:28	75
ITFA	190	4 hr	980	2201	60:40	63:37	60
Lipase PPL	160	7 days	3 % w/w	12600	90:10	93:07	50



Where R= $CH_2COOBzl$

Figure 3.5 Copolymer of Lactide and Aspartic Acid Depsipeptide

Copolymers with higher lactide content (more than 65 mole % in the copolymer) were solid in nature; as compared to other copolymers with lactide content below 65 moles. **Figure 3.5** shows structure of copolymer of lactide-aspartic acid copolymer. Yield of copolymerization was good. Compared to enzyme, Iron catalyst was more effective in completing the polymerization in a shorter time.

3.4.4 Deprotection of Lactide Copolymers

Deprotection of lactide-aspartic acid depsipeptide copolymers was carried out to remove benzyl group from protected copolymer. NMR spectra of copolymer before and after deprotection were shown in **Figure 3.6** and **3.7.** NMR spectrum of protected copolymer in **Figure 3.6** showed presence of aromatic protons around 7.4 ppm along with sharp peak for solvent $CDCl_3$ at 7.25 ppm. It was clearly seen from **Figure 3.7** that representative peaks of aromatic groups around 7.3 ppm vanished. Only one sharp peak, indicative of solvent $CDCl_3$ remained after deprotection of the copolymer. It was evident from comparison of the figures that deprotection of the copolymers was successful.

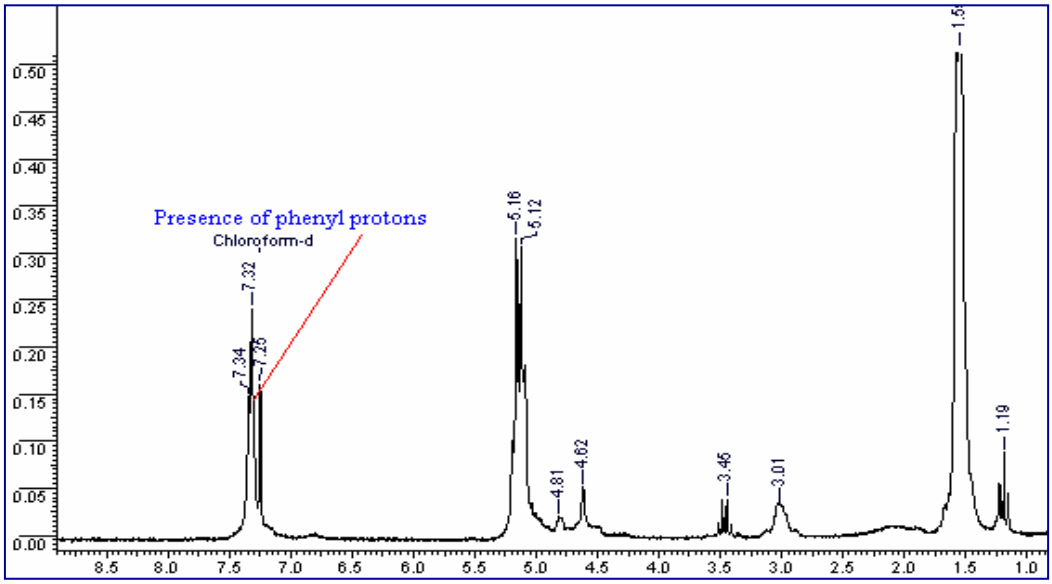


Figure 3.6 Protected Lactide - Aspartic Acid Depsipeptide Copolymer

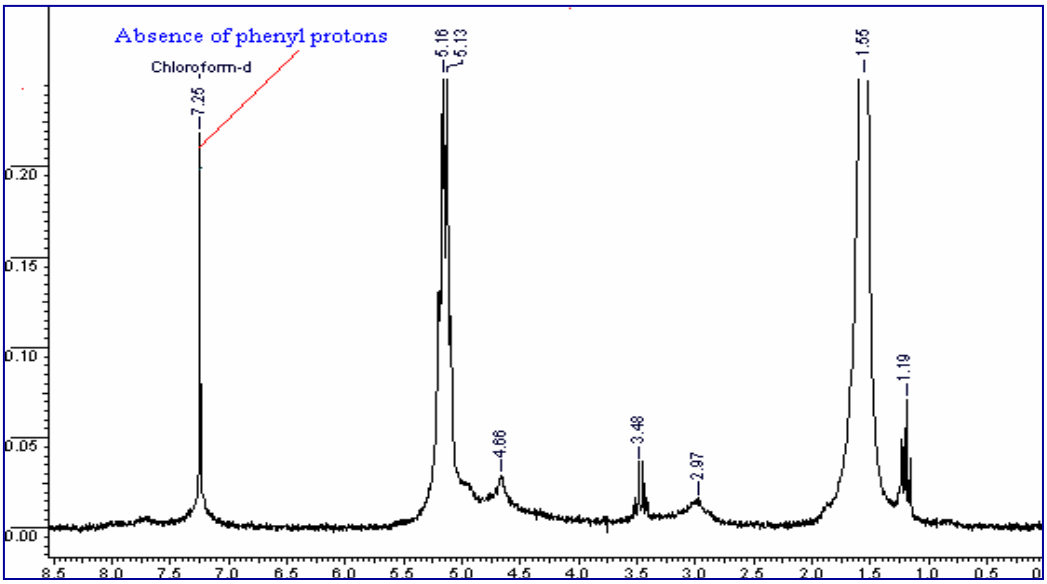


Figure 3.7 Deprotected Lactide-Aspartic Acid Depsipeptide Copolymer

3.4.5 Modification of Lactide Copolymers

Deprotected lactide copolymers were modified with fatty alcohol and effect of modification was studied by DSC.

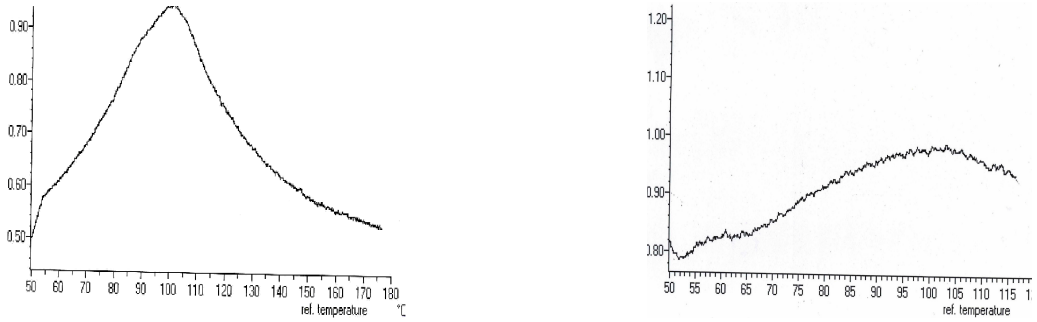


Figure 3.8 DSC of Copolymer Before and After Modification by Fatty Alcohol

Effect of modification was reflected in thermograms of polymers. Polymer showed sharp melting peak around 100 ^{0}C for polymer before modification, which was indicative of crystalline nature of the deprotected copolymer. After modification with fatty alcohol, the peak indicative of T_m of the copolymer, disappared. Hence it was evident from **Figure 3.8** that copolymer turned from crystalline to amorphous when modified with fatty alcohol.

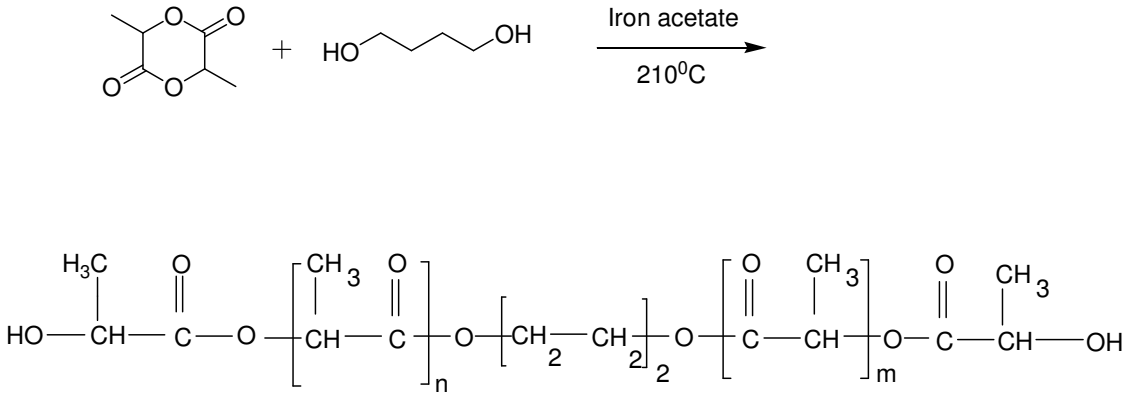
This result proved that lactide modification by copolymerization could lower down crystallinity of polymers to great extent. We decided to explore this idea by exploring another structural modification of lactide polymer.

3.4.6 Synthesis of Lactide Macromonomer

3.4.6.1 Synthesis of Lactide Diol

Lactide was reacted with 1, 4 Butanediol using iron acetate as catalyst by ring opening polymerization. Lactide and 1, 4 Butanediol amounts were varied from 50:1 to 50:12 moles. The results of molecular weight, acid value and T_g were

tabulated in **Table 3.3**. Schematic presentation of synthesis of lactide diol from lactide and 1,4 Butanediol was shown in **Figure 3.9**. Iron acetate was used as catalyst. The difunctional compound 1,4 Butanediol reacted with the lactide, and the product of this reaction was telechelic oligomer chains, which had only one kind of end group. On further polymerization, the lactic acid monomers or oligomers were linked to these telechelic polymer chains by the reaction of the hydroxyl groups. As a result, at the end of the polymerization there were polymer chains, which contained mainly one kind of end group.



Lactide diol

Figure 3.9 Synthesis of Lactide Diol

It was readily observed from **Table 3.3** that as the amount of 1, 4 Butanediol in the polymer increased, molecular weight of lactide diol decreased. Thus molecular weight of lactide diol could be controlled by bringing variations in the feed composition with respect to amount of 1, 4 Butanediol.

From 50:1 to 50:6 composition, Lactide diol were solid in nature, but after that all lactide diols were semisolid in nature due to increased proportion of 1,4 Butanediol. Tg of these polymers also decreased from polymer 1 to polymer 5, after that

measurement of Tg was not possible as the polymers were semisolid and sticky in nature.

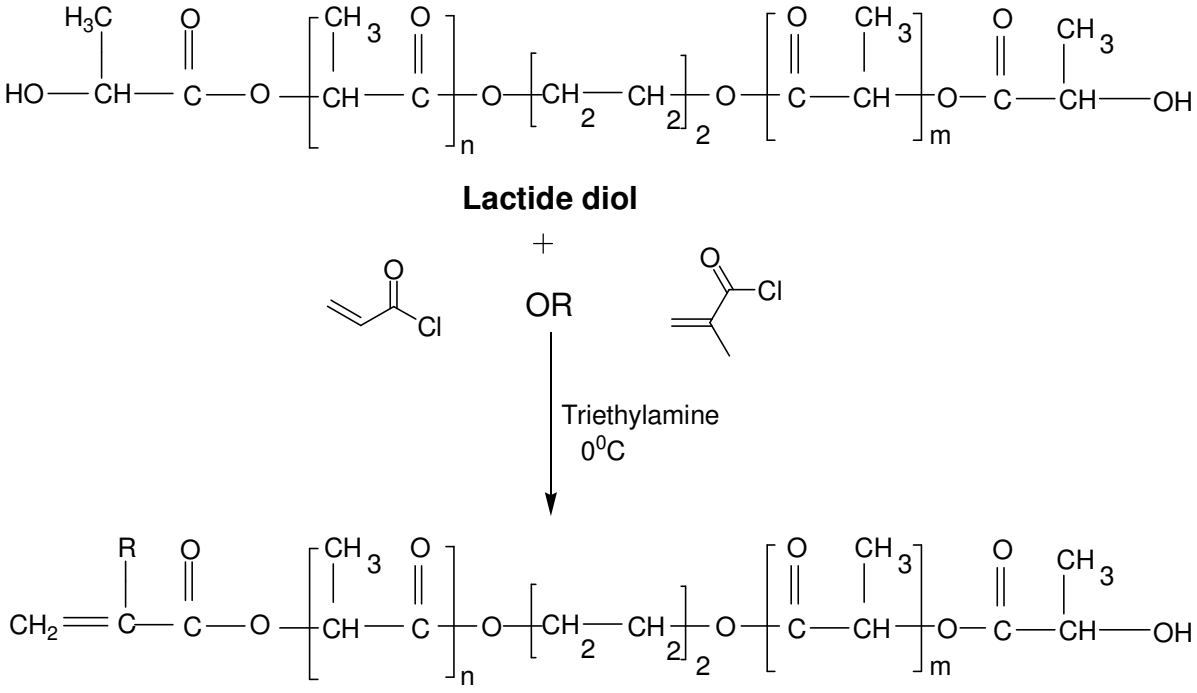
Acid numbers of these polymers were very low, which was indicative of hydroxyl termination of these polymers.

Table 3.3 Synthesis of Lactide Diol

Polymer	Lactide (mol)	Butanediol (mol)	Mn (GPC) G/mol	Mw (GPC) G/mol	Acid number	Tg (^{0}C)
1	50	1	9436	14000	1.36	43.37
2	50	2	3251	5190	1.12	36.72
3	50	3	1039	1801	1.05	31.08
4	50	4	600	1725	1.6	23.10
5	50	6	1232	1817	1.25	21.35
6	50	8	749	1207	1.32	--
7	50	9	662	980	1.52	--
8	50	10	487	818	1.58	--
9	50	12	446	671	1.02	--
10	50	14	397	563	1.11	--

3.4.6.2 Synthesis of Lactide Acrylate / Methacrylate

Lactide diol was converted to lactide macromer in the form of lactide acrylate or methacrylate by condensation with acryloyl chloride or methacryloyl chloride respectively. Schematic presentation of this reaction was shown in **Figure 3.10**.



Where R= CH_3 or H

Figure 3.10 Synthesis of Lactide Macromer (Lactide Acrylate / Methacrylate)

3.4.7 Characterization

3.4.7.1 NMR Spectroscopy

3.4.7.1.1 Lactide-Aspartic Acid Depsipeptide

^{1}H NMR spectrum of lactide copolymer was used as a quantitative tool to find out composition of lactide and aspartic acid depsipeptide in the copolymer. The structure of copolymer and corresponding NMR peaks of the copolymer shown in **Figure 3.11** were compared for this purpose. It was evident from figure that 2 methine protons corresponding to 2 (-CH) groups of lactide appeared at 5.16 ppm

and 6 methyl protons corresponding to 2 (-CH3) groups from lactide were seen at 1.56 ppm. In case of aspartic acid depsipeptide, 2 methylene protons of (-CH2) were observed around 3 ppm. These peak positions were compared to assign integration and compositions were calculated. These compositions were recorded in **Table 3.2**.

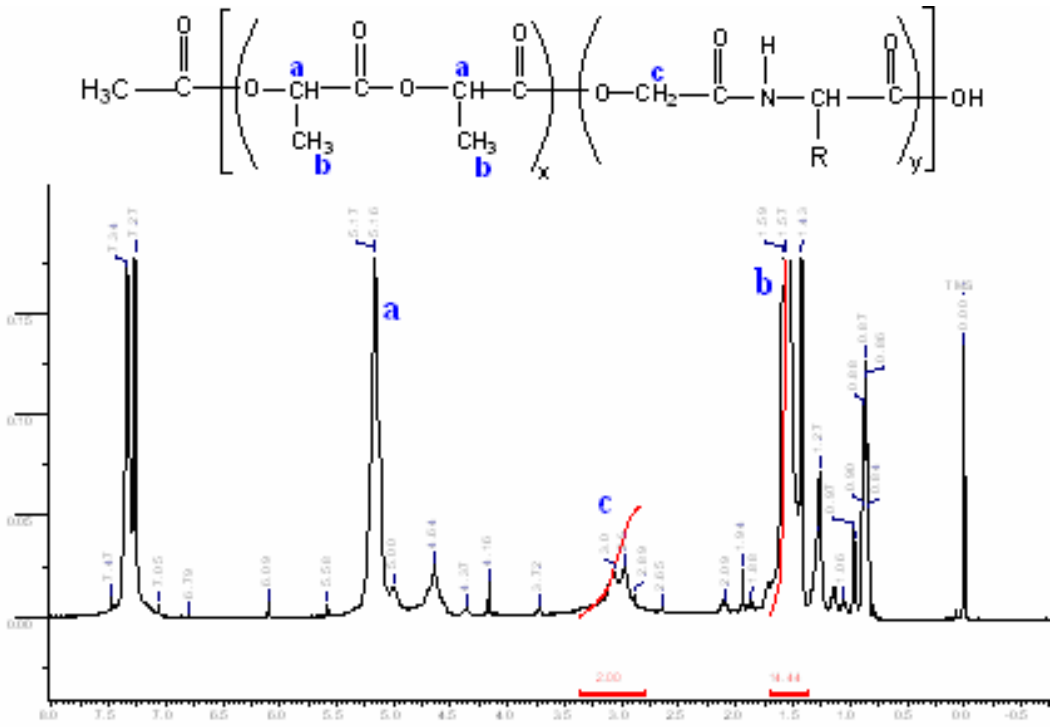


Figure 3.11
NMR Spectrum of Lactide-Aspartic acid Depsipeptide Copolymer

3.4.7.1.2 Synthesis of Lactide Macromer

NMR spectroscopy can also be used as a qualitative analytical tool to check formation of reaction intermediates and end products. There were three spectra as shown in **Figure 3.12**.

Lactide monomer spectrum showed only two important peaks at 5.16 and 1.56 ppm positions corresponding to methine and methyl protons of lactide. It was readily observed from **Figure 3.12** that when lactide was reacted with 1, 4 butanediol, peaks around 4.25 ppm were introduced in the spectrum. This was due to

introduction of 4 (- CH_2) groups of butanediol. Hence it was clear that lactide was successfully converted in lactide diol. Third spectrum was of lactide macromer. In this, lactide diol was condensed with methacryloyl chloride to give lactide methacrylate, called as lactide macromer.

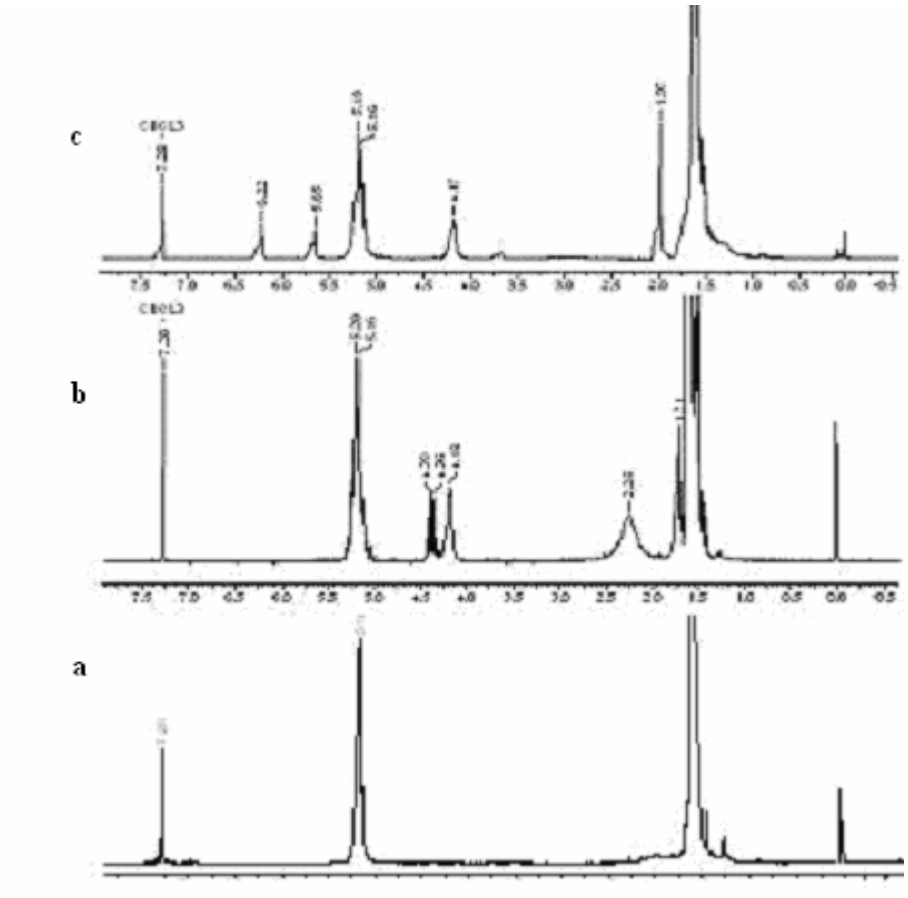


Figure 3.12 NMR Spectra of Lactide Monomer (a), Lactide Diol (b) and Lactide Macromer (c)

Conversion of end hydroxyl group of lactide diol to unsaturated lactide methacrylate was confirmed by introduction of two peaks in between 5.5 and 6.5 ppm. Thus it was confirmed qualitatively that lactide macromer was synthesized from lactide diol in last step with the help of NMR technique.

3.4.7.2 FTIR Spectroscopy

Fourier transform infrared spectroscopy was used for qualitative analysis of lactide modification reactions. Cyclic lactide monomer was polymerized by ring opening melt polymerization technique and was reacted with 1, 4 Butanediol. This introduced end hydroxyl groups in the polymer to give rise to lactide telechelic polymer (lactide diol) with reduced crystallinity. This lactide diol was further condensed with acid chloride to introduce end functionality in lactide. All these conversions and intermediate formations were confirmed by FTIR spectroscopy.

Figure 3.13 showed spectra of lactide monomer, lactide diol and lactide macromer. Synthesis of lactide diol and subsequently lactide macromer was confirmed by FTIR spectroscopy.

It was clearly observed from **Figure 3.13** that lactide monomer spectrum showed characteristic peak at 1750 cm^{-1} for C=O (carbonyl stretching) of ester. These FTIR spectra can be used as qualitative tool to check if the differences in the end groups could be seen in every stage of lactide modification.

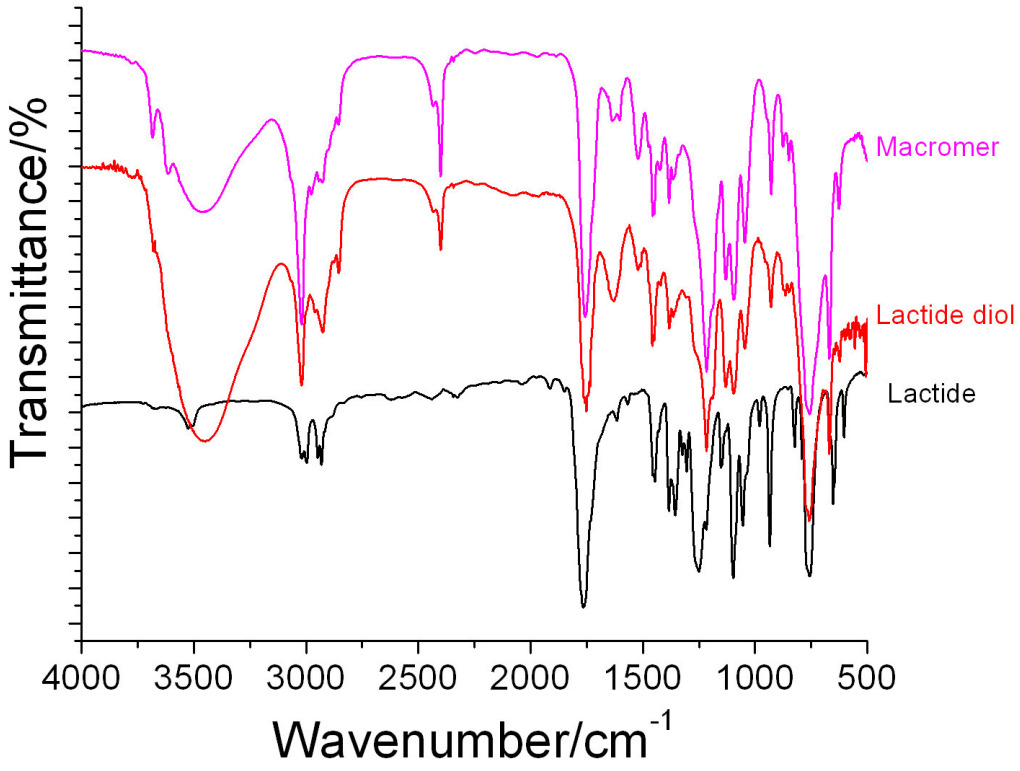


Figure 3.13
IR Spectra of Lactide, Diol and Macromer in the Range 4000 to 500 cm^{-1}

In spectrum of lactide diol, characteristic broad hydroxyl absorption peak around 3500 cm^{-1} was observed which indicates that lactide diol contained (-OH) end group which was absent in lactide spectrum. Along with this, spectrum for lactide diol also exhibited characteristic absorption peaks of ester (at 1750 and 1090 cm-1 for –C=O and C–O-C) and $–CH_2$-, $-CH_3$ groups (at 2850-3050 cm^{-1}). In the next step, lactide macromer was synthesized from lactide diol. Accordingly in the spectrum, intensity of hydroxyl absorption peak around 3500 cm^{-1} was decreased as hydroxyl group at one end of lactide diol was utilized in acrylate / methacrylate formation. At the same time peak at 1637 cm^{-1} for unsaturation (present in the macromer) was observed in **Figure 3.13** along with peak at 1750 cm^{-1} for C=O (carbonyl stretching) of ester.

It was readily observed from FTIR spectra that, only one end hydroxyl group of lactide diol was utilized during macromer synthesis and formation of lactide macromer was indicated by specific peak for unsaturation at 1637 cm^{-1}.

Thus, FTIR spectra provided evidences for synthesis of lactide macromer from lactide at every step. Introduction of important peaks at every step in this synthetic work exhibited qualitative proof to draw important conclusions about successful synthesis of lactide diol and then lactide macromer as important end product.

3.4.7.3 Elemental Analysis

Elemental analysis of iron catalysts was carried out to confirm C and H content. The results were compared with literature reports.

Table 3.4 Elemental Analysis of Iron Initiators

Iron isobutyrate

Analysis	Theoretical	Experimental
C	17.0 %	15.55 %
H	0.0 %	0.48 %

Iron trifluoroacetate

Analysis	Theoretical	Experimental
C	41.8 %	40.82 %
H	6.1 %	7.41 %

Table 3.4 indicates elemental analysis results for iron isobutyrate and iron trifluoroacetae synthesized in the lab. The reports were well in agreement with the literature, which was one of the ways to prove successful synthesis of iron catalysts in the lab.

3.5 Conclusions

We modified highly crystalline lactide polymers by two different routes in order to lower down crystallinity of lactide and to design excipient suitable for oral drug delivery. Modification was carried out in two ways, 1) the copolymerization with hydrophilic monomer and 2) synthesis of lactide macromonomer by introduction of unsaturation. We characterized these modified copolymers and macromers by NMR, FTIR, DSC, VPO and GPC. We could demonstrate that lactide-aspartic acid depsipeptide copolymers had turned amorphous after modification with fatty alcohol. This result provided stimulus for another plan for modification of lactide polymers. We synthesized and characterized lactide polymers with hydroxyl ends (prepolymers) and then introduced functional unsaturation at one end. This provided lactide macromer with one functional end, which could be copolymerized with desirable monomer to tailor lactide polymer as needed.

In summary, synthesis and characterization of modified lactide polymers and macromer highlights following important points:

1. Iron isobutyrate and iron trifluoroacetate were synthesized and their efficiency was evaluated and compared with iron acetate during lactide homopolymerization and copolymerization.
2. Iron catalysts were used in all lactide polymerization reactions and yield of homopolymerization reactions was good with development of high molecular weight polymers with narrow polydispersity index.
3. Lipase catalysts were also used along with iron catalysts for lactide homopolymerization. But it was observed that iron catalysts were more beneficial with respect to yield, molecular weight, polydispersity index, low reaction temperatures and less reaction time.
4. Lactide was copolymerized with aspartic acid depsipeptide in presence of iron catalyst and it was modified with cetyl alcohol after deprotection. Copolymers were low molecular weight and solid in nature. Polymers became sticky as aspartic acid content increased in the series of the compositions.

5. Crystalline lactide copolymers modified with fatty alcohol were amorphous in nature and showed no crystalline melting point peak in the Thermogram.

6. This result suggested that the crystallinity of the lactide polymer could be reduced by alternative copolymerization methods. This would involve synthesis of lactide macromer containing unsaturation at one end and further copolymerization with functional monomers to achieve desirable dissolution profiles.

7. Lactide was polymerized by ring opening polymerization method using iron catalyst in the presence of 1, 4 Butanediol to give lactide diol which had hydroxyl groups at both ends.

8. Molecular weight of lactide diol varied depending on amount of 1, 4 Butanediol added during polymerization. It was observed that increased amount of 1, 4 Butanediol resulted in decreased molecular weight of lactide diol.

9. At the same time, increased amount of 1, 4 Butanediol decreased crystallinity of lactide, this was evident from decrease in T_g values of lactide diol.

10. Lactide diol was condensed with acryloyl chloride or methacryloyl chloride to get lactide macromer with unsaturation at one end. Due to the presence of unsaturation, this lactide macromer is an active moiety, which can take part in copolymerization reaction.

11. Lactide macromonomer is low molecular weight and semisolid in nature. It is non crystalline in nature. Synthesis of lactide macromer from lactide diol was confirmed by NMR and FTIR.

3.6 References

Bosewell G.A., R.M. Scribner **1973,** US Patent 3,773,919

Frazza E.J. , Schmitt E.E., J. Biomed. Mater. Res. Symp. **1971,** *1*, 43

Haris, Parvez I.; Vogt, S.; Berger, S.; Wilke, I.; Larcher, Y.; Weisser, J.; Schnabelrauch, M. Bio-Medical Materials and Engineering **2005**, *15***,** 73

Kimura, Y.; Matsuzaki, Y.; Yamane, H.; Kitao, T. Polymer, **1989,** *30*, 1342

Kricheldorf, H.R.; Krieser, I. Makromol.Chem. **1987,** *188*, 1861

Kricheldorf, H.R.; Berl, M.; Scharnagl, N. Macromolecules **1988,** *21*, 286

Kobayashi, H.; Hyon, S.H.; Ikada, Y.J. Biomed Mater.Res. **1991**, *25*, 1481

Ouchi, T.; Nozaki, T.; Ishikawa, A.; fujimoto, I.;Ohya, Y. Journal of Poly.Sci.Part A: Poly.Chem. **1997**, *35*, 377

Song, C.X.; Chen, H.Y.; Feng, X.D. Polym.Commun. **1983,** *3*, 177

Stolt, M.; Sodergard, A. Macromolecules **1999,** *32*, 6412

Tasaka, F.; Miyazaki, H.; Ohya, Y.; Ouchi, T. Macromolecules **1999**, *32*, 6386

Okada H, Inoue Y., Heya T., Ueno H., Ogawa Y.and Toguchi H., Pharm. Res,**1991,** *8*, 584

Ouchi T., Hidetake M., Hidetoshi A., Fumitaka T., Hamada A., Ohya Y. Journal of Polymer Science: Part A: Polymer Chemistry, **2002,** *40*, 1218

Shalaby S.W and Johnson A., Biomedical polymers: Designed to degrade systems, Carl Hanser Verlag, Munich **1994**, 1

CHAPTER 4

pH Sensitive Lactide Copolymers for Cefuroxime Axetil Delivery

4.1 Introduction

Drug delivery takes a variety of forms, depending on the agent to be delivered and the administration route. Different routes of administration like the oral, parenteral, nasal and transdermal are available but the oral route remains the most attractive for drug delivery because of its ease, convenience, and non invasiveness.

Oral dosage forms are designed according to the nature of the drug, the nature of application and the need for any special effects. The common oral dosage forms can be classified into two categories solid and liquid. Tablets and capsules are solid dosage forms. Liquid dosage forms involve mixtures like solutions, suspensions and emulsions. The solid dosage forms are further modified depending on the therapeutic action desired, like controlled, extended or delayed release and these can be devised as fast dissolving, chewable, dispersible, hard gelatin capsules and soft gel filled capsules. However, patients at the extremes of age, such as children and the elderly, often experience difficulty in swallowing solid oral dosages forms. For these patients the drugs are mostly provided in liquid dosage forms. When the drug is bitter (Gao, 2006) the exposure of the active drug ingredient to the taste buds, leads to unpleasant taste.

Taste is an important parameter governing the compliance. The disagreeable taste of drugs causes difficulties in swallowing or causes patients to avoid their medication thereby resulting in low patient compliance. Conventional taste masking techniques such as use of sweeteners, amino acids, flavoring agents are often unsuccessful in masking the taste of highly bitter drugs like quinine, barberin, etoricoxib, antibiotics like levofloxacin, ofloxacin, sparfloxacin, ciprofloxacin, cefuroxime axetil, erythromycin and clarithromycin. Hence various other methods for taste masking have been tried earlier, which include use of ion exchange resins (Jaskari, 2001), complexation of bitter drugs with pharmaceutically acceptable excipients (Duchene, 1999) and coating of drugs by lipids and various polymeric materials. Of these, the coating is the most widely used technique for taste masking. Coating of the active ingredient can be done by any of the techniques known in the art like

microencapsulation (Kawashima, 1989), hot melt granulation, Fluid bed coating, and spray drying.

pH sensitive polymeric excipients can be used as coating of the drugs. Choice of polymeric excipients depends on site of drug delivery. Many acrylic and methacrylic acid copolymers have been explored for intestinal drug delivery because these polymers dissolve at pH conditions prevalent in intestine. Thus polymers containing anionic monomers which ionize at alkaline conditions bring out the dissolution of the polymer and release the drug are used for intestinal drug delivery. In the same way, polymers containing cationic monomers, which will ionize in acidic conditions, can be used for gastric delivery of drug molecules like cefuroxime axetil. Such pH sensitive polymers which dissolve in acidic medium are called as polybases. Polybases like poly (4-vinylpyridine) get ionized at low pH (Pinkrah, 2003). These vinyl pyridine polymers undergo a phase transition below pH 5 owing to protonation of pyridine groups (Gohy, 2002)

Table 4.1 Important Cationic Monomers pK_a Value of Homopolymers

Monomer	pH-sensitive group	pK_a	Reference
N, N-Dimethyl aminoethyl methacrylate	$-N(CH_3)_2$	6.6	Butun,1999
N, N-Diethyl amino ethyl methacrylate	$-N(CH_2CH_3)_2$	6.9	Butun,1999
2-/4-Vinyl pyridine	Pyridine ring	5	Satoh 1989
Chitosan	$-NH_2$	6.3	Lopez-Leon 2005

Thus pH sensitive monomers can be used in taste masking applications depending on site of drug delivery. Basic monomers like 4 –vinyl pyridine can be used for pH dependent delivery of certain antibiotics in gastric region.

There are certain drugs, which pose challenges during the formulation due to their physico-chemical characteristics like cefuroxime axetil, a second-generation cephalosporin antibiotic. Cefuroxime has relatively high dose requirement, further increasing the difficulty in administering the therapeutically effective dose. It exhibits the tendency to gel in contact with moisture, necessitating that the dosage form disintegrates into particles rapidly and releases the drug at a faster rate before the gelling occurs. Another problem associated with cefuroxime relates to extremely bitter taste of the drug making it necessary to formulate cefuroxime in a coated delivery system to make it palatable. Such active molecule which is required to be administered as a rapid release formulation to overcome the low bioavailability needs to have a protective polymer coating which releases the active ingredient at a rapid rate without compromising the bioavailability, and masking the unpleasant taste of the active ingredient. Cefuroxime axetil has a limited absorption region in the gastrointestinal tract as the enzyme esterase, hydrolyses it to cefuroxime (Dantzig, 1994), which cannot be absorbed across the tract thereby reducing its bioavailability.

Cefuroxime axetil already has a low bioavailability of 32-50% and hence further reduction in the bioavailability due to the formulation aspects should be minimized.

The taste masking formulations should be so designed that the bioavailability of the drugs is not compromised and the use of certain polymers like the enteric coatings should not affect the time to peak. Further the drug should be sufficiently absorbed to ensure effective therapeutic concentration in the plasma. It is established that bactericidal killing is rapid, intensive and increases proportionately to the concentration (Vogelman, 1986 & 1988). In the presence of high concentration of the drug, the killing is complete and almost instantaneous. In drugs like cefuroxime axetil, rapid and complete absorption and high systemic concentration are important to elicit the desired therapeutic effect.

Many efforts are made till date to taste mask cefuroxime axetil by researchers. These are tabulated in **Table 4.2**.

From the examples in **Table 4.2** it is clear that there exists a need to develop an improved taste masking pharmaceutical composition for bitter and unpalatable drug

like cefuroxime axetil that can remain stable during storage, allow for the proper release of the drug, and are cost and use efficient.

In our work, we could synthesize pH sensitive lactide copolymers which dissolved only above pH 3 and were insoluble below this pH. Characterization of these polymers was

Table 4.2 Taste Masking Efforts for Cefuroxime axetil

Taste Masking Technique	Drug Release	Reference
Coating with lipids or mixture of lipids	High temp. required for melting affects stability of drug	James, 1989
Drug adsorbed on a resin and coated by mixture of ethyl cellulose and latex	Controlled release not favorable for drugs with limited absorption window	Wen, 1999
Microencapsulation using cellulose acetate trimellitate, HPMCP-5 & 55	Cefuroxime axetil release in intestine	Cuna, 1996
Encapsulation in pH sensitive acrylic microspheres	Cefuroxime axetil release in alkaline medium	Alonso, 1997
Drug core coated with HPMC and shellac	Rapid drug release desirable.	Khan, 2002
Encapsulation of drug in methyl methacrylate, HPMC and VP	Rapid Drug release in stomach, Non biodegradable polymers.	Kulkarni, 2005

done by NMR, FTIR, DSC and VPO. Dissolution study revealed that these polymers dissolve depending on monomer content. We encapsulated cefuroxime axetil in microspheres of lactide-VP polymers and studied drug release at acidic pH. We could formulate this drug in the form of dry syrup for reconstitution and evaluate taste masking effect of the copolymer. These lactide-VP copolymers act as

novel, taste masking, low molecular weight reverse enteric coating excipients useful for taste masking applications.

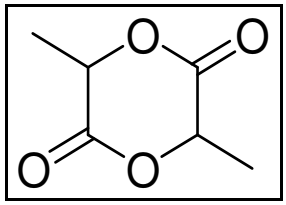
4.2 Experimental

4.2.1 Materials

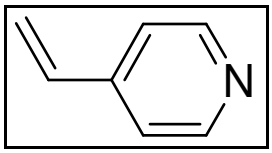
L-lactide (3S-cis-3, 6-Dimethyl-1, 4-dioxane-2, 5-dione 98%), 1, 4 butanediol, 4-vinyl pyridine (VP), and Iron acetate (99.995%) were procured from Aldrich Chemicals, USA and used without further purification. Azo bis Iso Butyronitrile (AIBN) was purchased from Sas chemicals Company, Mumbai. Structures of monomers and initiator are presented in **Figure 4.1**. Benzoyl chloride and hydroquinone were purchased from Merck Ltd and Qualigen Chemicals, Mumbai respectively. Solvents like Tetrahydrofuran and N, N dimethyl formamide were procured from S, D fine chemicals, India.

The drugs cefuroxime axetil (4-(carbamoyloxymethyl)-8- [2-(2-furyl)-2-methoxyimino-acetyl] amino -7-oxo- 2-thia-6-azabicyclo [4.2.0] oct -4-ene-5-carboxylic acid,

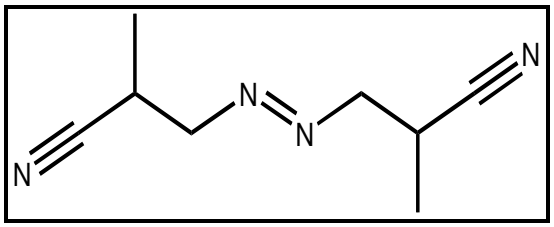
ciprofloxacin hydrochloride (1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid) and clarithromycin {6-(4-dimethylamino-3-hydroxy- 6-methyl-tetrahydropyran-2-yl) oxy-14-ethyl-12,13-dihydroxy-4-(5-hydroxy-4-methoxy-4,6-dimethyl-tetrahydropyran-2-yl) oxy-7-methoxy-3,5,7,9,11, 13-hexamethyl-1- oxacyclotetradecane-2,10-dione} were obtained from Lupin Labs, India, Pune. Chemical structures of the drugs used in the work are presented in **Figure 4.2**.



L-lactide

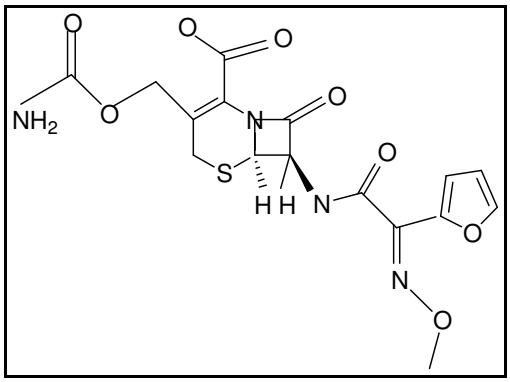


4-vinyl pyridine

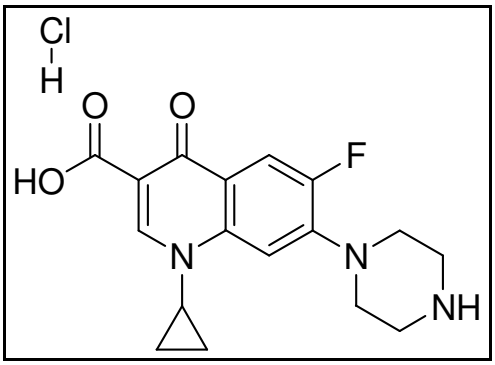


AIBN

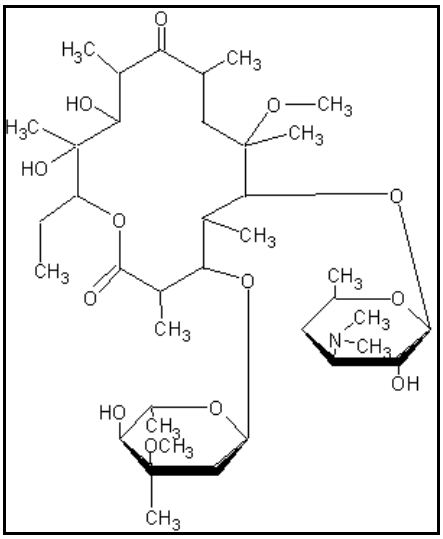
Figure 4.1 Structures of Monomers and Initiator used in Synthesis



Cefuroxime axetil



Ciprofloxacin hydrochloride



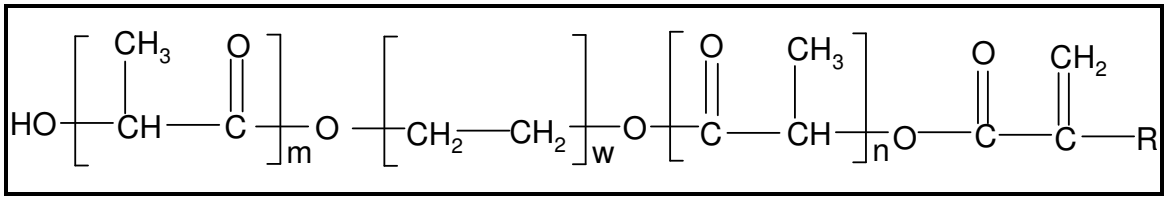
Clarithromycin

Figure 4.2 Structures of Drugs Encapsulated in the Copolymer

4.2.2 Synthesis of Lactide-VP Copolymers

4.2.2.1 Synthesis of Lactide Macromer

Lactide macromer (lactide acrylate and lactide methacrylate) was synthesized as per procedure described in chapter 3.



w = 2 and R = H or CH_3

Figure 4.3 Structure of Lactide Macromer

4.2.2.2 Synthesis of Lactide-VP Copolymers

Copolymers of lactide macromer (**Figure 4.3**) with VP were synthesized by free radical polymerization. Lactide macromers of molecular weight 500, 800 and 1200 were chosen for copolymerization. Lactide acrylate or lactide methacrylate macromer (M1) and VP (M2) were dissolved in DMF and 2 mole % AIBN was added to it. This reaction mixture was purged with nitrogen for 10 minutes and the test tube was sealed with Teflon. The reaction was carried out at 65 ^{0}C for 24 hours. Then the reaction mixture was concentrated under reduced pressure using rotavapour. The concentrated mixture was precipitated in deionised water. Polymer was then dried under vacuum to recover the product.

Lactide macromer and VP were copolymerized in different mole ratios from 10:90 to 80:20. Two types of copolymers were obtained from these polymerizations.

a. Lactide acrylate-VP (LAc-VP)

b. Lactide methacrylate-VP (LMAc-VP)

4.2.3 Encapsulation of Drugs in Lactide-VP Microspheres

Microspheres of lactide-VP polymers were prepared by emulsification solvent evaporation technique. The lactide polymer was dissolved along with the drug in an organic solvent (methanol and dichloromethane in the ratio 1:1). This organic phase was then added dropwise to light liquid paraffin under constant mechanical stirring rate of 800 rpm at room for 3-4 hours. The solvent was allowed to evaporate and chilled n-hexane or petroleum ether was added to this system and stirring was continued for another hour. The microspheres so obtained were separated by filtration, washed by pet ether or Hexane and dried under vacuum for up to 24 hours. These microspheres were stored in a well closed container under vacuum.
Three drugs – Cefuroxime axetil, ciprofloxacin hydrochloride and clarithromycin were encapsulated in lactide-VP microspheres using the method described above.

4.2.4 Reconstitution of Lactide Formulation

Taste masked pharmaceutical composition of lactide microspheres was prepared by using microspheres containing drug equivalent to 4 doses by using reconstitution medium of pH 4.5 comprising of sucrose 85% w/v, vanilla flavor qs, citric acid qs and polyvinyl pyrrolidone 2%. Final taste of the reconstituted syrup was checked by putting the formulation on tongue by 5 different volunteers and evaluating the taste parameter.

4.3 Characterization

4.3.1 Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectra of Lactide-VP copolymers were recorded on Bruker DRX –500 spectrometer operating at a proton frequency of 125.4 MHz using $CDCl_3$ as a solvent.

4.3.2 Fourier Transform Infra Red (FTIR) Spectroscopy

For FTIR analysis, 5 % (w/v) copolymer solution in chloroform (Spectroscopic grade) was put on KBR pellet for analysis. Fourier transform infrared analysis was carried out using a Shimadzu FT-IR-8300 spectrometer at resolution of 4 cm^{-1}.

4.3.3 Vapour Pressure Osmometer (VPO)

Molecular weight of lactide-VP copolymers was determined using Knauer Vapor Pressure Osmometer K-7000. Stock solution of copolymer (10 mg/ml) was prepared in Chloroform (Spectroscopy grade) and successive dilutions of polymer in this solvent were analyzed at selected constant temperature (37^0C). Benzil was used as standard for calibration of instrument. Molecular mass of a sample can be determined with a known concentration of the substance using calibration value.

4.3.4 Reactivity Ratio Determination

Kelen Tudos and Finemann Ross methods were used for finding out reactivity ratios of lactide macromer and VP monomer in the copolymer by calculation method. We were interested to know reactivity ratios and correlate it with low incorporation of VP monomer. Hence instead of doing special reactivity ratio measurements at low conversions, we went ahead with calculations depending on NMR results showing actual incorporation of VP monomer in the copolymer. Mole ratios of both, macromer and monomer in feed and in the product were used to find out reactivity ratios of the reactants.

4.3.5 Differential Scanning Calorimetry (DSC)

A Perkin Elmer DSC-2 was used for studying the melting and crystallization behavior of the lactide copolymers. The temperature and energy scales were calibrated with the standard procedures. The melting studies were performed in the

temperature range of -50 to 240 °C with the help of intercoolers arrangement at the heating rate of 10 °C/min in the N_2 atmosphere.

4.3.6 Dissolution Study

Dried lactide-VP copolymers (50 mg) were put in 5 ml buffer of respective pH. Dissolution pattern of these lactide copolymers was studied with respect to time and dissolution time was noted.

4.3.7 Scanning Electron Microscopy (SEM)

Surface morphology of lactide – VP microspheres was studied at an accelerating voltage of 20kV. (Leica, UK, model-stereoscan 440)

4.3.8 Optical Microscopy

The microspheres were spread uniformly on glass slide and observed under 10 X magnification of the microscope (Leica, UK, model). Particle size of 50 particles was recorded to get idea about average particle size of microspheres.

4.3.9 Drug Loading

Drug loading in the microspheres was determined by dissolving known amount of microspheres in methanol and sonicating it for few seconds. Supernatant solution was analyzed on UV spectrophotometer. The concentration of cefuroxime axetil and ciprofloxacin hydrochloride in microspheres was determined at 278 nm. In the similar way drug loading of microspheres containing clarithromycin was calculated using UV spectrophotometer at 270 nm.

4.3.10 Drug Release

Cefuroxime axetil release from the microparticles was determined in 900 ml of 0.07 N hydrochloric acid, at 37 ± 0.5°C, using USP type II apparatus rotated at 75 rpm. The samples were withdrawn at 15, 30, 45, 60 and 90 min. The amount withdrawn each time was replaced with fresh medium to maintain the sink conditions.

Ciprofloxacin hydrochloride release from the microparticles was determined in 900 ml of 0.1 N hydrochloric acid buffer, at 37± 0.5°C, using USP type II apparatus rotated at 100 rpm. The samples were withdrawn at 15, 30, 45, and 60, min. The amount withdrawn each time was replaced with fresh media to maintain the sink conditions.

Clarithromycin release from the taste masked particles was determined in 900 ml of acetate buffer pH 2.8, at 37± 0.5°C, using USP type II apparatus rotated at 100 rpm. The samples were withdrawn at 15, 30, 45 and 60 min. The amount withdrawn each time was replaced with fresh media to maintain the sink conditions.

4.3.11 Drug Leaching from Reconstituted Suspension

Drug release from reconstituted composition was studied over a period of 7 days to check for leaching of drug from microspheres during storage time.

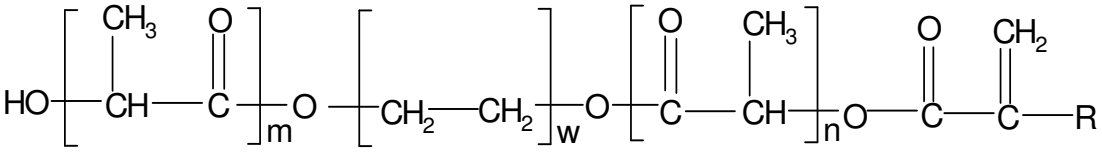
4.4 Results and Discussion

4.4.1 Free Radical Copolymerization

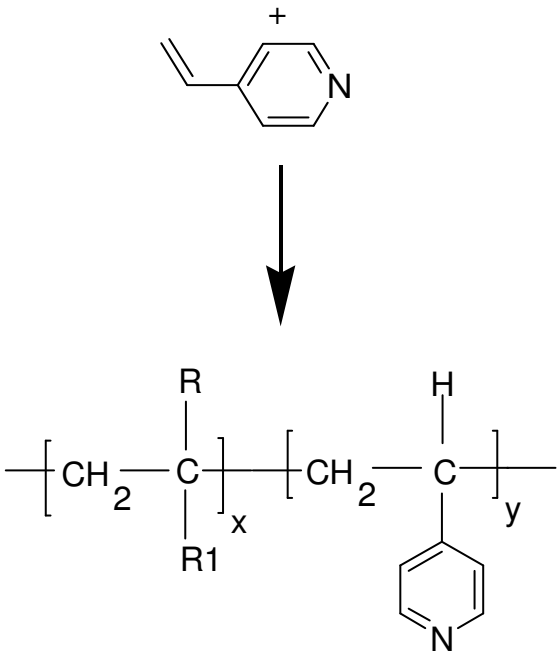
VP was copolymerized with lactide macromer using DMF as solvent and AIBN as initiator to obtain lactide copolymer. Unsaturated acrylate or methacrylate part of lactide macromer reacted with vinylic unsaturation of VP to give a linear polymer. Lactide chain remained as pendent part in the copolymer. The pendent lactide chain was very hydrophobic; whereas VP was basic and hydrophobic in nature. The copolymers synthesized in this work using different mole ratios of lactide macromer

and VP (10:90 to 50:50) were solid, but the copolymers having mole ratio of lactide macromer: VP 60:40 to 80:20 were sticky in nature. Yield of the copolymerization reaction was 82 %. Polymers had good surface coating property, but the film formed could not be lifted up. But these could be used for microencapsulation of drugs and explored for possible drug delivery applications.

Reaction mechanism of copolymerization reaction is shown schematically in **Figure 4.4**.



m = 2 to 5, n = 2 to 4 w = 2 R = H or CH_3



Where

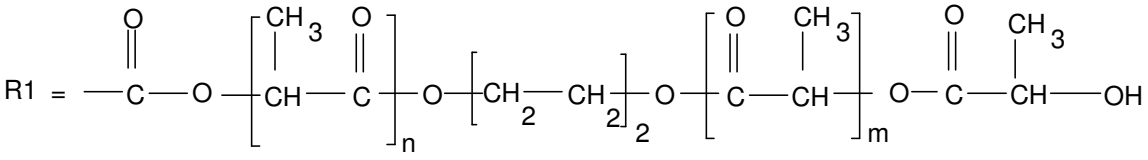


Figure 4.4 Reaction Mechanism of Lactide Macromer- VP Copolymerization

4.4.2 Encapsulation of Drugs in Lactide- VP Microspheres

Drugs were encapsulated in lactide microspheres by emulsion solvent evaporation method. Drug loading was in the rage of 30 to 45 %. Microspheres were spherical in shape and convenient for handling. The choice of the copolymers for the synthesis of the microsphere was based on VP content of the copolymer and results of dissolution pattern. Emulsion solvent evaporation method chosen for encapsulation was based on polymer properties. Lactide-VP copolymers were soluble in acidic pH less than 3 in aqueous buffers and insoluble above this pH. Hence organic solvent was selected as internal phase in encapsulation process and light liquid paraffin as external continuous phase. Pet ether was suitable non solvent for these polymers. Separation method for microspheres was convenient and caused minimum loss of materials.

4.4.3 Reconstitution

Microspheres were reconstituted in syrup base using vanilla flavor. This was for taste masking purpose and useful for pediatric patients in the form of syrup for reconstitution. Citric acid was used for maintaining pH of suspension in the range 4.5 to 5.5. This made the syrup more palatable. The taste of the reconstituted dosage form as checked by volunteers was favorable to indicate patient acceptability and taste masking achieved by microencapsulation of extremely bitter drug like cefuroxime axetil.

4.4.4 Characterization

4.4.4.1 NMR Spectroscopy

Composition of the copolymer and subsequently monomer content was calculated using proton NMR technique. Spectrum of lactide-VP copolymer showed characteristic peaks for lactide at 1.56 and 5.16 ppm. The peak at 1.56 corresponds

to 6 protons of 2 (methyl) groups; while peak at 5.16 ppm indicated 2 protons of 2 (methine) groups in the lactide chain. VP showed two main peaks corresponding to 2 (methine) groups at 7.51 ppm and 8.71ppm. Peak for methine of lactide at 5.16 ppm could be compared to methine of VP at 8.71 ppm and integrated to get copolymer composition of the copolymer.

It could be observed from **Figure 4.5** that integration of peak corresponding to methine protons of VP at 8.37 ppm could be compared with lactide peak at 5.16 ppm to find out composition of copolymer.

From the subsequent calculations for monomer content it was clear that incorporation of VP in the copolymer was dependent on molecular weight of the lactide macromer. Incorporation of the monomer decreased as the molecular weight of the lactide macromer used in the copolymer increased.

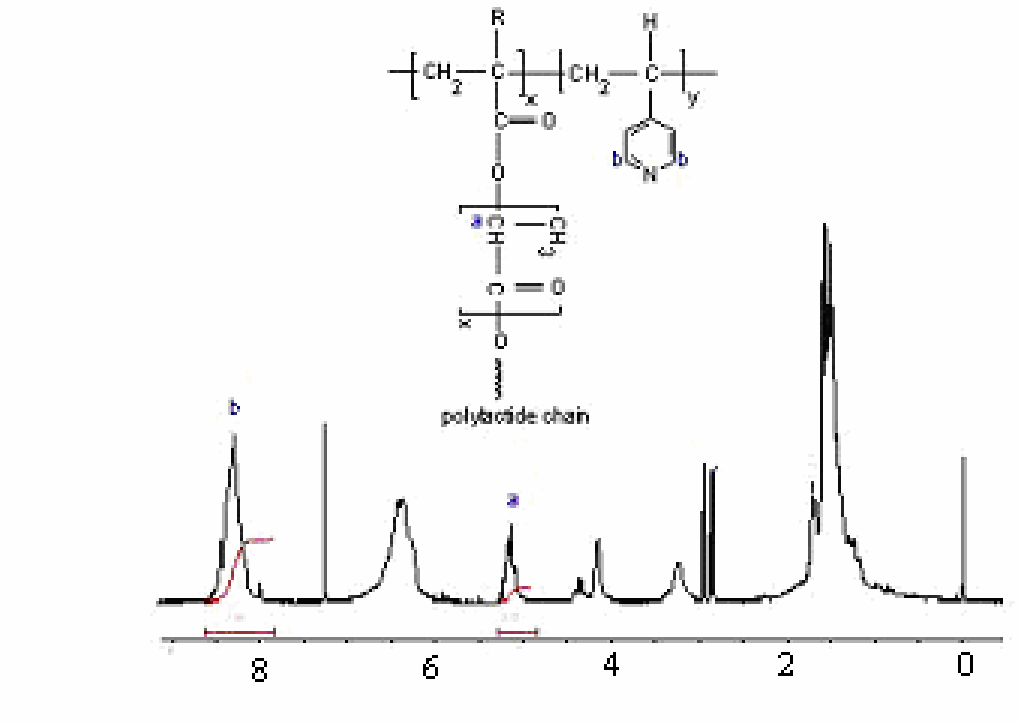


Figure 4.5 NMR Spectrum of Lactide Methacrylate-VP Copolymer

4.4.4.2 FTIR Spectroscopy

Synthesis of copolymer and incorporation of VP in the copolymer was confirmed by FTIR spectroscopy. It was clearly seen in **Figure 4.6** that the macromer showed characteristic -OH peak at 3500 cm^{-1}, peak at 1750 cm^{-1} for C=O (carbonyl stretching) of ester and 1637 cm^{-1} for unsaturation (present in the macromer). In the copolymers, apart from –OH and ester carbonyl stretching there was an additional band at 1600 cm^{-1} which was attributed to the ring stretching of VP. From above **Figure 4.6,** it was observed that the peak at 1637 cm^{-1} for unsaturation (C=C) as seen in spectrum of macromer disappeared in rest of the spectra of copolymers.

The presence of -OH peak and absence of double bond peak (1637 cm^{-1}) clearly indicated that the copolymerization reaction occurred through the vinylic double bond and –OH group did not take part in the copolymerization.

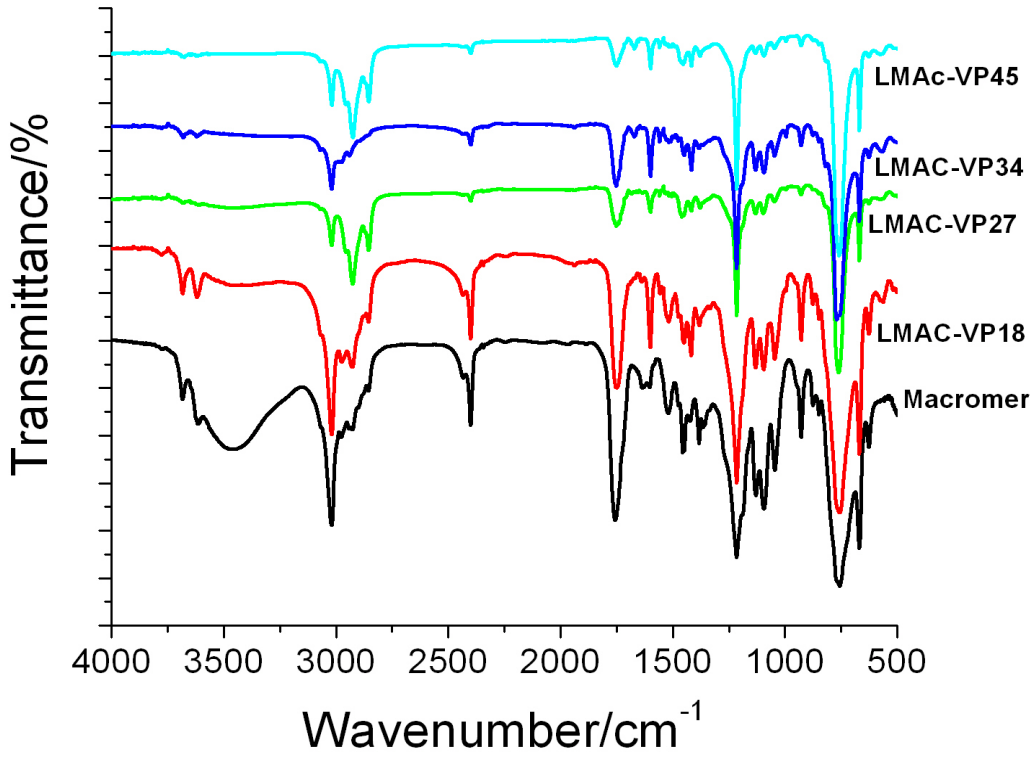


Figure 4.6 IR Spectra of Lactide Macromer and Copolymers in the Range 4000–500 cm^{-1}

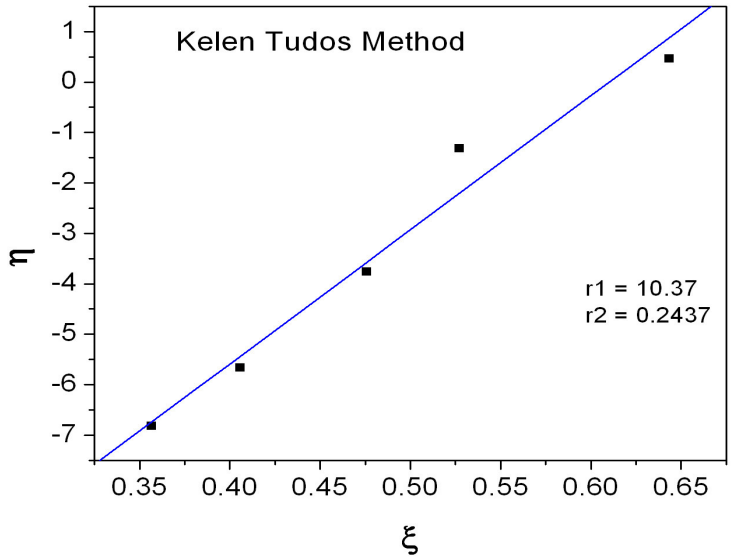
Figure 4.6 also showed the absence of ring stretching at 1600 cm^{-1} in the macromer. It was readily observed from the figure that intensity of ester carbonyl stretching peak at 1750 cm^{-1} as seen in macromer spectrum gradually decreased as VP content in copolymer compositions increased.

4.4.4.3 Vapour Pressure Osmometery (VPO)

Molecular weight of Lactide-VP copolymers was determined using Vapour Pressure Osmometer. The results tabulated in **Table 4.4 - 4.8** indicate that molecular weight of the copolymers increased in direct proportion to VP content of the polymer.
It was evident from all the tables that reactivity of VP was very low as compared to that of the lactide macromer. Further with increasing molecular weight of lactide macromer in the, the incorporation of VP decreased especially, beyond 2000.
It could be said that Lactide –VP copolymers were low molecular weight and development of molecular weight was mainly dependent on incorporation of VP monomer in the copolymers.

4.4.4.4. Reactivity Ratio

Reactivity ratios of lactide macromer and VP were determined by calculation using two different methods. Even if we did not restrict our copolymerization reactions to low conversions for purpose of applying Kelen Tudos and Finemann Ross methods, we surprisingly got very good plots to get idea about reactivity ratios. It could be readily observed from Figure 4.7 that reactivity ratio for lactide macromer was much higher (around 10) as compared to VP (around 0.2) as calculated by both methods. This could be the explanation for sluggishness and low incorporation of VP in the copolymer as seen in the **Table 4.4 to 4.8**.



r1 = Reactivity ratio of Lactide Macromer

r2 = Reactivity Ratio of VP

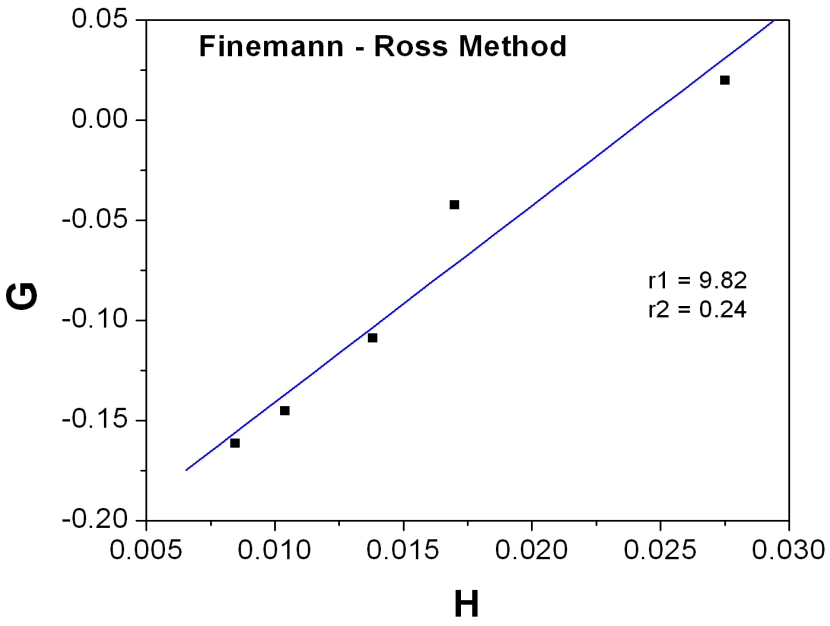


Figure 4.7 Reactivity Ratio of Lactide Macromer and VP

4.3.4.5 DSC Study

Lactide copolymers were characterized for T_g values and results are tabulated in **Table 4.3**. Thermal properties of the copolymers are representatives of their suitability for pharmaceutical processing. Polymers with fairly high T_g values are useful as excipients as these can withstand higher temperatures during formulations and remain stable without losing their integrity and physical form.

It is clearly observed from **Table 4.3** that lactide- VP copolymers showed T_g values in the range of 24 to 85^0C depending on VP content of the copolymers. T_g of copolymers decreased in direct proportion to VP content of the copolymer.

4.4.4.6 Dissolution Study

Dry lactide-VP copolymers were evaluated for dissolution pattern in various buffers of pH ranging from 1.2 to 7.4. It was observed that these copolymers only dissolved below pH 3 and were insoluble in rest of the buffers. Hence lactide –VP copolymers were pH sensitive.

Table 4.4 and 4.5 show that lactide acrylate-VP copolymers with higher VP content (above 10 % w/w) first swelled in acidic pH and dissolved after 24 hours. When VP content was very high (above 50% w/w), polymer swelled in acidic pH and remained insoluble even after a long time. Dissolution time for all these copolymers was dependent on VP content of the copolymer. Polymers with low VP content dissolved fast (within 15 minutes) as compared to those with high VP content. Lactide copolymers with very low

VP content (as low as 1 % w/w) showed pH sensitivity and became soluble in acidic buffer within 15 minutes.

Specific swelling and dissolution pattern of lactide polymers as discussed above was dependent on molecular weight of lactide used in the copolymer composition. It could be observed from **Table 4.6** that as molecular weight of lactide macromer in the copolymer increases beyond 1000, polymers did not swell, but they only dissolved and dissolution time was dependent on the VP content of the copolymer.

It was evident from **Table 4.7** that polymers with very low VP content did not show pH sensitive nature. This was especially in case of the copolymers containing high molecular weight lactide macromer (more than 2000).

Table 4.3 T_g Values of Lactide Copolymers

Copolymer	VP content %w/w	T_g (^{0}C)
LMAc(710) -VP	62	57.17
LMAc(710) -VP	31	51.54
LMAc(710)-VP	19	44.42
LMAc(710)-VP	14	24.74
LMAc (710)-VP	13	23.91
LAc (790) -VP	41	84.71
LAc(790) -VP	34	78.28
LAc(790) -VP	27	63.28
LAc(790) -VP	10	34.72
LAc(860) -VP	45	72.48
LAc(860) -VP	16	47.63
LAc(860) -VP	7	32.08

LMAc (710) - Lactide methacrylate of mol. wt. 710

LAc (790) - Lactide acrylate of mol. wt. 790

Table 4.4 Dissolution Behavior of Polymers in Acidic Buffer

Composition - lactide acrylate: 4 vinyl pyridine

Mol.wt. of lactide acrylate	Composition of the copolymer (in moles)		VP content % w/w	Mol. wt. of copolymer	Dissolution behavior at pH 1.8
	In feed	By NMR			
650	5:95	7:93	66	7916	Polymer swelled within 1 hour and remained swelled even after 24 hours, it did not dissolve
700	10:90	41:59	18	7451	Polymer swelled significantly in 1 hour and dissolved completely after24 hours
750	20:80	53:47	11	4760	Polymer swelled within 30 minutes and dissolved partly after 24 hours
700	20:80	58:42	09	1607	Polymer swelled within 1 hour and then dissolved completely after 4 hours
700	30:70	78:22	04	1119	Polymer dissolved within 30 minutes
700	40:60	93:07	01	1058	Polymer dissolved within 15 minutes
700	60:40	94:06	0.9	1015	Polymer dissolved within 15 minutes
700	50:50	99:01	0.15	980	Polymer did not dissolve

All oligo (lactide) acrylate copolymers did not swell or dissolve in buffers of pH 4.8, 6.8 or 10.

Table 4.8 shows dissolution pattern of lactide methacrylate-VP copolymers. These copolymers did not swell even at higher VP content, but they only dissolved depending on VP content of individual copolymers. Polymers having higher VP

content took more time for dissolution (2 hours), whereas those with low VP content dissolved faster (in 30 minutes). This needs further investigation.

Table 4.5 Dissolution Behavior of Polymers in Acidic Buffer

Composition- lactide acrylate: 4 vinyl pyridine

Mol. wt. lactide acrylate	Composition of the copolymer (in moles)		VP % w/w	Mol. wt. of copolymer	Dissolution behavior at pH 1.8
	In feed	NMR			
920	02:98	12:88	45	5826	Polymer swelled marginally and dissolved in 2 hours
790	02:98	16:84	41	7861	Polymer swelled and dissolved in 90 minutes
790	05:95	20:80	34	6524	Polymer swelled marginally and dissolved in about 2 hours
790	08:92	26:74	27	6180	Polymer swelled Marginally and dissolved in 1 hour
790	10:90	38:62	18	6539	Polymer swelled and dissolved in 1 hour
614	07:93	43:57	18	7643	Polymer swelled after 20 minutes, it did not dissolve
920	05:95	36:64	17	5270	Polymer did not swell, it dissolved in 90 minutes
790	15:85	53:47	11	5387	No swelling, soluble in 45 minutes
614	20:80	68:32	07	1790	Swelled marginally and dissolved in 2 hours

Table 4.6 Dissolution Behavior of Polymers in Acidic Buffer

Composition -Lactide acrylate: 4 vinyl pyridine

Mol. wt. of lactide acrylate	Composition of the copolymer (in moles)		VP content % w/w	Molecular weight of copolymer	Dissolution behavior at pH 1.8
	In Feed	By NMR			
1300	4:96	17:83	30	3531	Polymer dissolved in 1 hour
1415	5:95	21:79	25	2650	Polymer dissolved in 20 minutes
1415	7:93	29:71	18	2558	Polymer dissolved in 10 minutes
1415	10:90	42:58	11	2507	Polymer dissolved in 10 minutes
1300	15:85	53:47	07	2321	Polymer dissolved in 5 minutes

Table 4.7 Dissolution Behavior of Polymers in Acidic Buffer

Composition- lactide acrylate -4 vinyl pyridine copolymers

Mol. wt. of lactide acrylate	Composition		VP content % w/w	Dissolution behavior at pH 1.8
	In feed	By NMR		
4600	20:80	93:07	0.17	Insoluble
4400	10:90	97:03	0.07	Insoluble
4000	20:80	96:04	0.09	Insoluble
2700	10:90	95:05	0.2	Insoluble
2700	05:95	91:09	0.5	Insoluble

Table 4.8 Dissolution Behavior of Polymers in Acidic Buffer

Composition - lactide methacrylate: 4 vinyl pyridine

Mol. wt. of lactide methacrylate	Composition of the copolymer (in moles)		VP content % w/w	Mol. wt. of copolymer	Dissolution time in minutes at pH 1.8
	Feed	NMR			
750	05:95	8:92	62	6859	120
750	10:90	24:76	31	4166	90
750	15:85	37:63	19	1784	90
750	20:80	47:53	14	1530	45
750	25:75	49:51	13	1472	30

4.4.4.7 SEM of Lactide-VP Microspheres

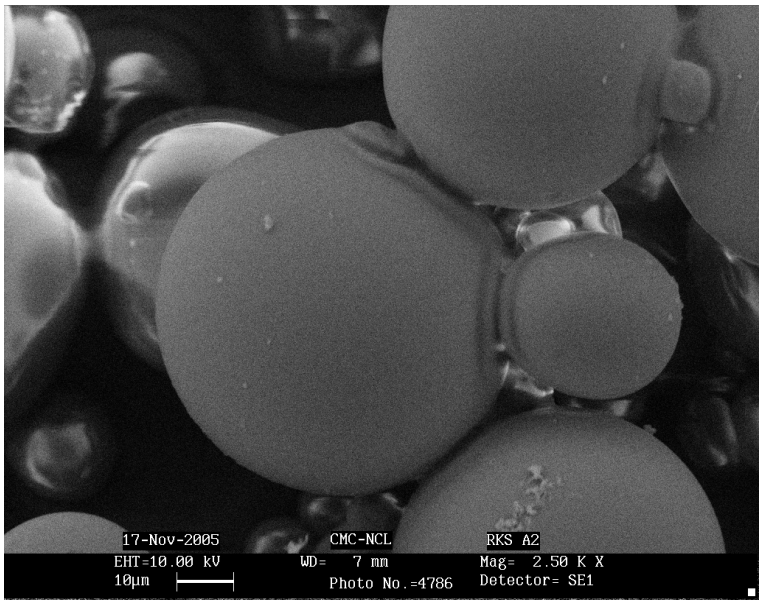


Figure 4.8 SEM of Lactide –VP Microspheres

Scanning Electron Microscopy reveals surface morphology along with particle size of the microspheres. As indicated in **Figure 4.8,** microspheres were spherical in shape and non porous, smooth in nature. Particle size was in the range of 50 µm to 300 µm.

4.4.4.8 Optical Microscopy

Particle size of 50 microspheres as measured by electronic microscope was in good agreement with SEM. Particles were spherical in shape with smooth surface and covered size range in between 50 to 400µm

4.4.4.9 Drug Release

Lactide –VP microspheres were evaluated for drug release in simulated gastric fluid. It was observed from **Tables 4.9, 4.11, 4.13, and 4.15 - 4.18** that about 95 % of Cefuroxime axetil, Ciprofloxacin hydrochloride and Clarithromycin were released in 45 to 60 minutes. These polymers are thus useful for immediate gastric delivery of the drugs. **Tables 4.9, 4.11 and 4.13** showed that about 78 to 90 % cefuroxime axetil was released in first 15 minutes when microspheres were exposed to simulated gastric fluid. Rest of the drug was released in next 30 minutes. **Tables 4.15-4.18** show release of Ciprofloxacin hydrochloride and Clarithromycin from lactide-VP microspheres. About 90 % of the drug was released in 60 minutes from the microspheres.

Drug release from lactide –VP microspheres was dependent on dissolution profile of these polymers. The polymers selected for microsphere preparation were readily soluble in acidic buffer, as revealed in dissolution study. Hence it was evident that polymer dissolution and drug release pattern were correlated well during our studies.

Lactide-VP copolymers were thus found to be suitable for immediate gastric delivery of drugs. More specifically, these were used for taste masking bitter drugs like Cefuroxime axetil, Ciprofloxacin hydrochloride and Clarithromycin. The formulation developed in this study- dry syrup for reconstitution is useful for pediatric patients.

4.4.4.10 Drug Release from Reconstituted Syrup

Reconstituted syrup was evaluated for drug leaching for seven days. It was evident from **Table 4.10, 4.12 and 4.14** that the drug released from reconstituted syrup during 7 days storage time was less than 2 %. Thus it was clear that formulation was a stable taste masked reconstituted syrup and did not release substantial amount of encapsulated drug in the syrup to decrease its palatability.

Table 4.9 Cefuroxime Axetil Release in Simulated Gastric Fluid

(Polymer: Drug ratio 2:1) (4VP content –12 % w/w)

Time (in min)	% Release
15	81
30	94
45	97

Table 4.10 Cefuroxime Axetil Release from Reconstituted Composition

Day	% Release
2	0.18
3	0.25
4	0.28
5	0.37
6	0.41
7	0.52

Table 4.11 Cefuroxime Axetil Release in Simulated Gastric Fluid

(Polymer: Drug ratio1:2) (4VP content – 12% w/w)

Time (min)	% Release
15	78.72
30	80.52
45	88.2
60	95.12

Table 4.12 Cefuroxime Axetil Release from Reconstituted Composition

Day	% Release
2	0.19
3	0.27
4	0.35
5	0.48
6	0.54
7	0.61

Table 4.13 Cefuroxime Axetil Release in Simulated Gastric Fluid

(Polymer: Drug ratio 2:1) (4VP content – 28 % w/w)

Time (min)	% Release
15	90
30	94
45	96

Table 4.14 Cefuroxime Axetil Release from Reconstituted Composition

Day	% Release
2	0.59
3	0.70
4	0.85
5	0.92
6	1.13
7	1.81

Table 4.15 Ciprofloxacin Release in Simulated Gastric Fluid

(Polymer: Drug ratio 1:1) (4VP content –12% w/w)

Time (min)	% Release
15	82.38
30	90.53
45	95.04

Table 4.16 Ciprofloxacin Release in Simulated Gastric Fluid

(Polymer: Drug ratio 2:1) (4VP content –12% w/w)

Time (min)	% Release
15	68.24
30	78.62
45	85.19
60	90.17

Table 4.17 Clarithromycin Release in Simulated Gastric Fluid

(Polymer: Drug ratio 2:1) (4VP content –12% w/w)

Time (min)	% Release
15	54.29
30	70.16
45	81.35
60	90.17

Table 4.18 Clarithromycin Release in Simulated Gastric Fluid

(Polymer: Drug ratio 1:2) (4VP content –12% w/w)

Time (min)	% Release
15	60.89
30	71.30
45	82.54
60	91.25

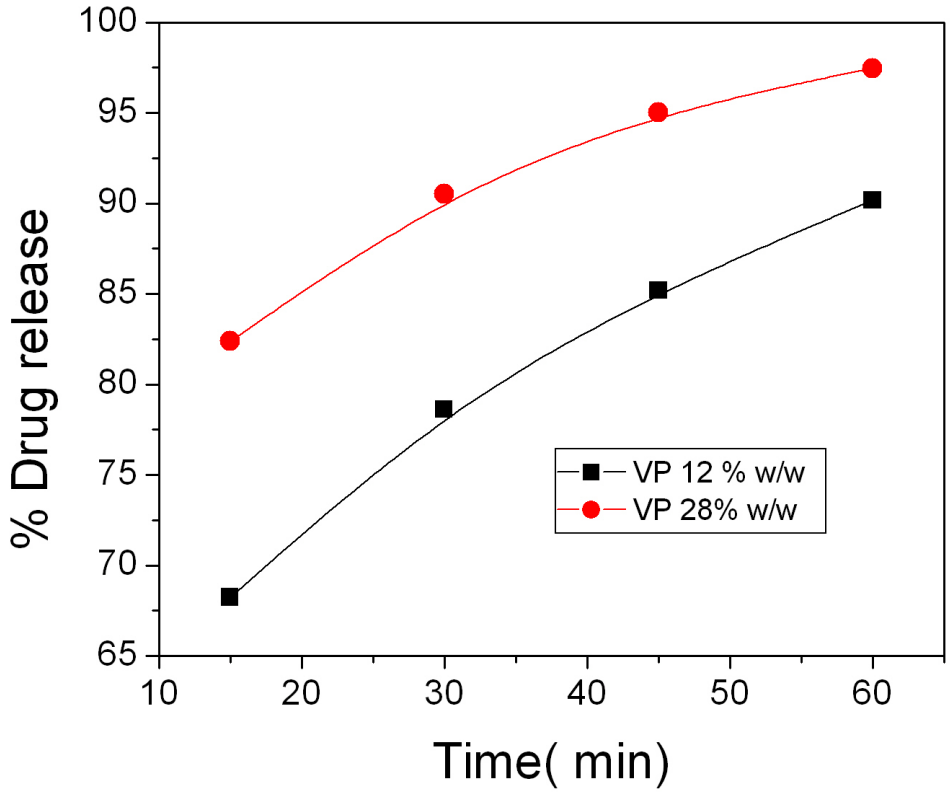


Figure 4.9 Cefuroxime Axetil Release at pH 1.8 and T= 37^0C

Figure 4.9 shows the release profile of Cefuroxime axetil from Lactide-VP microspheres at T= 37^0C and pH 1.8. As the VP content of the copolymer system used for encapsulation of the drug increased, the cumulative release of Cefuroxime axetil increased as a function of time. This increase in drug release could be attributed to the hydrophilicity of the polymer after protonation of VP. This study clearly indicated that the cumulative drug release could be manipulated by changing the VP content of the system.

When drug was encapsulated in lactide-VP microspheres, it was released immediately at acidic pH through the polymer matrix by dissolution mechanism. About 96% drug was released in 60 minutes at acidic pH. Such type of high drug concentration is desirable in case of drugs which have limited absorption window in upper GIT to achieve maximum therapeutic use of the drug.

4.5 Conclusions

Lactide –VP copolymers were synthesized and characterized for structure elucidation, molecular weight, monomer content, and reactivity ratio and dissolution profile. These copolymers exhibited pH sensitive nature. The polymers were soluble only below pH 3 and insoluble above this pH. Dissolution of the polymers was dependent on basic monomer content and molecular weight of lactide macromer used in the copolymer. The polymers had good surface coating property, which was exploited for drug delivery applications by encapsulating drugs in polymer microspheres.

Bitter drugs like Cefuroxime axetil, Ciprofloxacin hydrochloride and Clarithromycin were selected for encapsulation in these copolymers. Formulation was in the form of dry syrup for reconstitution. pH sensitive lactide copolymers could achieve taste masking of bitter drugs. Drug release from these microspheres was studied at acidic pH. It was observed that in acidic medium about 90 to 96% drug was released immediately depending on composition of microspheres. These formulations could be explored for immediate gastric delivery. Mechanism of drug release from lactide –VP microspheres might be dissolution of matrix in acidic medium due to presence of basic 4 vinyl pyridine moiety in the copolymer.

Immediate release of drug from microspheres was dependent on monomer content and molecular weight of the copolymer used in the formulation. These dry syrup formulations could be reconstituted at the time of consumption to increase patient compliance towards highly bitter drugs like Cefuroxime axetil. The lactide copolymers act as reverse enteric polymers and can be explored as pharmaceutical excipients for taste masking applications.

In summary, characterization, formulation and evaluation of lactide-VP copolymers highlight following points:

1. Lactide –VP microspheres were pH sensitive in nature. The polymers became soluble only in acidic pH of stomach. Polymers were insoluble above pH 3.

2. Lactide copolymers exhibited pH sensitivity at very low (about 1 % w/w) VP content and the polymers were low molecular weight.

3. These lactide copolymers could be called as reverse enteric polymers based on their dissolution property in stomach.

4. Dissolution pattern and time of lactide-VP copolymers was dependent on monomer content and molecular weight of lactide macromer used in the copolymer.

5. Molecular weight of the lactide-VP copolymers varied depending on VP content of the polymer. Copolymers with higher VP content resulted into higher molecular weight as compared to polymers with low VP content.

6. Incorporation of the basic monomer, 4 vinyl pyridine was dependent on molecular weight of lactide macromer. At the higher molecular weight of lactide macromer, it was observed that incorporation of VP in the copolymer is very low.

7. Lactide macromer was significantly more reactive than 4-vinyl pyridine, which was confirmed by reactivity ratio determination.

8. Drugs could be encapsulated in these lactide copolymers and microspheres exhibited immediate gastric release of about 96 % drug within 60 minutes.

9. This formulation worked as dry syrup for reconstitution which would be useful for pediatric patients who find it difficult to swallow solid dosage forms.

10. Lactide –VP polymers synthesized in this work could be explored as reverse enteric coating pharmaceutical excipients for taste masking of extremely bitter drugs like cefuroxime axetil.

11 After reconstitution of the dry syrup, it exhibited minimum amount of drug leaching over storage period.

12. pH sensitive, low molecular weight lactide-VP copolymers could be used for taste masking of bitter drugs and enhanced patient compliance and bioavailability of antibiotic drugs.

4.6 References

Alonso M. J., Lorenzo-Lamosa M. L, Cuna M.,. Vila-Jato J. L , Torres D. Journal of Microencapsulation **1997**, *14*, 607

Butun, V., Armes, S. P. Macromolecules **1999**, *32*, 4302

Cuna M., Lorenzo M. L., Vila Jato J. L., Torres D., Alonso M. J. Acta Technologiae et Legis Medicamenti. **1996**, *VII*, 3

Dantzig A. H., Duckworth D. C., Linda B. , Biochimica et Biophysica Acta **1994**, *1191*, 7

Duchene D., Wouessidjewe D., Ponchel G. J. Contr. Release **1999, *62,*** 263

Gao Y., Cui F., Guan Y., Yang L., Wang Y., Zhang L. International Journal of Pharmaceutics **2006,** *318,* 62

Gohy J., Lohmeijer B.G.G., Varshney S.K., Decamps B., Leroy E., Boileau S., Schubert

U.S. Macromolecules **2002**, *35*, 9748

James M. B. **1989,** U.S. Patent 4,865,851

Jaskari T., Vuorio M., Kontturi, K. Manzanares J.A. ,J. Hirvonen, J. Contr. Release **2001,***70,* 219

Kawashima Y., Niwa T., Handa T., Takeushi H., Iwamoto T. Itoh K. J. Pharm. Sci. **1989,***78* , 68

Kulkarni M. G, Menjoge A. R. **2005** US Patent Appl. 0136,114

Lopez U.S., Carvelvo E T.,. Seijo B. L., Ortega, J., Bastos L Journal of Colloid and Interface Science **2005**, *283*, 344

Pinkrah V.T., Snowden M.J., Mitchell J.C., Seidel J., Chowdhry B.Z., Fern G.R., Langmuir **2003,** *19* , 585

Satoh, M., Yoda, E., Hayashi, T., Miyama, J. Macromolecules **1989**, *22*, 1808

Vogelman B., William A. C. Journal of Pediatric **1986**, *108*, 835

Vogelman B., William A. C, Ebert S., Gudmundsson S., Leggett J. Journal of Infectious Diseases **1988**, *158*, 831

Wen B. **1999**, U.S. Patent 6,001,392

CHAPTER 5

Formulation and Evaluation of Cefuroxime Axetil Tablets: Roleof Novel Lactide Polymers as Compatible Excipients

5.1 Introduction

A variety of pharmaceutical active substances intended for oral administration, are often formulated in a solid or liquid dosage form. Solid dosage forms can be tablets**,** coated tablets**,** pellets, or granules. Generally, the term "tablet" includes not only tablets but also similar discrete bodies of other shape known by different names, such as "caplets" (e.g. capsule-shaped tablets), lozenges, and pills. Such solid forms are able to persist under normal handling conditions but disintegrate at the desired site, time or combination of both.

Typically, tablets will contain a medicament, along with other excipients to promote the formulation and release the medicine after ingestion at desired site. Additionally, the tablet may be coated with a bioactive or inert material to improve appearance, taste or improve shelf life of the tablet (Andersson, 1999).

Many active pharmaceutical ingredients are unpalatable in their natural state. After a tablet disintegrates or dissolves in the saliva, the active ingredient in the tablet remains in the oral cavity until it is swallowed. It is estimated that there are about 10,000 taste buds on tongue, roof of the mouth, cheeks, and throat, and each bud has 60-100 receptor cells. These receptor cells interact with molecules dissolved in the saliva and produce a positive or negative taste sensation. Hence contact of bitter active drug with taste buds should be avoided. A pleasant taste inside the mouth becomes critical for patient compliance. Unless the active ingredient is tasteless or does not have undesirable taste, taste-masking techniques should be used (Gao, 2006).

Current taste masking is often achieved by a few methods, such as using sweet-tasting substances as diluents, adding flavors, or encapsulating the unpleasant drug into microparticles or granules. All of them have their own advantages and limitations together. An ideal taste masking technology should provide the active ingredient without grittiness and with good mouth feel. The amount of taste masking materials used in the dosage forms should be kept low to avoid excessive increase in tablet size.

Simple approaches for taste masking include adding flavoring or sweetening ingredients to the compositions. When simple approaches are ineffective, various

other approaches are used to modify the release profiles and / or to mask the bad taste of active pharmaceutical ingredients for oral drug administration. One of the methods that have been applied in the pharmaceutical industry is to change the active ingredients into a complex with ion-exchange resins for preparing drug/ion-exchange resin complexes (Jaskari, 2001).

Attempts have been made to mask the highly bitter or unpleasant tasting drugs during administration to a patient in need of such drugs. Present taste masking technology generally uses microencapsulation techniques which relies primarily on polymer coating materials applied from non-aqueous solutions (Kawashima 1989). This may be in the form of coating for tablets or drug may be encapsulated in microspheres where bitter taste of the drug is masked. Examples of coatings used for taste masking of bitter drugs are presented in **Table 5.1**

Table 5.1 Use of Coating for Taste Masking Techniques

Formulation	Taste masking methodology	Principle/Problems	Reference
Chewable tablets made from coated granules	Blend of cellulose acetate and / or cellulose acetate butyrate and hydroxy propyl cellulose	Release of drug in saliva resulting in bitter taste	Roche, 1991
Oral rapid release particle formulation containing bitter drug core and film coat	Core with swelling agent and coat consists of ethyl cellulose and a water soluble substance	Presence of water soluble substance in coat makes film permeable to saliva giving bitter taste	Shirai, 1992
Pharmaceutical coating for oral taste masked formulation	Coat is a combination of triglycerides and a polymer	Instability of coat during storage and variation of coat performance due to interpersonal variations	Mauger, 1998
Coated Cefuroxime axetil tablets	Drug core and double layered film coat of hydroxypropyl Methyl cellulose and shellac	First film coat masks bitter taste and second film coat serves to delay the rupture time beyond 40 seconds	Khan, 2002
Cefuroxime axetil microspheres	Cellulose acetate trimellitate, HPMCP-50, HPMCP-55 for encapsulation	Taste masking and drug release in intestine	Cuna, 1996

The past efforts described in **Table 5.1** for taste masking are not satisfactory due to the possibility of drug leakage during storage or administration, which result in failure of taste masking. Cefuroxime axetil from tablet is expected to release fast so that it would not gel and decrease efficiency of the formulation.

With the purpose to overcome these difficulties, cationic co-polymers synthesized from dimethyl amino ethyl methacrylate and neutral methacrylic acids have been employed as a coating material for taste masking of bitter active ingredients. **Table 5.2** quotes such examples where DMAEMA copolymers were used for taste masking of bitter drugs.

Table 5.2 DMAEMA for Taste Masking Purpose

Formulation	System	Principle	Reference
Coated chewable tablets of Ibuprofen	A polymer mixture of DMAEMA and neutral MAA ester and a cellulose ester	Reverse enteric coating soluble in the stomach but relatively insoluble in the mouth	Hoy, 1996
Film coated Desloratadine formulation	Coat is a mixture of ethylcellulose (film forming water insoluble) and polymethacrylic acid copolymer (water insoluble pH dependent)	Coating layer intact in mouth and dissolves in stomach at pH below 5	Paruthi, 2004

As evident from Table 5.2, DMAEMA along with other neutral methacrylates (Eudragit E) is used as reverse enteric coating. This polymer shows swelling at pH 5. Percentage of DMAEMA in Eudragit E is high (35% w/w), which results in negative drug interaction with some of the drugs (Alonso, 1997). Low molecular weight DMAEMA polymers having low basic monomer content and their utility as excipient in pharmaceutical drug delivery has not been investigated in the past.

It is evident from above examples that there exists a need to develop an improved taste masking pharmaceutical composition for bitter and unpalatable drug like Cefuroxime axetil that can remain stable during storage, allow for the proper release of the drug, and are cost and use efficient.

It is further understood that there is a need for the development of a taste masking polymer such that the bitter taste is completely masked by the polymer at the pH of saliva in mouth in case of the solid dosage forms. It should be compatible with drug so that it will protect the drug in a biologically active form, also from the moisture in the dosage form and release the drug rapidly in the stomach.

We decided to copolymerize biodegradable aliphatic hydroxy carboxylic acids like lactic acid with basic monomer DMAEMA to obtain copolymers which combine properties of both the materials. Lactide is being used for many applications such as surgical sutures, drug delivery devices, tissue supports, and implants for internal bone fixation (Shalaby, 1994 and Dunn, 1995)

Polylactides are highly crystalline and their degradation rates are too low, which are not suitable for their applications in oral delivery (Tandya, 2006). There is need to modify lactide polymers to enhance their degradation properties by lowering the crystallinity. Biodegradable polymer networks and composites were prepared from lactide oligoesters terminated with unsaturated functional groups (Han, 1997 and Coullerez, 2000). Copolymerization is another approach for modification of lactide polymers, which we have tried in this work.

This work describes composition of copolymer synthesized using oligomeric lactide macromer and basic monomer. It also demonstrates that at very low concentration of the basic monomer (about 12 % w/w) this copolymer exhibits unusual dissolution behavior. Contrary to the solubility behavior of Eudragit E polymers, these polymers are soluble over a wide pH range. Because of their unusual dissolution behavior, they can be used as excipients in pharmaceutical drug delivery systems. Surprisingly we found that lactide -DMAEMA (Dimethyl amino ethyl methacrylate) copolymers synthesized by us are compatible with Cefuroxime axetil and they do not produce any negative interaction as reported in case of other commercially available polymers containing dimethyl amino ethyl group. These lactide-

DMAEMA copolymers can be used as compatible polymeric excipient for gastric delivery of bitter drug Cefuroxime axetil.

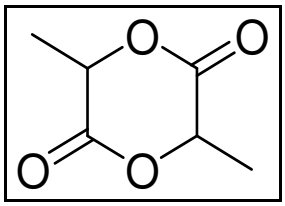
Lactide copolymers were synthesized and characterized for copolymer composition, molecular weight and dissolution profile. These polymers were formulated as tablet for oral administration. Tablets were coated by using pH sensitive lactide-VP copolymers which dissolve only at pH less than 3 which is much more acidic than pH of mouth. Variations in the tablet compositions were made and drug release from these tablets at gastric pH was evaluated. Drug release at salivary pH was also studied to check efficiency of the coating. Thus lactide-DMAEMA copolymers were synthesized, characterized and evaluated for Cefuroxime axetil oral delivery.

5.2 Experimental

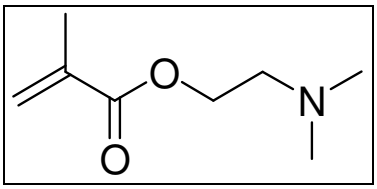
5.2.1 Materials

L-lactide (3S-cis-3,6-Dimethyl-1,4-dioxane-2,5-dione 98%), 1,4 butanediol, N,N Dimethyl amino ethyl methacrylate and Iron acetate (99.995%) were procured from Aldrich Chemicals , USA and used without further purification. Azo bis Iso Butyronitrile (AIBN) was purchased from Sas chemicals Company, Mumbai. Structures of monomers and initiator are presented in **Figure 5.1**. Benzoyl chloride and hydroquinone were purchased from Merck Ltd and Qualigen Chemicals, Mumbai respectively. Solvents like Tetrahydrofuran and N, N dimethyl formamide were procured from S, D fine chemicals, India.

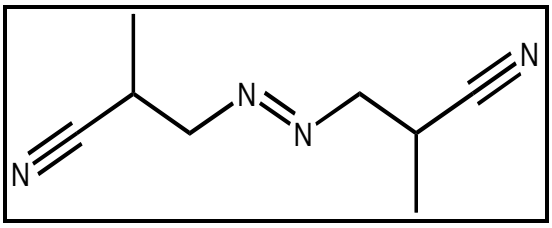
The drug cefuroxime axetil (4-(carbamoyloxymethyl)-8- [2-(2-furyl)-2-methoxyimino-acetyl] amino -7-oxo- 2-thia-6-azabicyclo [4.2.0] oct -4-ene-5-carboxylic acid) was a gift from Lupin Labs, Pune. Structure of drug is presented in **Figure 5.2**.



L-lactide

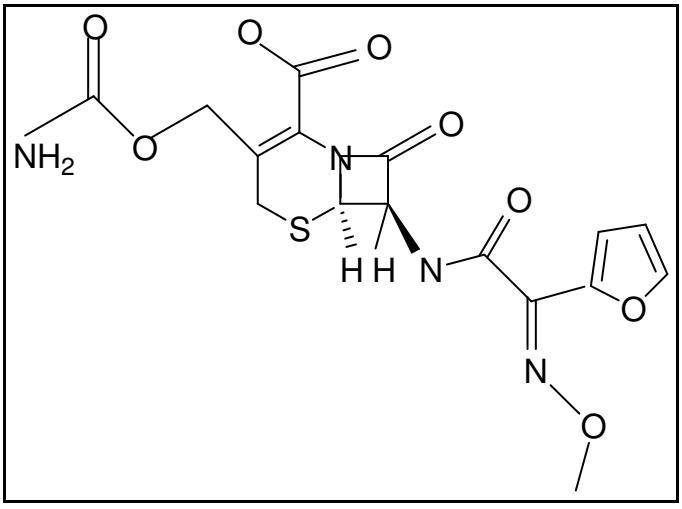


DMAEMA



AIBN

Figure 5.1 Structures of Monomers and Initiator in Macromer Synthesis



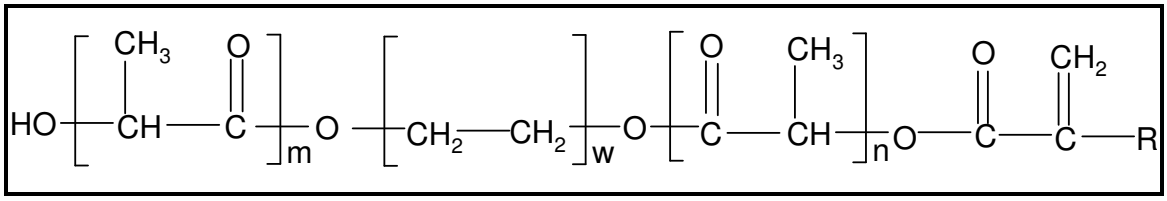
Cefuroxime axetil

Figure 5.2 Structure of Cefuroxime axetil

5.2.2 Synthesis of Lactide-DMAEMA Copolymers

5.2.2.1 Synthesis of Lactide Macromer

Lactide macromer (lactide acrylate and lactide methacrylate) was synthesized as per procedure described in chapter 3.



w = 2 and R = H or CH_3

Figure 5.3 Structure of Lactide Macromer

5.2.2.2 Synthesis of Lactide-DMAEMA Copolymers

Copolymers of lactide macromer (**Figure 5.3**) with DMAEMA were synthesized by free radical polymerization. Lactide macromer of molecular weight range 500, 800 and 1200 was chosen for copolymerization. Lactide acrylate or lactide methacrylate macromers (M1) and DMAEMA (M2) were dissolved in DMF and 2 mole % AIBN was added to it. This reaction mixture was purged with nitrogen for 10 minutes and the test tube was sealed with Teflon. The reaction was carried out at 65 ^{0}C for 24 hours. Then the reaction mixture was concentrated under reduced pressure using rotavapour. The concentrated mixture was precipitated in diethyl ether. Polymer was then dried under vacuum to recover the product.

Lactide macromer and DMAEMA were copolymerized in different mole ratios from 10:90 to 80:20. Two types of copolymers were obtained from these polymerizations.

a. Lactide acrylate-DMAEMA (LAc-DMAEMA)

b. Lactide methacrylate-DMAEMA (LMAc-DMAEMA)

5.2.2.3 Formulation of Cefuroxime Axetil Tablets

Cefuroxime axetil tablets were prepared by direct compression method. The drug and polymer were dissolved in common organic solvent. This drug-polymer solution was added drop wise to anhydrous lactose by continuous trituration in mortar pestle. Thus drug and polymer were adsorbed on anhydrous lactose and a granular matrix was obtained after evaporation of the solvent. This mass was punched under pressure to get a tablet by direct compression. This tablet was coated by using Lactide-VP polymer solution in organic solvent. Ladling method was used for coating (Alvarez-Fuentes, 2004). Tablet was dried under vacuum for 24 hours to obtain final solid dosage in the form of taste masked coated tablet. Five tablet compositions were formulated by varying the amounts of lactose (inert carrier), DMAEMA polymer and coating solution concentration. **Table 5.3** describes formulae for these 5 tablet compositions.

Table 5.3 Cefuroxime Axetil Tablet Formulations

Formulation	**Polymer (mg)**	**Lactose (mg)**	**Coating solution (% w/v)**
Tablet 1	125	250	10
Tablet 2	175	250	08
Tablet 3	250	250	08
Tablet 4	125	500	10
Tablet 5	125	750	10

Drug - 125 mg in all formulations

5.3 Characterization

5.3.1 Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectra of Lactide-DMAEMA copolymers were recorded on Bruker DRX – 500 spectrometer operating at a proton frequency of 125.4 MHz using $CDCl_3$ as a solvent.

5.3.2 Vapour Pressure Osmometry (VPO)

Molecular weight of lactide-VP copolymers was determined using Knauer Vapour Pressure Osmometer K-7000. Stock solution of copolymer (10 mg/ml) was prepared in Chloroform (Spectroscopy grade) and successive dilutions of polymer in this solvent were analyzed at 37^0C. Benzil was used as standard for calibration of instrument. Molecular mass of a sample can be determined with a known concentration of the substance using calibration value.

5.3.3 Dissolution Study

Dried lactide-DMAEMA copolymers (50 mg) were immersed in 5 ml buffer of respective pH. Dissolution pattern of these lactide copolymers was studied with respect to time and dissolution time was noted.

5.3.3 Compatibility with Drug

Lactide-DMAEMA copolymer (20 mg) was dissolved in chloroform. Equal amount of Cefuroxime axetil was mixed with this copolymers solution. System was observed for colour change, if any, for 48 hours. There was no discoloration of drug due to presence of lactide-DMAEMA copolymer in solution with the drug.

5.3.4 Drug Content

Drug content of the tablets was determined by dissolving the tablet in methanol and sonicating it for few seconds. Supernatant after filtration was analyzed on UV spectrophotometer. The concentration of Cefuroxime axetil in the tablet was determined at 278 nm. This experiment was repeated for 10 tablets and average was calculated.

5.3.5 Drug Release

Cefuroxime axetil released from the tablets in simulated gastric fluid was determined in 900 ml of 0.07 N hydrochloric acid, at 37 ± 0.5°C, using USP type II apparatus rotated at 75 rpm. The samples were withdrawn at 15, 30, 45, 60 and 90 min. The amount withdrawn each time was replaced with fresh media to maintain the sink conditions.

5.3.6 Drug Leaching at Salivary pH

Cefuroxime axetil released from the tablets in saliva was determined at pH 5.8 using phosphate buffer. The tablet was suspended in buffer and system was placed at 37°C, in shaker bath adjusted at 75 rpm. The samples were withdrawn at 5, 10, 15 and 20 min. They were filtered and the filtrate was analyzed at 275 nm using UV spectrophotometer.

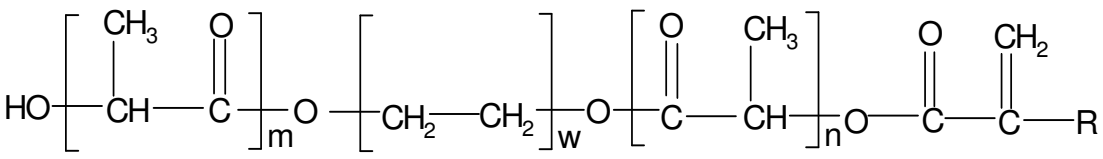
5.4 Results and Discussion

5.4.1 Free Radical Copolymerization

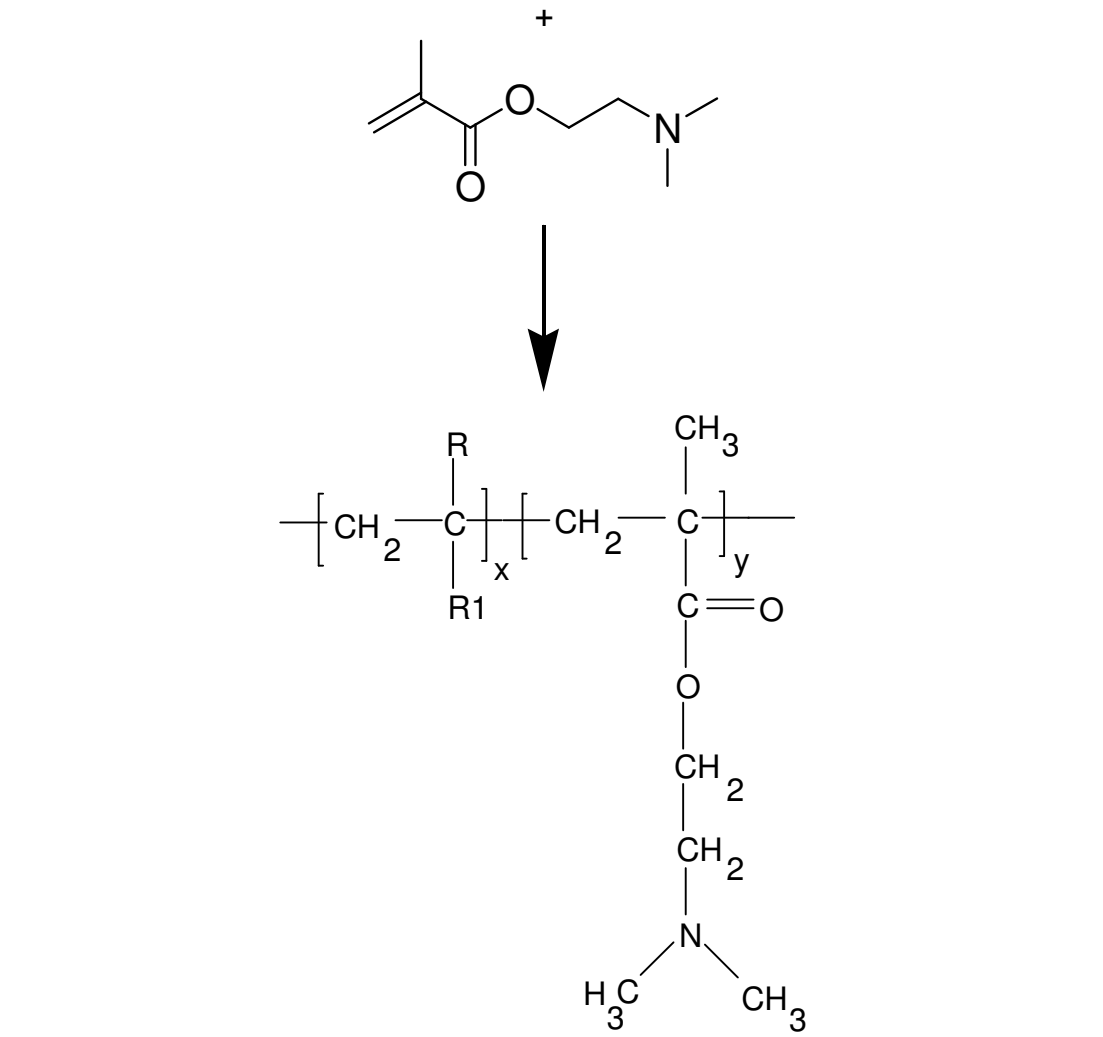
DMAEMA was copolymerized with lactide macromer using DMF as solvent and AIBN as initiator to get lactide copolymer. Unsaturated acrylate or methacrylate part of lactide macromer reacted with vinylic unsaturation of DMAEMA to yield a

linear polymer. Lactide chain remained as pendent part in the copolymer. This pendent lactide chain is very hydrophobic; whereas DMAEMA part is basic and hydrophilic in nature. Different mole ratios of lactide macromer and DMAEMA (10:90 to 80:20) were used to synthesize the copolymers. Yield of the copolymerization reaction was 70 to 80 %. Reaction mechanism of copolymerization reaction is shown schematically in **Figure 5.4**.

As copolymers were compatible with drug under study and were also soluble in aqueous buffers over entire pH range, it was decided to explore these polymers for gastric delivery of Cefuroxime axetil in tablet form. The copolymer was used as a matrix in which drug was uniformly dispersed and drug release studied.



m = 2 to 5, n = 2 to 4 w = 2 R = H or CH_3



Where

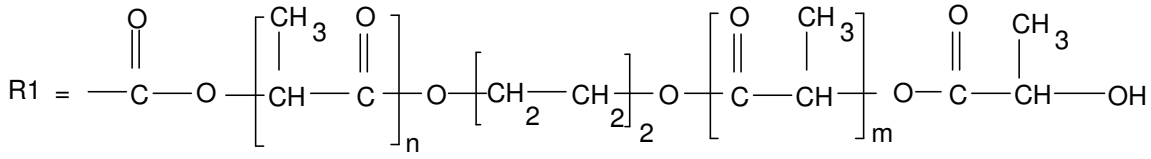


Figure 5.4 Reaction Mechanism of Lactide - DMAEMA Copolymerization

5.4.2 Formulation of Cefuroxime Axetil Tablets

Drug and polymer were adsorbed on anhydrous lactose and these granules were punched by direct compression method. Coating on the tablets was done by ladling method. The tablets were spherical and convex in shape. The coating layer was thin and uniform over the tablet.

This is a matrix type tablet in which drug is adsorbed on inert pharmaceutical carrier which will act as diluent to increase bulk of dosage form. Polymer is mixed with the drug uniformly using common solvent. This polymer is pH independent lactide-DMAEMA copolymer and is compatible with cefuroxime axetil. The main purpose of using this polymer is to show that DMAEMA copolymers can be used for cefuroxime axetil delivery, which is a novel finding. Till now, it was reported that DMAEMA polymers cause discoloration of cefuroxime axetil and therefore are not suitable for this drug delivery. It is shown for first time in this work that lactide-DMAEMA copolymers can be used as polymeric excipients in cefuroxime axetil formulations. As these copolymers are soluble over wide pH range from 1.2 to 7.4, these can deliver the drug at intended site in GIT by appropriate modification in formulation.

The formulation modification done in present work is application of outer coating to cefuroxime axetil tablets. The coating material is pH sensitive lactide-VP copolymer which is discussed earlier in chapter 4. This copolymer is soluble only below pH 3 and is insoluble above this pH. This polymer can act as suitable excipient for gastric delivery of therapeutic agent. It was formulated as dry syrup for reconstitution containing cefuroxime axetil .The bitter drug was taste masked by using microspheres of pH sensitive lactide-VP copolymers.

In this formulation, lactide-VP copolymers are used as outer coating material for two purposes. This copolymer avoids release of bitter drug at salivary pH and releases it in stomach, which is intended site of drug release. Another important use

is it masks the unpleasant bitter taste of Cefuroxime axetil and thus makes this formulation a taste masked solid dosage form.

Thus by using two types of lactide copolymers, the taste masked cefuroxime axetil tablets were formulated for gastric delivery of the drug.

5.4.3 Characterization

5.4.3.1 NMR Spectroscopy

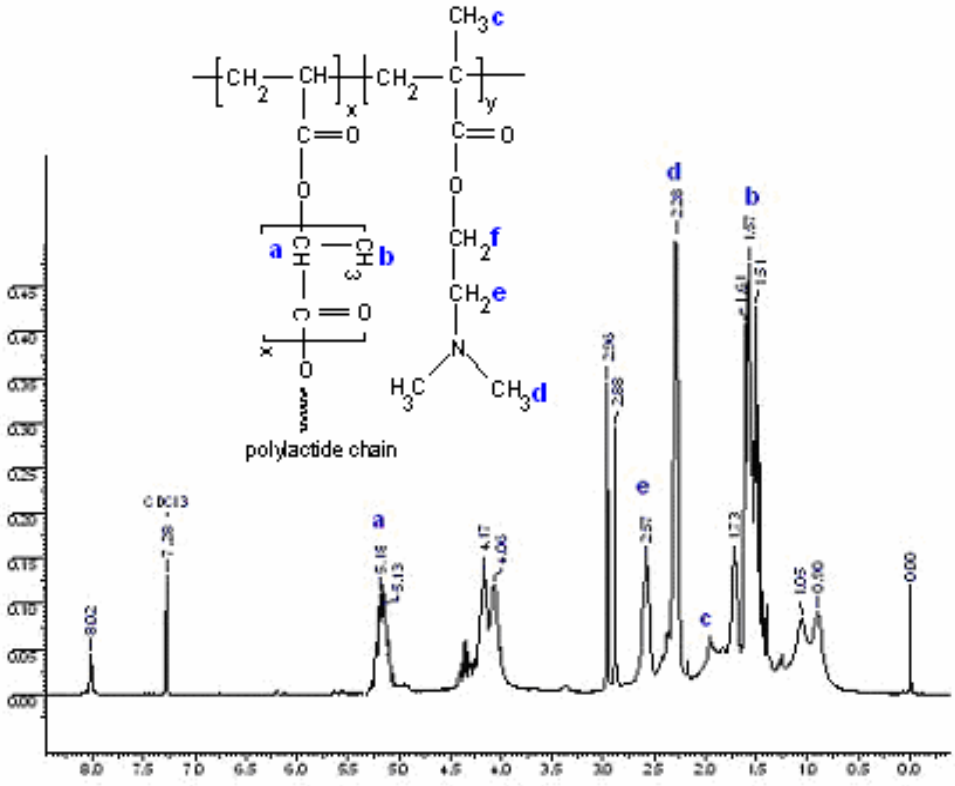


Figure 5.5 NMR spectrum of lactide-DMAEMA copolymer

Composition of the copolymer and subsequently monomer content was calculated using proton NMR technique. Spectrum of lactide-DMAEMA copolymer showed characteristic peaks for lactide at 1.56 ppm and 5.16 ppm. The peak at 1.56 ppm corresponds to 6 protons of 2 (methyl) groups; while peak at 5.16 ppm indicates 2 protons of 2 (methine) groups in the lactide chain.

In the spectrum, peaks corresponding to different groups in DMAEMA part are as follows- peak for C-CH_3 (methyl) is seen at 1.93 ppm and peak for N-CH_3 (2 methyl groups) is seen in the spectrum at 2.28 ppm. Similarly the peak for N-CH_2 (methylene) at 2.57 ppm and for O-CH_2 (methylene) at 4.26 ppm is observed in **Figure 5.5**.

Composition of the copolymer was calculated by integrating the peaks corresponding to respective monomers as mentioned in above description.

Integration of 2 methine groups corresponding to –CH of lactide (for 2 protons) was correlated with 1 methylene group of DMAEMA corresponding to 2 protons of N-CH2.

NMR spectrum of the copolymer as shown in **Figure 5.5** was used for calculation of monomer composition in lactide-DMAEMA copolymer.

DMAEMA content of the copolymer compositions was calculated using NMR peaks as shown in **Figure 5.5**. It was observed from the calculations that incorporation of DMAEMA was dependent on molecular weight of lactide macromer used in the copolymer. DMAEMA incorporation in the copolymer significantly decreases when molecular weight of lactide macromer increases beyond 2000.

5.4.3.2 Vapour Pressure Osmometry (VPO)

Molecular weight of Lactide-DMAEMA copolymers was determined using Vapour Pressure Osmometer. The results are tabulated in **Table 5.4 and 5.5.** It can be readily observed that molecular weight of the copolymers increased in direct proportion with DMAEMA content of the polymer.

It is evident from **Table 5.4 - 5.6** that incorporation of DMAEMA was dependent on molecular weight of lactide macromer. Copolymers with high molecular weight lactide macromer (more than 2000), showed negligible incorporation of DMAEMA as compared to copolymers containing low molecular weight lactide macromer (around 700).

Table 5.4 and 5.5 show that lactide copolymers were low molecular weight and development of molecular weight was mainly dependent on incorporation of DMAEMA monomer in the copolymers. Molecular weight of the copolymer decreased as DMAEMA content of the copolymer decreased in the series of the copolymer compositions.

Highest molecular weight observed in the table was around 5000. It can be said that the lactide-DMAEMA copolymers are low molecular weight and these can be used as excipients in oral drug delivery systems depending on their dissolution profile.

5.4.3.3 Dissolution Study

Dissolution pattern of lactide-DMAEMA copolymers was studied in various buffers of pH between 1.2 and 7.4 and dissolution time was noted.

It can be readily observed from **Table 5.4-5.6** that these copolymers dissolve in all buffers irrespective of pH. Thus lactide-DMAEMA copolymers behave as pH independent copolymers.

Table 5.4 shows that LAc-DMAEMA copolymers dissolve readily in all buffers. Dissolution time ranges from 30 to 60 minutes depending on DMAEMA content of the copolymer. The copolymers with higher content of DMAEMA dissolve in less time as compared to copolymers with low DMAEMA content. Dissolution time of the copolymers was observed to be independent of molecular weight of the copolymers. Lac - DMAEMA copolymers were soluble in all buffers only when DMAEMA content was more than 12 % w/w. The polymers were found to be insoluble in all buffers when monomer content was below this limit.

Table 5.5 shows dissolution profile of LMAc-DMAEMA copolymers in aqueous buffers. These polymers also dissolve in all buffers of pH 1.2 to 7.4. Dissolution time of the copolymers vary depending on DMAEMA content. This can be attributed to hydrophilicity of DMAEMA monomer, which helps the polymer to readily become soluble in aqueous buffers. This becomes obvious from **Table 5.6**. When DMAEMA content of the copolymers is negligible, polymers do not dissolve

in any buffer. This low incorporation of DMAEMA is due to presence of high molecular weight lactide macromer in the copolymer.

Molecular weight of lactide macromer plays very important role in the incorporation of comonomer in the copolymer system. Low molecular weight macromer allows entry of higher amount of DMAEMA in the lactide copolymer; whereas high molecular weight macromer restrict incorporation of comonomer and retards the solubility of the system in water due to low content of DMAEMA.

Table 5.4

Dissolution Behavior of Polymers in Buffers of pH 1.2, 4.8, 6.8 and 7.4

Composition: LAc- DMAEMA

Molecular Weight of lactide acrylate	**Composition of the copolymers (moles)**		**DMAEMA content % w/w of the copolymer**	**Molecular weight of copolymer**	**Dissolution time (min) in buffers**
	In feed	**By NMR**			
750	10:90	26:74	39	4699	30
700	20:80	27:73	38	4598	30
700	30:70	43:57	23	3135	45
700	40:60	52:48	17	2555	60
700	50:50	59:41	14	2372	60
700	60:40	62:38	12	2251	Insoluble
700	60:40	64:36	11	2190	Insoluble
700	70:30	67:33	10	2165	Insoluble
700	80:20	96:04	0.03	2079	Insoluble

Table 5.5

Dissolution Behavior of Polymers in Buffers of pH 1.2, 4.8, 6.8 and 7.4

Composition: LMAc: DMAEMA

Composition (moles)		DMAEMA % w/w	Molecular weight of copolymer	Dissolution time (min)
In feed	By NMR			
10:90	8:92	72	4865	10
20:80	28:72	36	2810	20
30:70	31:69	33	2746	20
40:60	36:64	28	2680	30
50:50[a]	41:59	24	2435	30
50:50[b]	58:42	12	2170	45

Macromer Mol wt a) 710 b) 800

Table 5.6 Dissolution Behavior of Polymers in Buffers

Composition: lactide acrylate: DMAEMA

Mol. wt of acrylate	Composition of copolymers (moles)		DMAEMA content % w/w of the copolymer	Solubility in all buffers
	In feed	By NMR		
4400	30:70	91:09	0.35	Insoluble
4000	40:60	89:11	0.48	Insoluble
2700	40:60	75:25	1.9	Insoluble
2700	30:70	65:35	3.0	Insoluble

5.4.3.4 Compatibility with Drug

Compatibility of drug with lactide-DMAEMA copolymer was studied to check suitability of these polymers for cefuroxime axetil drug delivery. It was clear from

the observation that polymer does not give any discoloration with Cefuroxime axetil. The lactide- polymer soluble at pH 1.2 to 7.4 and with low DMAEMA content (14 % w/w) was mainly tested for this purpose. The reason behind this was, we are specifically interested in demonstrating that lactide copolymers, which are evaluated in present study in the form of cefuroxime axetil solid dosage form, have very low DMAEMA content. At such low monomer content, these polymers show novel dissolution profile, as discussed earlier. This is novel in context of DMAEMA copolymers existing in the market as reverse enteric polymers. These polymers have 35% w/w DMAEMA and it is reported that these show negative interaction with cefuroxime axetil. Incompatibility of these polymers is observed in the form of discoloration.

Lactide copolymers synthesized in this work exhibit novel dissolution profile at low DMAEMA content and are compatible with cefuroxime axetil. Hence it is evident that the lactide copolymers are particularly suitable for Cefuroxime axetil delivery. Copolymers were used in cefuroxime axetil formulation and evaluated for drug release. Tablets were coated with pH sensitive lactide-VP copolymers to taste mask bitter drug and make it palatable for oral delivery.

Thus, main purpose of this work was to demonstrate utility of lactide-DMAEMA copolymers in cefuroxime axetil delivery for first time.

5.4.3.5 Drug Content

Drug content of the 10 tablets was determined by using UV spectrophotometer. The concentration of Cefuroxime axetil in the tablet was determined at 278 nm. It was observed that drug content of the tablets was uniform and there was no variation from tablet to tablet.

5.4.3.6 Drug Release

Cefuroxime axetil tablets were formulated using pH independent lactide-DMAEMA copolymers in the matrix and pH sensitive lactide-VP copolymers as external coating for taste masking purpose. Drug release from these tablets was studied in

simulated gastric fluid. It was readily observed from **Table 5.7** that about 80% drug was released in first 15 minutes, followed by 97% drug release in 60 minutes. Hence this formulation was suitable for immediate gastric delivery of cefuroxime axetil.

Drug release pattern varied depending on composition of the tablet. Proportion of either drug: polymer or drug: inert carrier was manipulated to study effect of tablet composition on drug release. It was seen from **Table 5.7 and 5.9** that drug release pattern slightly varied depending on polymer: drug proportion in the tablet. Drug release was faster when drug and polymer were used in equal amount as compared to the tablet where polymer amount was more than drug.

Table 5.10 - 5.12 indicated drug release from tablets containing varying amounts of anhydrous lactose. It could be said that amount of anhydrous lactose present in the formulation affected drug release rate. As amount of this inert carrier in the formulation increased, it lowered down drug release rate proportionately.

From drug release data for Cefuroxime axetil tablet formulations it was evident that immediate gastric release of drug took place with slight variation in drug release rate with respect to formulation variations like drug, polymer, and coating solution amount. At the same time, effect of lactose amount in the formulation was more significant as shown in **Figure 5.8**.

5.4.3.7 Drug Leaching at Salivary pH

Drug leaching from the formulation in saliva was checked by immersing the taste masked tablet in pH 5.8 buffer. This was for proving efficiency of outer lactide polymer coat applied for taste masking purpose. It can be readily observed from Table 5.6 that even after 20 minutes observation time, very little drug was released at pH 5.8. Hence it is evident that when this taste masked tablet formulation would come in contact with tongue while swallowing, it will not release significant amount of drug to sense bitterness of drug and thus taste masking purpose will be fulfilled. Such solid tablet formulation will thus be palatable with better patient compliance.

Table 5.7 Cefuroxime Axetil Release in Simulated Gastric Fluid

Formulation 1

Time (min)	% Release
15	81.2
30	86.0
45	94.6
60	97.1

Table 5.8 Cefuroxime Axetil Release in 5.8 pH Buffer

Formulation 1

Time (min)	% Release
5	0.02
10	0.08
15	0.14
20	0.24

Table 5.9 Cefuroxime Axetil Release in Simulated Gastric Fluid

Formulation 2

Time (min)	% Release
15	78.72
30	83.27
45	87.49
60	94.38

Table 5.10 Cefuroxime Axetil Release in Simulated Gastric Fluid

Formulation 3

Time (min)	% Release
15	75.72
30	81.30
45	86.29
60	93.66

Table 5.11 Cefuroxime Axetil Release in Simulated Gastric Fluid

Formulation 4

Time (min)	% Release
15	72.26
30	78.52
45	84.17
60	87.35

Table 5.12 Cefuroxime Axetil Release in Simulated Gastric Fluid

Formulation 5

Time (min)	% Release
15	68.13
30	72.47
45	77.60
60	82.03

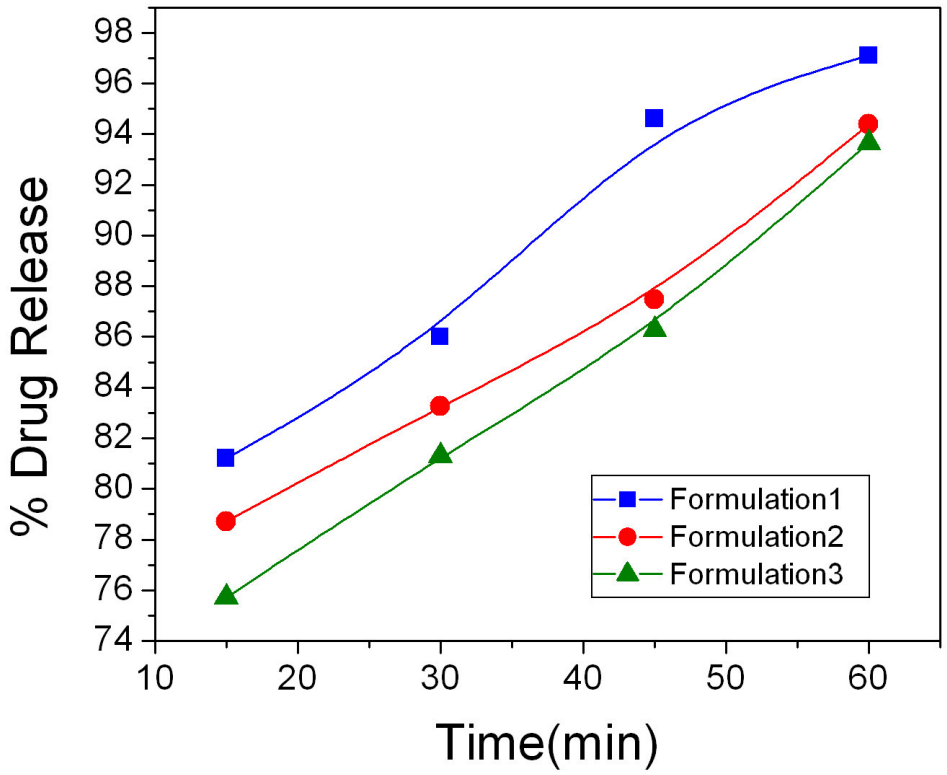


Figure 5.6 Cefuroxime Axetil Release at pH 1.8 and T= 37^{0}C

The release profile of Cefuroxime axetil from Lactide-DMAEMA tablets is shown at T= 37^{0}C and pH 1.8 in **Figure 5.6**. It can be readily observed that formulation 1 exhibits fast and better drug release profile as compared to formulation 2 & 3. Formulation 1 releases 81 % drug in first 15 minutes as compared to formulation 2 and 3 which release 75 to 78 % drug in same time period. Hence it can be said that increased amount of lactose as inert carrier may have some minimum inhibitory effect on drug release rate. This can be attributed to the fact that this is a matrix tablet in which drug, polymer and anhydrous lactose are in close association with each other and drug has to diffuse through this matrix to get released from tablet dosage form. At the same time there doesn't seem to be any effect of polymer coating thickness on the drug release rate from the tablet. This may be due to dissolution property of lactide-VP polymer used as coating for these tablets. These polymers dissolve rapidly, once they reach acidic pH of gastric region. Hence

coating thickness may not affect drug release rate. Thus it is observed from Figure 5.6 that all tablet compositions show immediate gastric delivery of drug.

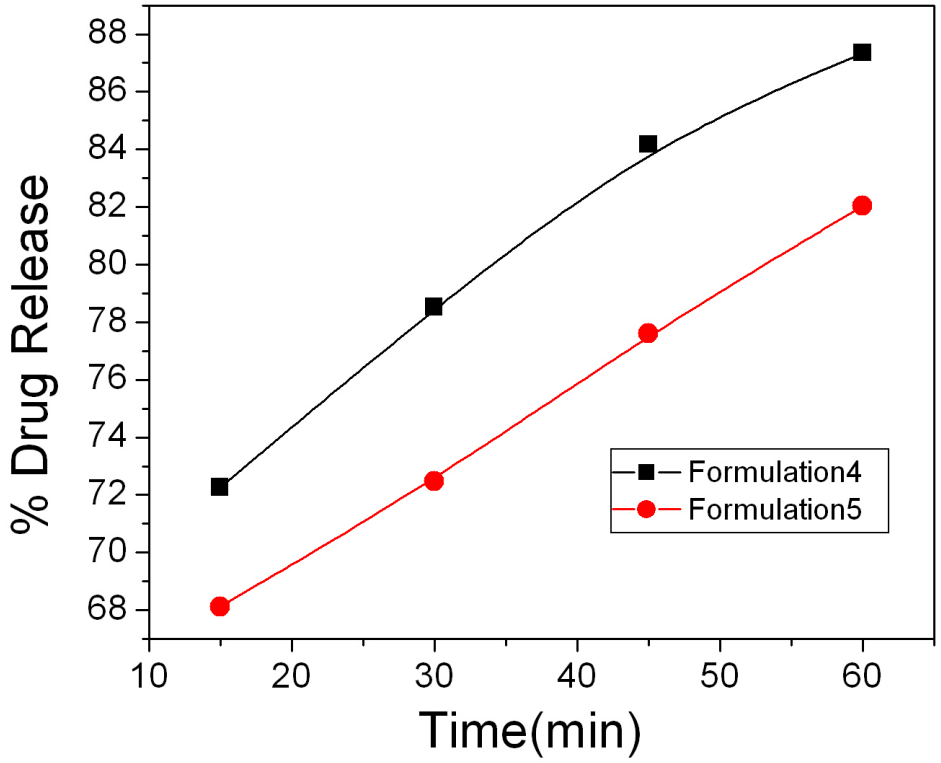


Figure 5.7 Cefuroxime Axetil Release at pH 1.8 and T= 37^{0}C

The release profile of Cefuroxime axetil from Lactide-DMAEMA tablets is shown at T= 37^{0}C and pH 1.8 in **Figure 5.7.** It is readily observed that rate of drug release from tablet 4 and 5 differs in first 15 minutes, as well as towards 60 minutes. Figure shows changes in cumulative % drug release with respect to time. Formulation 4 and 5 differ in composition with respect to amount of lactose present in formulation, but amount of drug, polymer and coating solution concentration remain constant. Higher amount of carrier substance lowers down rate of drug release from formulation.

Difference in drug release based on compositional changes with respect to lactose is shown in **Figure 5.8**.

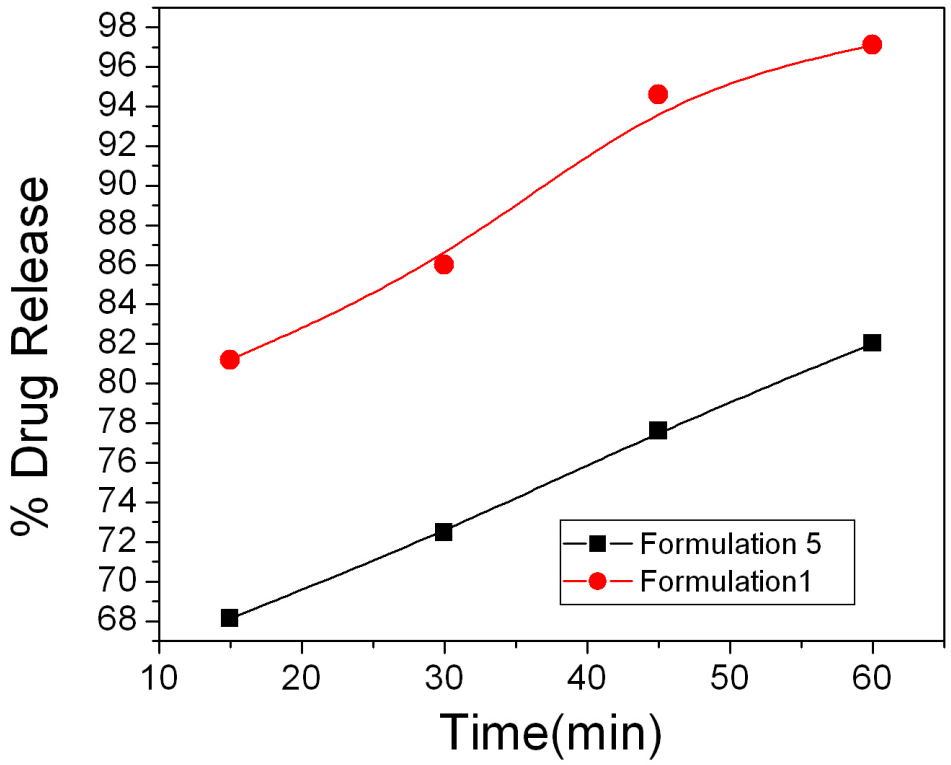


Figure 5.8 Effect of Anhydrous Lactose on Drug Release from Formulation 1 and 5

From **Figure 5.8** it is clear that increased amount of lactose in the formulation affects rate of drug release. As the amount of anhydrous lactose in tablet matrix increases from 250 mg to 750 mg (as observed in Formulation 1 and 5 respectively), drug release over the time period of 60 minutes was lowered from 97 to 82 % .This change in the drug release can be attributed to mechanism of drug release from the formulation. Drug has to diffuse through the matrix of anhydrous lactose and it will be released from tablet when lactide-VP and lactide-DMAEMA polymers dissolve. Drug diffusion through inert carrier matrix will take time as amount of carrier substantially increases and this will consequently result in lowered rate of drug release as indicated in the figure.

5.5 Conclusion

Lactide –DMAEMA copolymers were synthesized and characterized for molecular weight, monomer content and dissolution profile. The polymers were soluble over entire pH range of 1.2 to 7.4. Dissolution time of the polymers was dependent on DMAEMA content in the copolymer. The polymers were found to be compatible with bitter drug cefuroxime axetil; hence it was decided to use these polymers to design solid dosage formulation for oral drug delivery.

A tablet formulation was designed using lactide-DMAEMA copolymers as matrix along with anhydrous lactose as inert carrier. Lactide-VP copolymers were used as coating to taste mask the drug and release it at acidic pH prevalent in the gastric region. Different tablet formulations were prepared by varying amounts of drug, polymer, inert carrier and coating solution concentration. Drug release from these tablets was studied at acidic pH. It was observed that in acidic medium about 80 to 95% drug was released immediately depending on composition of tablets. These formulations could be explored for immediate gastric delivery. Mechanism of drug release from tablets would be a combination of diffusion of the drug and dissolution of lactide-DMAEMA polymer in acidic medium. Tablets of cefuroxime axetil were taste masked by applying outer coating of lactide-VP copolymers which did not release the drug at salivary pH, but released it only when it reached gastric region. Thus the tablets were taste masked and would result in better patient compliance towards extremely bitter cefuroxime axetil.

Drug release from tablets was affected by changes in the composition of the tablet especially with respect to amount of inert carrier used in the formulation. pH independent lactide-DMAEMA copolymers acted as reverse enteric polymers in this composition and mechanism of drug release from the tablet composition was by diffusion through the matrix and also dissolution of the copolymer at acidic pH. These polymers were compatible with cefuroxime axetil, hence could be explored as pharmaceutical excipients for taste masking applications.

In summary, characterization, formulation and evaluation of lactide-DMAEMA copolymers highlighted following points:

1. Lactide copolymers, with DMAEMA content more than 12 % w/w were found to be soluble in aqueous buffers of entire pH range from 1.2 to 7.4. Hence these could be called as pH independent lactide copolymers.

2. Lactide –DMAEMA copolymers were low molecular weight and development of molecular weight was dependent on DMAEMA content of the copolymer. It was observed that as DMAEMA content decreased, it resulted in copolymers with lower molecular weight as compared with copolymers with higher DMAEMA content.

3 Incorporation of DMAEMA decreased as the molecular weight of lactide macromer increased in the copolymer. Hence copolymers containing higher molecular weight lactide macromer (more than 2000) were found insoluble in all buffers due to very low incorporation of DMAEMA.

4. Copolymers with higher DMAEMA content dissolved faster in all aqueous buffers as compared to copolymers with lower DMAEMA content. This dissolution profile could be attributed to hydrophilicity of DMAEMA monomer.

5. Lactide-DMAEMA copolymers were found to be compatible with the drug-cefuroxime axetil and this observation led to test their suitability in Cefuroxime axetil formulation.

6. Idea of Cefuroxime axetil delivery was explored in the form of matrix tablet formulation in which lactide-DMAEMA copolymers were adsorbed on anhydrous lactose along with drug.

7. The tablet was coated by lactide –VP copolymers for taste masking purpose and to avoid drug leaching at salivary pH as these polymers were soluble only below pH 3 as described in chapter 4. Thus these lactide-VP polymers performed the vital role of deciding fate of dissolution of lactide –DMAEMA copolymers and did not allow them to release drug at salivary pH in spite of their dissolution behavior at all pH ranges, as shown in dissolution study.

8. It was readily seen from the release study that about 95 % drug was released immediately from the tablet formulation at gastric pH over the period of 60 minutes.

9. Very little drug was released at salivary pH which proved that tablet coating was useful for masking of bitter taste of cefuroxime axetil. Thus the formulation

explored use of combination of two lactide polymers for two different purposes. It could give rise to taste masked solid dosage form containing Lactide-DMAEMA polymers compatible with cefuroxime axetil.

10. Different tablet compositions with variations in amount of anhydrous lactose and coating layer were formulated for the purpose of evaluating their effect on drug release. It was observed that these formulation variations had no significant effect on drug release from the formulation. % Drug release varied from 75 to 82 % in first 15 minutes and cumulative drug release varied from 88 to 97 % over 60 minutes study time with respect to formulation changes.

11. Lactide-DMAEMA and lactide-VP copolymers in combination were used to give rise to a matrix tablet formulation for oral cefuroxime axetil delivery. This was a taste masked formulation for oral delivery of bitter drug which delivered substantial amount of drug over 60 minutes at gastric pH.

12. Literature reports that DMAEMA copolymers such as Eudragit E cannot be used for cefuroxime axetil delivery due to negative interactions. Surprisingly the DMAEMA copolymers synthesized by us did not show any negative interaction for cefuroxime axetil. It would be interesting to validate the findings in more details and investigate the reasons for this behavior further.

5.6 References

Andersson M., Josefson M., Langkilde F.W., Wahlund K.G. Journal of Pharmaceutical and Biomedical Analysis 1999, *20*, 27

Alonso M.J., Lorenzo-Lamosa M.L.,.Cuna M, Vila Jato J.L., Torres D., Journal of Microencapsulation **1997**, *14*, 607

Alvarez-Fuentes J., Fernández-Arévalo M., González-Rodríguez M.L., Cirri M., Mura P. Journal of Drug Targeting **2004**, *12*, 607

Coullerez G., Lowe C., Pechy P., Kausch H.H. , Hilborn J .J. Mater. Sci: Mater. Med. **2000**, *11***,** 505

Cuna M., Lorenzo M. L., Vila Jato J. L., Torres D., Alonso M. J., Acta Technologiae et Legis Medicamenti. **1996**, *VII*, 3

Dunn R.L. In: J.O. Hollinger, Editor, Biomedical applications of synthetic biodegradable polymers, CRC Press, Boca Raton **1995**, 17

Han D.K., Hubbell J.A. Macromolecules **1997**, *30,* 6077

Hoy; Michael R. **1996,** U.S. Patent 5, 489, 436

Jaskari T., Vuorio M., Kontturi K., Manzanares J.A. and Hirvonen J. J. Contr. Release **2001,** *70,* 219

Kawashima Y., Niwa T., Handa T., Takeushi H., Iwamoto T. and Itoh K., J. Pharm. Sci. **1989,** *78* , 68

Khan Abdul Rehman **2002**, Patent Application WO 02/43707

Mauger; John W. **1998,** U.S. Patent 5,728,403

Paruthi, M. K. **2004,** US Patent Application No**.** 20040258752

Roche; Edward J. **1991,** U.S. Patent 5,075,114

Shalaby S.W., Johnson A. In: Shalaby S.W., Editor, Biomedical polymers: Designed to degrade systems, Carl Hanser Verlag, Munich **1994**, 1

Shirai Y. **1992,** U.S. Patent 5,082,669

Tandya A., Mammucari, R., Dehghani, F., Foster, N.R., International Journal of Pharmaceutics **2007**, *328*, 1

Yan G., Cui F., Ying G., Lei Y., Wang Y., Zhang L. International Journal of Pharmaceutics **2006,** *318,* 62

CHAPTER 6

pH Sensitive Lactide Polymers for Intestinal Drug Delivery

6.1 Introduction

Stimuli responsive or smart polymers are being explored as polymeric excipients in many biomedical and pharmaceutical areas, especially in site specific drug delivery systems. This is because these polymers undergo a conformational change in response to changes in external environment such as pH, temperature, light, and metabolites (Kang, 2001). Among these, pH sensitive polymers have attracted growing interest in both scientific and technological fields (Chiu, 2001). pH responsive conformation accompanied by solubility changes is common behavior in biopolymers. These polymers consist of ionizable groups that can accept and donate protons in response to environmental pH. As the environmental pH changes, the degree of ionization in a polymer bearing weakly ionizable groups is dramatically altered (Gil, 2004). The polymers containing ionizable groups form polyelectrolytes in aqueous medium. There are two types of pH responsive polyelectrolytes; weak polyacids and weak polybases. Weak polyacids such as poly (acrylic acid) are ionized in neutral and basic pH (Philippova, 1997). Polyacids bearing carboxylic group with pK_a around 5–6 are the most representative weak polyacids. The polymers containing acrylic acid and methacrylic acid have been most frequently reported as pH responsive polymers. Carboxylic pendant groups accept protons at low pH and release at basic pH.

Table 6.1 lists ionizable anionic monomers used in the synthesis of pH-sensitive polymers useful in pharmaceutical applications.

pH responsive polymers contain functional groups which undergo structural change in response to pH. This property of polymers can be used in drug delivery systems to target the release of drugs to intended sites along the gastrointestinal tract. The concept of using pH as a trigger to release a drug in the colon is based on pH conditions that continuously vary from acidic (1-3) to near neutral and basic (5-8) along the gastrointestinal tract.

Pharmaceutical uses of acrylic polymers are widespread and these copolymers are available in the market under different brand names depending on the composition and manufacturer. Applications of acrylic polymers in ocular, nasal, buccal, gastro-intestinal, epidermal and transdermal, vaginal or cervical drug delivery continue to

be explored. Acrylic acid and methacrylic acid copolymers are used as excipients in variety of ways ranging from personal care products to intestinal drug delivery. These copolymers solubilize in intestine and release encapsulated drug. Molecular weights of these copolymers are high. Content of acidic monomers like acrylic acid and methacrylic acid that contributes to pH dependent behavior in these copolymers is 25 to 55 % w/w.

Table 6.1 Important Anionic Monomers / Polymers and Respective pK Value of Corresponding Homopolymers

Monomer	pH-sensitive group	pK_a	Reference
Acrylic acid	-COOH	4.7	Peppas, 1998
Methacrylic acid	-COOH	6.15/6.35	Ketchalsky, 1947
Sodium styrene sulfonate	$-SO_3^-Na^+$	<1	Kang, 2002
2-acrylamido-2-methyl-1- propane sulphonic acid	$-SO_3H$	2.86	McCormick, 1986

In case of the references cited above, the drug release profile was not suitable for extended intestinal drug delivery. These polymers were also not able to protect the drug from gastric environment.

For intestinal drug delivery, anionic polymers of methacrylic acid and methacrylates containing -COOH group are available in the market which dissolve immediately when they reach near neutral or neutral pH in intestine and release the drug. Other pH independent copolymers of acrylate and methacrylates containing quaternary ammonium groups which are being explored, swell both in acidic as well as basic pH. Thus these polymers are not suitable for delivery of acid labile drugs. Other type of copolymers of acrylates and methacrylates containing quaternary ammonium group in combination with sodium carboxymethylcellulose exhibit pH

independent dissolution behavior and these too can not protect acid labile drugs. Hence no acrylate or methacrylate polymers are available currently to satisfy the need.

Table 6.2 Acrylic acid and Methacrylic Acid Copolymers in Drug Delivery

Polymer System	Drug Release	Applications	Reference
Combination coating of PVA,MAA and EtAc on Verapamil HCl	Slow release in acid & faster release in alkaline medium	pH independent drug release in GIT	Dashevsky, 2004
p (MAA-g-EG) hydrogels conatining Insulin	No release in stomach, fast release within 2 hours in intestine	pH dependent oral insulin delivery	Lowman, 1999
Microparticles of equimolar amount of MAA-g-EG	Release retarded in stomach & fast release in intestine	pH dependent oral insulin delivery	Morishita, 2002
Above Microparticles with higher amount of MAA	Fast release in acidic and alkaline medium	pH independent oral insulin delivery	Morishita, 2002
Formulations with PAA/ CA or PAA / PEO	Drug release in acidic and alkaline medium	pH independent oral sustained release	Rogers, 2003
EC & HPMC in tablet core and MA& MMA in coat	Immediate release in acidic & alkaline medium. Sustained release at pH 7.5	pH independent oral sustained release Diclofenac tablet	Kawakami, 2005
Microspheres using coating of pH dependent anionic polymer	Drug release only above pH 5.5	pH dependent controlled oral NSAID delivery	Shafer, 2004
Formulation with enteric coating	Minimum release in stomach & slow release in intestine	pH dependent Milnacipran formulation	Hirsh, 2006

From the foregoing it is clear that there is a need to design polymers, which unlike conventional enteric polymers will dissolve over extended time periods. Such polymers will be useful for the release of drugs over varying time periods to satisfy needs of a wide variety of intestinal drug delivery systems like delayed and extended release. Such polymeric excipients will also protect the drugs from harsh acidic pH of stomach (e.g. proteins and peptide drugs like Insulin), as well as protect gastric region from harmful side effects of some drugs (e.g. NSAID category).

Although NSAIDs are often used for their anti-inflammatory, analgesic, and / or antipyretic effects, they could cause gastrointestinal (GI) bleeding through a variety of mechanisms related to their topical and systemic effects. The GI bleeding may depend on the length of the treatment and on the particular drug. This problem is important in cases where the therapy must be continued for a long period of time. For example, osteoarthritis and rheumatoid arthritis in the elderly is often treated with long-term NSAID therapy, as chronic treatment is needed to control pain and inflammation and to improve quality of life. Diclofenac sodium is one of the most commonly prescribed extremely potent and effective drugs for its analgesic, anti-inflammatory and anti-rheumatic effects. This drug has strong action and low toxicity compared with Indomethacin and therefore is widely used in current medical practice. Diclofenac is used for long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis and spondylitis. It is also considered to be useful for the short-term treatment of acute musculoskeletal injury, acute painful shoulder, postoperative pain and dysmenorrhea. However, Diclofenac produces side effects in about 20% of patients that require cessation of medication. It is believed that the gastrointestinal toxicity is due to decrease in the biosynthesis of cytoprotective prostaglandins.

There is a need to develop modified release formulations of NSAIDs to avoid drug release and subsequent side effects in stomach and release drug either immediately or over extended time period only in intestine. Modification of lactide in the form of functional macromonomer and its copolymerization with acidic monomer was

therefore explored to achieve dissolution mediated drug release.

Lactide is a biodegradable and FDA approved monomer for use in polymers for pharmaceutical applications. The polymers are not suitable in the present form for oral drug delivery because of highly crystalline nature. The rate of degradation is such that the release of the drug over gastric emptying time is not possible (Anderson, 1997). It is desirable to modify the structure such that the drug is released by a mechanism other than degradation, so that the polymer is useful for oral drug delivery. Lactide copolymers are being used for parenteral applications commercially and their oral dosage forms are under investigations. Some of the lactide polymers and their applications are listed in **Table 6.3**.

Table 6.3 Lactide Polymers in Drug Delivery

Copolymer system	**Drug release mechanism**	**Application**	**Ref.**
H bonded inter-polymer complex between P (MAA) & triblock PLA-b-PEG-b-PLA	Hydrolysis in aqueous medium	To maintain acidic pH in body cavities like vagina	Huang, 2003
PLGA microcapsules with saline/propylene glycol / glycerine	Biodegradation of microcapsule	Dry eye treatment	El-Sherif, 2003
Oligolactide methacrylate macromer	Excellent biocompatibility	Scaffolds for bone tissue engineering	Schnabelrauch, 2002
(PLA-g-P (NIPAm-co-MAA) nano particles	25% release in acidic medium & slow release for 4 days. No release at pH 7.4	Intracellular delivery of anti-cancer drug 5FU	Lo, 2005
Graft polymer of polyethylene glycol Methyl glycidyl ether with L-lactide	Biocompatible polymer with controlled crystallinity	Sutures and drug delivery systems.	Park, US 6221977

Thus in above examples, lactide polymers released the drug in alkaline as well as acidic pH which is not desirable for acid labile drugs. Also low molecular weight lactide macromonomers are used in the literature as scaffolds in tissue engineering. These macromers alone do not exhibit any pH dependent behavior.

We synthesized and evaluated copolymer compositions comprising oligomeric lactide macromer and acidic monomer. This resulted in pH sensitive lactide polymers. Our work demonstrated that even at very low concentration of the acidic monomer (about 1 % w/w), the copolymer dissolves at pH > 6 over time periods ranging from 30 to 1440 minutes. These pH sensitive polymers were used for drug encapsulation and drug release was studied. From the results we could interpret that these copolymers will satisfy the need for an excipient in intestinal drug delivery. These polymers avoid release of gastro-irritant drug in stomach and release them in intestinal region over an extended time period depending on composition of copolymer. Thus lactide copolymers are potential biocompatible pH sensitive excipients useful for intestinal drug delivery systems.

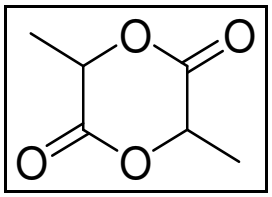
6.2 Experimental

6.2.1 Materials used

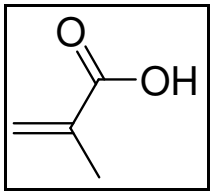
L-lactide (3S-cis-3,6-Dimethyl-1,4-dioxane-2,5-dione 98%), 1,4 butanediol, Acrylic acid (AA), Methacrylic acid (MAA) and Iron acetate (99.995%) were procured from Aldrich Chemicals , USA and used without further purification. Azo bis Iso Butyronitrile (AIBN) was purchased from Sas chemicals Company, Mumbai. Structures of monomers and initiator are presented in figure 6.1. Benzoyl chloride and hydroquinone were purchased from Merck Ltd and Qualigen Chemicals, Mumbai respectively. Solvents like Tetrahydrofuran and N, N dimethyl formamide were procured from S, D fine chemicals.

The drugs Diclofenac Sodium (2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt), and Celecoxib(4-[5-(4-methylphenyl)-3-(trifluoromethyl)

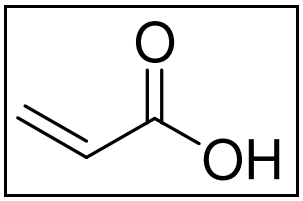
pyrazol-1-yl] benzene sulfonamide were obtained from Lupin Labs, India, Pune. Chemical structures of the drugs used in the work are presented in **Figure 6.2**.



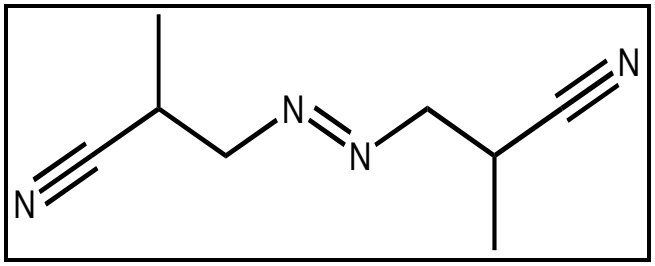
L-lactic acid



Methacrylic acid

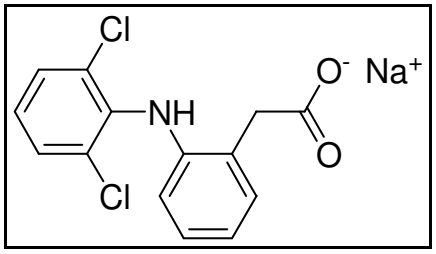


Acrylic acid

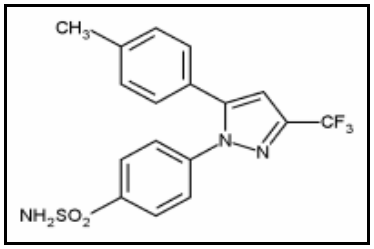


AIBN

Figure 6.1 Structures of Monomers and Initiator



Diclofenac sodium



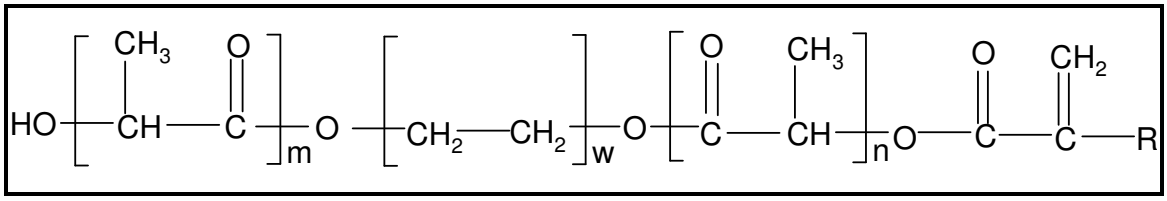
Celecoxib

Figure 6.2 Structures of Drugs used for Microencapsulation

6.2.2 Synthesis of Lactide-AA / MAA Copolymers

6.2.2.1 Synthesis of Lactide Macromer

Lactide macromer (lactide acrylate and lactide methacrylate) was synthesized as per procedure described in chapter 3.



w = 2 and R = H or CH_3

Figure 6.3 Structure of Lactide Macromer

6.2.2.2 Synthesis of Lactide-AA / MAA Copolymers

Copolymers of lactide macromer with Acrylic acid and Methacrylic acid were synthesized by free radical polymerization. Lactide macromers of molecular weight range 500, 800 and 1200 were chosen for copolymerization. Lactide acrylate or lactide methacrylate macromer (M1) and AA / MAA (M2) were dissolved in DMF and 2 mole % AIBN was added to it. This reaction mixture was purged with nitrogen for 10 minutes and the test tube was sealed with Teflon. The reaction was carried out at 65 ^{0}C for 24 hours. Then the reaction mixture was concentrated under reduced pressure using rotavapour. The concentrated mixture was precipitated in diethyl ether. Polymer was then dried under vacuum to get product.

Lactide macromer and AA / MAA were copolymerized in different mole ratios from 10:90 to 80:20. Four types of copolymers were obtained from these polymerizations.

a. Lactide acrylate-AA

b. Lactide methacrylate-AA

c. Lactide acrylate-MAA

d. Lactide methacrylate-MAA

6.2.3 Encapsulation of Drugs in Lactide-AA / MAA Microspheres

Microspheres of lactide- AA / MAA polymers were prepared by emulsification solvent evaporation technique. The lactide polymer was dissolved along with the drug in an organic solvent (methanol and dichloromethane in the ratio 1:1). This organic phase was then added dropwise to light liquid paraffin under constant mechanical stirring rate of 800 rpm at room temperature for 3-4 hours. The solvent was allowed to evaporate and chilled n-hexane or petroleum ether was added to this system and stirring was continued for another hour. The microspheres so obtained were separated by filtration, washed by pet ether or Hexane and dried under vacuum for up to 24 hours. These microspheres were stored in a well closed container under vacuum.

Two drugs - Diclofenac sodium and Celecoxib were encapsulated in lactide-AA / MAA microspheres using the method described above.

6.3 Characterization

6.3.1 Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectra of Lactide- AA / MAA copolymers were recorded on Bruker DRX – 500 spectrometer operating at a proton and carbon frequency of 500.13 and 125.4 MHz respectively using DMSO-d_6 or $CDCl_3$ as a solvent.

6.3.2 Fourier Transform Infra Red (FTIR) Spectroscopy

For FTIR analysis, 5 % (w/v) copolymer solution in chloroform (Spectroscopic grade) was put on KBR pellet or the polymer compositions which were not soluble in chloroform were mulled in KBr and a pellet was formed for analysis. Fourier

transform infrared analysis was carried out using a Shimadzu's FT-IR-8300 spectrometer at resolution of 4 cm^{-1}.

6.3.3 Vapor Pressure Osmometry (VPO)

Molecular weight of lactide-AA / MAA copolymers was determined using Knauer Vapor Pressure Osmometer K-7000. Stock solution of copolymer (10 mg/ml) was prepared in Chloroform or Dimethyl sulphoxide (Spectroscopy grade) and successive dilutions of polymer in this solvent were analyzed at selected constant temperature (37^0C). Benzil was used as standard for calibration of instrument. Molecular mass of a sample can be determined with a known concentration of the substance using calibration value.

6.3.4 Differential Scanning Calorimetry (DSC)

A Perkin Elmer instrument was used for studying the melting and crystallization behavior of the lactide copolymers. The temperature and energy scales were calibrated with the standard procedures. The melting studies were performed in the temperature range of -50 to 240 °C with the help of intercoolers arrangement at the heating rate of 10 °C/min in the N_2 atmosphere.

6.3.5 Dissolution Study

Dried lactide-AA / MAA copolymers (50 mg) were immersed in 5 ml buffer of respective pH. Dissolution pattern of these lactide copolymers was studied with respect to time and dissolution time was noted.

6.3.6 Scanning Electron Microscopy (SEM)

Surface morphology of lactide –AA / MAA microspheres was studied at an accelerating voltage of 20kV. (Leica, UK, model-stereoscan 440)

6.3.7 Optical Microscopy

The microspheres were spread uniformly on glass slide and observed under 10 X magnification of the microscope (Leica, UK, model). Particle size of 50 particles was recorded to get idea about average particle size of microspheres.

6.3.8 Drug Loading

Drug loading in the microspheres was determined by dissolving known amount of microspheres in methanol and sonicating it for few seconds. Supernatant solution was analyzed on UV spectrophotometer. The concentration of Diclofenac sodium in microspheres was determined at 254 nm. In a similar manner drug loading of microspheres containing Celecoxib was calculated from absorbance at 275 nm.

6.3.9 Drug Release

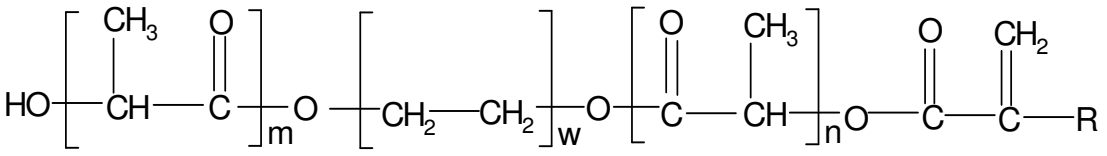
Study of drug release from the microspheres was first carried out in 0.1 N hydrochloric acid buffer for two hours, at 37 ± 0.5°C, using USP type II apparatus rotated at 50 rpm. Subsequently drug release was determined at 6.8 pH phosphate buffer for next four hours at 37 ± 0.5°C, under same conditions. The samples were withdrawn at fixed time intervals. The amount withdrawn each time was replaced with fresh media to maintain the sink conditions. Samples were analyzed on UV spectrophotometer at 254 nm and cumulative Diclofenac sodium release from microspheres was determined using calibration curve for the drug.

Celecoxib release from microspheres was determined by placing composition consisting of Celecoxib and polymer in 0.1 N HCl 100 ml for 2 hours and then in 6.8 pH phosphate buffer at 37± 0.5°C, using USP type II apparatus rotated at 100 rpm. Samples were withdrawn from phosphate buffer solution (pH 6.8) at fixed time intervals. Amount withdrawn each time was replaced with fresh media to maintain sink conditions.

6.4 Results and Discussion

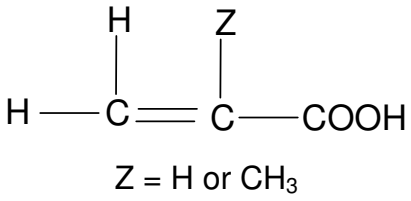
6.4.1 Free Radical Copolymerization

AA / MAA was copolymerized with lactide macromer using DMF as solvent and AIBN as initiator. Unsaturated acrylate or methacrylate part of lactide macromer reacted with unsaturation of AA / MAA to give a linear polymer. Lactide chain remained as pendent part in the copolymer. Reaction mechanism of copolymerization reaction is shown schematically in **Figure 6.4**.

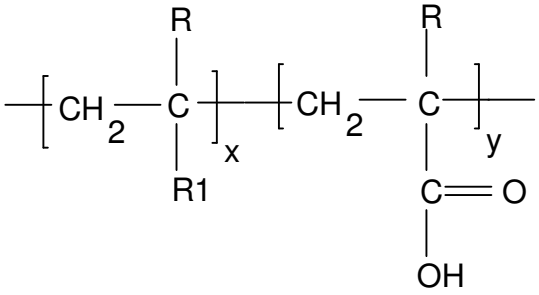


m = 2 to 5, n = 2 to 4 w = 2 R = H or CH_3

+



Z = H or CH_3



where

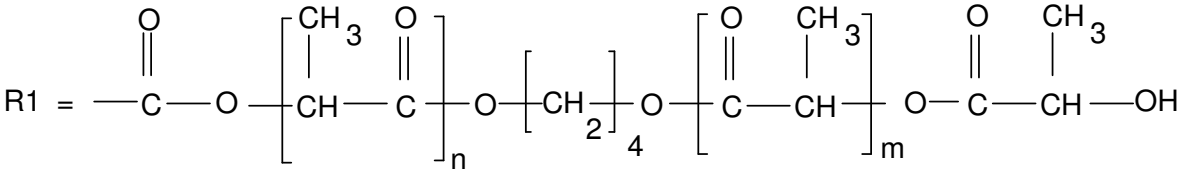


Figure 6.4

Schematic Presentation of Lactide - AA/MAA Copolymerization

The pendent lactide chain is very hydrophobic; whereas AA / MAA part is hydrophilic in nature. All the copolymers synthesized in this work using different mole ratios of lactide macromer and AA / MAA (10:90 to 80:20) were solid in nature. Yield of the copolymerization reactions was 75 %. Polymers had good surface coating property, but the film formed could not be lifted. The polymers can be used for microencapsulation of drugs and can be explored for possible drug delivery applications.

6.4.2 Encapsulation of Drugs in Lactide-AA / MAA Microspheres

Drugs were encapsulated in lactide microspheres by emulsion solvent evaporation method. Drug loading was in the range 28 to 40 %. Microspheres were spherical in shape and convenient for handling. The choice of the copolymers for microsphere synthesis was based on AA / MAA content of the copolymer and results of dissolution pattern. Lactide-AA/MAA copolymers were soluble in alkaline pH above 6 in aqueous buffers as well as in some organic solvents. Hence organic solvent was selected as internal phase in encapsulation process and light liquid paraffin as external continuous phase. Pet ether or diethyl ether was suitable non solvent for these polymers. Separation method for microspheres was easy with minimum loss of materials.

6.4.3 Characterization

6.4.3.1 NMR Spectroscopy

Composition of the copolymer was calculated using ^{13}C NMR spectroscopy. From figure no. 6.5, it was observed that spectrum of lactide-AA / MAA copolymer showed characteristic peaks for lactide at 174 ppm representative of Carbon atom of (-COO) group and free carboxyl groups (C=O) of acrylic or methacrylic acid were represented by a peak around 170 ppm in the spectrum. Monomer (AA / MAA) content and composition of the lactide copolymer can be calculated using above characteristic peaks of lactide and acids.

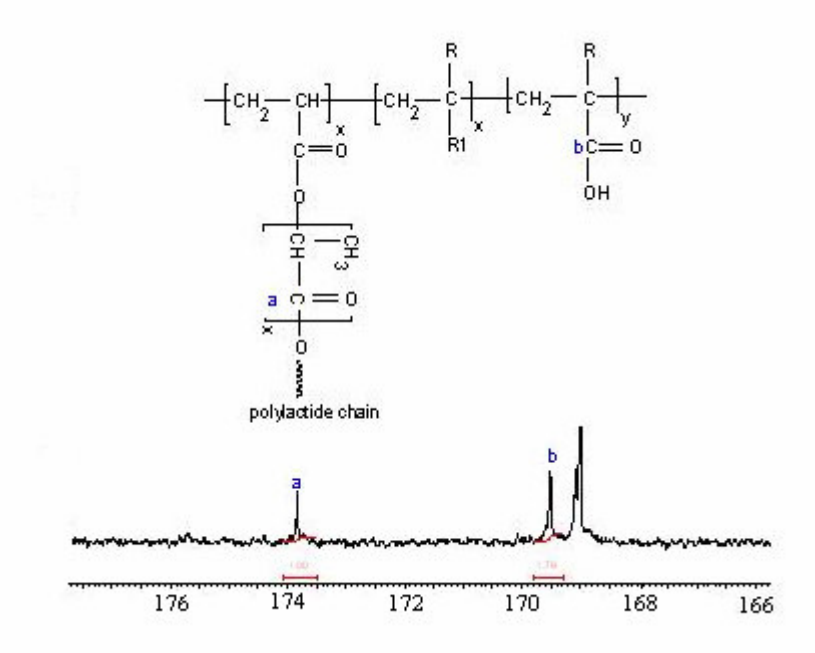


Figure 6.5 NMR Spectrum of LMAc-MAA Copolymer

As shown in **Figure 6.5**, integration of the lactide peak at 174 ppm can be compared with the integration of AA/ MAA peak at 170 ppm. Lactide peak was assigned integration value 1 representing 1 Carbon atom to get corresponding integration value for carbon atom of acid. In this manner polymer composition was calculated using ^{13} C NMR spectrum.

From these values, AA / MAA content of copolymers could be calculated. Results of copolymer compositions and monomer contents of these copolymers are tabulated in **Table no.6.5 to 6.8**. It could be observed from these tables that monomer incorporation in the copolymers decreased depending on molecular weight of lactide macromer used in the composition.

Synthesis of copolymer or incorporation of AA / MAA in copolymer was confirmed by FTIR spectroscopy. Macromer showed characteristic -OH peak at 3500 cm^{-1}, peak at 1750 cm^{-1} for C=O (carbonyl stretching) of ester and 1640 cm^{-1} for unsaturation

6.4.3.2 FTIR Spectroscopy

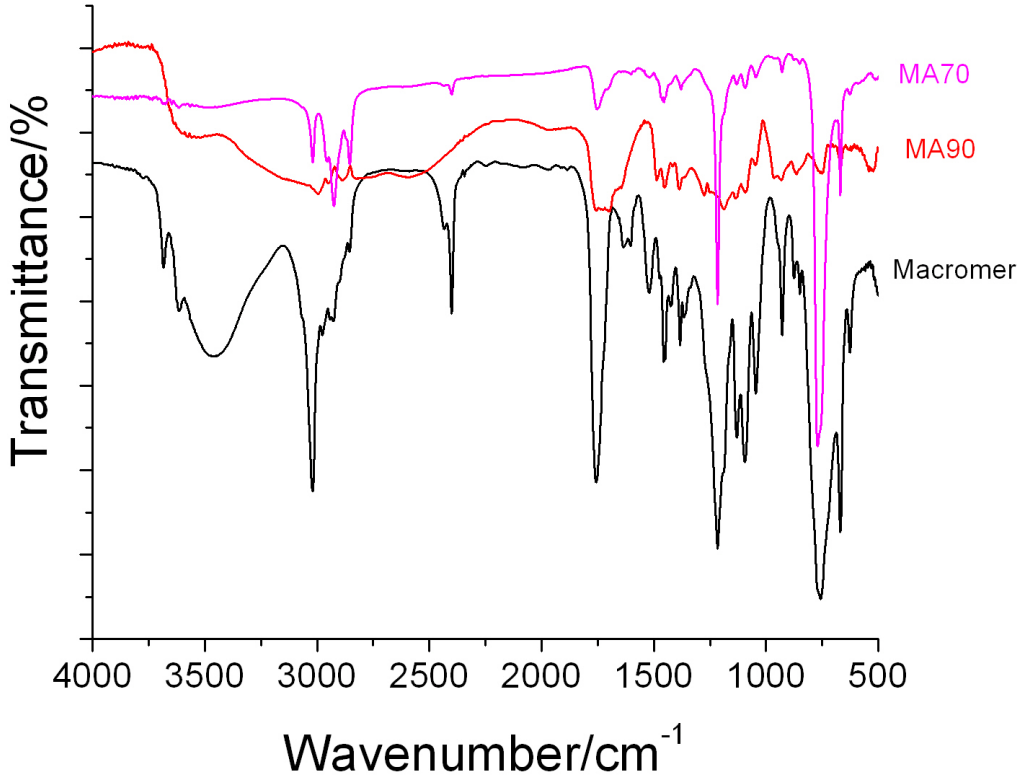


Figure 6.6

IR Spectra of Lactide Copolymer in the Range 4000-500 cm^{-1}

(present in the macromer) as shown in **Figure 6.6**. In the copolymers, apart from –OH and ester carbonyl stretching, there is an additional band at 1730 cm^{-1}, which is attributed to the carbonyl stretching of methacrylic acid. From above figure it is observed that peak at 1640-1680 for unsaturation (C=C) as seen in spectrum of macromer disappeared in rest of the spectra of copolymers.

The presence of -OH peak and absence of double bond peak (1680 cm^{-1}) clearly indicated that the copolymerization reaction occurred through the vinylic double bond and –OH group did not take part in the copolymerization.

Figure also showed the absence of acid carbonyl stretching at 1730 cm^{-1} in the macromer. It is readily seen from the figure that intensity of acid carbonyl stretching peak at 1730 cm^{-1} gradually increased with increasing MAA content in copolymer compositions. Similar study was carried out in the literature for evaluation of methyl methacrylate –MAA copolymers by FTIR method (Rufino, 2003).

6.4.3.3 Vapor Pressure Osmometry (VPO)

Lactide-AA / MAA copolymers were characterized for molecular weight and results are tabulated in **Table 6.5 to 6.8**.

It could be readily seen from **Table 6.5 and 6.7** that as AA content of the copolymers increased, molecular weight of the copolymers increased. In all cases, the copolymers synthesized from macromer of 1200 molecular weight could develop copolymers with fairly high molecular weights as compared to copolymers with 500 and 800 macromer.

It was observed from **Table 6.6 and 6.8** that MAA containing copolymers could develop higher molecular weight as compared to AA containing copolymers. Molecular weights of the copolymers were dependent on molecular weight lactide macromer used in the copolymer.

6.4.3.4 DSC Analysis

Lactide copolymers were characterized for T_g values and results were tabulated in **Table 6.4**. Thermal properties of the copolymers are representatives of their suitability for pharmaceutical processing. Polymers with fairly high T_g values are useful as excipients in dosage formulations.

It was clearly observed from the table that lactide- MAA copolymers showed T_g values in the range 18 to 150^0C depending on MAA content of the copolymers. T_g of copolymers decreased in with MAA content of the copolymer. Copolymers synthesized from lactide macromer of higher molecular weight possessed higher T_g values even at lower MAA content.

Table 6.4 T_g Values of Lactide –MAA Copolymers

Copolymer	AA/ MAA content % w/w	T_g (^{0}C)
LAc (710)-MAA	12	141.63
LAc (710)-MAA	10	80.47
LAc (710)-MAA	6	36.12
LMAc (870)-MAA	27	146.73
LMAc (870)-MAA	17	36.30
LMAc (870)-MAA	07	18.84
LMAc (1200)-MAA	04	32.99

LAc (710) –Lactide acrylate of molecular weight 710

LMAc (870) – Lactide methacrylate of molecular weight 870

6.4.3.5 Dissolution Study of Lactide –AA/MAA Copolymers

Lactide-AA/MAA copolymers were evaluated for dissolution pattern using buffers of pH 1.2, 5.8, 6.8 and 7.4. It was observed that these copolymers did not dissolve at pH 1.2 and 5.8. But the copolymers dissolved above pH 6, hence dissolution study was carried out with respect to time at pH 6.8 and 7.4.

Observations were recorded in table 6.5 to 6.8. Dissolution pattern of these copolymers was dependent on molecular weight of lactide macromer and copolymer, monomer composition and pH of dissolution medium. Polymers

dissolved faster in pH 7.4 as compared to pH 6.8 which is because of greater ionization effect at pH 7.4 as compared to pH 6.8.

Table 6.5 and 6.6 show dissolution data of copolymers based on lactide acrylate macromer copolymerized with AA or MAA. Copolymers synthesized from moderate to higher molecular weight lactide macromer (710, 837 and 1260) took more time for complete dissolution in both buffers as compared to copolymers with low molecular weight lactide macromer (555 and 625). Dissolution time was also dependent on molecular weight of copolymer in case of compositions containing lactide macromer 555 or 625. In these compositions even when AA or MAA content was high, polymers took more time for dissolution due to higher molecular weight of the polymer. For the remaining polymers in the series dissolution time was dependent on acidic monomer content of the copolymers. Due to hydrophilic nature of AA and MAA, the copolymers having higher content of acidic monomer dissolved faster as compared to copolymers with lower content of acidic monomer. Copolymers having very low acidic monomer content didn't dissolve at all in either of the buffers.

Tables 6.7 and 6.8 show dissolution pattern of lactide methacrylate copolymers at pH 6.8 and 7.4. It was observed that the copolymers with low acid content and composed of low molecular weight lactide macromer did not dissolve in any alkaline buffer. As the molecular weight of lactide macromer further increased, content of acidic monomer decreased accordingly which affected dissolution time. Still, lactide methacrylate-acrylic acid combination of **Table 6.7** dissolved in alkaline buffer at very low acidic content (0.3 % w/w), which is noteworthy.

All these lactide-AA / MAA copolymers dissolved in alkaline buffers over varying time periods. These copolymers were pH sensitive and low molecular weight.

Table 6.5 Dissolution Behaviors of Polymers in Buffers

Composition –LAc: acrylic acid

Molecular weight of lactide acrylate	**AA content % w/w of the copolymer**	**Copolymer Mol. Wt**	**Dissolution time in buffers (min)**	
			pH 6.8	**pH 7.4**
555	63	4176	140	90
555	34	2088	90	60
555	19	1116	--	120
555	14	1041	--	--
555	06	1028	--	--
837	18	2850	120	90
837	12	1744	150	120
837	17	1972	270	240
837	16	1926	345	330
837	11	1690	1440 (partly)	1440 (partly)
837	10	1521	--	--
1260	0.17	9175	--	--
1260	0.16	7942	--	--
1260	0.0576	3080	--	--
1260	0.0536	2957	--	--
1260	0.0512	2940	--	--

--- indicates the copolymer does not dissolve in given pH buffer

Table 6.6 Dissolution Behavior of Polymers in Buffers

Composition – LAc: methacrylic acid

Molecular weight of lactide Acrylate	**MAA content % w/w of the copolymer**	**Copolymer Mol. Wt**	**Dissolution time in buffers (min)**	
			pH 6.8	**pH 7.4**
625	9	12378	120	60
625	5.3	7644	50	75
625	4.8	4520	70	50
520	7	1765	60	30
625	4	3182	------	65
520	6	1440	150	75
625	4	2168	-------	70
625	6	2052	-------	90
520	5	1139	-------	------
710	12	6249	75	60
710	10	6083	70	80
710	6	5419	95	90
1260	2.1	10678	240	180
1260	1.28	7231	---	240 (partly)
1260	0.98	5100	---	---
1260	0.92	2070	---	---
1260	0.98	1987	-----	---

Table 6.7 Dissolution Behavior of Polymers in Buffers

Composition – LMAc: acrylic acid

Molecular weight of lactide methacrylate	**AA content % w/w of the copolymer**	**Copolymer Mol. Wt**	**Dissolution time in buffers (min)**	
			pH 6.8	**pH 7.4**
581	39	5935	50	85
581	19	3783	180	60
581	09	2341	--	95
581	04	2186	--	--
870	22	6357	60	50
870	20	6077	75	60
870	18	4734	90	80
870	13	3250	360 (partly)	95
870	05	3172	---	210
1270	0.299	9482	300	250
1270	0.176	7672	--	310
1270	0.0287	4354	--	--
1270	0.0869	3283	--	--
1270	0.044	3194	--	--

Table 6.8 Dissolution Behavior of Polymers in Buffers

Composition – LMAc: methacrylic acid

Molecular weight of lactide methacrylate	**MAA content % w/w of the copolymer**	**Copolymer Mol. Wt.**	**Dissolution time in buffers (min)**	
			pH 6.8	pH 7.4
581	46	7496	95	50
581	30	6140	180	180
581	09	3965	300	180
581	04	3127	330	300
870	27	7125	135	60
870	17	6804	150	90
870	19	4117	360	80
870	07	2780	--	180
870	03	2635	--	210
1270	1.78	9137	210	120
1270	1.57	6279	250	180
1270	0.59	4170	--	----
1270	0.28	3972	--	--
1270	0.21	3876	--	--

6.4.3.5 SEM of Lactide-AA / MAA Microspheres

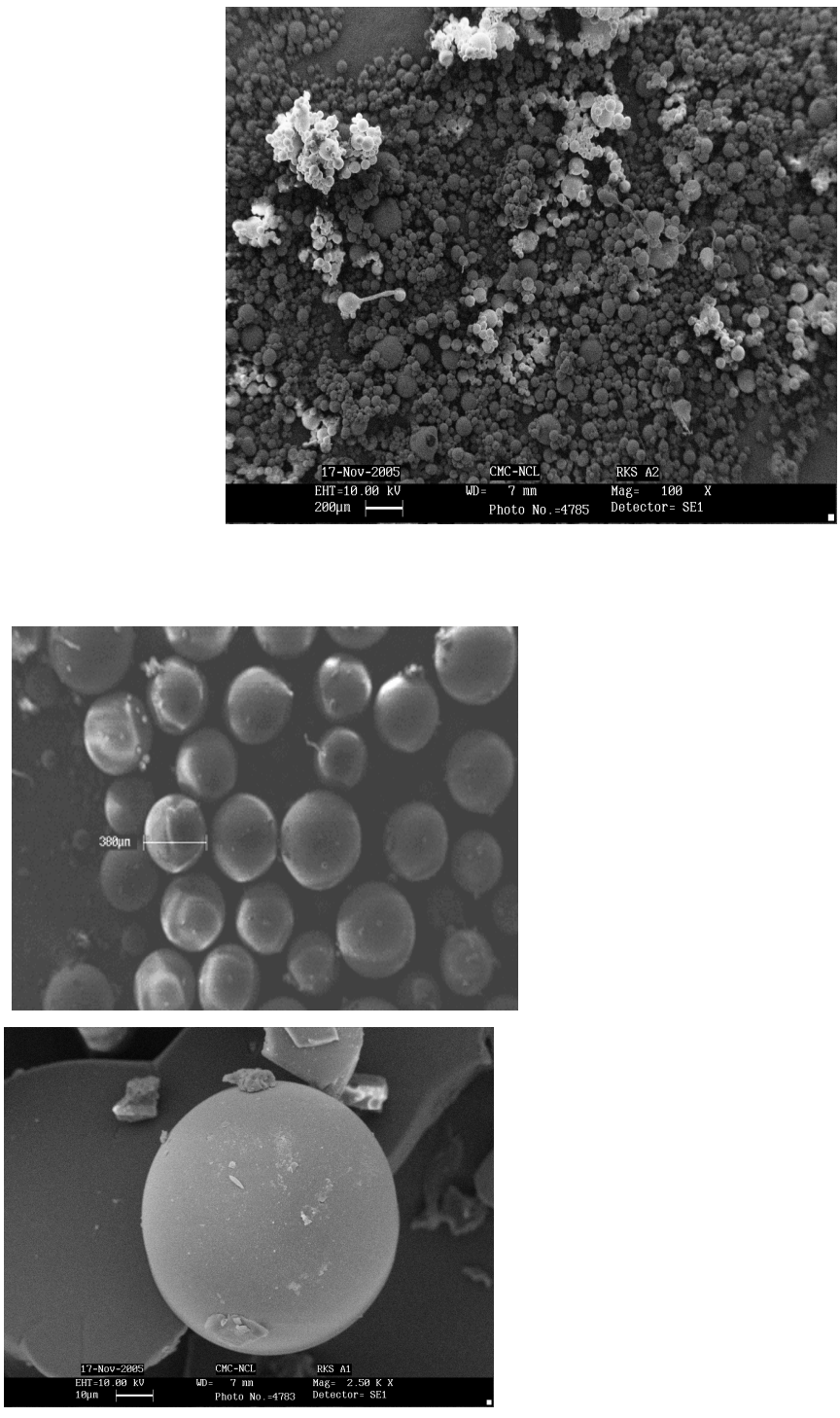


Figure 6.7 Microspheres of Lactide –MAA Containing DS

Lactide –AA/MAA copolymers were used for encapsulation of drugs and evaluated by SEM for surface morphology. The microspheres were spherical in shape and non porous in nature. The particle size was found to be in range of 150 to 400 microns by electron microscopy.

6.4.4 Drug Release

Drug release from lactide-AA / MAA microspheres was studied in acidic medium for first two hours and then in alkaline medium for 4 to 5 hours. Microspheres exhibited minimum (3 to 4 %) drug release in acidic medium. Drug release in alkaline medium was found to be dependent on composition of copolymer used for encapsulation of drug. Two types of release pattern in alkaline medium were observed as recorded in **Table 6.10, 6.12, 6.14, 6.16, 6.18 and 6.20**. It was clearly seen from these tables that depending on composition drug was released either immediately within 60 minutes or slowly over extended time period of 3 to 4 hours . About 70 to 80 % Diclofenac sodium or Celecoxib was released slowly over a period of 4 to 5 hours from microspheres in alkaline medium.

Lactide-AA / MAA copolymers exhibiting specific dissolution profiles were selected for microsphere synthesis to achieve desirable drug release patterns. Conclusion could be drawn that polymer dissolution and drug release data were correlated which was very clear from all observations in tabular form.

Lactide copolymers exhibited varied dissolution profiles depending on their composition. This phenomenon was used for exploring use of these lactide polymers for delayed and extended release of encapsulated drug in intestine. Mechanism of drug release from lactide microspheres was dissolution of polymer in alkaline medium, which took place over varying time period, ranging from 30 minutes to 1440 minutes, depending on acidic monomer content of the polymer.

These pH sensitive copolymers could be used for delayed or extended release of drug in intestine. Choice of the copolymers for microsphere synthesis will depend on type and condition of disease to be treated by using such delivery system in patients

Table 6.9 DS Release in Simulated Gastric Fluid *

Time(min)	% Release
15	1.2
30	1.8
60	2.5
90	2.9
120	3.2

*Polymer composition- oligo (lactide) acrylate: methacrylic acid,

(Polymer: Drug 2:1) (MAA content 10% w/w),

Mol. wt. of copolymer: 6083

Table 6.10 DS Release in Simulated Intestinal Fluid

Time (min)	% Release
15	78.13
30	84.37
60	93.71

Table 6.11 DS Release in Simulated Gastric Fluid *

Time (min)	% Release
15	0.8
30	1.4
60	1.8
90	2.3
120	2.7

* Polymer composition- oligo (lactide) methacrylate: methacrylic acid

(Polymer: Drug ratio 1:1) (MAA content –10% w/w),

Mol. wt. of polymer - 7125

Table 6.12 DS Release in Simulated Intestinal Fluid

Time (min)	% Release
15	84.27
30	88.12
60	91.35
90	95.80

Table 6.13 DS Release in Simulated Gastric Fluid*

Time(min)	% Release
15	0.62
30	0.80
60	1.14
90	1.86
120	2.05

* Polymer composition- oligo (lactide) acrylate: methacrylic acid,
(Polymer: Drug ratio 2:1) (MAA content –2% w/w),
Polymer mol.wt. 10678

Table 6.14 DS Release in Simulated Intestinal Fluid

Time(min)	% Release
15	10.62
30	21.30
60	37.19
90	52.04
120	67.95
180	75.29
240	80.18

Table 6.15 DS Release in Simulated Gastric Fluid*

Time(min)	% Release
15	1.31
30	1.70
60	2.15
90	2.45
120	2.80

*Polymer composition- oligo (lactide) methacrylate: methacrylic acid,

(Polymer: Drug 2:1) (MAA content 1.5% w/w),

Polymer mol.wt. - 9137

Table 6.16 DS Release in Simulated Intestinal Fluid

Time(min)	% Release
15	22.46
30	38.92
60	51.07
90	59.22
120	67.18
180	72.05
240	77.24

Table 6.17 Celecoxib Release in Simulated Gastric Fluid*

Time(min)	% Release
15	1.27
30	2.41
60	2.85
90	3.47
120	4.09

* Polymer composition- oligo (lactide) acrylate: methacrylic acid,

(Polymer: Drug ratio 2:1) (MAA content –7% w/w),

Polymer mol.wt. 1765

Table 6.18 Celecoxib Release in Simulated Intestinal Fluid

Time(min)	% Release
15	76.26
30	85.90
60	91.14
90	96.85

Table 6.19 Celecoxib Release in Simulated Gastric Fluid *

Time (min)	% Release
15	0.72
30	0.90
60	1.25
90	1.93
120	2.18

* Polymer composition- oligo (lactide) methacrylate: methacrylic acid,

(Polymer: Drug 1:1) (MAA content 2% w/w),

Polymer mol. wt. – 6279

Table 6.20 Celecoxib Release in Simulated Intestinal Fluid

Time(min)	% Release
15	18.35
30	22.58
60	31.09
90	45.72
120	59.29
180	67.10
240	71.26

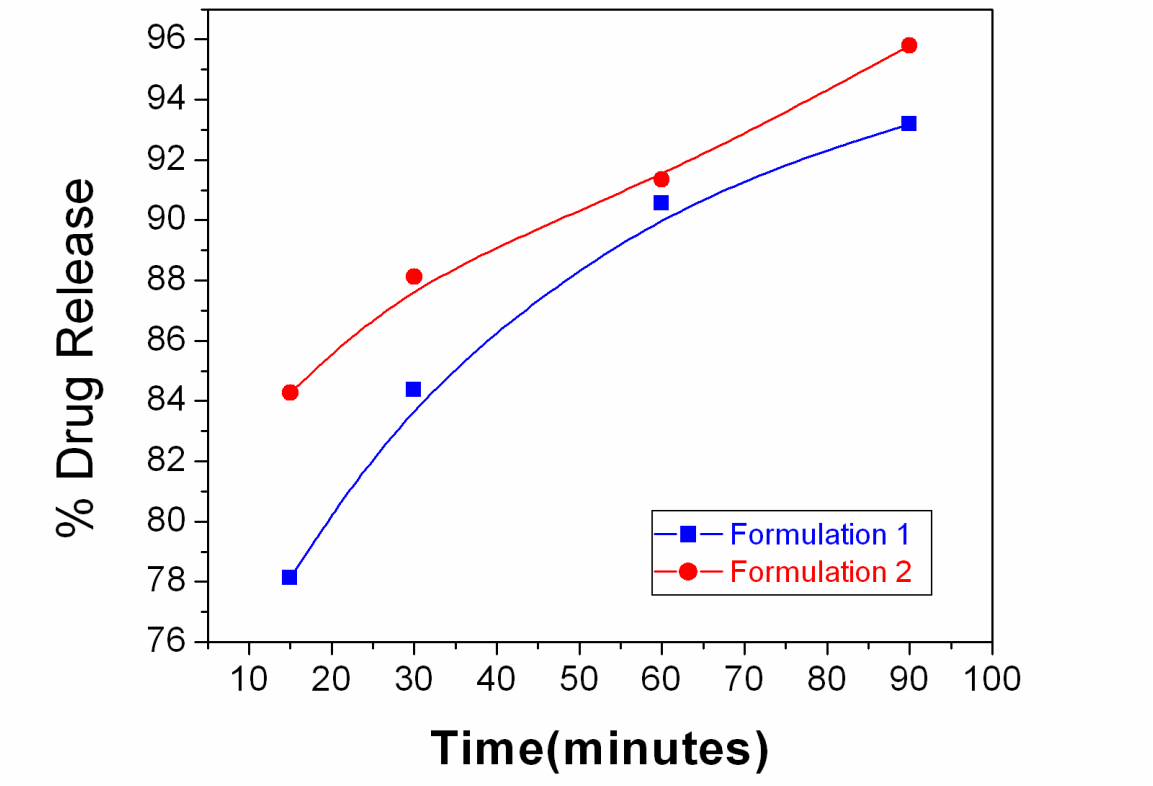


Figure 6.8 Delayed Release Pattern from Lactide –MAA Microspheres

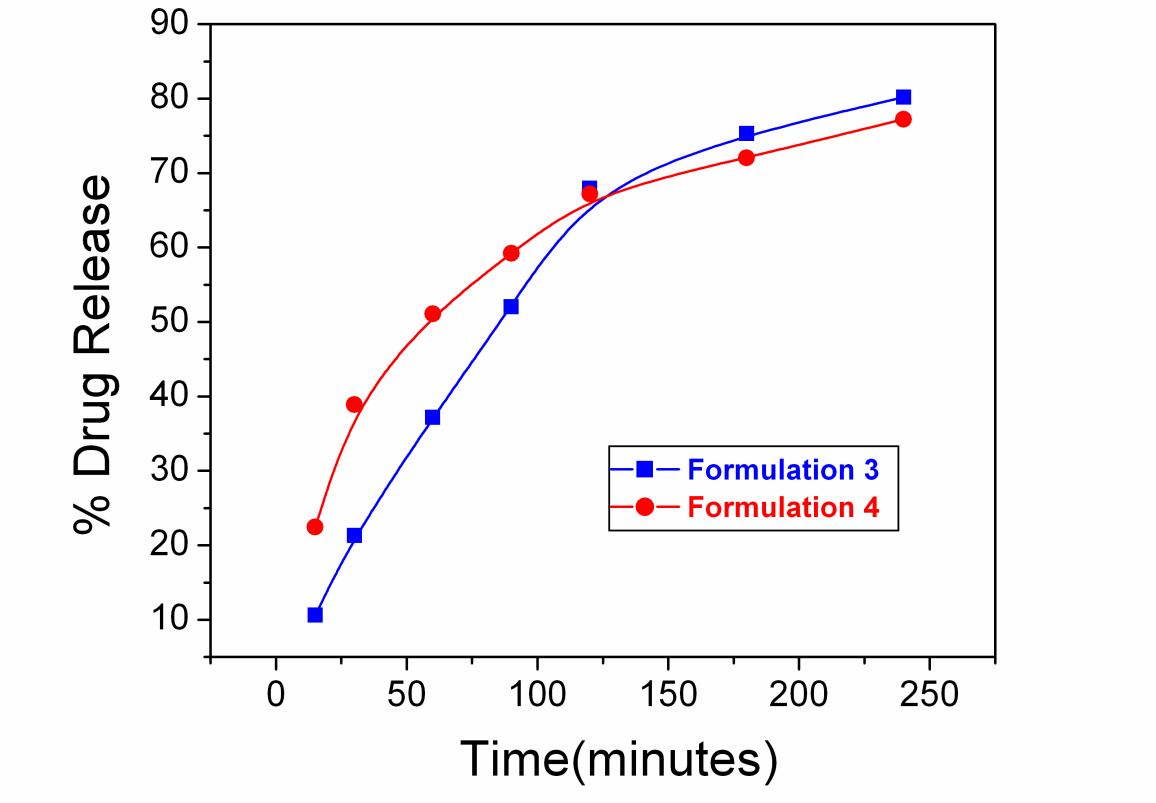


Figure 6.9 Extended Release Pattern from Lactide –MAA Microspheres

Figures 6.8 and 6.9 show the release profile of Diclofenac from Lactide-AA / MAA copolymer at T= 37^0C and pH 6.8. It could be readily observed that as the MAA content of the copolymer system used for encapsulation of the drug increased, the cumulative % release of Diclofenac sodium increased as a function of time. This increase in drug release could be attributed to the hydrophilicity of MAA. This study clearly indicated that the cumulative drug release was affected by changing the hydrophilicity of the system.

When drug was encapsulated in lactide-MAA system in the form of microspheres, it was released either immediately or slowly through the polymer matrix by dissolution mechanism. This type of drug release in intestine is refered to as delayed or extended release.

Delayed drug release is especially useful to treat acute disease conditions and extended drug release is desirable in disease conditions like rheumatoid arthritis or osteoarthritis.

Encapsulation of NSAIDs like Diclofenac sodium and Celecoxib is important for minimizing exposure of drug in acidic environment of stomach and preventing subsequent side effects. Negligible amount of drug was released in stomach through this formulation. Further same family of polymer yielded different release profiles when the compostion was varied. This is advantageous. Drug release profiles can be manipulated by using same polymer of variable composition to benefit variety of disease conditions and minimize side effects.

6.5 Conclusions

Lactide – AA / MAA copolymers were synthesized and characterized for molecular weight, monomer content and dissolution profile. These copolymers exhibited novel dissolution profile. Polymers were soluble only above pH 6 over variable time period ranging from 30 to 1440 minutes. Dissolution of the polymers was dependent on composition and acidic monomer content. The polymers had good surface coating property and this was used for drug delivery applications by encapsulating drugs in polymer microspheres.

Drugs from NSAID category were selected for this application and drug release from microspheres was investigated in acidic and alkaline medium. It was observed that negligible amount of drug was released at acidic pH of stomach. In alkaline medium, drugs were released either immediately or slowly over extended time of 4 to 5 hours depending on composition of microspheres. About 75 to 80 % drug was released at intestinal pH in 4 hours of release study. These formulations could be explored for delayed or extended release in intestine. Mechanism of drug release from lactide –AA / MAA microspheres might be dissolution of polymer matrix.

Delayed or extended release of drug from microspheres was dependent on acid content and molecular weight of the copolymer used in the formulation. These

formulations could be explored to treat acute conditions like pain associated with osteoarthritis or chronic conditions like rheumatoid arthritis using NSAID drugs.

In summary, characterization and evaluation of lactide-AA / MAA copolymers highlights following points:

1. We synthesized pH sensitive lactide polymers by copolymerizing lactide macromer with acrylic acid and methacrylic acid. These copolymers were evaluated in the form of microspheres for drug release profiles.
2. Lactide-AA/MAA copolymers dissolved only above pH 6 and remained insoluble below pH 6. Dissolution time varied from 30 to 1440 minutes depending on composition of the copolymer.
3. Incorporation of acidic monomer in the copolymer was dependent on the molecular weight of lactide macromer. It was observed that as molecular weight of lactide macromer increased, incorporation of acidic monomer (AA/MAA) decreased in the copolymer.
4. FTIR characterization of lactide copolymers revealed that copolymerization took place through unsaturation of lactide macromer with vinylic unsaturation of the acidic monomer. Hydroxyl end of macromer remained free during this reaction.
5. Dissolution pattern of lactide copolymers was influenced by the monomer composition and molecular weight of the polymer. Copolymers containing higher amount of acidic monomer dissolved faster as compared to copolymers containing lower acid content. This could be attributed to hydrophilicity of AA or MAA, which enhanced dissolution of copolymers.
6. Drug release pattern from lactide copolymers was based on copolymer composition used in microspheres. Drug was released either immediately or over extended time period. Such type of formulation would be useful for delayed or extended intestinal delivery of NSAID drug to treat acute or chronic conditions related to osteoarthritis or rheumatoid arthritis.
7. Side effects like gastric irritation of NSAIDs would be minimized using such formulations, as negligible quantitiy of drug was released in gastric region.

8. Delayed and extended drug delivery systems could be formulated by using same type of lactide polymer, just by changing the composition, which was reported for first time by us in this work.

9. pH sensitive, low molecular weight lactide copolymers synthesized in this work having very low acid content could be used as pharmaceutical coating excipient to deliver drugs in intestine at two different rates as per disease status.

6.6 References

Anderson J. M. , Shive M.S. Advanced Drug Delivery Reviews **1997**, *28(1),* 5

Chiu H.C., Wu A.T., Lin Y.F. Polymer **2001**, *42*, 1471

Dashevsky A., Kolter K., Bodmeier R. European Journal of Pharmaceutics and Biopharmaceutics **2004**, *58(1)*, 45-49

El-Sherif D. M., El-Mansoury J. A. **2003**, U.S. Patent Application 20030143280

Gil E. S., Hudson S. M. Prog. Polym. Sci., **2004**, *29*, 1173

Huang Y., Kim J. **2003,** U.S. Patent Application 20030232088

Hirsh U. S. **2006**, Patent Application 20060024366

Kang S.I., Bae Y.H. Macromolecules **2001**, *34*, 8173

Kang, M.S.; Choi, Y-J.; Moon, S-H. J. Membr. Sci. **2002**, *207*, 157

Kawakami, et al U.S Patent Application 20050214368

Ketchalsky A. Spitnik P. J. Polymer Sci. **1947**, *2*, 432

Lo C., Lin K., Hsiue G. Journal of Controlled Release, **2005**, *104(3)*, 477

Lowman A. M., Morishita M., Kajita M., Nagai T., Peppas N. A. Journal of Pharmaceutical Sciences **1999**, *88(9)*, 933-937

Matthias S., Sebastian V., Yves L., Ingo W. Biomolecular Engineering **2002**, *19*, 295

McCormick, C. L.; Elliott, D. L. Macromolecules **1986**, *19*, 542.

Morishita M., Lowman A. M., Takayama K., Nagai T., Peppas N. A. Journal of Controlled Release **2002**, *81(1-2)*, 25-32.

Park, Jung-Ki; Cho, Kuk Young; Kim, Chang-Hyeon U.S. Patent 6221977

Peppas, N. A.; Wright, S. L. Eur. J.Pharmaceutics and Biophamarmaceutics **1998**, *46*, 15.

Philippova O.E., Hourdet D., Audebert R. and. Khokhlov A.R, Macromolecules **1997**, *30*, 8278.

Rogers V., Dor P. J., Fix, Joseph A.; Kojima, Hiroyuki; Sako, Kazuhiro. PCT Int. Appl. **2003**, WO 2003041656.

Rufino E. S. and. Monteiro E. E. C Polymer, **2003,** *44 (23)* , 7189.

Shafer U. S. **2004,**Patent Application 20040062778

CHAPTER 7

Swellable Lactide Copolymers for Oral Drug Delivery

7.1 Introduction

Hydrogels are three dimensional network systems, which swell but do not dissolve in water (Hoffman, 2002). In the polymeric network hydrophilic groups are present which are hydrated in an aqueous environment. The crosslinks need to be present to avoid dissolution of the hydrophilic polymer chains into the aqueous phase. In physically crosslinked systems (Mathur, 1998), hydrophobic groups can act as pseudo crosslinks and decrease solubility of hydrophilic component in water. Such hydrophobically modified water soluble systems (Tanaka, 1992) swell but do not dissolve in aqueous medium.

Recent years have witnessed significant advances made in controlled drug delivery technology using polymeric hydrogels (Hoffman, 2002). Stimuli responsive polymeric hydrogels, which swell or shrink in response to changes in the environmental conditions (Jeong, 2002), have been extensively studied and used as smart materials for various biomedical applications (Gupta, 2002). These polymeric hydrogels are being prepared from a limited number of synthetic polymers and their derivatives such as copolymers of methacrylic acid, acrylamide and N-isopropylacrylamide (Ito, 1997; Yakohata, 1986; Chung, 1994). The design of new biodegradable and biocompatible stimuli-sensitive polymeric systems plays a key role in the development of biomaterials useful for many applications.

N-vinyl pyrrolidone (NVP) is a nonionic, hydrophilic and biocompatible monomer, which results in poly vinyl pyrrolidone homopolymer after polymerisation. Poly (N-vinyl-2-pyrrolidone) (PVP) (Chauhan, 2005) has a high binding affinity for water and several other small and large molecules. NVP is used in many applications like in the production of polyvinyl pyrrolidone (PVP) polymers and copolymers, for pharmaceuticals, wound healing agents, bioadhesives, washing additives, food additives, cosmetics, and paint dispersions (Kao, 1997; Shantha, 2000; Ameye, 2002). N-vinyl pyrrolidone has gelling tendency and high water affinity. It is biocompatible and used in different applications like plasma expander and in drug delivery systems (Joseph, 1999; Raghunath, 1985; Aykara, 2005; Eguiburu, 1996). Various applications of NVP copolymers are summarized in **Table 7.1**.

Because of hydrophilic nature, NVP yields water-soluble polymers (Erout,1996) after copolymerization with other monomers like 3 dimethyl amino propyl methacrylate (DMAPMA) useful in personal care products (Liu, 2002). Block polymers of NVP with other monomers like D, L-lactide (Benahmed, 2001) and hydroxy propyl methacrylamide exhibit amphiphilic nature. These amphiphilic systems containing hydrophobic and hydrophilic segments behave as micelles useful for loading poorly water- soluble drugs.

Table 7.1 NVP Copolymers in Various Applications

Copolymer	Application	Reference
NVP-NVS	Water soluble polymers	Liu, 2002
NVP-DMA & NVP-TMA	Fim formation	Touchal1, 2004
NVP-PEG-Chitosan	Oral drug delivery	Shantha, 2000
NVP-AA	Hydrogel drug carrier	Joseph, 1999
NVP-DMAEMA-IA	Drug delivery	Aykara, 2005
NVP- Lactide	Micellar drug loading	Benahmed, 2001
NVP- Lactide HPMC macromer	Graft copolymer synthesis	Erout, 1996

NVP hydrogels developed so far for drug delivery have been based on crosslinked systems. Formulation of drug delivery systems based on these poses problems since these materials are insoluble in organic solvents while they swell in aqueous media. Recently a lot of studies concerning the application of stimuli responsive hydrogels as novel drug delivery systems have been carried out. By using their ability to swell or collapse in response to external factors such as pH, temperature, ionic strength, electrical field, or chemical compounds, the release of the drugs in a specific site or at a fixed rate can be controlled (Gil, 2004; Peppas, 1999).

In this work graft polymers of lactide were synthesized by reacting lactide macromer with NVP by free radical polymerization. These copolymers were characterized by NMR, IR and VPO, for monomer composition, structural elucidation and molecular weight respectively. These copolymers do not dissolve in water, but swell to different extents. Swelling ratio in different buffers was determined and polymers were used to encapsulate Diclofenac sodium, which is one of the drugs from NSAID category. Polymer in the form of microspheres was evaluated for drug release in simulated gastric and intestinal fluid. Lactide-NVP copolymers were found to be suitable for extended release of Diclofenac sodium in intestine over 5 hours.

7.2 Experimental

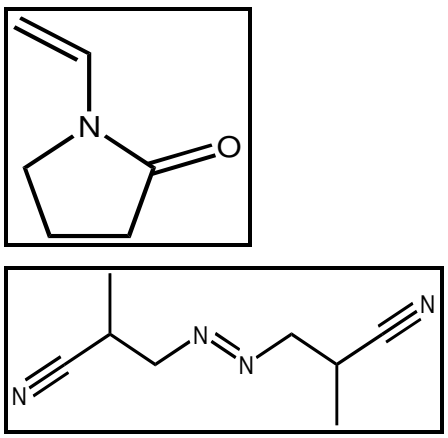
7.2.1 Materials

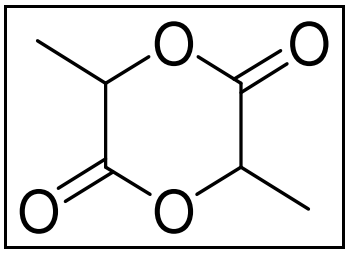
L-lactide (3S-cis-3,6-Dimethyl-1,4-dioxane-2,5-dione 98%) , 1,4 butanediol ,N-vinyl pyrrolidone (1-Vinyl 2-Pyrrolidone), iron acetate (99.995 %), acrylic acid and methacrylic acid were procured from Aldrich Chemicals, USA and used without further purification.

Azo bis Iso Butyronitrile (AIBN) was purchased from Sas chemicals Company, Mumbai

Benzoyl chloride was obtained from Qualigens Chemicals, Mumbai and Hydroquinone from Merck Limited, India. Solvents like Tetrahydrofuran and N, N dimethyl formamide were procured from S, D fine chemicals, India.

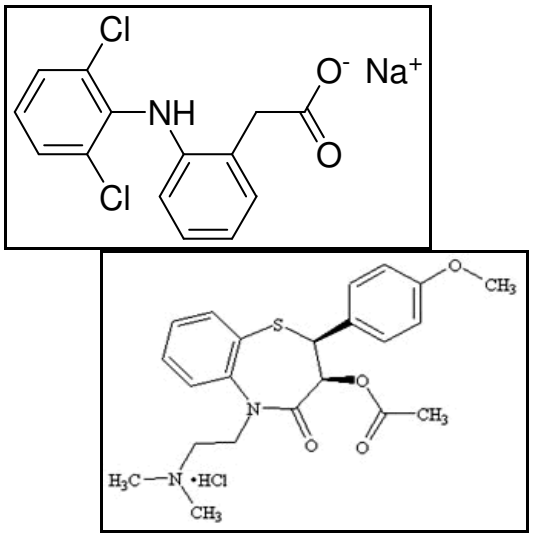
The drugs Diclofenac Sodium DS (2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt),Diltiazem hydrochloride Dilti. HCL(1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-,mono hydrochloride, (+)-cis) and Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl] benzene sulfonamide were obtained from Lupin Labs, India, Pune.



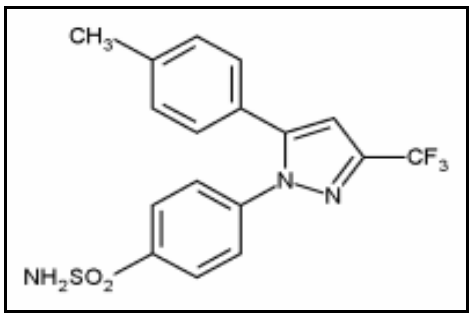


NVP L-lactide AIBN

Figure 7.1 Chemical Structures of Monomers and Initiator



Diclofenac sodium **Diltiazem hydrochloride**



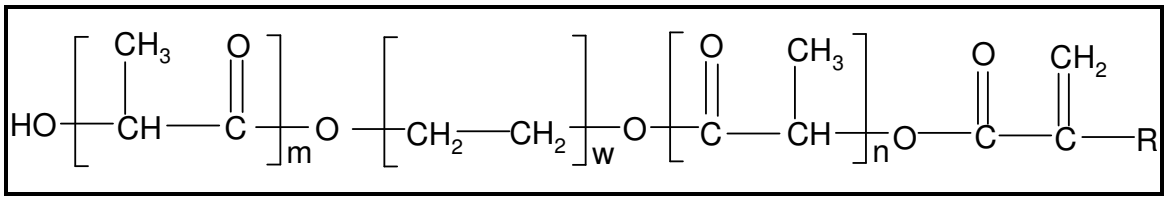
Celecoxib

Figure 7.2 Chemical Structures of Drugs

7.2.2 Synthesis of Lactide-NVP Copolymers

7.2.2.1 Synthesis of Lactide Macromer

Lactide macromer (lactide acrylate and lactide methacrylate) (Schnabelrauch, 2002) was synthesized as per procedure described in chapter 3.



w = 2 and R = H or CH_3

Figure 7.3 Structure of Lactide Macromer

7.2.2.2 Synthesis of Lactide-NVP Copolymers

Copolymers of lactide macromer with NVP were synthesized by free radical polymerization. Lactide macromers of molecular weight range 500, 800 and 1200 were chosen for copolymerization. Lactide acrylate or lactide methacrylate macromer (monomer M1) and N-vinyl pyrrolidone (monomer M2) were dissolved in DMF and 2 mole % AIBN was added. This reaction mixture was purged with nitrogen for 10 minutes and the test tube was sealed with Teflon. The reaction was carried out at 65 ^{0}C for 24 hours. Then the reaction mixture was concentrated under reduced pressure using rotavapour. The concentrated mixture was precipitated in diethyl ether. Polymer was then dried under vacuum to recover the product.

Lactide macromer and NVP were copolymerized in different mole ratios from 10:90 to 80:20. Two types of copolymers were formed from these polymerizations.

a. Lactide acrylate-NVP

b. Lactide methacrylate-NVP

Polymer composition is presented in **Table 7.2 and Table 7.3.**

Table 7.2 Lactide Acrylate -NVP Copolymerization

polymer	M1 mol. wt.	M1:M2 In Feed (moles)	M1 In feed mol x 10^{-3}	M2 In feed mol x10^{-2}	Initiator mol x10^{-4}
LAc:NVP	**561**	**10:90**	**1.78**	**1.60**	**3.55**
LAc:NVP	**561**	**20:80**	**1.78**	**0.71**	**1.78**
LAc:NVP	**561**	**30:70**	**1.78**	**0.41**	**1.18**
LAc:NVP	**561**	**40:60**	**1.78**	**0.26**	**0.89**
LAc:NVP	**561**	**50:50**	**1.78**	**0.17**	**0.71**
LAc:NVP	**561**	**60:40**	**1.78**	**0.11**	**0.59**
LAc:NVP	**855**	**10:90**	**1.16**	**1.05**	**2.33**
LAc:NVP	**855**	**20:80**	**1.16**	**0.47**	**1.16**
LAc:NVP	**855**	**30:70**	**1.16**	**0.27**	**0.77**
LAc:NVP	**855**	**40:60**	**1.16**	**0.18**	**0.58**
LAc:NVP	**855**	**50:50**	**1.16**	**0.16**	**0.46**
LAc:NVP	**855**	**60:40**	**1.16**	**0.08**	**0.38**
LAc:NVP	**1281**	**10:90**	**0.78**	**0.72**	**1.56**
LAc:NVP	**1281**	**20:80**	**0.78**	**0.31**	**0.78**
LAc:NVP	**1281**	**30:70**	**0.78**	**0.18**	**0.52**
LAc:NVP	**1281**	**40:60**	**0.78**	**0.11**	**0.39**
LAc:NVP	**1281**	**50:50**	**0.78**	**0.08**	**0.31**
LAc:NVP	**1281**	**60:40**	**0.78**	**0.05**	**0.26**

LAc = Lactide acrylate macromer (M1)

NVP = N-vinyl pyrrolidone (M2)

LAc: NVP = copolymer of macromer and NVP

Table 7.3 Lactide Methacrylate –NVP Copolymerization

Polymer	M1 mol. wt.	M1:M2 In Feed (moles)	M1 In feed mol x 10^{-3}	M2 In feed mol x10^{-2}	Initiator mol x10^{-4}
LMc:NVP	574	10:90	1.74	1.56	3.48
LMc:NVP	574	20:80	1.74	0.69	1.74
LMc:NVP	574	30:70	1.74	0.40	1.15
LMc:NVP	574	40:60	1.74	0.26	0.87
LMc:NVP	574	50:50	1.74	0.17	0.69
LMc:NVP	574	60:40	1.74	0.11	0.58
LMc:NVP	574	70:30	1.74	0.07	0.49
LMc:NVP	574	80:20	1.74	0.04	0.43
LMc:NVP	870	10:90	1.11	1.03	2.28
LMc:NVP	870	20:80	1.11	0.46	1.14
LMc:NVP	870	30:70	1.11	0.26	0.07
LMc:NVP	870	40:60	1.11	0.17	0.06
LMc:NVP	870	50:50	1.11	0.11	0.05
LMc:NVP	870	60:40	1.11	0.08	0.04
LMc:NVP	1294	10:90	0.78	0.69	1.54
LMc:NVP	1294	20:80	0.78	0.30	0.77
LMc:NVP	1294	30:70	0.78	0.18	0.51
LMc:NVP	1294	40:60	0.78	0.11	0.38
LMc:NVP	1294	50:50	0.78	0.08	0.30
LMc:NVP	1294	60:40	0.67	0.04	0.22
LMc:NVP	1294	70:30	0.67	0.02	0.19

LMc = Lactide methacrylate macromer (M1)

NVP = N-vinyl pyrrolidone (M2)

LMc: NVP = copolymer of lactide macromer and NVP

7.2.3 Encapsulation of Drugs in Lactide-NVP Microspheres

Microspheres of lactide-NVP polymers were prepared using emulsification solvent evaporation technique. The lactide polymer was dissolved along with the drug in an organic solvent (methanol and dichloromethane in the ratio 1:1). This organic phase was then added dropwise to light liquid paraffin under constant mechanical stirring rate of 800 rpm at room temperature for 3-4 hours. The solvent was allowed to evaporate and chilled n-hexane or petroleum ether was added to this system and stirring was continued for another hour. The microspheres so obtained were separated by filtration, washed by pet ether or Hexane and dried under vacuum for up to 24 hours. These microspheres were stored in a well-closed container under vacuum.

Three drugs were encapsulated in lactide-NVP microspheres using the method described above.

7.3 Characterization

7.3.1 NMR Spectroscopy

NMR spectra of NVP copolymers were recorded on Bruker DRX –500 spectrometer operating at a proton and carbon frequency of 500.13 and 125.4 MHz respectively using $CDCl_3$ as a solvent.

7.3.2 FTIR Spectroscopy

For FT-IR analysis, 5 % (w/v) copolymer solution in chloroform (Spectroscopic grade) was deposited on KBR pellet. Fourier transform infrared analysis was carried out using a Shimadzu's FT-IR-8300 spectrometer at resolution of 4 cm^{-1}.

7.3.3 Vapour Pressure Osmometry

Molecular weight of lactide-NVP copolymers was determined using Knauer Vapor Pressure Osmometer K-7000. Stock solution of copolymer (10 mg/ml) was prepared in Chloroform (Spectroscopy grade) and successive dilutions of polymer in this solvent were analyzed at selected constant temperature (37^0C). Benzil was used as standard for calibration of instrument. Molecular mass of a sample can be determined with a known concentration of the substance using calibration value.

7.3.4 Swelling Study

Swelling study of lactide-NVP copolymers was performed in buffers of pH range 1.2 to 7.4. The swelling ratio of the polymers at varying pH was found by exposing dry polymer to buffer solutions. About 5 mg of polymer was put in 5 ml buffer of pH 1.2, 5.8, 6.8 and 7.4. After fixed time intervals swollen polymers were wiped gently and weighed to calculate swelling ratio.

The swelling ratio (q) of membranes was calculated using the following equation,

$$q = \frac{W_2}{W_1} \text{ X } 100 \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{ (I)}$$

Where W2 = (wt. of wet polymer – wt. of dry polymer)

W1= (wt. of dry polymer)

7.3.5 Scanning Electron Microscopy (SEM)

Surface morphology of lactide –NVP microspheres was studied using an accelerating voltage of 20kV. (Leica, UK, model-stereoscan 440)

7.3.6 Optical Microscopy

The microspheres were spread uniformly on glass slide and observed under 10 X magnification of the microscope (Leica, UK, model). Particle size of 50 particles was recorded to get idea about average particle size of microspheres.

7.3.7 Drug Loading

A known amount of microspheres was added in methanol and sonicated for few seconds. Supernatant solution was analyzed on UV spectrophotometer. The concentration of Diclofenac sodium in microspheres was determined at 254 nm to calculate loading of. In the similar way drug loadings of microspheres containing Diltiazem and Celecoxib were calculated using UV spectrophotometer at 240 and 275 nm respectively.

7.3.8 Drug Release

Study of drug release from the microparticles was first carried out in 0.1 N hydrochloric acid buffer for two hours, at 37 ± 0.5°C, using USP type II apparatus rotated at 50 rpm. Subsequently drug release was determined at 6.8 pH phosphate buffer for next four hours at 37 ± 0.5°C, under same conditions. The samples were withdrawn at fixed time intervals. The amount withdrawn each time was replaced with fresh media to maintain the sink conditions. Samples were analyzed on UV spectrophotometer at 254 nm and cumulative Diclofenac sodium release from microspheres was determined using calibration curve for the drug.

Diltiazem release from microspheres was determined by placing them in 0.1 N HCl 100 ml for 2 hours and then in 6.8 pH phosphate buffer at 37± 0.5°C, using USP type II apparatus rotated at 75 rpm. Samples were withdrawn from 6.8 pH phosphate buffer solution at 15, 30, 45 and 60, 120 and 240 min. Amount withdrawn each time was replaced with fresh media to maintain sink conditions.

Celecoxib release from microspheres was determined by placing composition consisting of celecoxib and polymer in 0.1 N HCl 100 ml for 2 hours and then in 6.8 pH phosphate buffer at 37± 0.5°C, using USP type II apparatus rotated at 100 rpm. Samples were withdrawn from 6.8 pH phosphate buffer solution at 15, 30, 45 and 60, 120 and 240 min. Amount withdrawn each time was replaced with fresh media to maintain sink conditions.

7.4 Results and Discussion

7.4.1 Free Radical Copolymerization

NVP was copolymerized with lactide macromer using DMF as solvent and AIBN as initiator to get lactide copolymer. Unsaturated acrylate or methacrylate part of lactide macromer reacted with vinyl unsaturation of NVP to give a linear polymer. Lactide chain remained as pendent part in the copolymer. This pendent lactide chain is very hydrophobic; whereas NVP is very hydrophilic in nature. All the copolymers synthesized in this work using different mole ratios of lactide macromonomer and NVP (10:90 to 80:20) were solid in nature. Yield of the copolymerization reactions was 70%. The polymers were soluble in various organic solvents, but were insoluble in water.

Reaction mechanism of copolymerization is shown schematically in **Figure 7.4**.

The copolymers had ability to coat the surface uniformly. So these can be used for microencapsulation of drugs and can be explored for possible drug delivery applications.

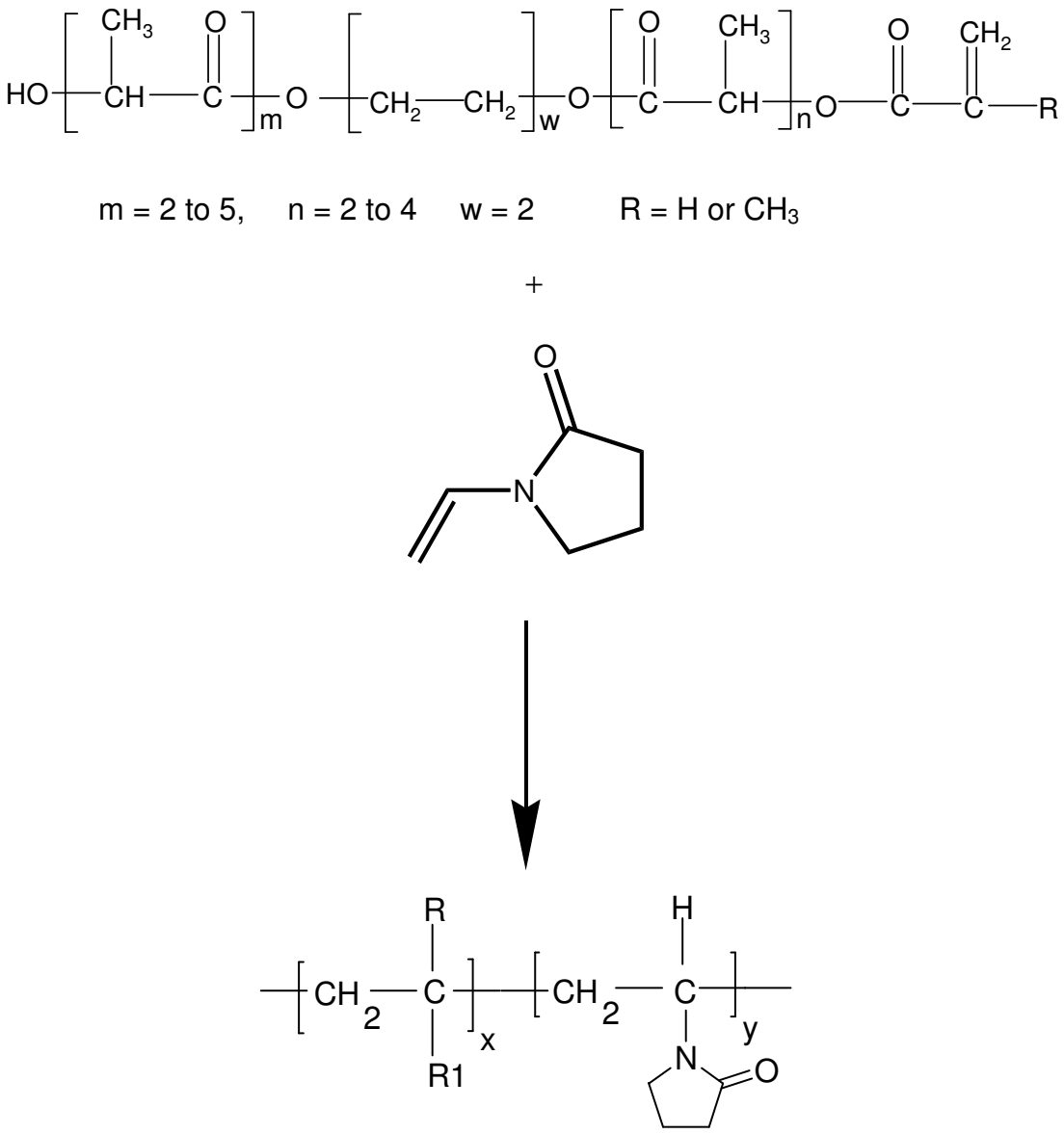


Figure 7.4 Schematic Representation of Lactide-NVP Copolymerization

7.4.2 Encapsulation of Drugs

Drugs were encapsulated in lactide microspheres by emulsion solvent evaporation method. Yield of the microencapsulation was good and drug loading was in the range of 35 to 50%. Physical properties and ease of handling of microspheres varied according to variations in polymer to drug ratios. It was observed that microspheres were easily broken when amount of polymer used was lower than the drug in formulation (1:0.5),

but these possessed good handling property when polymer : drug ratio was 4:1 to 1:1.

Method of encapsulation was chosen based on polymer properties. Emulsion water evaporation method was found to be ideal for a polymer, which swelled in water, but was soluble in organic solvents useful in this method. Light paraffin oil as continuous phase could be easily removed by washing with pet ether. Pet ether or diethyl ether is suitable nonsolvent for these polymers. Separation of microspheres in this method was easy with minimum loss of materials while washing and filtering out from system.

7.4.3 Characterization

7.4.3.1 NMR Spectroscopy

Composition of the copolymer was calculated using ^{1}H proton NMR spectroscopy. Spectra of the lactide-NVP copolymers showed characteristic peaks for lactide at 1.56 and 5.16 ppm. The peak at 1.56 ppm corresponds to 6 protons of 2 (methyl) groups; while peak at 5.16 ppm indicates 2 protons of 2 (methine) groups in the lactide chain. Various peaks representing protons in the NVP monomer were at following positions- 2.23 ppm, 2.10 ppm and 3.4 ppm for 2 protons each of (methylene) in pyrrolidone ring, 6.96 ppm, 4.26 ppm and 4.1 ppm corresponding to protons of vinyl part. Integration of lactide peak at 5.16 ppm for two protons was

correlated with 2 protons of (methylene) for NVP at 3.4 ppm and composition of the copolymer and subsequently monomer content was calculated.

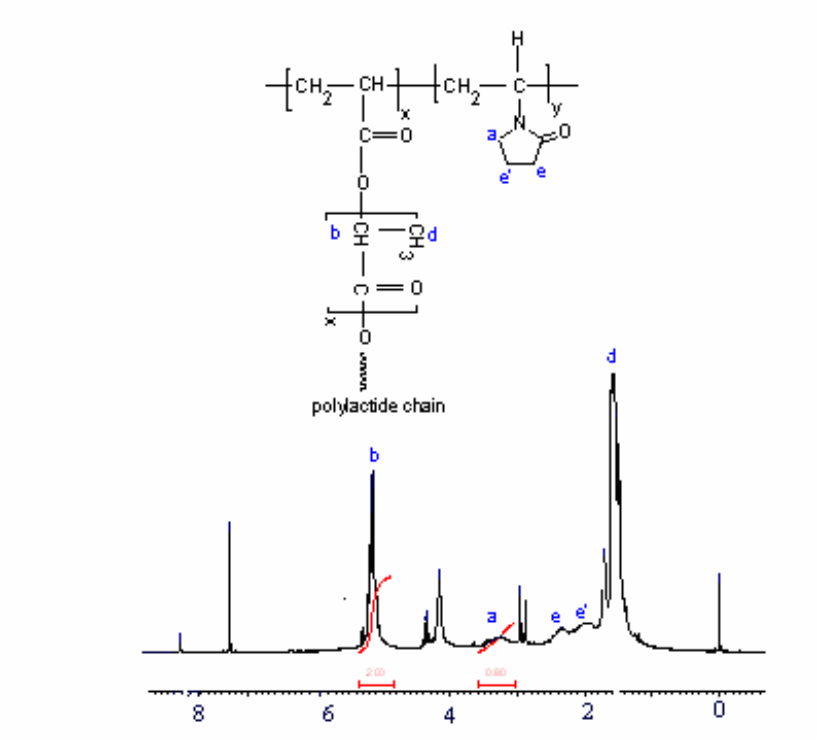


Figure 7.5 NMR Spectrum of LAc: NVP Copolymer

(30:70 composition), LAc molecular weight 1281

It was observed that in all copolymer compositions, incorporation of NVP in the product was low as compared to molar ratios of two monomers in feed. NVP is a sluggish molecule with low reactivity in the copolymerization reactions (Touchal1, 2004; Erout, 1996; Bauduin, 1996; Mahmoud, 1985). This resulted in low incorporation of NVP.

Incorporation of NVP was observed to be dependant on molecular weight of the lactide macromer. It was found that with an increasing molecular weight of lactide macromer, incorporation of NVP in the copolymer decreased.

7.4.3.2 FTIR Spectroscopy

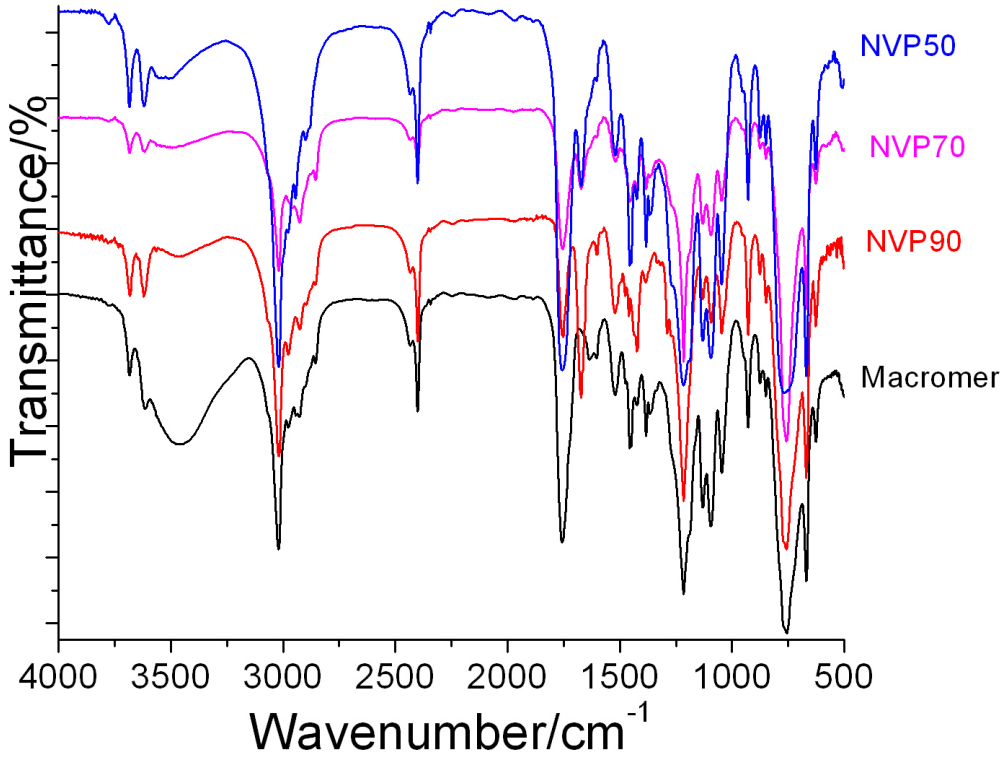


Figure 7.6

IR Spectra of Lactide Macromer and Copolymers in the Range 4000-500cm^{-1} Incorporation of NVP in copolymer was confirmed by FTIR spectroscopy technique. Macromer showed characteristic -OH peak at 3500 cm^{-1}, peak at 1750 cm^{-1} for C=O (carbonyl stretching) of ester and 1640- 1680 cm^{-1} for unsaturation (present in the macromer) as shown in **Figure 7.6**. In the copolymers, apart from –OH and ester carbonyl stretching there was an additional band at 1650 cm^{-1} which could be attributed to the carbonyl stretching of pyrrolidone ring. From above figure it was observed that peak at 1640-1680 for unsaturation (C=C) as seen in spectrum of macromer disappeared in rest of the spectra of copolymers.

The presence of -OH peak and absence of double bond peak (1680 cm^{-1}) clearly indicated that the copolymerization reaction occurred through the vinylic double bond and –OH group did not take part in the copolymerization.

Figure also showed the absence of pyrrolidone (amide) carbonyl stretching at 1650 cm^{-1} in the macromer. With an increase in NVP content of the feed, the intensity of pyrrolidone carbonyl stretching in the spectrum increased, which clearly indicated the increase in the NVP incorporation.

7.4.3.3 Vapor Pressure Osmometry (VPO)

NVP copolymers were characterized for molecular weight and results are tabulated in tables 7.4-7.9. It could be readily seen from tables that copolymers having lower NVP content were of higher molecular weight as compared to the copolymers with higher NVP content. It was observed that lactide methacrylate- NVP copolymer system could develop higher molecular weights as compared to lactide acrylate-NVP system. Highest molecular weight recorded in the table was about 13000. Molecular weights of the copolymers were dependent on lactide macromer molecular weight used in the copolymer.

7.4.3.4 Swelling Study

The copolymers only swelled but did not dissolve in water. Swelling ratio of the copolymers was studied in aqueous buffers of pH range 1.2 to 7.4 at fixed time intervals upto 6 hours. Results were tabulated in tables 7.4 to 7.9.

From tables, it was observed that the copolymers swelled to different extent depending on composition of the copolymer and pH of surrounding medium.

Lactide Acrylate- NVP System

According to **Table 7.4, 7.5 and 7.6,** the copolymers having higher NVP content swelled to greater extent in alkaline medium as compared to acidic medium. This was observed when molecular weight of lactide macromer was 500 to 800. But when lactide molecular weight increased to 1200, swelling ratio was more in alkaline medium even at low NVP content.

Lactide Methacrylate-NVP System

As seen in tables 7.7-7.9, copolymers having higher NVP content and lower molecular weight exhibited higher swelling ratio in alkaline medium as compared to acidic medium when lactide macromer weight was around 500 to 800. In case of lactide macromer molecular weight 1200, polymers having lower NVP content exhibited comparatively higher swelling ratio as compared to swelling ratio of lactide acrylate-NVP polymers.

No specific trend for swelling ratio was observed in lactide-NVP system. This could be attributed to absence of any ionic species in the copolymer. Lactide methacrylate and NVP, both are neutral by nature, and hence these copolymers are not expected to show any specific pH dependent swelling behavior.

The copolymers of specific composition exhibiting significant swelling in alkaline medium as compared to acidic medium were selected for drug encapsulation.

NVP is a hydrophilic monomer, which readily dissolves in water. However, presence of hydrophobic lactide macromer in the copolymer system prevents its dissolution in water, via hydrophobic associations. In addition to this, there may be inter-intra molecular H- bonding within the polymer system, which leads to physically crosslinked lactide hydrogel.

Table7.4 Swelling Ratio of LAc (561): NVP Copolymers

Copolymer	Buffer pH	NVP content % w/w	Polymer Mol.Wt.	Swelling Ratio % (time- hrs)			
				1	2	4	6
ANVP 90	1.2	30.19	4176	274	329	380	419
ANVP 90	5.8			120	176	210	255
ANVP 90	6.8			282	350	426	521
ANVP 90	7.4			194	239	314	365
ANVP 70	1.2	19.57	5094	129	183	211	243
ANVP 70	5.8			142	195	261	378
ANVP 70	6.8			230	258	285	391
ANVP 70	7.4			136	214	279	373
ANVP 50	1.2	16.92	6216	157	173	186	188
ANVP 50	5.8			164	182	227	265
ANVP 50	6.8			271	308	329	420
ANVP 50	7.4			116	285	360	419
ANVP 30	1.2	7.51	7327	143	205	233	316
ANVP 30	5.8			149	176	233	252
ANVP 30	6.8			222	226	342	448
ANVP 30	7.4			105	354	441	454

ANIP- Copolymer of lactide acrylate (20 moles) with N-isopropyl acrylamide (80 moles) (in feed)

Table 7.5 Swelling Ratio of LAc (855): NVP Copolymers

polymer	Buffer pH	NVP Content % w/w	Polymer Mol.Wt.	Swelling Ratio % (time- hrs)			
				1	2	4	6
ANVP 90	1.2	24.14	2059	248	344	423	604
ANVP 90	5.8			187	270	270	358
ANVP 90	6.8			224	347	347	427
ANVP 90	7.4			198	430	459	487
ANVP 80	1.2	8.93	2407	571	720	885	1040
ANVP 80	5.8			132	342	555	605
ANVP 80	6.8			250	394	425	494
ANVP 80	7.4			410	498	509	537
ANVP 70	1.2	6.01	3725	244	309	332	344
ANVP 70	5.8			245	388	466	540
ANVP 70	6.8			420	455	469	483
ANVP 70	7.4			416	467	477	600
ANVP 60	1.2	5.04	3811	157	242	580	623
ANVP 60	5.8			389	466	532	732
ANVP 60	6.8			244	356	362	379
ANVP 60	7.4			340	340	364	371
ANVP 50	1.2	4.36	3892	240	246	247	417
ANVP 50	5.8			232	280	304	409
ANVP 50	6.8			222	272	350	514
ANVP 50	7.4			208	259	326	419
ANVP 40	1.2	2.84	3917	265	635	635	770
ANVP 40	5.8			373	450	732	923
ANVP 40	6.8			235	257	286	455
ANVP 40	7.4			207	307	456	711

ANVP 90 - copolymer of lactide acrylate (10 moles) and NVP (90 moles) (in feed)

Table 7.6 Swelling Ratio of LAc (1281): NVP Copolymers

Copolymer	Buffer pH	NVP content %w/w	Polymer Mol.Wt.	Swelling Ratio % (time- hrs)			
				1	2	4	6
ANVP 90	1.2	13.36	6395	239	330	376	458
ANVP 90	5.8			223	300	319	469
ANVP 90	6.8			74	161	190	218
ANVP 90	7.4			245	278	290	433
ANVP 80	1.2	3.58	8907	85	160	280	361
ANVP 80	5.8			52	204	385	508
ANVP 80	6.8			219	371	685	778
ANVP 80	7.4			200	345	348	660
ANVP 70	1.2	3.10	9126	89	154	261	457
ANVP 70	5.8			62	179	272	469
ANVP 70	6.8			268	319	335	601
ANVP 70	7.4			211	358	473	580

Table 7.7 Swelling Ratio of LMAc (574): NVP Polymers

Copolymer	Buffer pH	NVP content % w/w	Polymer Mol.Wt.	Swelling Ratio % (time- hrs)			
				1	2	4	6
MANVP 90	1.2	38.72	2735	61	96	110	132
MANVP 90	5.8			24	57	83	104
MANVP 90	6.8			62	101	120	235
MANVP 90	7.4			193	210	278	302
MANVP 80	1.2	31.52	3862	70	73	90	168
MANVP 80	5.8			79	132	197	221
MANVP 80	6.8			109	111	199	203
MANVP 80	7.4			175	217	319	334
MANVP 70	1.2	15.68	4190	107	292	351	409
MANVP 70	5.8			225	227	251	399
MANVP 70	6.8			172	275	478	580
MANVP 70	7.4			208	211	256	284
MANVP 60	1.2	6.36	5482	43	54	140	164
MANVP 60	5.8			42	215	218	286
MANVP 60	6.8			45	46	157	243
MANVP 60	7.4			33	117	127	134
MANVP 50	1.2	5.18	6627	200	258	300	332
MANVP 50	5.8			109	160	372	538
MANVP 50	6.8			217	231	238	287
MANVP 50	7.4			340	345	505	516
MANVP 40	1.2	4.61	7013	293	310	504	530
MANVP 40	5.8			134	154	559	578
MANVP 40	6.8			317	324	465	583
MANVP 40	7.4			155	334	486	591
MANVP 30	1.2	2.10	8125	310	339	382	529
MANVP 30	5.8			100	139	269	313
MANVP 30	6.8			75	165	510	538
MANVP 30	7.4			87	176	179	271
MANVP 20	1.2	1.13	8387	354	377	384	465
MANVP 20	5.8			194	231	232	237
MANVP 20	6.8			90	103	224	241
MANVP 20	7.4			149	198	379	404

Table 7.8 Swelling Ratio of LMAc (877): NVP Copolymers

Copolymer	Buffer pH	NVP content % w/w	Polymer Mol.Wt.	Swelling Ratio % (time- hrs)			
				1	2	4	6
MANVP 90	1.2	27	2965	134	229	241	305
MANVP 90	5.8			202	216	226	246
MANVP 90	6.8			329	490	----	-----
MANVP 90	7.4			498	719	----	-----
MANVP 80	1.2	11.32	3376	165	175	216	216
MANVP 80	5.8			333	336	352	496
MANVP 80	6.8			411	444	444	483
MANVP 80	7.4			571	684	788	922
MANVP 70	1.2	5.19	4407	151	215	290	372
MANVP 70	5.8			107	110	230	242
MANVP 70	6.8			152	170	234	262
MANVP 70	7.4			301	329	394	476
MANVP 60	1.2	2.03	5791	106	129	179	228
MANVP 60	5.8			181	253	273	285
MANVP 60	6.8			199	408	567	790
MANVP 60	7.4			526	646	784	833
MANVP 50	1.2	0.952	6213	136	204	232	268
MANVP 50	5.8			135	153	207	360
MANVP 50	6.8			262	386	387	410
MANVP 50	7.4			170	178	232	303
MANVP 40	1.2	0.80	6687	65	88	112	250
MANVP 40	5.8			189	284	316	343
MANVP 40	6.8			129	145	201	227
MANVP 40	7.4			122	123	204	230

MANVP90- copolymer of lactide methacrylate (10 moles) and N-vinyl Pyrrolidone (90 moles) (in feed)

------- Denotes polymer swelled and broken down to particles making it difficult to calculate swelling ratio.

Table 7.9 Swelling Ratio of LMAc (1294): NVP Copolymers

Copolymer	Buffer pH	NVP content %w/w	Polymer Mol.Wt.	Swelling Ratio % (time- hrs)			
				1hr	2hr	4hr	6hr
MANVP90	1.2	16.8	7482	136	181	476	554
MANVP90	5.8			265	307	383	388
MANVP90	6.8			227	319	450	421
MANVP90	7.4			405	427	482	485
MANVP80	1.2	9.67	7714	532	538	554	592
MANVP80	5.8			100	282	383	388
MANVP80	6.8			117	249	421	450
MANVP80	7.4			482	485	662	719
MANVP70	1.2	7.1	8617	232	284	290	554
MANVP70	5.8			617	682	729	736
MANVP70	6.8			308	412	528	566
MANVP70	7.4			215	282	346	524
MANVP60	1.2	6.5	9290	69	309	388	755
MANVP60	5.8			182	485	515	515
MANVP60	6.8			203	221	242	359
MANVP60	7.4			205	261	464	637
MANVP50	1.2	4.62	10325	318	463	549	559
MANVP50	5.8			13	18	23	50
MANVP50	6.8			394	402	489	644
MANVP50	7.4			106	155	272	586
MANVP40	1.2	3.01	11937	305	320	330	425
MANVP40	5.8			148	169	277	464
MANVP40	6.8			245	266	394	617
MANVP40	7.4			100	130	302	715
MANVP30	1.2	2.74	12490	518	524	587	616
MANVP30	5.8			175	194	306	724
MANVP30	6.8			320	330	395	497
MANVP30	7.4			511	528	561	561

7.4.3.5 Scanning Electron Microscopy

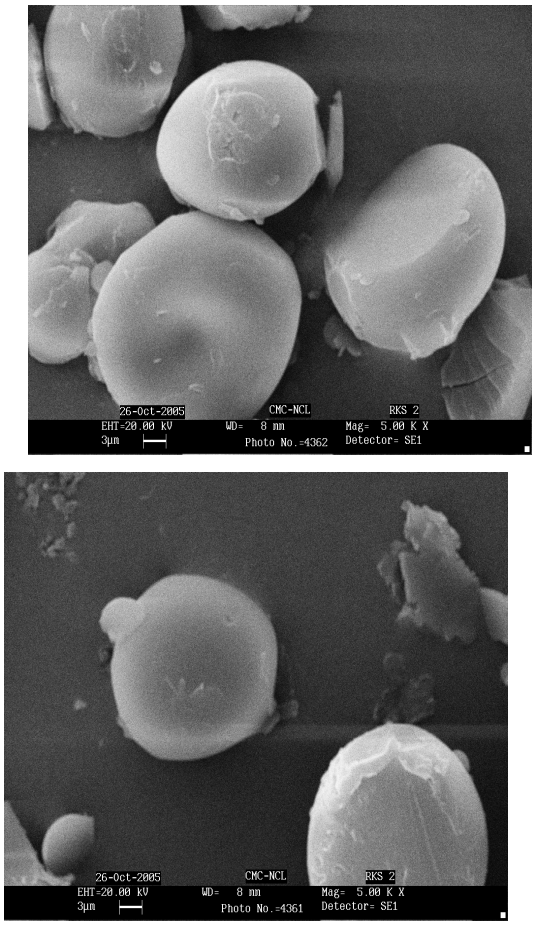


Figure 7.7 SEM of Lactide-NVP Microspheres

The surface morphology of microspheres was examined by SEM, which indicates that the NVP microspheres containing Diclofenac sodium were spherical in shape and non porous. The size of microspheres was in the range of 200 nm to 600 nm.

7.4.4 Drug Release

Drug release from lactide-NVP microspheres was studied in acidic medium for first two hours and then in alkaline medium. Microspheres exhibited minimum (5 to 6 %) drug release in acidic medium. About 80 % Diclofenac sodium was released slowly over a period of 5 hours from microspheres in alkaline medium.

Drug release from lactide-NVP microspheres was dependent on swelling ratio of the copolymer in respective medium.

NVP copolymers selected for microspheres preparation exhibited very minimum swelling in acidic medium and profuse swelling in alkaline medium.

Due to swelling nature of the copolymer, mechanism of drug release through the microsphere might be drug diffusion. Drug was released slowly over extended time period (about 5 hours) from microspheres.

Table 7.10 DS Release in Simulated Gastric Fluid*

Time(min)	% Release
15	2.2
30	2.8
60	3.5
90	4.0
120	4.8

Table 7.11 DS Release in Simulated Intestinal Fluid

Time(min)	% Release
15	10.27
30	19.13
60	25.64
90	30.44
120	41.90
180	58.25
240	68.01
300	76.29

*Polymer composition- oligo (lactide) acrylate: NVP

(Polymer: Drug 2:1) (NVP content 3.6 % w/w)

Table 7.12 DS Release in Simulated Gastric Fluid*

Time(min)	% Release
15	3.5
30	3.8
60	4.2
90	5.0
120	5.7

Table 7.13 DS Release in Simulated Intestinal Fluid

Time(min)	% Release
15	18.25
30	21.33
60	28.44
90	35.17
120	46.38
180	61.40
240	70.57
300	80.29

* Polymer composition- oligo (lactide) methacrylate: NVP

(Polymer: Drug 2:1) (NVP content 11 % w/w)

Table 7.14 Diltiazem. HCl Release in Simulated Gastric Fluid*

Time(min)	% Release
15	1.8
30	2.5
60	2.9
90	3.5
120	4.1

Table 7.15 Diltiazem. HCl Release in Simulated Intestinal Fluid

Time(min)	% Release
15	27.0
30	29.51
60	37.64
90	43.15
120	68.36
180	79.80
240	84.12
300	88.62

* Polymer composition- oligo (lactide) methacrylate: NVP

(Polymer: Drug 1:1) (NVP content 3% w/w)

Table 7.16 Diltiazem. HCl Release in Simulated Gastric Fluid*

Time(min)	% Release
15	3.7
30	4.6
60	5.2
90	6.8
120	7.4

Table 7.17 Diltiazem. HCl Release in Simulated Intestinal Fluid

Time(min)	% Release
15	32.0
30	39.22
60	47.95
90	54.17
120	70.04
180	78.29
240	86.15
300	90.58

*Polymer composition- oligo (lactide) acrylate: NVP

(Polymer: Drug 2:1) (NVP content 5% w/w)

Table 7.18 Celecoxib Release in Simulated Gastric Fluid*

Time(min)	% Release
15	1.8
30	2.5
60	3.7
90	4.0
120	5.2

Table 7.19 Celecoxib Release in Simulated Intestinal Fluid

Time(min)	% Release
15	13.82
30	20.13
60	34.65
90	49.17
120	54.90
180	65.28
240	72.01
300	84.35

*Polymer composition- oligo (lactide) methacrylate: NVP

(Polymer: Drug 1:1) (NVP content 17 % w/w)

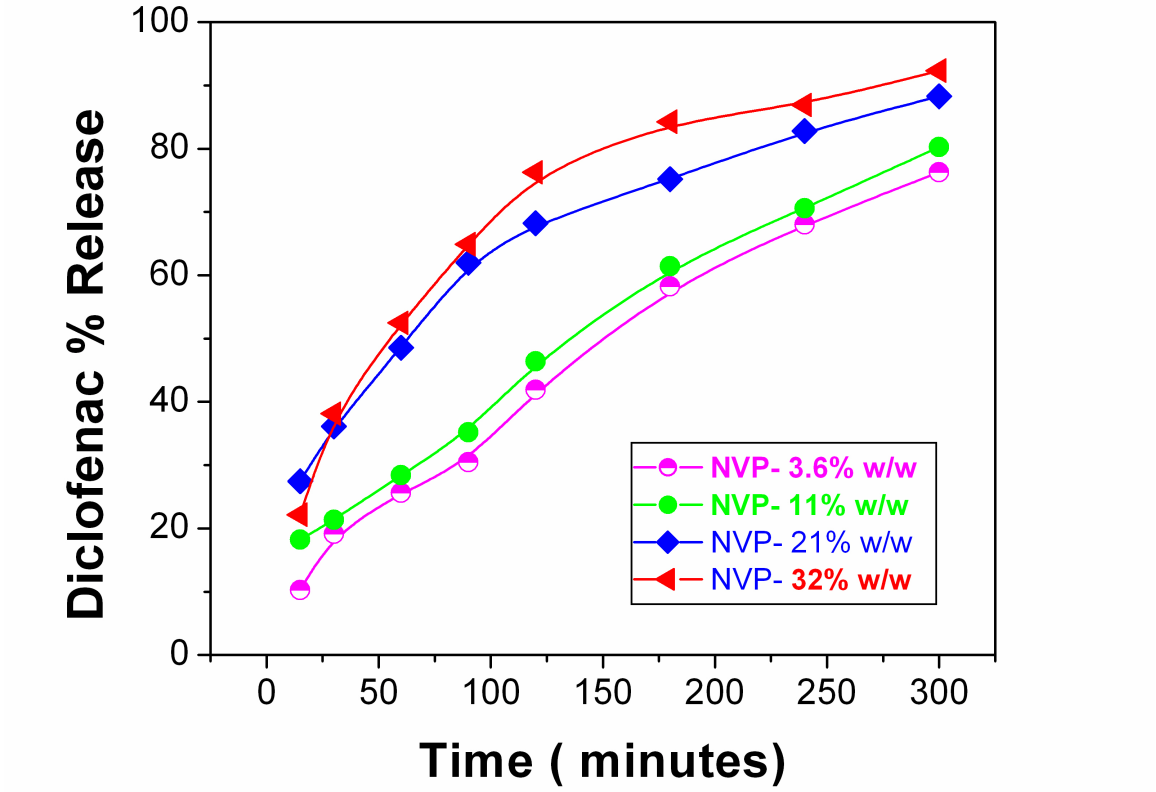


Figure 7.8 Drug Release from Lactide-NVP Microspheres

Figure 7.8 shows the release profile of Diclofenac from Lactide-NVP copolymer at T= 37^0C and pH 6.8. It would be readily observed that as the NVP content of the copolymer system used for encapsulation of the drug increased, the cumulative release of Diclofenac sodium increased as a function of time. This increase in drug release could be attributed to the hydrophilicity of NVP. This study clearly indicated that the cumulative drug release could be affected by changing the hydrophilicity of the system.

When drug was encapsulated in lactide-NVP hydrogel system in the form of microspheres, it was released slowly through the hydrogel network by diffusion mechanism. Hence pattern of drug release observed in the study was extended type.

Such type of release is especially useful in chronic disease conditions like rheumatoid arthritis or osteoarthritis for slow or extended release of drug Diclofenac sodium or celecoxib. Extended drug release of antihypertensive drug such as Diltiazem hydrochloride is useful for controlling blood pressure of hypertension patients.

Encapsulation of NSAID drugs like Diclofenac sodium and Celecoxib is important for minimizing exposure of drug in acidic environment of stomach and preventing subsequent side effects. Minimal amount of drug is released in stomach through this formulation, which is desirable.

7.5 Conclusions

Lactide –NVP copolymers were synthesized and characterized for molecular weight, monomer content and structure elucidation. Lactide copolymers modified with NVP exhibited swelling in aqueous medium; while these were soluble in organic solvents. Hence this copolymer system could be called as hydrophobically modified NVP hydrogel system. This feature of polymers was supported by swelling ratio data carried out at definite time intervals in various buffers ranging from 1.2 to 7.4. Swelling ratio of the copolymers was dependent on pH of surrounding medium and composition of the copolymer. The polymers had good surface coating property and this was used for drug delivery applications by encapsulating drugs in polymer microspheres.

Drugs from NSAID and antihypertensive categories were selected for this application and drug release from microspheres was investigated. It was observed that drugs were released at extended rate from the formulations over 5 hours. Negligible amount of drug was released at acidic pH of stomach, which was beneficial in case of NSAIDs as it to avoided side effects in gastric region. About 85 to 90 % drug was released at intestinal pH. These formulations could find applications for extended drug release in intestine. Mechanism of drug release from lactide –NVP microspheres is expected to be diffusion through the physically crosslinked matrix system, which can be explored to treat chronic conditions like

rheumatoid arthritis or osteoarthritis using NSAID drugs. Extended release of antihypertensive drug is also advisable for maintaining blood pressure of hypertension conditions.

In summary, characterization and evaluation of lactide-NVP copolymers highlight following points:

1. Lactide-NVP copolymers acted as physically crosslinked hydrogels resulting in swelling in aqueous medium. But these copolymers were soluble in organic solvents.
2. Incorporation of NVP in copolymer was comparatively low because of sluggish nature of NVP. This incorporation further reduced as molecular weight of lactide macromonomer increased in the system.
3. Swelling ratio of lactide copolymers was dependent on pH of surrounding medium and composition of the copolymer.
4. Lactide copolymers had good surface coating property and could be explored for encapsulation of drug molecules in formulation design.
5. Microspheres exhibited extended drug release (about 90%) over a period of 5 hours at pH of intestine; whereas very minimum (about 5 %) drug was released at acidic pH.
6. The extended intestinal drug release would be potentially useful for treatment of chronic diseases like arthritis and also for maintenance of blood pressure in hypertensive patients.
7. Gastric side effects of NSAID drugs like Diclofenac sodium and celecoxib can be minimized by formulating these drugs in coated form, which will release minimum amount in stomach.
8. Extended drug release from microspheres of lactide copolymers was by diffusion mechanism through physically crosslinked system of polymer.
9. Lactide-NVP hydrogels would be convenient for pharmaceutical processing as they are soluble in organic solvents unlike other hydrogel systems.

7.6 References

Ameye D., Voorespoels J., Foreman P., Jasi J., Richardson P., Garesh S. J. Cont. Rel. **2002**, *79*, 73

Aykara T. C, Ibrahim A. J Polym Sci Part B: Polym Phys. **2005**, ***43***, 2819

Bauduin G., Boutevin B., Belbachir M., Rachid M. Eur. Polym. J.**1996,** *32*, 501

Benahmed A., Ranger M., Leroux J.C. Pharmaceutical Research, **2001**, 18 ,323

Brannon-Peppas, L.; Peppas, N. A. Biomaterials **1990**, *11*, 635

Chauhan G. S., Singh B., Kumar S. Journal of Applied Polymer Science, **2005**, *98*, 373

Chung D.J., Ito Y., Imanishi Y. J. Appl. Polym. Sci. **1994**, *51*, 2027

Eguiburu J. L., Berridi M. J. F., Roman J. S. Polymer, **1996**, *37,* 3615

Erout M. N., Troesch A., Pichot C., Cros P.Bioconjugate Chem. **1996,** *7*, 568

Erout M. N., Abdelhamid E., Pichot C., Klauro M.F. Polymer **1996,** *37* , 1157

Gil, E. S.; Hudson, S. M.; Progress in Polymer Sci. **2004**, *29*, 1173

Gupta P., Vermani K., Garg S. Drug Discovery Today **2002**, *7(10)*, 569

Hoffman A. S. Advanced Drug Delivery Reviews **2002**, *43*, 3

Ito Y., Park Y. S., Imanishi Y. Macromol. Rapid Commun. **1997**, *18*, 221

Jeong B., Gutowska A. Trends in Biotechnology **2002**, *20*, 305

Joseph J., Reactive & Functional Polymers **1999**, *39*, 99

Kao F., Manivannan G., Sawan S. P. J Biomed Mater Res (Appl Biomater) **1997**, *38,* 191

Liu K.C., Anderson L.R, Hardy E. Reuven E. Y. U.S. Pat. No.5, 609,865

Mahmoud A. Al-lssa, Thomas P. Davis, Malcolm B. Huglin and Daniel C. F. Yip Polymer, **1985**, *26*, 1869

Mathur A. M., Hammonds K. F., Klier J., Scanton, A. B. J. Controlled Release **1998**, *54*, 177

Matthias S., Sebastian V., Yves L., Ingo W. Biomolecular Engineering, **2002**, *19*, 295

Raghunath K., Rao K. P., Nagarajan B., Thomas K. J. Eur. Polym. J. **1985**, *21,* 195

Shantha K.L., Harding D.R.K. International Journal of Pharmaceutics **2000,** *207*, 65

Tanaka, T. in “Polyelectrolyte Gels:Properties, Preparation and Applications”, Harland, R. S.; Prud’homme, R. K. (Edi.) **1992**, ACS Symp. Series 480, Amer. Chem. Soc., Washington, D. C. 1

Touchal1 S., Jonquie`res A., Cle´ment R., Lochon P. Polymer **2004,** *45*, 83

Yokahata, Y.; Noguchi, H.; Seki, T. Macromolecules **1986**, *19*, 493

CHAPTER 8

Conclusions and Directions for Future Work

8.1 Conclusions

We focused on synthesis, characterization and evaluation of modified lactide polymers for oral drug delivery. Although lactide polymers are biodegradable and FDA approved, these are being explored mainly for controlled drug delivery by parenteral route. This is because of highly crystalline nature of lactide polymers, which degrade at very slow rate ranging from few days to months. But these polymers can be tailored as to lower crystallinity and enhance rate of degradation so that these will be useful as excipients in oral dosage forms.

Copolymerization is one of the ways to introduce hydrophilicity and lower crystallinity in the polymer. Thus copolymerization of lactide with aspartic acid depsipeptide lowered crystallinity of polymers as was demonstrated by thermal characterization of the copolymers.

This result provided insight for modification of lactide polymer structure. Instead of direct copolymerization of lactide with other comonomers, we synthesized lactide macromer containing unsaturation at one end. This macromer was then copolymerized with acidic, basic and hydrophilic monomers. Dissolution properties of lactide copolymers were studied and delivery systems based on dissolution profile of lactide copolymers were formulated. We demonstrated that lactide copolymers were useful as coating excipients for immediate gastric delivery, as well as extended and delayed intestinal drug delivery. These excipients also masked the taste of bitter drugs like Cefuroxime axetil in immediate gastric delivery. Formulations for extended or delayed drug delivery in intestine were obtained by varying polymer composition. The drug release was governed by polymer dissolution, or drug diffusion depending on polymer composition.

The overall conclusions of this work are summarized below.

1. Lactide homopolymers and copolymers containing aspartic acid depsipeptide were synthesized using iron catalysts and were thermally characterized to check the effect of lactide modification on lowering crystallinity of the polymers. Highly crystalline lactide polymers could be converted to amorphous form by copolymerization. Lactide macromer containing a reactive unsaturated end was

synthesized from lactide diol using iron catalyst. It was observed that molecular weight and T_g of the lactide diol decreased in direct proportion to the amount of 1, 4 butanediol in the reaction. Lactide diol turned from solid to semisolid state as amount of 1, 4 butanediol increased. Lactide macromer synthesized by the condensation of lactide diol (molecular weight 500, 800 and 1200) varied in consistency from liquid, semisolid to solid because of variations in molecular weight. Lactide acrylate or lactide methacrylate synthesized in this way had one hydroxyl end and another reactive unsaturated end, which was confirmed by FTIR and NMR analysis. Low molecular weight lactide macromer could be further used for copolymerization with acidic, basic and hydrophilic monomers to achieve desirable dissolution profiles, which could be explored for oral drug delivery.

2. Lactide macromer was copolymerized with the basic monomer, 4 vinyl pyridine (VP) by free radical copolymerization. The lactide-VP copolymers having VP content more than 1 % w/w were pH sensitive and soluble only in acidic pH below 3. The copolymers were characterized by VPO, NMR and FTIR, for molecular weight, polymer composition and structure elucidation. The dissolution profile data showed that the copolymers containing more than 20 % w/w VP, only swelled in acidic medium, but didn't dissolve. The copolymers containing less than 20 % w/w VP dissolved readily in 5 to 30 minutes in acidic buffer. Thus these polymers can be called reverse enteric polymers. Dissolution time was dependent on VP content and molecular weight of the copolymers. Incorporation of VP in lactide copolymers was governed by the molecular weight of lactide macromer. Monomer incorporation in copolymers containing high molecular weight (1200) macromer was very low as compared to copolymer containing low molecular weight (500) macromer. It was confirmed by reactivity ratio determination using Kelen Tudos and Finmann Ross method that reactivity ratio of VP was very low as compared to that of the lactide macromer.

Cefuroxime axetil was encapsulated in Lactide-VP microspheres and drug release was evaluated. About 96 % drug was released in 60 minutes. These microspheres could be reconstituted using syrup base, adequate flavor and viscosity building excipient. This formulation masked the bitter taste of Cefuroxime axetil and

released the same immediately at the gastric pH. This would be useful as dry syrup for pediatric patients who can not swallow solid dosage forms.

3. Lactide-DMAEMA copolymers were synthesized using lactide macromer and DMAEMA. These copolymers exhibited novel dissolution profile at DMAEMA content more than 12 % w/w. Lactide-DMAEMA copolymers dissolved over entire pH range 1.2 to 7.4. Incorporation of DMAEMA decreased as the molecular weight of lactide macromer increased in the copolymer. Hence copolymers containing higher molecular weight lactide macromer (more than 2000) were found insoluble in all buffers due to very low incorporation of DMAEMA. Copolymers with higher DMAEMA content dissolved faster in all aqueous buffers as compared to copolymers with lower DMAEMA content. This dissolution profile could be attributed to hydrophilicity of DMAEMA monomer.

Lactide copolymers were also found to be compatible with cefuroxime axetil. With this important observation, it was decided to use these polymers in cefuroxime formulation. Matrix tablet were formulated in which copolymer and drug were adsorbed on inert carrier and punched by direct compression method. This tablet was coated by ladling method, using lactide –VP copolymer.

Use of lactide-VP copolymers in this tablet formulation served two purposes- a) taste masking of bitter drug cefuroxime axetil and b) to avoid leaching of bitter drug at salivary pH and to release it only in stomach. Lactide –DMAEMA polymers were compatible with polymer. Drug release experiment exhibited about 95 % drug release in 60 minutes; whereas negligible amount of drug was leached from the tablet at salivary pH, which proved efficiency of lactide-VP coating in the formulation.

Novelty of this work lies in the tailored dissolution profile of the polymers designed and synthesized as well as the formulations developed. Two types of lactide copolymers were used in combination to formulate taste masked matrix tablet containing cefuroxime axetil. Lactide- DMAEMA and lactide-VP copolymers were explored for two different purposes. This resulted in a stable, taste masked cefuroxime axetil tablet containing DMAEMA as one of the component. This is

significant since the polymer containing DMAEMA, Eudragit E is known to degrade Cefuroxime axetil.

4. Lactide macromer was copolymerized with acidic monomers like acrylic acid and methacrylic acid by free radical copolymerization. These copolymers were evaluated for composition, molecular weight and dissolution profile. The copolymers dissolved only at pH greater than 6. Moreover, these copolymers dissolved over extended time periods ranging from 30 minutes to 1440 minutes in buffers of pH above 6. Incorporation of monomers in the copolymers was governed by the molecular weight of the lactide macromer. Dissolution time was dependent on composition and molecular weight of the copolymer. Copolymers containing higher amount of acidic monomer dissolved faster as compared to copolymers containing lower acidic monomer content. This could be attributed to hydrophilicity of AA or MAA.

Microspheres were formulated using the polymers which exhibited requisite dissolution profiles. Drugs from NSAID category like diclofenac sodium were encapsulated in these copolymers. Drug release in simulated intestinal fluid was either delayed or extended and appears to be controlled by the dissolution of polymer matrix.

Novelty of this work lies in the synthesis of pH sensitive lactide polymers and drug release pattern achieved. Thus we synthesized and evaluated lactide polymer acting as novel enteric coating excipient useful for oral drug delivery. This enteric coating exhibited either delayed or extended release as compared to commonly used enteric coatings, which dissolve rapidly above pH 5- 5.5 and release the drug almost instantaneously.

5. We copolymerized lactide macromer with NVP. These copolymers swelled, but did not dissolve in any buffer. Swelling ratio of the copolymers varied depending on NVP content and pH of buffer. These copolymers were soluble in organic solvents like chloroform, acetone, methanol and dimethyl formamide. Thus lactide-NVP copolymers acted as physically crosslinked hydrogels resulting in swelling in aqueous medium. Incorporation of NVP in copolymer was comparatively low because of sluggish polymerization of NVP. The incorporation

further decreased as molecular weight of lactide macromonomer increased. We formulated microspheres containing these copolymers and encapsulated drugs from NSAID category. Microspheres exhibited extended drug release (about 90%) over a period of 5 hours at pH of intestine; whereas only about 5 % drug was released at acidic pH. Such type of extended drug release would be useful for treatment of chronic disease conditions like rheumatoid arthritis.

6. Novelty of this work lies in synthesis of swellable lactide polymers. This type of swelling lactide polymer has been not yet reported in the literature. These copolymers are well suited for pharmaceutical processing, as they are soluble in organic solvents. The copolymers act as physically crosslinked hydrogels due to hydrophobic-hydrophilic balance. Thus we could synthesize lactide-based excipient useful for protection of stomach lining from NSAID drugs. Unlike conventional enteric coating excipients available in the market, these copolymers release drug over extended time period at intestinal pH.

8.2 Directions for the Future Work

This work could be further extended as follows:

1. We copolymerized lactide macromer with acidic, basic and hydrophilic monomers and characterized these copolymer, which exhibited novel dissolution profiles depending on type of comonomer and monomer content in the copolymer. It will be useful to evaluate reactivity ratios in these systems, which will provide insight about microstructure of copolymer system.

2. We studied pH sensitive lactide –VP copolymers and evaluated microspheres for taste masking and immediate gastric delivery of cefuroxime axetil. Copolymers containing higher proportion of VP only swell, but do not dissolve in acidic pH like other lactide-VP compositions with lower VP content. Swelling lactide-VP copolymers can be evaluated to deliver the drug at slow rate by designing gastroretentive dosage forms. This formulation can include other

pharmaceutical excipients to achieve desirable swelling ratio and mucoadhesiveness useful for successful dosage form design.

3. The lactide- DMAEMA copolymers dissolve over entire pH range from 1.2 to 7.4. We explored these copolymers for immediate gastric delivery of cefuroxime axetil as polymers were compatible with drug. Further it would be interesting to use these polymers as an alkalizing agent in core along with drug as a substitute to commonly used alkaline hydroxides. The copolymers can be used as stabilizing agents in the formulation core to protect acid labile drugs like antacids.

4. In the present work, Lactide-AA / MAA copolymers were evaluated for delayed and extended intestinal drug delivery depending on dissolution behavior of the copolymers. Lactide-NVP copolymers were also explored for intestinal drug delivery, which resulted in extended drug release pattern. Potential of these lactide-AA/MAA copolymers for delivery of other acid sensitive molecules like peptide drugs can be further investigated. Experiments can be also designed to study drug release over extended time period to encapsulate acid sensitive drugs. It would be also interesting to investigate mechanism underlying drug release from lactide hydrogels by varying NVP contents in the copolymer system.

5. Novel pH sensitive lactide copolymers and hydrogels synthesized in this work dissolve at specific pH depending on type of monomer used in the copolymer system. Lactide-VP and lactide-DMAEMA copolymers were used for gastric delivery of the drugs, whereas lactide-AA/MAA and lactide-NVP copolymers were used for intestinal drug delivery. By appropriate combination of drugs and excipients, composite dosage forms can be developed, which will release more than one drug at different sites along the length of the GI tract depending on pH conditions prevalent at the specific site. pH sensitive lactide polymers can thus be explored for site specific delivery of drugs from multidrug formulation.