Synthesis and Evaluation of Polymers for Novel Drug Delivery Systems

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Submitted By

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Statement by the candidate

As required by the University Ordinance 770, I wish to state that the work embodied in this thesis titled **"Synthesis and Evaluation of Polymers for Novel Drug Delivery Systems"** forms my own contribution to the research work carried out under the guidance of **Dr. Mohan G. Kulkarni,** at the National Chemical Laboratory, Pune. This work has not been submitted for any other degree of this or any other University. Whenever references have been made to previous works of others, it has been clearly indicated as such and included in the Bibliography.

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Dedicated to my parents

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Abbreviations

ACP	Acetaminophen
AIBN	Azobisisobutyronitrile
BMA	n-butyl methacrylate
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CIP	Ciprofloxacin hydrochloride
DLT	Diltiazem hydrochloride
DMF	Dimethyl formamide
DSC	Differential scanning calorimeter / y
FTIR	Fourier transform infrared spectroscopy
GGA	Gas generating agent / y
GRS	Gastroretentive system / s
GRT	Gastric retention time
h	hour / s
HCl	Hydrochloric acid
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methylcellulose
MAA	Methacrylic acid
min.	Minutes
MMA	Methyl methacrylate
mol.	Molecular
M_n	Number average molecular weight
M_w	Weight average molecular weight
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
NCE	New chemical entity
NDDS	Novel drug delivery system / s
NMR	Nuclear magnetic resonance spectroscopy
NREP	New reverse enteric polymer
OFN	Ofloxacin

PEG	Poly (ethylene glycol)
PEO	Poly (ethylene oxide)
PLAMAMA	Poly (methacrylic acid-g-lactide methacrylate)
PVP	Poly (vinyl pyrrolidone)
SEM	Scanning electron microscope / y
S No.	Serial number
TEA	Triethylamine
T_g	Glass transition temperature / s
THF	Tetrahydrofuran
THP	Theophylline
USFDA	United states food and drug administration
USP	United states pharmacopeia
UV	Ultraviolet
VER	Verapamil hydrochloride
VP	4-Vinylpyridine
Wt	Weight

Chapter 1

Literature review

1.1 Importance of novel drug delivery systems

The number of new drugs approved by USFDA has declined from 53 to just 21 per year from 1996 to 2010 (Hughes, 2008 and Thayer 2011) and the cost of new drug development has risen from $800 Mn to $2 Bn (Adams and Brantner, 2006). To mitigate the escalating costs and risks of new drug development, the pharmaceutical companies focus on life cycle management of existing drugs to maximize the value addition from R&D investments. The approaches to life cycle management of drugs include chemical modification, pharmacokinetic modification, improved bioavailability, increased API purity and development of less invasive routes of administration (Fleming and Ma, 2002).

The objective of formulation scientist is to improve the drug safety and efficacy of drugs. Novel drug delivery systems (NDDS) are formulated to enhance bioavailability and pharmacokinetic modification of existing products. NDDS development takes relatively shorter time and involves lower cost as compared to the development of NCE. To increase the safety and efficacy profile of drugs, one or more NDDS are developed. These include sustained release, delayed release, pulsatile release, orally disintegrating systems and gastroretentive systems. Diltiazem hydrochloride is one of the best examples of using NDDS as a strategy for extending the product life cycle and enhancing profitability. The NCE patent expired in 1986 and the product life cycle of Diltiazem hydrochloride (DLT) was extended by introduction of products such as Cardizem® CD, Tiazac® and Cardizem® LA which were based on different NDDS. Cardizem® was prescribed thrice a day for treatment of hypertension and generated $ 260 Mn in 1988. Hoechst and Elan introduced Cardizem® SR, an extended release formulation for twice a day version in 1989 and revenues peaked to $ 400 Mn and continued till 1991. Biovail introduced once a day version, Cardizem CD which further raised the revenues to $ 900 Mn by 1996 (Baichwal and Deborah, 2001).

Polymers play an important role in controlling the drug release from drug delivery systems. The first sustained release capsule for dextro-amphetamine sulphate (Dexedrine) (GSK website, history of company) was introduced in the market by Smithkline and French in 1952. It was formulated by coating a drug onto nonpareil sugar beads and further coated with glyceryl stearate and wax. After Dexedrine, several sustained release systems have been developed. This helped patients to

reduce multiple dosing to once a day dosing with better absorption and safety profiles. Alza Corp. developed osmotic systems to achieve zero order release.

1.2 Importance of oral drug delivery systems

Despite phenomenal advancements in the inhalable, injectable, transdermal, nasal and other routes of administration, the oral drug delivery remains well ahead among these delivery routes. If oral route is viable option, most companies choose oral route and if it is not immediately viable option, the pharmaceutical companies often invest resources in making it viable. Oral products represent the largest segment of the drug delivery market and are expected to see considerable growth especially for sustained release dosage forms and oral forms of injectable drugs (figure 1.1). Oral drug delivery is presently valued at $49 Bn and is expected to reach $92 Bn by 2016 with growth rate of 11.3 %. The growth in the oral drug delivery market is primarily driven by newer technologies enabling sustained release formulations of oral drugs and oral formulations of injectable only drugs (Global business Intelligence report, Nov 2010).

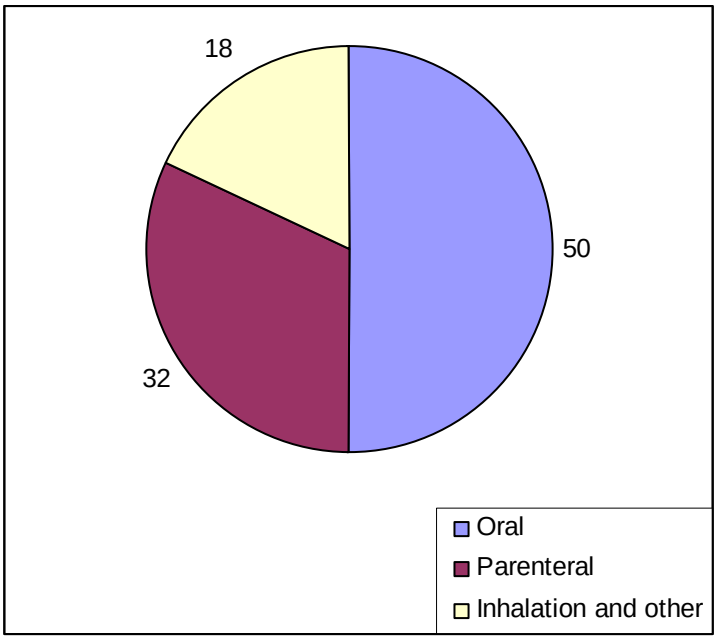


Figure 1.1: US drug delivery market: Sales

Peptides and proteins have become drugs of choice for the treatment of new diseases as a result of their high selectivity and potent action. Also a wide variety of new protein / peptide drugs are commercially produced as a result of advancements in biotechnology. More than two biologic license applications per year are approved by

USFDA since 1996 (Hughes, 2008). Pre-systematic degradation and poor intestinal permeability necessitates parenteral delivery of proteins and peptides. With developments of different kind of functionally modified polymers, the oral delivery of proteins and peptides might be possible in near future (Morishita and Peppas, 2006).

Drug discovery efforts are directed towards designing new drugs which can be orally administered without the need of specialized delivery technology. This would otherwise add cost and time for drug development in addition to drug discovery. When an oral drug delivery technology is needed, it is common for pharmaceutical companies to develop in-house technology. It is worth the effort because technology is likely to be useful in the future since majority of products in the pipeline are administered orally. The pharmaceutical companies are continuously looking for differentiated products using NDDS which improve the safety and efficacy and are useful to extend the life cycle of the drugs. This can be achieved by use of innovative technologies which possess differentiated features vis-à-vis existing technologies for oral delivery of drugs. Oral drug delivery systems have advantages such as ease of administration, painless administration, versatility to accommodate variety of drug candidates, patient compliance and lower cost.

1.3 Rationale for site specific drug delivery systems

The development of systems which release drug at constant rate was the major focus in early eighties. However, the realization that drug absorption is affected by physicochemical and physiological factors such as pH dependent solubility, instability in gastrointestinal tract, transit time of dosage form, pH and surface area of gastrointestinal tract, presence of enzymes and microflora in the colon, has necessitated the development of site specific and chronotherapeutic delivery systems (Dressman et al, 1993). Thus, advancement in the understanding of these factors has shifted the focus from zero order release to site specific and chronotherapeutic drug delivery to further enhance the safety and efficacy of drugs (Gupta et al, 2002). Site specific delivery includes drug delivery selectively to stomach, intestine or colon and is especially desirable for drugs which exhibit pH dependent solubility, stability and absorption. Site specific release is achieved using both pH sensitive and pH independent polymers.

Drugs having restricted absorption window are delivered using site specific systems that release the drug along the gastrointestinal tract where the absorption is

maximum so as to enhance the drug bioavailability and minimize adverse effects. Gastroretentive delivery systems are formulated for the improvement of safety and efficacy of drugs which exhibit poor absorption in lower gastrointestinal tract. Transit time in the small intestine seems to be affected neither by food intake nor by the nature of dosage form. Hence, systems are formulated which release drug in sustained manner in the intestine to enhance bioavailability of drugs.

Oral pulsatile systems are designed to treat diseases which exhibit circadian recurrence of symptoms (Youan, 2004). These systems provide a predetermined lag time followed by rapid release of drugs. The lag time of these systems can not be precisely controlled because of highly variable residence time of formulation in the GI tract. Gastric emptying of the formulation is the most important factor which affects the residence time of dosage forms. Hence, Zou et al (2008) recommended pulsatile systems which release drug in the stomach by increasing its residence time by formulating floating systems. This leads to enhanced absorption of drugs which exhibit maximum absorption in the stomach.

1.4 Gastroretentive sustained release systems

1.4.1 Rationale for gastroretentive sustained release systems

The transit time of the dosage form of orally administered products depends on factors such as physical state of the dosage form, presence of food, sex, size and shape of the dosage form. The drugs which exhibit poor absorption in the lower gastrointestinal tract exhibit poor oral bioavailability due to rapid gastric emptying. The process of gastric emptying is markedly different in fasted and fed state. In the fasted state, it is characterized by series of events known as migrating motor complex (MMC) followed by contractions of mild to severe magnitude which results in emptying of gastric contents. The phase I is basal phase which occurs for 30 to 60 min and is free from any electric, contractile or secretory activity. Phase II is preburst phase and occurs for 20 to 40 min with intermittent contractions during which contractions increase in frequency and amplitude. Bile enters the duodenum during this phase and gastric mucus discharge occurs throughout phase II and III. Phase III is burst phase of 10 to 20 min with intense contractions and heavy mucus discharge. It is also known as housekeeper wave as it sweeps off undigested food. Phase IV is transition period of 0 to 5 min between phase III and start of phase I of next cycle. Feeding sets off this motility pattern and delays the gastric emptying. When sustained release product is administered in the fasted state, the MMC may be

in any of its phases. This may affect gastric residence time of dosage form. This negatively affects the bioavailability of drugs which exhibit restricted absorption window in lower intestine. Therefore, by increasing the gastric residence time of dosage forms we can improve the bioavailability of such drugs (Chawla et al., 2003).

Sustained release of drugs in stomach in order to enhance the safety and efficacy is useful for following drug categories: a) drugs used for local action in stomach, e.g., 5-flourouracil, antacids, b) drugs which are unstable in lower part of gastrointestinal tract, e.g., captopril, c) drugs which are insoluble at intestinal conditions (acid soluble basic drugs), e.g., Propranolol HCl, metoprolol, diazepam, d) drugs which exhibit variable bioavailability, e.g., sotalol HCl, levodopa, and e) drugs having site specific absorption in stomach or upper part of small intestine, e.g., atenolol, salbutamol (Singh and Kim, 2001).

1.4.2 Approaches to gastroretentive sustained release systems

Gastroretentive sustained release drug delivery systems are based on different approaches to achieve gastric retention and sustained drug delivery in the stomach. These approaches include use of systems which float due to lower density than gastric content, mucoadhesive systems, expandable systems and high density systems. Detailed description of each is described below.

1.4.2.1 Floating sustained release systems

The density of gastric content is 1.004 g/cc and the drug delivery systems which have density lower than 1.004 g/cc float on the gastric contents while the drug is released in sustained manner from gastroretentive sustained release systems. The concept of floating was first described by Donald Davis in 1964 for pills to overcome swallowing difficulty (US patent 3418999).

The commonly used polymers for fabrication of floating sustained release systems include swellable and gellable polymers. These are modified cellulose derivatives, poly (ethylene oxide) and polysaccharides. Most common approach to preparation of floating systems is to mix drug and polymers intimately and compress into tablets. These tablets swell and float after oral administration and release the drug in sustained manner. Floating results as product density lower than unity is achieved and the drug is released by diffusion or erosion from swollen tablets. The mechanism of floating and drug release is explained in figure 1.2.

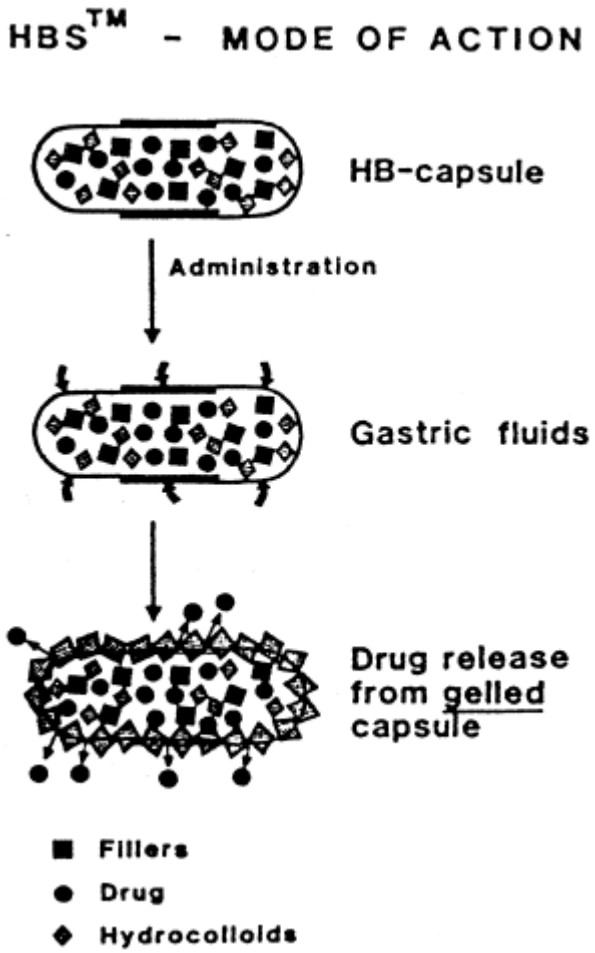


Figure 1.2: Working principle of hydrodynamically balanced system
(Adapted from Bogentoft, 1982)

Based on architecture, floating systems are categorized as matrix and reservoir systems. The matrix type floating systems are discussed below.

Atyabi et al (1996) described floating TPH loaded ion exchange resin beads. The ion-exchange resin (Dowex) beads were loaded with bicarbonate and theophylline. The maximum amount of TPH that could be bound to ion exchange resin without affecting their floating ability was 150 mg/g of resin. These beads were coated with semipermeable membrane using Eudragit RS polymer. These beads on contact with gastric fluid caused exchange between bicarbonate and chloride ions and resulted in formation of CO_2, which was trapped within the membrane causing the beads to float. These beads released TPH for 24 h. Since the drug loading was low, this approach was not practiced.

Fukuda et al (2006) described a pH sensitive polymer such as Eudragit EPO as release modifier in floating hot melt extrudates of Chlorpheniramine maleate. The hot melt extrudates were prepared using microcrystalline cellulose and sodium bicarbonate. Increase in the content of Eudragit EPO caused increase in drug release rates; however the buoyancy was reduced.

Ali et al (2007) described hydrodynamically balanced system for metformin using polymer blends. The capsules composed of 78 % w/w MET and 22 % w/w Methocel K4M or Polyox WSR 303 resulted in rapid MET release. Incorporation of 5 % w/w ethyl cellulose along with Methocel K4M resulted in rapid buoyancy and sustained release over a period of 12 h. Thus, two polymers were required to achieve sustained release of VER when formulated as matrix tablet, because of high solubility of VER.

Patel et al (2009) developed a verapamil floating tablet based on Methocel K4M, and xanthan gum (3:2) in order to increase the gastric retention time of the dosage form and to sustain the drug release. The drug loading was 38 % w/w and polymer loading 32 % w/w. Buoyancy was achieved by incorporating 22 % w/w effervescent agents in the tablet. The tablet exhibited buoyancy time of 26 sec and sustained the VER release for 24 h.

Sriammornsak et al (2007) described floating calcium pectinate gel as carrier for Metronidazole. Incorporation of sodium bicarbonate or calcium carbonate into pectin solution resulted in formation of porous or dense beads after drying. The highly porous freeze dried beads exhibited acceptable floating characteristics but released drug rapidly within 1 h. The drug release could be sustained for 2 h using pectin and calcium carbonate but resulted in poor floating characteristics.

US patent 4140755 assigned to Hoffman La Roche (1979) described a bilayer floating tablet having bulk density lower than that of gastric fluid, and which therefore remained floated in gastric fluid and had a specific gravity of 1.004 to 1.010. The system was composed of Riboflavin-5-phosphate and hydrophilic hydrocolloid layer and drug-free second layer. The hydrocolloids used were sodium carboxymethylcellulose, methyl cellulose and hydroxypropylmethylcellulose 4000 cps. On contact with gastric fluid, the outermost hydrophilic colloid layer hydrated to form soft gelatinous mass and retained the integrity of the tablet and released the drug for 5 h.

US patent 4126672 assigned to Hoffman La Roche (1978) disclosed a sustained release capsule for diazepam. The composition was composed of 5-60 % w/w

pharmaceutically acceptable inert substances, 0-60 % w/w fatty substance having low density, and 20-75 % w/w of hydrocolloids. The hydrocolloid was selected from hydroxypropylcellulose, methylcellulose, hydroxymethylcellulose, guar gum, hydroxypropyl methylcellulose and sodiumcarboxymethylcellulose. The homogeneous mixture on contact with water swelled, floated and sustained the drug release over a period of 7 h.

Reservoir devices to achieve sustained release using GRS are discussed below.

Krogel and Bodmeier (1999) described floating / pulsatile drug delivery based on effervescent cores. The mechanical properties of polymers such as puncture strength and % elongation at break determined the drug delivery type. Eudragit RL with 20% acetyltributyl citrate (ATBC) with high elongation values and high water permeability was found suitable for floating drug delivery. The coated tablets exhibited buoyancy time within 15 min but released the drug rapidly. Bilayer tablet was designed with a layer containing drug and Methocel K4M or cellulose acetate and second layer of effervescent agent with PEG 4000. The bilayer tablet was coated with plasticized Eudragit RL. Incorporation of 50 % w/w cellulose acetate in the core could not sustain the drug release for extended period. Methocel K4M incorporation caused sustained release for 6 h but the tablet settled after 2-4 h in both cases. The rapid release was attributed to high permeability of drug through Eudragit RL coating and hence it was not suitable for fabrication of reservoir type sustained GRS. Meka et al (2009) developed floating minitablets for Furosemide. Furosemide has solubility of 23 μg/ml at acidic pH which was increased to 216 μg/ml by preparing solid dispersion of Furosemide and PVP K30 in the ratio 1:5. Matrix type minitablets were prepared using Methocel K100M and Ethyl cellulose. These minitablets were further coated with Eudragit RL30D. The tablets floated in 4 min and sustained the release over a period of 12 h. This system also used multiple polymers.

Sungthongjeen et al (2008) described TPH tablets based on lactose. These tablets were coated with three successive layers viz., protective layer (Methocel E15LV), gas forming layer (Methocel E15LV and sodium bicarbonate) and Eudragit RL30D. Thus, this approach used multiple polymers and multiple steps but had low drug loading (7 % w/w). TPH release was attributed to Methocel E15LV and occurred by diffusion and the floating was due to entrapment of generated gas in the polymeric

membrane. TPH tablets exhibited acceptable floating characteristics. TPH has low solubility. Therefore 46 % w/w Lactose was used in core as osmotic agent to achieve sustained release for 8 h.

Goole et al (2008) described coated multiple unit sustained release floating minitablets for Levodopa. The minitablet was composed of 3 mm drug core and coating of Eudragit RL30D surrounding the core. The drug loading was 37.5 % w/w and polymer loading 20 % w/w. Also, 46 % w/w Lactose had to be incorporated in the core to create osmotic pressure as Levodopa has low solubility (3 mg/ml). These minitablets floated in 20 min and sustained the release for 20 h.

Rouge et al (1998) described Atenolol minitablets composed of Methocel F4M and coated with a blend of Eudragit NE30D and Eudragit RS. The drug and polymer loading of Atenolol tablets was 12.5 % and 87 % w/w respectively. This blend did not swell, but ruptured as a result of high internal pressure caused by swelling of HPMC matrix. The buoyancy time was delayed by coating with Eudragit NE30D and Eudragit RS blend but could not sustain the drug release for extended period.

Sawicki and Glod (2004) investigated acrylic polymers Eudragit NE30D, Eudragit L30D55 and Eudragit RL as coatings for the preparation of floating sustained release VER pellets. Due to high permeability of VER through Eudragit NE30D and Eudragit RL, it was rapidly released. VER pellets coated with a 1:1 blend of Eudragit NE30D and Eudragit L30D55 resulted in BT of 3 min and sustained the release over a period of 6 h, attributed to presence of Eudragit L30D55 in the blend which remained collapsed in acidic pH, resulted in lower porosity of the coating and lowered diffusion of VER. Hence a blend of polymers had to be used for preparation of floating sustained release pellets of VER.

Lunio and Sawicki (2006) used polymeric blends of different Eudragits to achieve sustained release of VER from pellets. Coating VER pellets using Eudragit RL alone or blends of a) Eudragit RL and Eudragit RS (in the ratio 1:1) resulted in rapid VER release although the pellets floated immediately. Eudragit RS when coated on VER pellets resulted in buoyancy time of 70 min but could release only 4 % VER in 4 h. Coating of VER pellets using blend of Eudragit RL and Eudragit RS (in the ratio 1:4) resulted in buoyancy time of 22 min and sustained VER release for 6 h after a lag time of 1 h. Use of higher proportion of Eudragit RS led to lag time of 1 h for VER release. To ensure VER release during the lag phase, 20 % by weight of

uncoated VER pellets had to be incorporated along with VER pellets coated with the blend. The manufacture of this system used multiple polymers and multiple steps.

1.4.2.2 Swellable sustained release systems

The swellable sustained release gastroretentive systems are based on principle of gastric retention due to increase in the size of the dosage form which enables gastric retention by size exclusion effect from pylorus of stomach. The systems with diameter of 13 mm are useful to increase the gastric residence time of dosage forms (Khosla and Davis, 1990).

Depomed Inc. developed a variety of systems based on swellable and shape based systems (US patents 5007790, 5972389, 7736667). US patent 5007790 described swellable microspheres composed of crosslinked polymers such as alginates, gelatin, chitin, carboxymethylcellulose and drug. These microspheres were filled into hard gelatin capsule. The matrix swelled to an extent which promoted gastric retention and released the drug in sustained manner in stomach upto 6 h. The physical integrity of matrix system was maintained for 1-4 h after the drug was released. The swollen matrix dissolved by hydrolysis or proteolytic digestion.

US patent 5972389 assigned to Depomed Inc. disclosed gastric retentive tablets for the controlled release of sparingly soluble and insoluble drugs. The formulation of this patent used polymeric matrix that swelled by imbibition of gastric fluid and caused increase in the size so as to promote gastric retention in patient's stomach in whom the fed state had been induced. The formulation gradually eroded over a prolonged period and sustained the release. Poly (ethylene oxide) (PEO) of molecular weight 9 X 10^5 to 8 X 10^6 was used for preparation of erodible matrix. The drugs claimed included ciprofloxacin, carbamazepine, nifedipine, alprazolam, ranitidine, clarithromycin, and metronidazole. This patent also covered soluble drugs that were rendered insoluble or sparingly soluble by enteric coating and dispersed in erodible PEO matrix. Thus, this patent used hydrophilic matrix which exhibited swelling followed by erosion so as to achieve release of insoluble drugs for prolonged period. This system used higher proportion (60 %w/w of total tablet) of PEO and modified shape system.

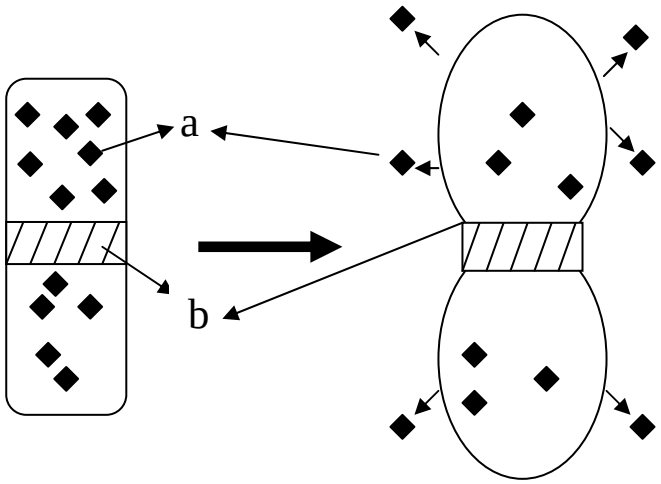
US patent 7736667 disclosed a shell and core dosage form for gastric retention which released the drug at constant rate. Reservoir systems were used to achieve zero order release from dosage forms. The dosage form was a dual matrix configuration. First matrix comprised a polymer core in which the drug was

dispersed. The second matrix encased first matrix. The casing was free from drug and was composed of swellable polymeric material which resulted in increased size required for gastric retention during fed condition in patients. The shell and core system was designed in such a way that it enabled controlled drug release. The shell and core were prepared from high molecular weight PEO, HPMC, hydroxyethylcellulose and hydroxypropyl cellulose. The drugs claimed included were metformin HCl, vancomycin HCl, captopril, acyclovir, tramadol, paclitaxel, etc. The patent also disclosed that at least 60 to 70 % of the total drug should be retained after first two hours of dissolution. This system required 70 % w/w polymer loading to achieve release at constant rate. This system was large in size (500-3000 mg weight) and could pose swallowing problems.

Alza Corp. (US patent 6120803) disclosed dosage form adapted for gastric retention which comprised active dispersed in swellable or soluble polymeric matrix along with a hydroattractant and an insoluble band circumscribing a portion of the surface of the polymer matrix. The polymer was selected from HPMC, HPC, PEO, poly (acrylic acid), pre-gelatinized starch and polyvinyl alcohol. The hydroattractant was selected from crosslinked sodium carboxymethylcellulose, microcrystalline cellulose and crosslinked povidone. The system sustained the drug release for a period of 12 h. The drugs claimed included acyclovir, ranitidine, bupropion, minocycline, etc. Functioning of this system is shown in figure 1.3. This composition used multiple polymers and multiple steps.

Chen and Park (2000) described gastric retention properties of superporous hydrogel (SPH) composites. SPH hydrogels contained numerous pores connected together to form channel structures. Water was absorbed into the dried SPHs by capillary wetting rather than by diffusion which caused upto 100 fold swelling of SPH extremely rapidly within minutes. The hydrogel based on Poly (acrylamide-co-3, sulfopropylacrylate) i.e. poly (AM-co-SPAK) was synthesized and its composite with crosspovidone was prepared. Acrylamide was used to impart strength and sulfopropylcarylate was used to impart strong electrolyte properties to achieve high swelling. High porosity was obtained by use of gas forming agent, sodium bicarbonate during polymerization. The SPH hydrogel composite was compressed without disrupting interconnected capillary channels. This was achieved by incorporating composite material in the hydrogel. The compression enabled reduction in size of hydrogel composites so that these could be filled into hard

gelatin capsule. SPH composite filled capsule in dogs in fed state exhibited gastric retention over 24 h and subsequently fragmented to clear from the stomach.



Device P Device Q

Figure 1.3: The gastroretentive device before (P) and after swelling (Q) and a) - drug molecule and b) - insoluble band (Adapted from US patent 6120803)

Ahmed and Ayres (2007) described modified geometry based gastroretentive device for riboflavin containing xanthan gum, locust bean gum, sodium lauryl sulfate and PVP. All these ingredients were mixed and dissolved in deionized water and heated at 85 °C. The drug was added in viscous solution which was poured into molds to achieve cubic, cuboidal, short cylinder and long cylinder shapes after drying. Cuboid shaped system (3.0 x 1.5 x 1.0 cm) exhibited fastest swelling and reached equilibrium swelling within 30 minutes whereas cubic and cylindrical shaped systems required upto 60 min for swelling. Riboflavin was released over 24 h from cuboid shaped system. This approach used high temperature and may be used for thermostable drugs only.

1.4.2.3 Floating and swelling sustained release systems

US patent 7776345 assigned to Sun Pharma Advanced Research Company disclosed a biphasic gastroretentive drug delivery system for baclofen. It was composed of swellable core containing drug, swellable polymer and gas generating agent. The core was further coated using immediate release drug layer wherein the drug was same as that in the core. The system on swelling caused entrapment of generated gas in the swollen matrix; lowered the density and resulted in floating. The swellable

polymer used in core was combination of hydrophilic polymer and highly swelling superdisintegrant. Hydrophilic polymer was selected from HPMC, HEC, HPC and superdisintegrant was selected from crosspovidone, crosslinked sodium carboxymethylcellulose and sodium starch glycolate. The biphasic release system floated within 10 min and released the drug over a period of 24 h. This approach used high proportion of polymer in the range 20-75 % w/w of the total system and used multiple polymers. The drug loading was only 2-3 % by weight of the total dosage form.

Liu and Fassihi (2008) described an asymmetric composite gastroretentive matrix for zero order release of highly soluble drug Alfuzocine HCl. The design was based on trilayer tablet using HPMC and PEO as matrix forming polymers. The performance of composite formulation was compared with marketed product Uroxatral® XR. Uroxatral® XR exhibited buoyancy time of 45 min and released drug in sustained manner for 24 h and the composite formulation floated within a minute and released the drug over a period of 24 h. The swelling / dissolution characteristics and release profiles achieved using simple monolithic matrix and composite systems are shown in figure 1.4.

US patent 6261601 assigned to Ranbaxy Laboratories disclosed orally administered controlled drug delivery system for spatial and temporal control. It offered once a day product for ciprofloxacin HCl and contained by weight 70 % drug, 0.2 to 0.5 % sodium alginate, 0.5 to 2 % xanthan gum, 10 to 25 % sodium bicarbonate and 5 to 20 % crosspovidone. The tablets released CIP over a period of 12 h. This system used multiple polymers.

Hascicek et al (2011) developed a modified release technology platform known as Dome Matrix®. It contained female and male modules assembled together in void configuration by friction interlocking and was formulated as swellable matrix for Clindamycin phosphate (CLM). These modules were made using Methocel K100M and lubricants. Attachment of additional female module sans drug to above matrix resulted in modulation of CLM release. The composition of such additional female module governed the release profile. Stacking additional module composed of inert polymer i.e. cellulose acetate propionate onto Dome Matrix® resulted in linearization of release profile. This system used multiple polymers and needed special tooling for manufacture. The schematic representation of Dome Matrix tablet is shown in figure 1.5.

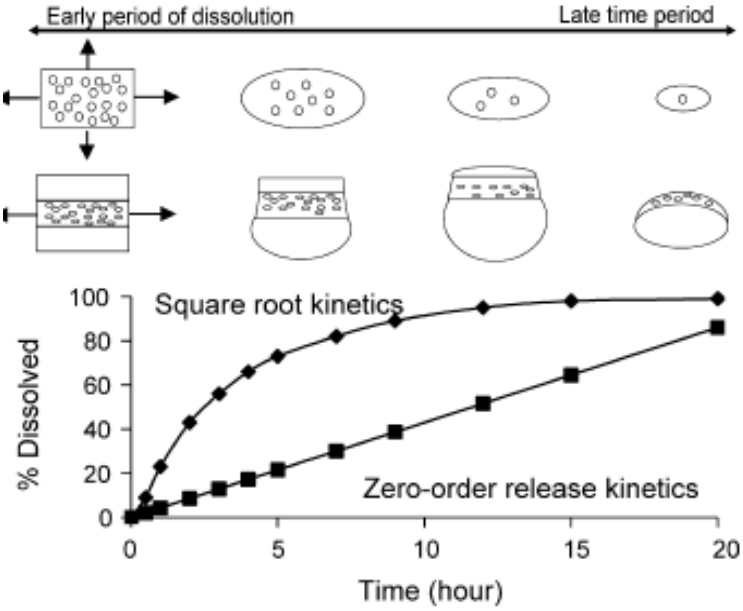


Figure 1.4: The matrix swelling / dissolution and drug release pattern from monolithic (HPMC based) system and composite (PEO based) system (Adapted from Liu and Fassihi, 2008)

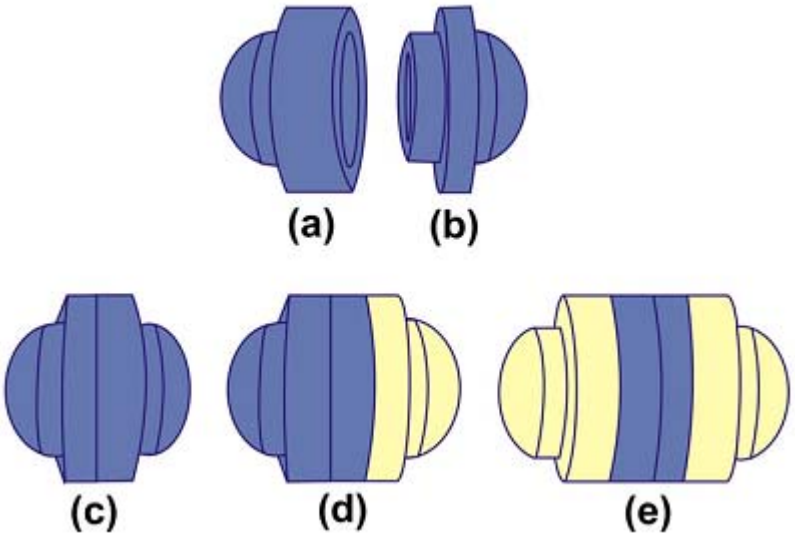


Figure 1.5: Schematic of female module (a), male module (b), void configuration assembly, made by sticking male and female modules concave base to concave base (c), Assembled system with additional barrier female module to one (d) or both (e) convex bases of void configuration (Adapted from Hascicek et al, 2011)

Arza et al (2009) described a swellable floating tablet for sustained delivery of ciprofloxacin HCl. The tablets were prepared using Methocel K100M,

crosspovidone and gas generating agent, sodium bicarbonate. Crosspovidone was used to enhance tablet swelling and Methocel K100M was release retarding polymer which also formed strong gel in order to maintain physical integrity of the system. These tablets floated within 15 sec and released CIP over a period of 12 h. The performance of this system was comparable to that of Cifran OD® and thus provided simple approach to gastroretentive sustained release of CIP as compared to Cifran OD®. The swelling of swellable CIP tablet is shown in figure 1.6.

Figure 1.6: Size of the Ciprofloxacin tablet before and after swelling
(Adapted from Arza et al, 2009)

1.4.2.4 Mucoadhesive sustained release systems

Sakkinen et al (2003) investigated microcrystalline chitosan (MCCh) for gastro retentive delivery of Furosemide. Drug loaded MCCh granules exhibited good *in vitro* mucoadhesive characteristics in isolated oesophagus, but did not adhere to gastric mucosa, and passed into the small intestine and released the drug. The *in vivo* study produced no evidence that MCCh granules can be used for gastroretentive delivery.

Chavanpatil et al (2006) described a bioadhesive floating matrix tablet for sustained release of ofloxacin. Ofloxacin is soluble at pH 2-5 and sparingly soluble at pH 7. The gellable polymers Methocel K100M and psyllium husk were used along with sodium bicarbonate. Psylium husk and Methocel K100M provided physical integrity

due to stronger gel formation so as to avoid gastric emptying from stomach. These tablets resulted in incomplete release (< 40 %) in 24 h. Crosspovidone was incorporated to accelerate drug release as a result of enhanced water penetration into the tablet. However, crosspovidone incorporation could not enhance drug release sufficiently. Further addition of channeling agent i.e. β-cyclodextrin enhanced the drug release and release profile comparable with marketed formulation Zanocin® was achieved. The combination of Methocel K100M and psyllium husk exhibited better bioadhesive characteristics than Methocel K100M or psyllium husk alone.

Cheuh et al (1995) suggested that floating systems to achieve gastric retention suffer from disadvantage that they are effective only when sufficient amount of fluid is available in the stomach; however buoyancy of the dosage forms may be impeded during gastric emptying, This serious limitation could be overcome by using mucoadhesive polymers to enable these systems to adhere to mucus lining of stomach wall (Chitnis et al (1991). Varshosaz et al (2009) investigated blend of Methocel K100M and sodium carboxymethylcellulose (Na CMC) for mucoadhesive gastroretentive system for CIP. CIP tablets containing only Methocel K100M and sodium bicarbonate released only 40-50% drug in 8 h. Thus NaCMC had to be incorporated in order to enhance tablet swelling and mucoadhesive characteristics. Increase in Na CMC content in the blend accelerated release of CIP. These tablets released CIP over a period of 8 h and exhibited good floating characteristics (50 sec).

Dhaliwal et al (2008) investigated mucoadhesive Acyclovir microspheres for gastroretentive sustained delivery. The microspheres prepared using thiolated chitosan exhibited higher mucoadhesive strength than those prepared using chitosan, Carbopol 71G and HPMC. Further, thiolated chitosan based microspheres were evaluated *in vivo* and it was observed that these microspheres exhibited 4 times higher $AUC_{0\text{-}24\ h}$ value than that exhibited by Acyclovir solution. Thus, formulating Acyclovir in the form of mucoadhesive microspheres resulted in sustained release over a period of 10 h, enhanced the contact between microspheres and intestinal mucosa as indicated by mucoadhesion studies and facilitated drug permeation through mucosa as evidenced by the fluorescence microscopy. These factors led to increased bioavailability of Acyclovir.

Pund et al (2011) described mucoadhesive system for gastroretentive delivery of Rifampicin. The system was composed of rapid release and mucoadhesive sustained release fractions to achieve loading and maintenance dose. The system released drug over a period of 6 h and exhibited gastric retention for 5 h as demonstrated by gamma scintigraphy.

1.4.2.5 Expandable sustained release systems

Klausner et al (2003) described unfolding gastroretentive dosage form for sustained release of levodopa. This was based on rigid devices for gastric retention. (Klausner et al, (2002). The system was composed of inner layer using drug and ethyl cellulose matrix (1:1), framed with rigid polymeric strips containing Poly (L-lactic acid- ethyl cellulose in ratio 9:1 and was covered on both sides by two shielding layers containing hydrolyzed gelatin, Eudragit S, glycerine and glutaraldehyde in ratios 48:30:20:2. The exterior of shielding layers was covered with antiadherent layer of microcrystalline cellulose. All membranes were prepared by dissolving the polymers in suitable solvents and subsequent casting and evaporation of solvent. The layers were attached to each other using small amount of dichloromethane or ethyl alcohol. The dimensions of system prior to folding were 5.0 cm X 2.5 cm. This system was folded and filled into size 000 capsule. This system was referred to as Accordion Pill™. The capsule on contact with gastric medium dissolved and the system expanded within 15 min and caused sustained release for 7 h. The expanded system exhibited gastric retention for 24 h in beagle dogs. Kagan et al (2006) carried out clinical evaluation of Gastroretentive Accordion Pill™ and showed that formulating Riboflavin in Accordion Pill™ doubled its bioavailability.

Gronig et al (2007) evaluated compressed collagen sponges for gastroretentive delivery of riboflavin. The system consisted oblong tablets which could be swallowed easily and expanded on contact with gastrointestinal fluid within few minutes to a length of 4-6 cm and were retained in stomach and released the drug over a period of 12 h. The increase in size before and after hydration is shown in figure 1.7.

These compressed sponges had only 10 % w/w/ drug loading and the preparation involved time consuming freeze drying process.

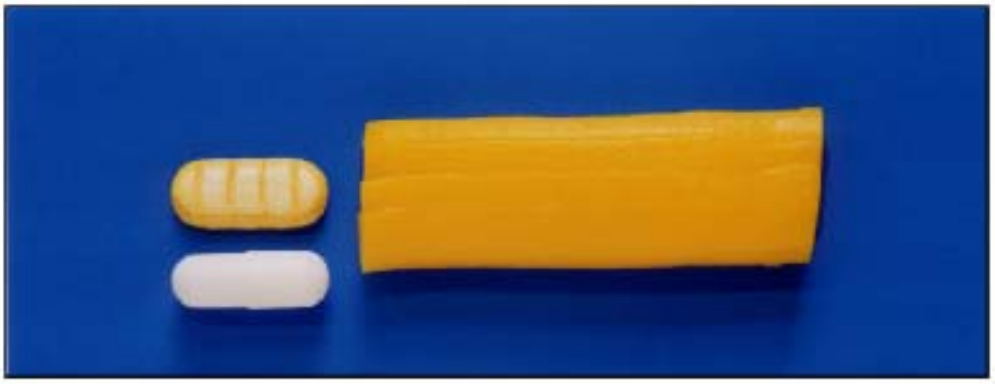


Figure 1.7: Collagen dosage form before and after expansion, capsule size no. 1 shown left below (Adapted from Gronig et al, 2007)

1.4.2.6 High density sustained release systems

High density systems sink to the bottom of stomach where these get entrapped in the folds of antrum and withstand peristaltic waves of stomach wall (Bardonnet et al, 2006). A density close to 2.5 g/cm^3 is required for such systems (Clarke et al, 1993). Guan et al (2010) developed gastroretentive Famotidine osmotic pump tablet based on high density Iron powder. It was composed of PEO, sodium chloride and Iron powder. The density of the tablet was > 2.5 g/cm^3. The tablets exhibited sustained release over a period of 12 h and gastric retention of 7 h as demonstrated by gamma scintigraphy.

1.4.3 Advantages and limitations of gastroretentive sustained release systems

The existing gastroretentive systems to achieve sustained release are based on matrix systems. In order to maintain balance between swelling and dissolution of these systems blends of HPMC and PEO have been used. The marketed product containing the blend is based on modified shape and floating mechanisms and needs to be administered in fed state so as to avoid rapid gastric emptying. These systems exhibit gastric retention and sustain the release over 6-8 h. The reservoir based systems could achieve gastric retention and sustain release of drugs having low solubility (Meka et al, 2009). The reservoir systems reported for highly soluble drugs could not sustain the release for extended periods although these systems exhibited acceptable floating characteristics (Krogel and Bodmeier, 1999, Sawicki, 2004, Sawicki and Lunio 2006).

A summary of patents on gastroretentive sustained release systems is presented in table 1.1.

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Table 1.1: Summary of patents on gastroretentive sustained release systems

S No	Patent No.	Assignee	Title
1	US6881420	Teva Pharma	Compositions and dosage forms for gastric delivery of irinotecan and methods of treatment that use it to inhibit cancer cell proliferation
2	US7674480	Teva Pharma	Rapidly expanding composition for gastric retention and controlled release of therapeutic agents, and dosage forms including the composition
3	US5972389	Depomed Inc.	Gastric-retentive, oral drug dosage forms for the controlled-release of sparingly soluble drugs and insoluble matter
4	US7776345	Sun Pharma	Gastric retention controlled drug delivery system
5	US6723340	Depomed Inc.	Optimal polymer mixtures for gastric retentive tablets
6	US7438927	Depomed Inc.	Methods of treatment using a gastric retained gabapentin dosage
7	US6548083	Alza Corp.	Prolonged release active agent dosage form adapted for gastric retention
8	US6120803	Alza Corp.	Prolonged release active agent dosage form adapted for gastric retention
9	US4767627	Merck Co.	Drug delivery device which can be retained in the stomach for a controlled period of time
10	US4758436	Merck Co.	Drug delivery device which can be retained in the stomach for a controlled period of time
11	US4735804	Merck Co.	Drug delivery device which can be retained in the stomach for a prolonged period.

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12	US7736667	Depomed Inc.	Shell-and-core dosage form approaching zero-order drug release
13	US7731989	Depomed Inc.	Gastric retained gabapentin dosage form
14	US7413751	Depomed Inc.	Methods of treatment using a gastric retained losartan dosage
15	US6997283	Alza Corp.	Gastric retention dosage form having multiple layers
16	US6635280	Depomed Inc.	Extending the duration of drug release within the stomach during the fed mode
17	US6488962	Depomed Inc.	Tablet shapes to enhance gastric retention of swellable controlled-release oral dosage forms
18	US6340475	Depomed Inc.	Extending the duration of drug release within the stomach during the fed mode
19	US5443843	Pfizer Inc.	Gastric retention system for controlled drug release
20	US5007790	Depomed Inc	Sustained-release oral drug dosage form
21	US5002772	Pfizer Inc.	Gastric retention system for controlled drug release
22	US6776999	Lohmann Therapy	Expandable gastroretentive therapeutic system with prolonged stomach retention time
23	US6685962	Yissum Res.	Gastroretentive controlled release pharmaceutical dosage forms
24	US6207197	West Pharma	Gastroretentive controlled release microspheres for improved drug delivery
25	WO2010064139	Intec Pharma	Zaleplon gastroretentive drug delivery system
26	WO2010064100	Intec Pharma	Baclofen gastroretentive drug delivery system
27	WO2010035273	Intec Pharma	Novel gastroretentive dosage forms
28	WO2009144558	Intec Pharma	Carbidopa/Levodopa gastroretentive drug delivery system

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29	WO2009008873	BASF Corp.	A gastroretentive composition on the basis of water soluble reaction product from a vinyl group containing precursor
30	WO2008148478	Lohmann Therapy	A gastroretentive system comprising an alginate body
31	WO2009084040	Rubicon Res	Once a day angiotensin receptor blockers
32	WO2007010400	Ethypharm	Gastroretentive formulations and process thereof
33	WO2007137216	Janssen Pharma	Gastroretentive sustained release formulations
34	WO2008027945	Novartis AG	Extended release oral drug delivery system for valsartan
35	WO200579752	Rubicon Res	Controlled release pharmaceuticals with improved bioavailability

1.5 Gastroretentive chronotherapeutic systems

1.5.1 Rationale for gastroretentive chronotherapeutic systems

Gastroretentive chronotherapeutic delivery is used to treat medical conditions such as arthritis, asthma, duodenal ulcer, rhinitis and cardiovascular diseases which exhibit changes in intensity of symptoms depending on circadian rhythm. Oral delayed and pulsatile release systems which exhibit a predetermined lag followed by the release of the drug are used for chronotherapeutic delivery of drugs (Youan, 2004). Gastric retention was used to achieve pH dependent lag time followed by rapid release of drugs once the system enters intestinal pH for design of chronotherapeutic system (Sher et al, 2007, Sharma and Pawar, 2006).

1.5.2 Approaches to gastroretentive chronotherapeutic systems

Gastroretentive chronotherapeutic delivery systems reported in the past relied on combination of floating and pulsatile mechanisms. These systems exhibited a lag time followed by rapid release of drug which had limited solubility at acidic pH and high solubility at neutral pH. Thus, gastric retention of such systems resulted in lag phase followed by release at simulated intestinal conditions.

Nakamichi et al (2001) developed Nicardipine HCl (NDP) extrudates using enteric polymer hydroxypropylmethylcellulose acetate succinate (HPMCAS), wheat starch and calcium phosphate dehydrate. These extrudates were porous in nature and floated over a period of 6 h at acidic pH and then settled. The release profile exhibited lag time at acidic pH followed by rapid release at intestinal pH. Thus a floating and pulsatile delivery was achieved.

Zou et al (2008) described bilayer tablet-in-tablet approach to pulsatile delivery of VER. This system was based on rapid release tablet dry coated with swellable polymer and a second buoyant layer. Methocel E15 was used as swellable polymer as dry coating to achieve lag time and Methocel K4M, Carbopol 934P and sodium bicarbonate were used in buoyant layer. Depending on the proportion of swellable polymer, the floating system exhibited lag time of 3-5 h followed by rapid release at acidic pH.

A multiparticulate floating pulsatile system for Meloxicam was developed using porous calcium silicate and calcium alginate for chronotherapy of rheumatoid arthritis. These beads exhibited lag time in the range 2-8 h at acidic pH followed by rapid release at intestinal pH. These systems had to use 85 % by weight of calcium silicate to achieve good floating characteristics (Sharma and Pawar, 2006).

Badve et al (2007) described floating pulsatile beads for Diclofenac sodium based on hollow calcium alginate beads. These beads exhibited lag time during floating in the stomach for 5 h followed by rapid release at pH 7.2 phosphate buffer. Similarly, Sher et al (2007) described floating pulsatile beads of Ibuprofen adsorbed on low density microporous polypropylene (Accurel MP 1000) which resulted in a lag time of 6 h followed by rapid release in pH 7.2 phosphate buffer. These approaches were useful for delivery of NSAIDs which exhibit gastric irritation as the drug was released only at intestinal pH.

1.5.3 Advantages and limitations of gastroretentive chronotherapeutic systems

The gastroretentive chronotherapeutic systems which exhibit a lag time as a result of gastric retention and drug release at intestinal pH can be used to treat diseases which exhibit circadian rhythm. These systems can be administered to achieve a lag time followed by release of drug when the intensity of symptoms of diseases is at peak. These systems are simple and easy to manufacture. Since floating time of these systems is expected to provide lag time, it is likely to be affected by rapid gastric emptying of beads due to their smaller size. The utility of these systems in real life applications needs to be validated.

1.6 Gastroretentive multiple pulsed systems

1.6.1 Rationale for gastroretentive multiple pulsed system

A gastroretentive multiple pulsed system was disclosed in the patent application WO2007/079082 by Advancis Pharmaceutical Corporation, which was based on Pulsys™ technology. This approach exploited the principle that bacteria when exposed to antibacterial agent's initial dose followed by sequential pulses were killed more effectively than when exposed to standard sustained dosage regimen. It is thus obvious that the drugs which exhibit restricted absorption window at lower gastrointestinal tract could be advantageously administered using gastroretentive multiple pulsed system. This approach is useful for all antimicrobial agents which exhibit such absorption window.

1.6.2 Approaches to gastroretentive multiple pulsed systems

WO2007/079082 claimed multiple pulsed composition for drugs. It exhibited at least three distinguishable C_{max} and T_{max} in pharmacokinetic release profile. This patent disclosed improved pulsatile delivery of active ingredients, such as immediate onset of release to achieve desired C_{max} and separation between multiple C_{max}. The first pulse was achieved using immediate release portion. The second pulse was

achieved from system which exhibited lag time followed by rapid release and third pulse was achieved using system which exhibited sustained releases after a predetermined lag. Time dependent polymeric coating containing dispersed swellable polymer was used to achieve second and third pulse. The lag time was achieved using insoluble polymeric coating followed by rupture of coating. The extent of rupture was governed by the ratio of soluble to insoluble film former or additives and thus the lag time and duration of drug release after the lag was manipulated. The polymers used were ethyl cellulose as film former and swellable polymers such as Crosscarmellose sodium.

1.6.3 Advantages and limitations of gastroretentive multiple pulsed systems

The gastroretentive multiple pulsed system could be used to enhance bioavailability of drugs which exhibit restricted absorption in lower gastrointestinal tract and avoid development of resistance by microbes against antimicrobial agents. It was desired to avoid pulse collapse between consecutive pulses. However this objective was only partly achieved as the pulses overlapped.

1.7 Drug delivery systems for sustained release at intestinal pH

1.7.1 Rationale for sustained release at intestinal pH

Conventional enteric polymer such as Eudragit L100 (copolymer of MMA and MAA in ratio 1:1) is insoluble at acidic pH and dissolves at pH > 6. Increase in the hydrophobic component MMA resulted in shifting threshold pH value at which the polymer dissolved to 6.5 in case of Eudragit S100 (copolymer of MMA and MAA in the ratio 2:1). Copolymers of methacrylic acid with hydrophobic macromonomers resulted in copolymers which exhibited a wide variety of swelling / dissolution characteristics at intestinal pH. These polymers were used to achieve sustained release under simulated intestinal conditions.

1.7.2 Approaches to sustained release at intestinal pH

Multiple polymers (Cellulose acetate phthalate and Ethyl cellulose) were used to achieve sustained release of Diclofenac sodium at pH 6.8 from drug tablet coated with polymer blend (Biju et al, 2004). To achieve sustained release of DLT at intestinal pH, approaches such as use of polymer coated systems, modified geometric shapes and drug polymer interactions were used.

Following systems were prepared exploiting drug polymer interactions. Sipahigil et al. (2006) evaluated pH sensitive poly (methacrylic acid-g-ethylene glycol) polymer to achieve sustained release of DLT. DLT microparticles were prepared by

imbibition which resulted in low (2 % w/w) drug loading. These particles released DLT over a period of 8 h at pH 7.4 phosphate buffer. Sousa et al (2005) described poly (NIPAm -co-MAA) copolymer for sustained release of DLT. The drug loading was carried out using imbibition. The drug loaded films released the drug over a period of 8 h at pH 7.4 phosphate buffer.

DLT sustained release systems which use modified geometries shapes are summarized below.

Kim (2005) described triple layered donut shaped tablets (TLDST) to achieve sustained release of DLT. TLDSTs was composed of three layers and prepared by dry coating and drilling 0.1 inch hole in the tablet. The core tablet consisted of HPMCAS and bottom and top layers were made form Ethyl cellulose. These tablets exhibited sustained DLT release over 16 h at intestinal pH.

US patent 5422123 assigned to Jagotec AG disclosed a DLT core composed of a) water swellable polymer and second polymer having both swelling and gelling characteristics in definite geometric form and b) a support platform applied to this core. The support platform was made from Methocel K100M, hydrogenated castor oil and ethyl cellulose. The DLT tablets sustained the release over 6 h in distilled water. Dilacor XR is marketed using this technology.

DLT sustained release systems based on polymeric coatings are summarized below.

DLT controlled release systems are covered by US patents 5288505, 5229791, 7108866 and dosage forms have been marketed as Cardizem by Biovail Corp. US patent 5288505 disclosed beads composed of DLT and wetting agent such as fatty acid ester of sucrose, fatty acid ester of polyoxyethylene. The beads were further coated with Eudragit NE30D, a rate controlling porous polymer. Eudragit NE is a neutral copolymer of ethyl acrylate and methyl methacrylate with a molecular weight of 800000. These beads released DLT over a period of 24 h and were used for night dosing regimen. US patent 7108866 disclosed DLT beads coated with swellable and diffusible polymeric coating composed of HPMC, HEC and Talc and Eudragit NE30D. The beads exhibited sustained release over 24 h in distilled water and meant for night dosing regimen.

US patent 5286497 assigned to Carderm Capital disclosed DLT beads which exhibit biphasic release. The product was based on combination of beads which exhibit sustained release and beads which exhibit delayed release. These beads were composed of drug and coated with blend of Eudragit RL and Eudragit RS (95:5) to

achieve 10-15 and 25 % w/w polymer loading. The beads with 10-15 % w/w polymer loading released 20-45 % DLT in 6 h, 25-50 % in 12 h and 35-70 % in 18 h and at least 70 % at 24 h in 0.1 N HCl. The beads with 25 % w/w polymer loading released 0-15 % DLT in 12 h, 0-45 % in 18 h, at least 45 % in 24 h and at least 70 % in 30 h in 0.1 N HCl. The system was suitable for sustained release of DLT over a period of 24 h i.e. once a day dosage regimen. Cardizem CD was marketed using this technology.

US patent 5364620 assigned to Elan disclosed sustained release system based on polymer coating. It was composed of rapid release portion (25 % by weight of total system) and sustained release fraction (75 % by weight of total system). The active cores were coated with a blend of Eudragit RS and Eudragit RL (8:2) in acetone: IPA (40:60) mixture or Ethyl cellulose and PVP K-30 (9:1) and cellulose acetate (9:1) in IPA. The coated beads sustained the release for 24 h at 0.05 M KCl solution, pH 7.0.

1.7.3 Advantages and limitations of systems for sustained release at intestinal pH

The systems based on coated product and modified geometric shaped system sustained release of DLT over 24 h. Products with variety of release profiles were developed and marketed earlier using these approaches. This has extended the life cycle of DLT and is one of the best examples of use of NDDS to exploit science and technology for profitability in the business. These systems used multiple polymers and multiple steps for the preparation.

1.8 The summing up

The literature reviewed described the current status of NDDS. Drugs which exhibit restricted absorption in lower gastrointestinal tract due to pH dependent solubility, instability in gastrointestinal tract exhibit low bioavailability and hence are formulated using gastroretentive systems (GRS) in order to increase the residence time in stomach and bioavailability. Different types of release viz. sustained, pulsatile and multiple pulsed release profiles have been achieved in the past using gastroretentive systems. 13 mm tablets were prepared to achieve dual mechanism for gastric retention (Khosla and Davis, 1990).

Currently available gastroretentive sustained systems are classified as matrix and reservoir type. Matrix type systems use multiple polymers at loading 15-90 % by weight to sustain the drug release over an extended period (US patent 6723340).

Polymers used for gastroretentive matrices include high molecular weight hydroxypropyl methylcellulose (HPMC) and poly (ethylene oxide), since systems based on HPMC alone are difficult to clear from the stomach after the drug release is complete. Since PEO swells and dissolves over an extended period, these blends have to be used judiciously to achieve desirable floating, swelling and dissolution of matrices and drug release profiles. These blends result in systems which swell over a prolonged period but do not dissolve completely. Hence there is a need to develop polymers which exhibit a wide variety of swelling / dissolution characteristics which could be used for preparation of such blends based on HPMC. Gastroretentive reservoir systems to achieve sustained release of highly soluble drugs use multiple polymers (Krogel and Bodmeier, 1999, Lunio and Sawicki, 2006, and Sawicki and Glod, 2004) are reported in literature. The matrix systems result in a burst release followed by sustained drug release for 24 h (Londhe et al, 2010 and Patel et al, 2009). It was suggested that reservoir systems be developed for highly soluble drugs in order to ensure better control on the drug release. Ideally the polymers to be used as coatings should have high swelling, permeability to dissolution medium and flexibility in dry and wet state and low CO_2 permeability (Sungthongjeen et al (2008) and Krogel and Bodmeier (1999). Polymers such as Eudragit RL30D and Eudragit NE30D have high permeability for dissolution medium and resulted in rapid drug release (Krogel and Bodmeier, 1999, Lunio and Sawicki, 2006, and Sawicki and Glod, 2004). Eudragit RS30D based system required buoyancy time of 70 min and also released only 4 % VER in 4 h. Thus, the existing polymers when used as blend could not sustain VER release over a prolonged period. Hence there exists a need to develop new polymers which would be useful as coating, provide acceptable floating as well as have the ability to sustain the drug release for prolonged period. This could be achieved by encapsulation of effervescent drug cores with a pH sensitive polymer which swells but does not dissolve, has high flexibility in dry and wet state and has ability to sustain the drug release.

Pulsatile type release systems have been exploited for the design of chronotherapeutic systems for the drugs used in the treatment of diseases which exhibit circadian rhythm. Systems reported earlier provided predetermined a lag time followed by drug release. These systems were formulated exploiting osmosis (Bi et al, 2007), colon targeting (Patel and Amin, 2011 and Mastiholimath et al, 2007) and erosion (Fukui et al, 2000) and combination of floating and pulsatile

principle (Sher et al, 2006, Sharma and Pawar 2006). These systems necessitated multiple components and their transit time in gastrointestinal tract could not be controlled as it was affected by variable gastric emptying process. Zou et al (2008) suggested use of a pulsatile system with gastroretentive characteristics to overcome the effect of variable gastric emptying. The system was based on tablet in tablet approach and was not easily amenable for large scale manufacture. Thus, there is a need to develop a polymer which could be used for chronotherapeutic delivery system which offers better control over transit time of dosage form. This could be achieved by encapsulation of the drugs in a pH sensitive polymer which swells and dissolve.

The systems which provide multiple pulsed release in stomach were exploited to avoid development of resistance in antibacterial therapies (WO2007/079082 assigned to Advancis Pharmaceutical Corp.). The product developed resulted in first rapid pulse from immediate release fraction, second pulse after a lag time from time dependent rupturable coating and third pulse which provided sustained release after a lag time using rupturable coatings. The extent of rupture was governed by the ratio of soluble to insoluble film coating or additives and thus the lag time and duration of drug release after the lag could be manipulated. While it was desired to avoid pulse collapse, the said patent could achieve this only partially as the pulse overlapped with each other. The inventors also emphasized the need to design systems which could provide multiple pulsed release, separate the pulses and extend the gastric residence time in order to increase bioavailability of drugs. Fabrication of such system would be possible if we could prepare pH sensitive polymers which exhibit a wide variety of swelling / dissolution characteristics. The drugs could be encapsulated using these polymers and release profiles with different lag times and release times could be obtained.

Sustained release in intestine was achieved using multiple polymers (Biju et al, 2004) and using complex geometric shapes of dosage forms (Kim, 2005). These systems used a combination of enteric polymer and swellable polymer or required multiple steps for fabrication of dosage forms. Conventional enteric polymer Eudragit L100 is random copolymer of MAA and MMA which dissolve above pH 6. Increase in the hydrophobic monomer (MMA) content of the polymer just increased the values of threshold pH at which polymer dissolved; e.g. Eudragit L100 dissolves above pH 6 and Eudragit S dissolves above pH 6.5. Methacrylic acid copolymers

could offer polymers with a wide variety of swelling / dissolution characteristics and could be useful to achieve sustained release at intestinal pH.

In summary, this chapter discussed current approaches, polymers used, advantages and limitations of polymers and systems and highlighted need of new polymers which can be used for development of new type of systems in NDDS.

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Chapter 2

Objectives and scope of investigation

After judicious review of literature on prior efforts for the development of NDDS, this investigation was undertaken to design, synthesize, characterize and evaluate new pH sensitive polymers for NDDS.

Present investigation focuses on design, synthesis and characterization of pH sensitive polymers and their evaluation for oral drug delivery systems. Acidic and basic pH sensitive polymers would be synthesized and their swelling and dissolution characteristics would be exploited for preparation of NDDS. pH sensitive polymers containing MMA, BMA and VP would be synthesized and evaluated for floating matrix tablet, floating sustained release system, chronotherapeutic delivery of drugs and gastroretentive multiple pulsed release systems. Also, methacrylic acid copolymers would be developed and evaluated for sustained release of drugs in the intestine.

More specifically, the present investigation has been undertaken with following objectives:

1. Design and synthesize pH sensitive polymers which exhibit a wide variety of swelling / dissolution characteristics at acidic pH. Polymers with following characteristics would be synthesized.

- Polymers which swell but do not dissolve
- Polymers which swell and dissolve
- Polymers which dissolve directly without swelling

2. Characterize pH sensitive polymers for composition, molecular weight, glass transition temperature and swelling / dissolution behavior.

3. Evaluate pH sensitive polymers as modulator of swelling / dissolution characteristics and drug release from gastroretentive matrices based on HPMC.

4. Evaluate pH sensitive polymers which swell but do not dissolve for reservoir type floating sustained delivery of drugs.

5. Evaluate pH sensitive polymers which swell followed by dissolution over an extended period at acidic pH for gastroretentive chronotherapeutic delivery.

6. Evaluate pH sensitive polymers which swell followed by dissolution over an extended period at acidic pH for gastroretentive multiple pulsed delivery.

7. Develop and evaluate multiple pulsed release systems based on above results.

8. Investigate factors influencing the performance of reservoir type floating systems. These include gas generating agent concentration in the tablet core, amount and type

of diluents, drug choice, polymer swelling / dissolution characteristics and coating level.

9. Monitor morphological changes during swelling / dissolution of polymer films by SEM. This will help to understand drug release mechanism.

10. Synthesize copolymers of methacrylic acid and oligolactide methacrylate macromer varying in methacrylic acid content and characterize the same for acid content, glass transition temperature, and swelling / dissolution behavior at neutral pH.

11. Evaluate these copolymers for sustained drug release under simulated intestinal conditions.

12. Elucidate the drug release mechanism for drug loaded copolymer films.

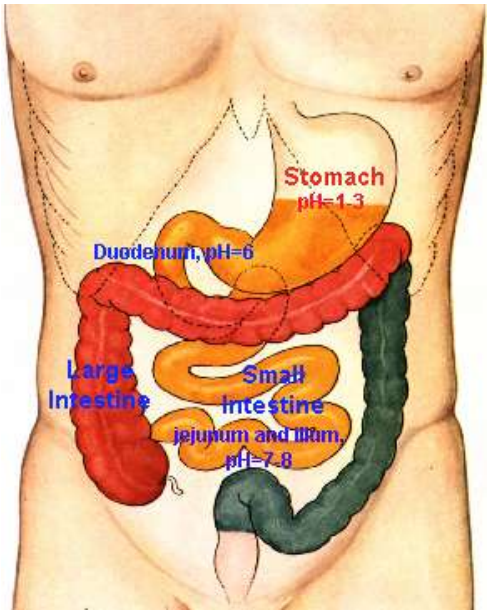
Chapter 3

Basic pH sensitive polymers: Synthesis and characterization

3.1 Introduction

3.1.1 Importance of pH sensitive polymers

The gastrointestinal tract presents variety of milieu depending upon the region. The pH values along gastrointestinal tract depend on the location and pH increases from stomach to rectum. The pictorial representation of changes in pH according to anatomy of gastrointestinal tract is shown in figure 3.1. Variation in pH along the gastrointestinal tract has led to development of pH dependent polymers for drug delivery.



Organ	pH
Stomach	1-3
Duodenum	6
Jejunum	7-8
Ileum	7-8

Figure 3.1: Pictorial representation of human gastrointestinal tract

3.1.2 Types of pH sensitive polymers

Enteric polymers were developed to protect the drugs from acidic environment of the stomach and release the drug in intestine. Enteric polymers remain collapsed at the acidic pH and dissolve at near neutral pH. Enteric polymers are based on methacrylic acid / acrylic acid, phthalate / acetate phthalate or acetate succinate derivatives with methyl methacrylate or hydroxypropylmethylcellulose (HPMC). Several formulations have exploited pH dependent dissolution behavior. Such systems include delayed release products for omeprazole, pantoprazole, rabeprazole, didanosine, etc. Another rationale for the preparation of enteric coated dosage forms is to avoid gastric irritation caused by pharmaceutical actives such as NSAIDs. Enteric polymers are

also useful for preparation of sustained release systems for drugs which show burst release in the stomach.

Reverse enteric polymers swell / dissolve at acidic pH and are insoluble / swellable at pH above 5.5. Eudragit EPO is a reverse enteric polymer. It is composed of MMA, BMA and DMAEMA. Due to cationic monomer DMAEMA, it swells at acidic pH. Eudragit EPO is used for taste masking of bitter drugs and as release modifier in floating systems (Fukuda et al, 2006). Menjoge and Kulkarni (2007) developed a self-associated cationic polymer, NREP (New reverse enteric polymer) and used for taste masking applications and inhibition of polymorphism of active pharmaceutical ingredient. NREP is composed of MMA, HEMA and VP. The protonation of nitrogen causes ionization of amino group and facilitates dissolution of polymer. As pK_a of VP is 5.45-5.65 (Park et al, 1999), which is lower than that of DMAEMA (pK_a 8.4) (Tomme et al, 2005), NREP dissolves at acidic pH rapidly than Eudragit EPO and is insoluble at neutral pH. This property of NREP was advantageous over Eudragit EPO and hence the former was utilized for preparation of taste masked suspensions. Thus, pH sensitive polymers which exhibit enteric and reverse enteric behavior are used for delayed release and taste masking applications.

3.1.3 Limitations of existing pH sensitive polymers

Currently available pH sensitive polymers are not suitable for preparation of gastroretentive formulations which would provide drug release in sustained or pulsatile manner. Eudragit EPO and NREP dissolve rapidly at acidic pH and can not be used to prepare gastroretentive sustained release systems. Also enteric polymers are impermeable to 0.1 N HCl and can not impart floating characteristics to formulations although can sustain drug release. Hence there exists a need for design of new pH sensitive polymers which would be useful for the preparation of gastroretentive systems for sustained and pulsatile release.

3.1.4 Our approach and role of basic pH sensitive polymers

It would be advantageous to prepare pH sensitive polymers which would exhibit a variety of swelling / dissolution properties in 0.1 N HCl. These polymers would find applications in gastroretentive systems. Dorozynski et al (2011) used blends of carrageenan with HPMC to prepare blends with a variety of swelling and erosion properties. The differences in swelling and erosion behavior were attributed to structures of carrageenans. Following similar approach, we proposed a series of polymers containing MMA, BMA and VP, wherein hydrophilic HEMA in NREP was

replaced with hydrophobic BMA. This would lead to swellable polymers rather than soluble ones. By varying VP content of polymers, the swelling / dissolution of polymers could be manipulated. Polymers with different MMA/BMA ratio could be prepared to yield variety of swelling / dissolution profiles. Thus we envisaged synthesis of pH sensitive polymers which i) swell, ii) swell and dissolve and iii) dissolve without swelling. The wide range of swelling / dissolution properties of pH sensitive polymers can be exploited for different applications which are discussed in subsequent chapters.

3.2 Experimental section

3.2.1 Materials

MMA, BMA, VP and deuterated chloroform ($CDCl_3$) were purchased from Aldrich Chemicals, India. 2, 2' azobisisobutyronitrile (AIBN) was purchased from a local supplier. N, N', dimethylformamide GR grade (DMF) and dichloromethane were purchased from Merck Chemicals, India.

3.2.2 Methods

3.2.2.1 Synthesis of basic pH sensitive polymers

The pH sensitive polymers of varying compositions were synthesized by conventional free radical polymerization of MMA, BMA and VP using 1 mole % AIBN in DMF at 65 ºC for 24 h. The polymers were precipitated in distilled water followed by washing with distilled water and were dried at room temperature.

3.2.2.2 Characterization of basic pH sensitive polymers

3.2.2.2.1 ^{1}H NMR analysis of polymers

The polymer compositions were determined using ^{1}H NMR spectroscopy (Bruker, 200 MHz). The samples were dissolved in deuterated chloroform.

3.2.2.2.2 FTIR analysis of polymers

Infrared spectra were recorded using Perkin Elmer FTIR spectrophotometer in diffused reflectance mode. 3 mg of sample with 100 mg potassium bromide was mixed thoroughly in mortar and pestle and small quantity of mixture was placed in sample holder and scanned in the region 4000 cm^{-1} to 400 cm^{-1}.

3.2.2.2.3 Glass transition temperatures of polymers

Differential scanning calorimeter (DSC), TA, Model Q10 was used to determine glass transition temperature of polymers at heating rate of 10 ºC/min from - 80 ºC to 200 ºC under nitrogen gas flow of 50 ml/min.

3.2.2.2.4 Molecular weights of polymers

The molecular weights of pH sensitive polymers were determined using gel permeation chromatography (GPC) using HPLC grade chloroform as a solvent at 1 ml/min flow rate. The samples were filtered through 0.45 micron filters.

3.2.2.2.5 Swelling / dissolution studies of polymer films

Swelling / dissolution studies of polymers varying in compositions were performed on polymer films of about 200 μm thickness prepared using solvent casting method. The study was carried out in 0.1 N HCl at 37 ± 0.5 ºC. The weights of polymer films were taken periodically after removing excess of medium gently with tissue paper. The degree of swelling (DS) was determined using following formula:

$$\text{Degree of swelling} = [(W_s - W_d)/W_d] \times 100$$

Where, W_d and W_s are weights of dry and swollen polymer respectively.

In case of polymer films which dissolve, percent dissolution was determined by following formula:

$$\text{Percent dissolution} = [(W_t - W_d)/W_d] \times 100$$

Where, W_d and W_t are weights of dry polymer and weight at time‘t’ respectively.

3.3 Results and discussion

Existing reverse enteric polymers such as NREP and Eudragit EPO dissolve at acidic pH and hence have limited applications in NDDS. Thus, pH sensitive polymers containing MMA, BMA and VP which exhibit a wide variety of swelling and dissolution characteristics at acidic pH were synthesized. The swelling and dissolution characteristics of these polymers could be exploited for the preparation of variety of NDDS.

3.3.1 Synthesis of basic pH sensitive polymers

The basic pH sensitive polymers were obtained as white free flowing powders. These were soluble in dichloromethane, chloroform and insoluble in water, diethyl ether.

3.3.2 ^{1}H NMR and FTIR analysis of polymers

The polymer compositions were determined using integrations of δ values at 3.59 ppm, 3.95 ppm and 8.44 ppm for MMA, BMA and VP respectively. The

compositions of polymers are shown in table 3.1. The chemical structure of pH sensitive polymer is shown in figure 3.2. The representative ^{1}H NMR and FTIR spectrum of a pH sensitive polymer is shown in figure 3.3 and 3.4 respectively. The polymers with different MMA to BMA ratios but same VP content were grouped as series A, B and C. Series A, B and C comprised 11-12, 18-19 and 30-34 mole % VP and different MMA/BMA ratios.

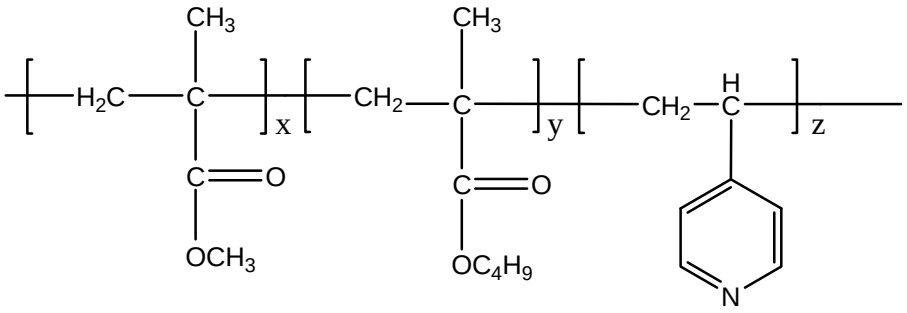


Figure 3.2: Chemical structure of basic pH sensitive polymer

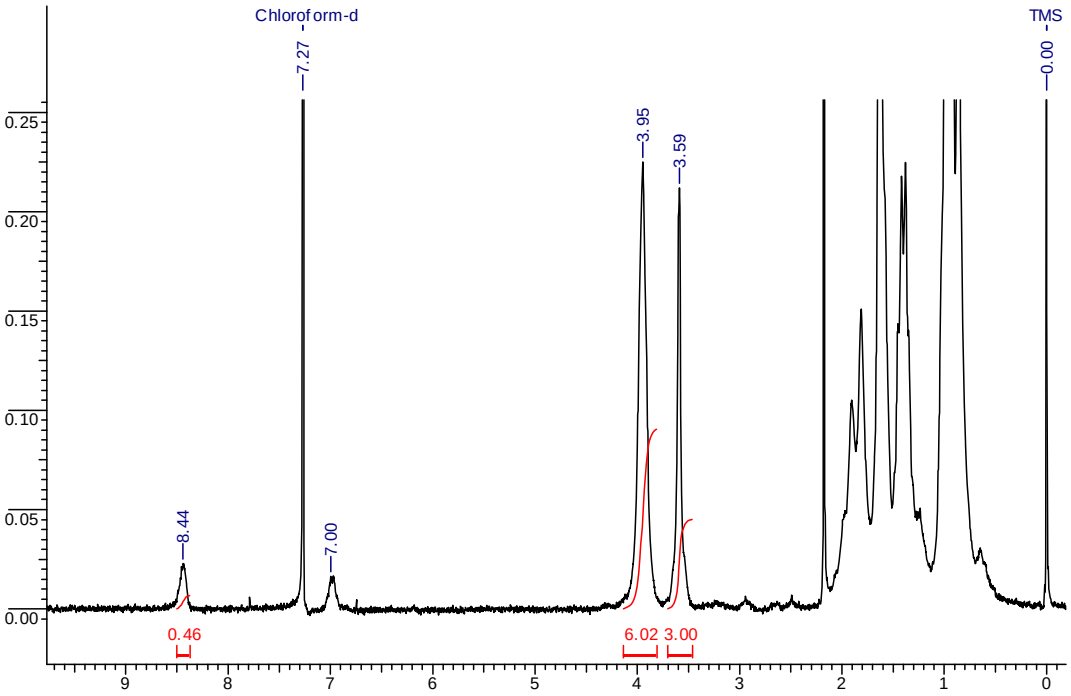


Figure 3.3: ^{1}H NMR spectrum of a basic pH sensitive polymer

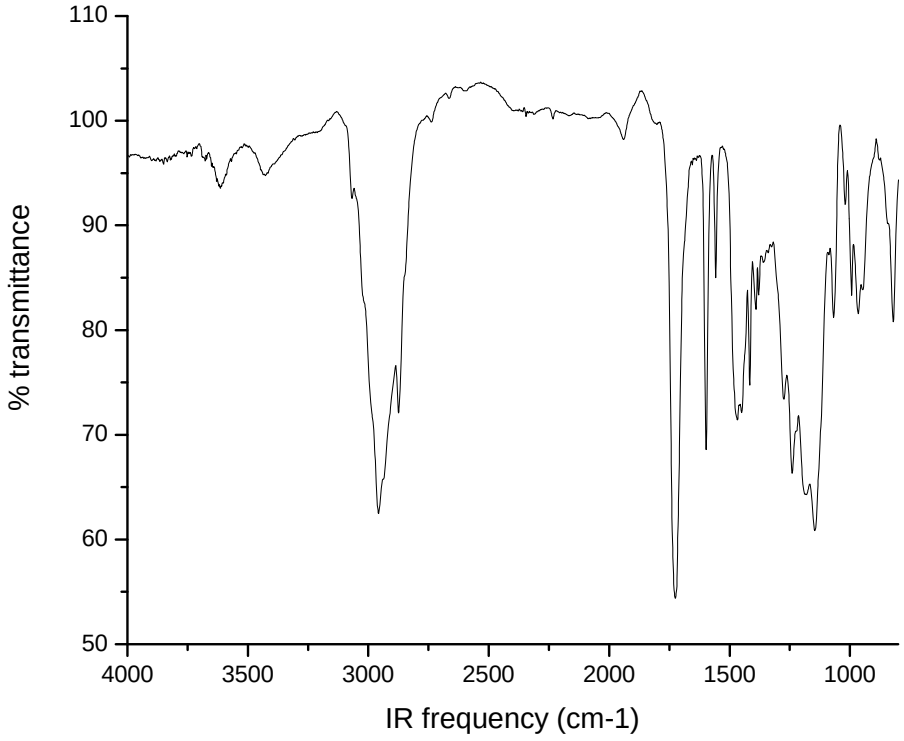


Figure 3.4: FTIR spectrum of a basic pH sensitive polymer

The FTIR spectrum of pH sensitive polymer exhibited following peaks:
A peak at 3614 cm^{-1} for free hydroxyl groups, 1716 cm^{-1} for free ester, peaks at 2858 cm^{-1} to 2962 cm^{-1} for methyl C-H asymmetric / symmetric stretch, 1419 cm^{-1} to 1465 cm^{-1} for methyl asymmetric / symmetric bend, 1188 cm^{-1} to 1272 cm^{-1} for C-O stretch, 1549 cm^{-1} to 1594 cm^{-1} and 994 cm^{-1} for characteristic of a pyridine ring.

3.3.3 Glass transition temperatures of polymers

The glass transition temperatures (T_g) of pH sensitive polymers were determined to evaluate the effect of polymer composition on the nature of polymers. The reported T_g of homopolymers of MMA, BMA and VP are 100 ºC (Kuo et al, 2003), 36 ºC (Fernandez-Garcia et al, 2002) and 157 ºC (Cesteros et al, 1993) respectively. The T_g values for polymers are summarized in table 3.1. At constant VP content, varying MMA/BMA ratio caused differences in T_g values. Increase in BMA caused reduction in T_g of pH sensitive polymers in series A-C. The T_g of pH sensitive polymers was in the range 35-101 ºC. Thus DSC revealed that the polymers exhibit both glassy and rubbery behavior depending on composition.

3.3.4 Swelling / dissolution studies of polymer films

This study was carried out to investigate effect of VP content and MMA/BMA ratio on swelling and dissolution characteristics of pH sensitive polymers (table 3.1). The swelling kinetics of series A and B polymers is shown in figures 3.5 and 3.6 respectively. The polymer films prepared using series A having VP content of 11-12 mole % swelled and did not dissolve for 24 h.

Table 3.1: Compositions and properties of basic pH sensitive polymers

S No	Polymer	MMA:BMA:VP (mole%)	Swelling/dissolution	MW (Da)	PI	T_g (°C)
1	A1	66:23:11	307 %	43650	1.93	88
2	A2	55:33:12	209 %	41430	1.85	79
3	A3	44:45:12	129 %	35850	1.76	63
4	A4	31:57:12	83 %	32200	1.73	57
5	A5	21:67:12	17 %	33400	1.75	50
6	A6	15:73:12	2 %	35200	1.81	47
7	A7	11:77:12	23 %	35300	1.83	46
8	A8	00:89:11	26 %	34800	1.83	35
9	B1	62:20:18	Swells 492 % and dissolves	31500	1.62	95
10	B2	51:31:18	Swells 295 % and dissolves	34800	1.70	82
11	B3	43:38:19	Swells 207 % and dissolves	36100	1.69	75
12	B4	27:54:19	Swells 264 % and dissolves	38100	1.70	61
13	B5	19:63:18	Swells 295 % and dissolves	46000	1.74	56
14	B6	15:67:18	Swells 703 % and dissolve	40580	1.79	51
15	C1	53:17:30	Soluble	25700	1.56	101
16	C2	45:22:33	Soluble	27200	1.61	91
17	C3	35:30:34	Soluble	30200	1.63	80
18	C4	22:43:34	Soluble	34300	1.60	68
19	C5	17:50:33	Soluble	34400	1.54	60

MW: molecular weight and PI: Polydispersity Index

The polymer films of series B having VP content of 18-19 mole % swelled followed by dissolution over 24 h. The polymer films prepared using series C polymers having VP content 30-34 mole % dissolved without swelling within an hour. Thus the VP content of polymers governed whether polymer swelled / dissolved and MMA/BMA

ratio in the polymers governed the rate and extent of swelling characteristics of polymers.

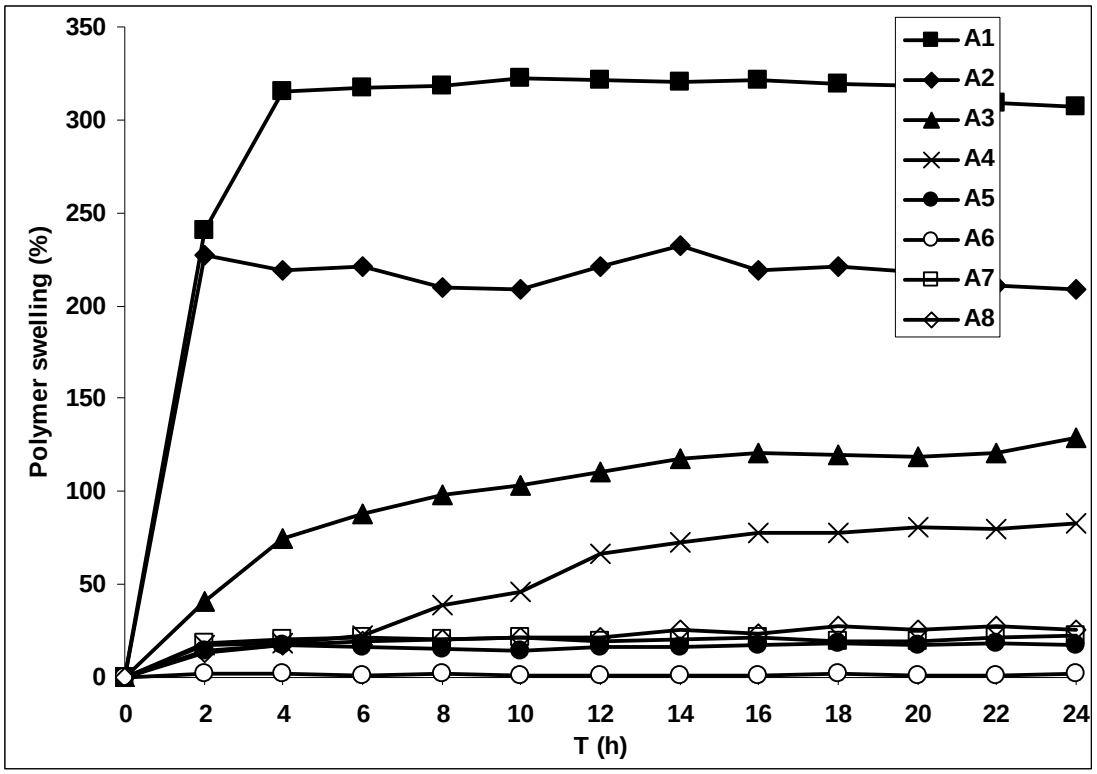


Figure 3.5: Swelling kinetics of series A polymer films

Increase in BMA content of polymers of series A caused lowering of equilibrium swelling. Series A polymers exhibited equilibrium swelling in the range 2-300 %. In the case of series B polymers, increase in BMA content resulted in reduction in swelling rate and increased the time to attain equilibrium swelling. The polymers exhibited equilibrium swelling in the range 200-700 %.

It was reported that an ideal polymer for reservoir GRS for sustained release should swell but should not dissolve (Krogel and Bodmeier, 1999). This was essential to sustain the drug release when polymer is in swollen state and to maintain integrity of system. Thus, the swelling characteristics of series A polymers were exploited as coatings for preparation of gastroretentive sustained delivery systems and are discussed in subsequent chapters.

The polymer coatings which swell and erode provide lag time followed by drug release. This behavior was used to provide pulsatile drug delivery (Fukui et al, 2000 and Cao et al, 2004). Also, pulsatile release could be exploited for the preparation of

chronotherapeutic systems (Bi et al, 2007). Thus polymers of series B were further evaluated as coatings for pulsatile and chronotherapeutic gastroretentive systems and are discussed in subsequent chapters.

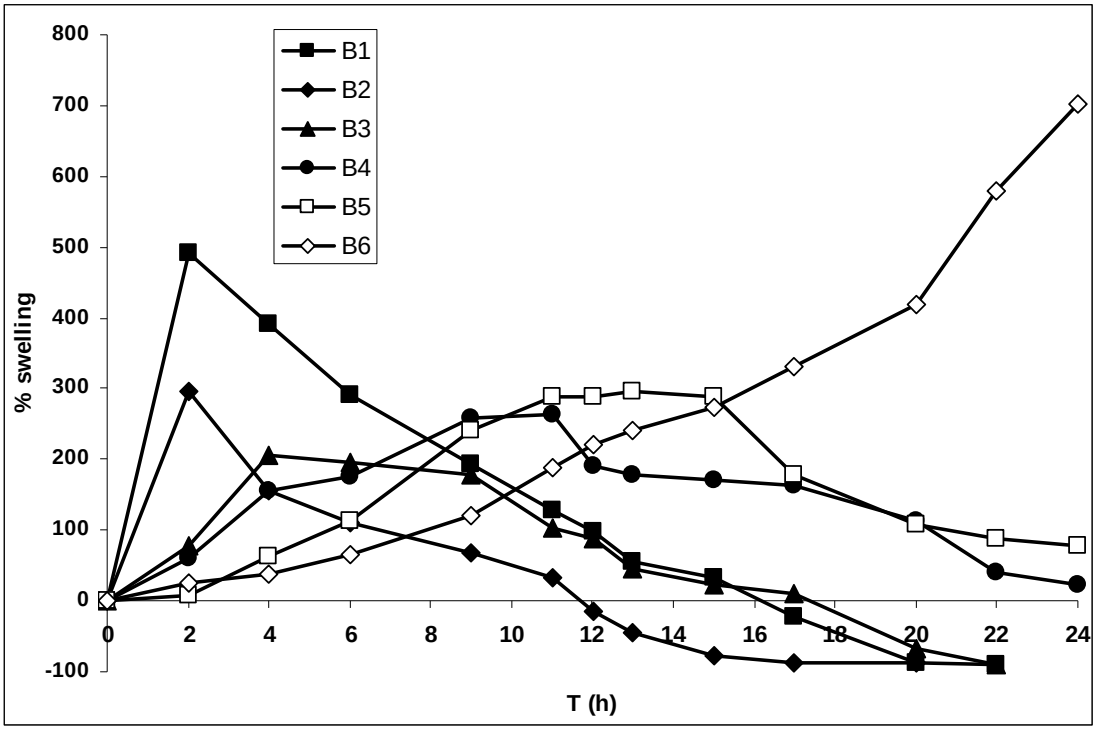


Figure 3.6: Swelling / dissolution of series B polymer films

The polymers of series C dissolved without swelling and were not suitable for sustained or pulsatile gastroretentive systems and hence were evaluated as modulator of swelling / dissolution and drug release characteristics of floating matrix tablets along with high viscosity HPMC. Also the series A and series B polymers were evaluated.

3.4 Conclusions

Three series of basic pH sensitive polymers containing MMA, BMA and VP have been synthesized and characterized for polymer composition, molecular weight, T_g and swelling and dissolution behavior at acidic pH. Depending on VP content, the polymers swelled / dissolved. Also varying MMA/BMA ratios yielded polymers which exhibited different equilibrium swelling / time to reach equilibrium swelling. The series A polymers having VP content 11-12 mole % swelled but did not dissolve while those with VP content 18-19 mole % swelled and dissolved over an extended period of 24 h. Polymers having VP content 30-34 mole % dissolved directly without

swelling. These polymer characteristics were exploited as a) modulators release of floating matrix tablets and polymeric coatings in the development of b) floating sustained delivery, c) chronotherapeutic drug delivery and d) gastroretentive multiple pulsed delivery and are discussed in chapters 4-7 respectively.

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Chapter 4

Modulation of properties of floating matrix tablets using basic pH sensitive polymers

4.1 Introduction

Oral drug delivery has been known for decades as the most convenient and widely used route of administration amongst all other routes that have been explored for the systemic drug delivery. All controlled release systems have limited effectiveness if the systems can not remain in the vicinity of the absorption site. Gastric emptying studies revealed that orally administered controlled release dosage forms are subjected to two complications: 1) short residence time and 2) unpredictable gastric emptying (Chawla et al, 2001). The absorption window of drugs is often restricted to stomach as a result of differences in solubility and stability of drugs in different regions of gastrointestinal tract, presence of enzymes, variation in pH and interaction with endogenous components such as bile salts. It is therefore necessary to devise means to retain such drugs in stomach for longer duration. Gastric retention system is one of the ways to ensure maximum drug absorption in gastrointestinal tract for the drugs which exhibit limited absorption in lower part of GI tract.

Gastroretentive drug delivery systems are desirable for several categories of drugs (Singh and Kim, 2001): 1) drugs for local action in stomach, e.g. 5-fluorouracil, antacids; 2) drugs unstable in lower part of gastrointestinal tract, e.g. captopril; 3) drugs insoluble in intestinal fluids, e.g. Propranolol HCl, metoprolol, diazepam; 4) drugs with variable bioavailability, e.g. sotalol hydrochloride, levodopa; and 5) drugs which exhibit site specific absorption in stomach or upper intestine, e.g. atenolol, levodopa, salbutamol, sotalol hydrochloride. Riboflavin (Kagan et al, 2006), metformin (Stepensky et al, 2001 and Marathe et al 2000), ciprofloxacin (Harder et al, 1990) and valacyclovir (Kagan and Hoffman, 2008) are preferably absorbed from stomach or proximal intestine.

Various approaches used to achieve gastric retention include a) floating systems, b) swelling and expanding systems, c) bioadhesive systems, d) modified shape systems and e) high density systems. The details of each approach to gastric retention are discussed below in brief.

Floating systems or hydrodynamically balanced systems have bulk density lower than gastric fluids and thus remain buoyant in stomach without affecting the gastric emptying rate for a prolonged period of time. After the release of the drug, residual system is emptied from stomach. This results in increase in gastric retention time (GRT) and a better control of fluctuations in plasma drug concentrations (Ali et al, 2007). Swelling type systems swell to an extent which prevents their exit from

stomach through pylorus and such systems are retained in stomach for prolonged period of time (US patent 6734340 and Arza et al, 2009). Bioadhesive systems are used to localize the delivery device within the stomach to enhance drug absorption in site specific manner (Lenaerts and Gurney, 1990). These systems use bioadhesive polymers that adhere to epithelial surface of the gastrointestinal tract. Modified shape systems have non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends which extend the GRT depending on size, shape and flexural modulus of drug delivery device (Cargill et al, 1998 and Caldwell et al, 1988). High density formulations include pellets which have a density greater than that of gastric contents. This is accomplished by using heavy inert materials such as barium sulfate, zinc oxide, titanium dioxide, iron powder (Guan et al, 2010).

Floating systems are the most widely investigated amongst these approaches. Most of the gastroretentive systems available in the market are based on floating mechanism (Singh and Kim, 2000). High viscosity grade HPMC is the most commonly used gelling agent for the preparation of floating systems. The floating system is effective only in the presence of sufficient fluid in the stomach; otherwise buoyancy of the dosage form is impeded during gastric emptying (Chueh et al, 1995). This serious limitation can be overcome by using a combination of floating system and other gastroretentive approaches (Chitnis et al, 1991). US patent 6723340 utilizes a combination of floating and tablet shape to ensure gastroretentivity. A combination of floating and bioadhesive matrix systems to prepare Ciprofloxacin HCl gastroretentive tablets by incorporation of Na CMC as bioadhesive agent with HPMC was reported (Varshosaz et al, 2009). Thus often a combination of two approaches is necessary to devise effective gastroretentive drug delivery systems.

4.1.1 Approaches to modulation of properties of floating matrix tablets

The floating matrix systems were prepared using HPMC along with additives such as superdisintegrants (Chavanpatil et al, 2006 and Arza et al, 2009), cellulose derivatives (Varshosaz et al 2009 and Jagdale et al, 2009), polysaccharides (Dorozynski et al, 2011) and polyethylene oxide (US patent 6723340). Also gas generating agents were used to promote floating of tablets.

A pH sensitive polymer such as Eudragit EPO was used in floating tablets based on hot melt extrudates along with Eudragit RSPO. Chlorpheniramine maleate tablets based on hot melt extrudates were prepared using Eudragit RSPO, Eudragit EPO, sodium bicarbonate and microcrystalline cellulose. Increase in content of Eudragit

EPO caused increase in drug release rates; however the buoyancy was compromised (Fukuda et al, 2006). Gas generating components typically sodium bicarbonate and anhydrous citric acid were used to improve floating characteristics. Formation of carbon dioxide after contact with aqueous medium caused entrapment of generated gas in the gel layer produced by HPMC, achieving density lower than gastric contents and subsequently buoyancy of the system.

Arza et al (2009) investigated superdisintegrant as additive for CIP floating matrices. Different Methocel grades varying in viscosities such as Methocel K100LV, Methocel K15M and Methocel K100M were evaluated for floating matrices using superdisintegrants (crosspovidone, sodium starch glycolate and crosscarmellose sodium) as swelling agents and gas generating substance (sodium bicarbonate). Superdisintegrants were required to enhance swelling and drug release from matrix. Tablets prepared with Methocel K100LV and Methocel K15M exhibited faster drug release, and as the concentration of Methocel polymers was increased, the drug release was retarded. Also, Methocel K15M exhibited poor swelling and rapid dissolution as compared to Methocel K100M. Therefore, Methocel K100M was used in combination with superdisintegrant to enhance swelling and drug release from the matrix. The blends of superdisintegrant and Methocel K100M resulted in swellable floating tablet which sustained release of CIP over 12 h. Incorporation of sodium bicarbonate resulted in floating lag time of few seconds.

Chavanpatil et al (2006) investigated crosspovidone as swelling agent for swellable bioadhesive Ofloxacin tablets based on Psyllium husk, Methocel K100M and sodium bicarbonate. Ofloxacin tablets with no crosspovidone showed slower drug release than marketed preparation. Thus, crosspovidone and β-cyclodextrin were added to increase swelling and subsequently ensure faster and complete drug release than Ofloxacin tablets sans crosspovidone and β-cyclodextrin. The faster and higher swelling of tablets led to enhanced diffusion of Ofloxacin.

Varshosaz et al (2009) investigated blend of Methocel K100M and sodium carboxymethylcellulose (Na CMC) for mucoadhesive gastroretentive system for CIP. CIP tablets containing Methocel K100M and sodium bicarbonate released only 40-50% drug in 8 h. Thus NaCMC had to be incorporated in order to enhance tablet swelling and impart mucoadhesive characteristics. Increase in Na CMC content in the blend accelerated released of CIP. These tablets released CIP over a period of 8 h and exhibited a buoyancy time of 50 seconds.

Jagdale et al (2009) investigated Propranolol HCl floating tablets based on Methocel K4M, hydroxypropylcellulose (HPC) and microcrystalline cellulose. Propranolol HCl tablets prepared with Methocel K4M alone, could swell and float, but resulted in incomplete drug release because of poor swelling of Methocel K4M matrix. Incorporation of HPC and MCC enhanced the swelling and helped retain the drug at the site for a longer time so as to extend the release of Propranolol HCl upto 18 h.

Dorozynkski et al (2011) investigated low viscosity grade HPMC (Metolose 65 SH400) blend with carageenan.

κ-carrageenan and HPMC blend showed floating and sustained release of drug for 8 h. λ-carrageenan promoted hydration of matrix followed by erosion of matrices. HPMC and carrageenan blends were reported for pH independent release by Bonferoni et al (1998) who demonstrated that erosion of carrageenan matrices was accelerated at acidic pH. It was also reported that erosion of carrageenan could be controlled by the incorporation of slowly eroding polymer HPMC (Nerurkar et al, 2005).

US patent 6723340 assigned to Depomed Inc. disclosed use of HPMC and polyethylene oxide for the preparation of oval shaped floating tablets. This combination offered unique benefits of drug release control and allowed tablet swelling to achieve gastric retention and gradual disintegration of dosage form so that it was cleared from the stomach after the drug release was complete. HPMC has low swelling and resulted in incomplete drug release. To overcome this limitation, PEO was used to enhance the drug release and floating characteristics.

4.1.2 Limitations of existing polymers for modulation of properties of floating matrix tablets

The existing approaches to modulation of properties of floating matrix tablets such as use of superdisintegrants, cellulose derivatives, polysaccharide and PEO exhibit limited applicability in terms of achieving desired release profiles and also most of these polymers except PEO resulted in systems which did not dissolve after the release was over. This may pose serious problem for clearance of dosage forms from stomach. Since PEO swells and dissolve, it can yield limited release profiles and swelling / dissolution characteristics of floating matrix tablets.

4.1.3 Our approach and role of basic pH sensitive polymers

The objective of this investigation was to design a basic pH sensitive polymer which swells in acidic medium and enhances the swelling of matrix when used along with HPMC and control the release of the drug and dissolve once the drug release is complete. The erosion of the polymer would ensure clearance of the system from the stomach.

We synthesized three types of pH sensitive polymers varying in swelling / dissolution characteristics as described in the chapter 3. While all pH sensitive polymers exhibited desired performance in terms of floating and drug release, there were reasons why different types of polymers were exploited. These are discussed in the results and discussion section. We formulated a series of CIP floating tablets with pH sensitive polymers that resulted in different extent of equilibrium swelling and dissolution characteristics. Hydroxypropyl methylcellulose (Methocel K15M) was used as gellable polymer. Mixture of sodium bicarbonate and anhydrous citric acid was used as gas generating system.

Ciprofloxacin HCl (CIP), a broad spectrum fluoroquinolone antibacterial agent is better absorbed from the stomach and proximal part of the intestine (Harder et al, 1990 and Varshosaz et al, 2006). The extended release formulations of CIP (Cipro XR and Proquin XR) are used for complicated and uncomplicated urinary tract infections (Bayer, 2005 and Esprit Pharma, 2005). It was therefore chosen as model drug for this investigation.

4.2 Experimental section

4.2.1 Materials

Magnesium stearate, sodium bicarbonate, anhydrous citric acid were purchased from Merck Chemicals, India. Lactose was purchased from S D Fine Chemicals Ltd, India. Ciprofloxacin HCl (CIP), Acetaminophen (ACP), Eudragit EPO and Methocel K15M were gift samples from Lupin Laboratories Ltd., India.

The basic pH sensitive polymers were synthesized and characterized as discussed in the chapter 3.

4.2.2 Methods

4.2.2.1 Preparation of floating matrix tablets

Floating matrix tablets were prepared using basic pH sensitive polymers of series A, B and C by direct compression method using pneumatic press. All ingredients were

weighed and mixed in a mortar and pestle. The tablets were compressed using 13 mm diameter dies. The tablet composition is given in table 4.1.

Table 4.1: Composition of floating matrix tablets

S No	Ingredient	Content (% w/w)
1	Drug	35
2	pH sensitive polymer	35
3	Methocel K15M	15
4	Sodium bicarbonate	7
5	Citric acid anhydrous	7
6	Magnesium stearate	1

CIP floating tablets using only Methocel K15M were also prepared. The effect of functionally related and commercially available polymer, Eudragit EPO was also compared. To investigate effect of drug type, Acetaminophen (ACP) floating tablets were prepared using C1, C3 and C5 polymers.

4.2.2.2 Swelling / dissolution studies of floating matrix tablets

Swelling / dissolution studies of CIP floating tablets prepared using pH sensitive polymers of series A, B and C were carried out as discussed in chapter 3.

4.2.2.3 Release and floating studies from floating matrix tablets

The drug release studies from floating matrix tablets were carried out using Electrolab dissolution apparatus, USP Type II, 50 rpm at 37 ± 0.5 ºC in 900 ml of 0.1 N HCl. 5 ml aliquots were withdrawn at predetermined time intervals. The dissolution medium was replenished with equal amount of fresh medium. The samples were filtered and analyzed by UV spectrophotometer at 277 and 244 nm for CIP and ACP respectively. The floating behavior of the tablets prepared using various basic pH sensitive polymers synthesized by us was monitored during the drug release experiments. The lag time to float the tablet was taken as buoyancy time (BT) and floating time (FT) was the time over which the tablet remained floated in the medium.

4.2.2.4 Interaction study between Methocel K15M and basic pH sensitive polymers

The interactions between Methocel K15M and a pH sensitive polymer, C4 were characterized by FTIR spectroscopy (Perkin Elmer spectrophotometer) using diffused reflectance mode. 3 mg of polymer blend and 100 mg potassium bromide was mixed thoroughly in mortar and pestle and small quantity of mixture was placed in sample

holder and scanned in the region 4000 cm^{-1} to 400 cm^{-1}. FTIR spectra were recorded for Methocel K15M, polymer C4 and their blend.

4.3 Results and discussion

Dorozynski et al (2011) investigated HPMC and carrageenan blends for L-dopa floating drug delivery systems. κ, λ and ι-carrageenans were evaluated for floating systems. Hydration studies of matrices prepared from HPMC and carrageenan blends revealed that after 120 min the degree of hydration was 21, 12 and 9 times for ι, κ and λ carrageenans respectively whereas the corresponding values were 16, 11 and 9 times at the end of 300 min. This showed that the order of swelling of the blends was governed by the type of carrageenan and was in the order ι > κ >λ. Erosion behavior of these blends revealed that at 300 min, all carrageenan blends eroded and % of weight remaining after 300 min was 45, 23 and 13 % for ι, κ and λ carrageenan blends. The matrices of κ-carrageenan and HPMC swelled continuously and the floatation of this formulation was ensured by the presence of dry core as evident from the MR images taken during dissolution studies. In case of ι and λ carrageenan based matrices, water penetration caused dissolution of dry core which resulted in loss of floating. The matrices based on all types of carrageenans floated immediately and sustained the drug release for 300 min. The difference in hydration behavior of carrageenans was due to structural differences and ability to form gels and hydration. This study revealed that the hydration and erosion behavior of HPMC and carrageenan blends determine the floating and drug release profiles. Following a similar approach, we synthesized a series of pH sensitive polymers containing MMA, BMA and VP for controlling the swelling and dissolution characteristics. MMA to BMA ratio was varied to manipulate sorption properties for polymers and VP was incorporated as pH sensitive monomer.

The compositions containing three different levels of VP were synthesized. Depending on VP content, polymers were grouped as series A, B and C polymers. Series A polymers swelled, series B polymers swelled and dissolved and series C polymers dissolved directly without swelling in 0.1 N HCl. Ciprofloxacin HCl (CIP) was chosen as model drug since its absorption is limited to stomach (Harder et al, 1990). Floating matrix tablets were prepared using Methocel K15M as gel forming polymer to maintain system integrity and pH sensitive polymer blend along with sodium bicarbonate and anhydrous citric acid as gas generating system. The carbon

dioxide gas generated was entrapped in the matrix gel and ensured floating of the tablets.

4.3.1 CIP floating matrix tablet prepared using Methocel K15M

4.3.1.1 Swelling / dissolution behavior of CIP tablet prepared using Methocel K15M

The effect of swelling behavior of CIP tablet prepared using Methocel K15M was investigated initially. The CIP floating tablet swelled within 2 h and the swelling practically remained constant for 24 h after small fraction dissolved out. The swelling behavior is shown in figure 4.1.

The swollen tablet did not dissolve upto 24 h and the tablets swelled 75-80 % of their original weight.

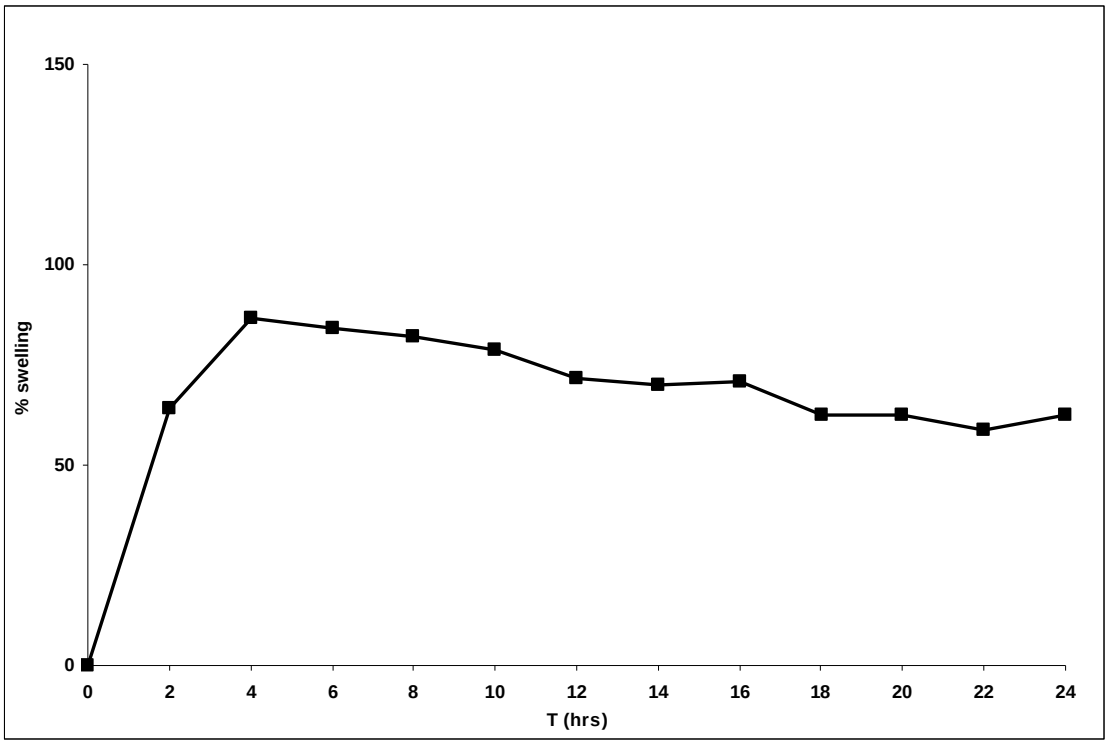

Figure 4.1: Swelling of CIP tablet prepared using Methocel K15M

The ideal floating matrix tablet should swell and float immediately followed by sustained drug release. The floating tablet should also dissolve after the drug release is complete to ensure its clearance from stomach.

4.3.1.2 Release and floating studies from CIP tablet prepared using Methocel K15M

CIP release from Methocel K15M based matrix is shown in figure 4.2.

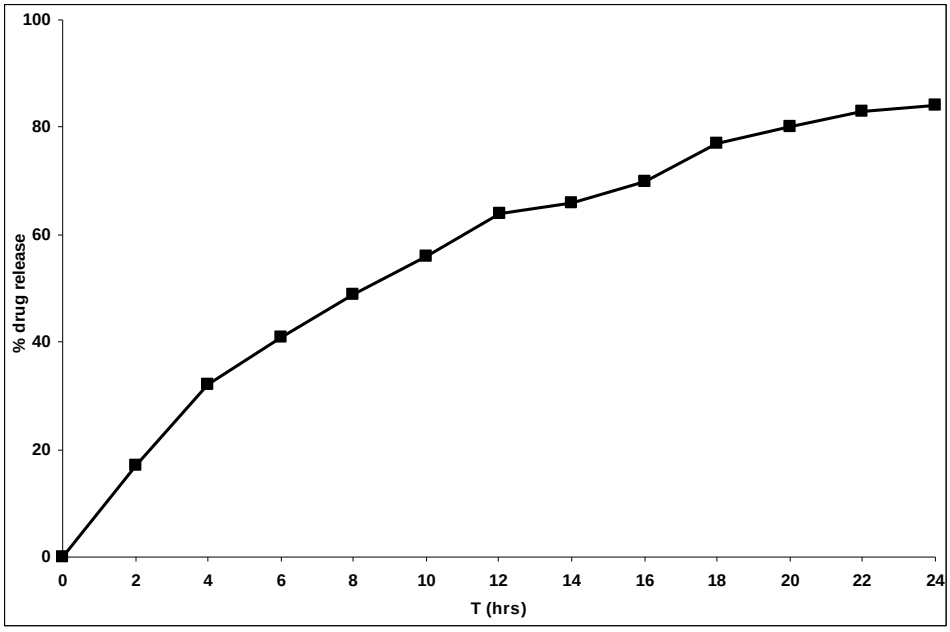

Figure 4.2: Release from CIP tablet prepared using Methocel K15M

CIP matrix tablet prepared using Methocel K15M floated within a minute. 80 % CIP release was observed from Methocel K15M in 24 h. To further enhance the drug release, we used Eudragit EPO along with Methocel K15M. This approach was similar to that reported by Jagdale et al (2009) who incorporated HPC and MCC in Methocel K4M to accelerate the release of Propranolol HCl. Chavanpatil et al (2006) also used crosspovidone and β-cyclodextrin along with Methocel K100M based Ofloxacin matrix tablets to accelerate drug release.

4.3.2 CIP floating tablet prepared using Methocel K15M and Eudragit EPO

Eudragit EPO is a cationic polymer which dissolves in acidic pH and thus may impart dissolution of the floating system as well as sustain the drug release. CIP tablet prepared using Methocel K15M and Eudragit EPO floated after 44 min. The CIP release from floating tablet prepared using blend of Methocel K15M and Eudragit EPO is given in figure 4.3.

The CIP tablet prepared using blend of Methocel K15M and Eudragit EPO exhibited poor floating properties. Burst release of about 60 % was observed within 2 h and the release was complete in 8-10 h. Thus Eudragit EPO was not suitable for preparation of CIP floating tablet because of poor floating as well as release characteristics. It was therefore necessary to vary the pH dependent swelling and dissolution characteristics of the polymers incorporated in Methocel K15M based matrix tablets.

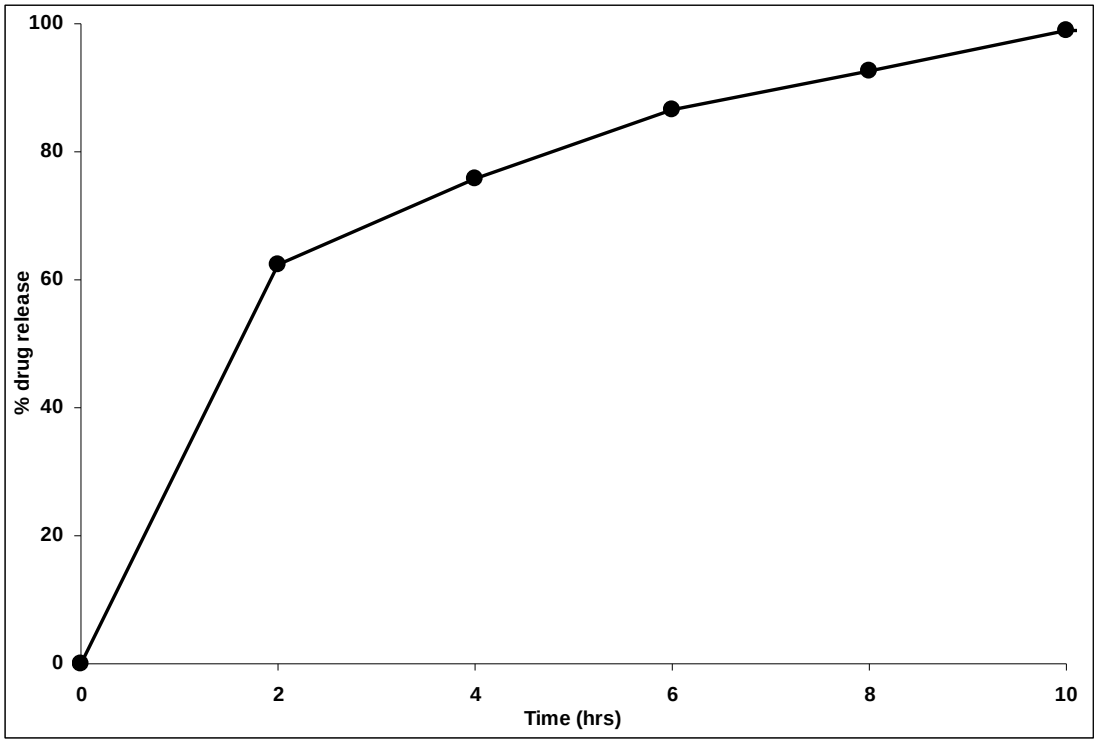

Figure 4.3: Release from CIP tablet prepared with Methocel K15M and Eudragit EPO

4.3.3 CIP floating matrix tablets prepared using Methocel K15M and series A polymers

The swelling and release characteristics of CIP floating matrix tablets prepared using series A polymers containing 12 mole % VP and MMA / BMA ratio of 3.0 to 0.3 are discussed below.

4.3.3.1 Swelling / dissolution studies of CIP tablets prepared using Methocel K15M and series A polymers

The swelling / dissolution of CIP floating tablets prepared using Methocel K15M and series A polymers is shown in figure 4.4.

Incorporation of series A polymers enhanced water penetration into tablets and resulted in higher swelling of CIP matrix tablets. The equilibrium swelling was achieved within 12 h in CIP floating tablets prepared with series A polymers. The tablets swelled to the extent of 150 to 200 % and remained swollen for 24 h. All the tablets prepared using series A polymers exhibited higher swelling than that prepared with Methocel K15M alone. The CIP matrix tablets swelled but did not dissolve which is critical for elimination of dosage form from the stomach. Therefore, we investigated series B polymers containing 18-19 mole % VP which we believed

would enhance the drug release as a result of swelling followed by dissolution of this series of polymers as reported earlier.

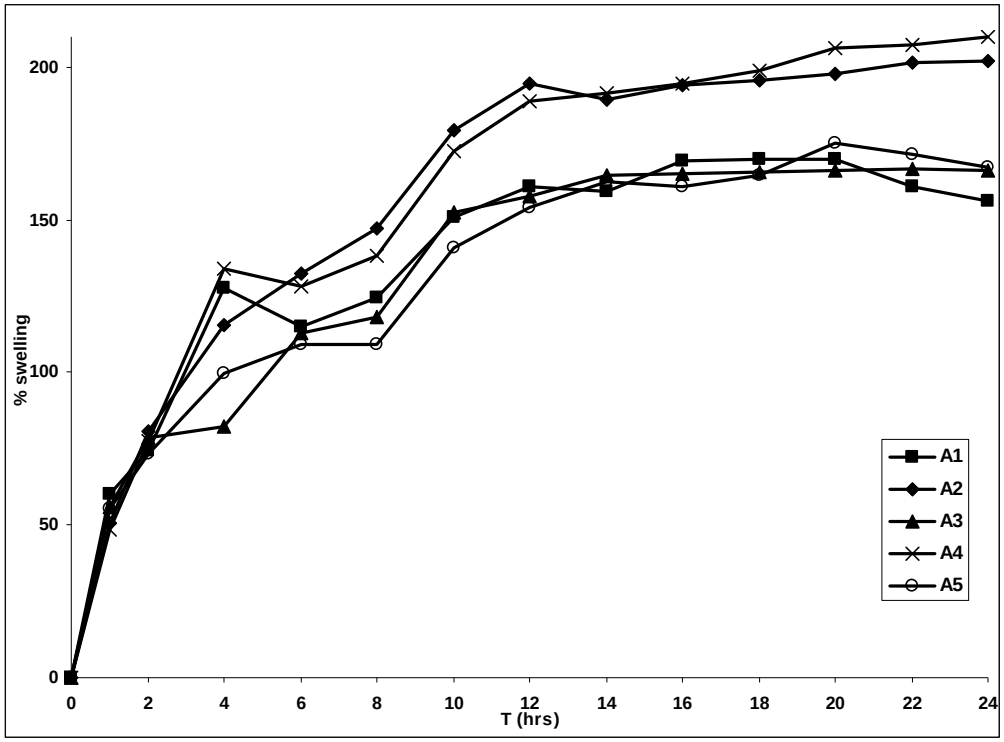

Figure 4.4: Swelling of CIP tablets prepared using Methocel K15M and series A polymers

4.3.3.2 Release and floating studies from CIP tablets prepared using Methocel K15M and series A polymers

The floating characteristics of CIP matrix tablets prepared using Methocel K15M and series A polymers are given in table 4.2. The drug release characteristics of CIP matrix tablets prepared using Methocel K15M and series A polymers are shown in figure 4.5.

All CIP tablets prepared using Methocel K15M and series A polymers floated immediately within a minute and remained floated for 24 h.

About 60-85 % of CIP was released from tablets prepared using Methocel K15M and series A polymers. The swollen polymers increased water uptake into floating matrices and increased drug release compared to release from matrices prepared using Methocel K15M alone. The incorporation of series A polymers sustained release of CIP as compared to the incorporation of Eudragit EPO. In the case of polymers A4 and A5 which exhibited lower degree of swelling, the drug release was not complete

even after 24 h. More importantly, the tablets did not dissolve at the end of 24 h. To increase drug release rate and to ensure that the tablets erode after drug release is complete, series B polymers containing 18-19 mole % of VP were evaluated.

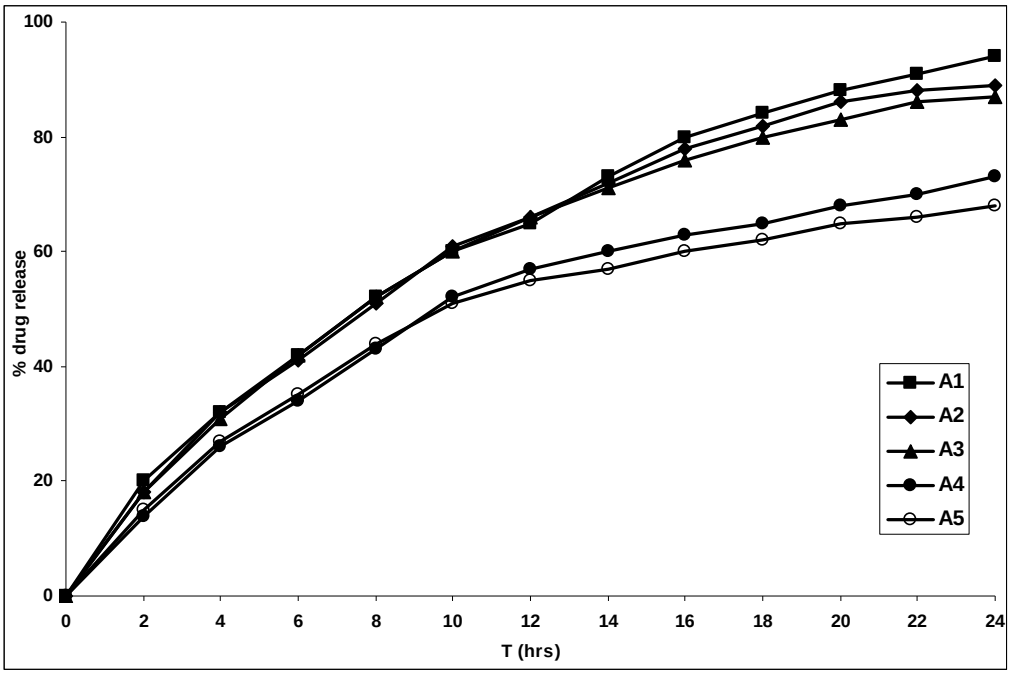

Figure 4.5: Release from CIP tablets prepared using Methocel K15M and series A polymers

Table 4.2: Floating of CIP tablets: Methocel K15M and series A polymers

Tablet code	BT (sec)	FT (h)
A1	29	24
A2	26	24
A3	39	24
A4	48	24
A5	26	24

4.3.4 CIP floating matrix tablets prepared using Methocel K15M and series B polymers

4.3.4.1 Swelling / dissolution studies of CIP tablets prepared using Methocel K15M and series B polymers

The swelling behavior of CIP floating tablets prepared using Methocel K15M and series B polymers is shown in figure 4.6.

The polymers of series B swelled and dissolved. The equilibrium swelling of series B based matrix tablets was achieved within 8 h as compared to 12 h in the case of series

A polymers and Methocel K15M matrices. The tablets remained swollen to the extent of 75 to 100 % of their original weight for 24 h. Thus, although the polymer films of series B swelled followed by dissolution, CIP floating matrix tablets exhibited only swelling but did not dissolve. This was because these polymers could not leach out of the gelling polymer HPMC in the tablets. The swelling / dissolution study of pH sensitive polymers showed that polymers of series A swelled and remained swollen for 24 h whereas polymers of series B swelled and dissolved.

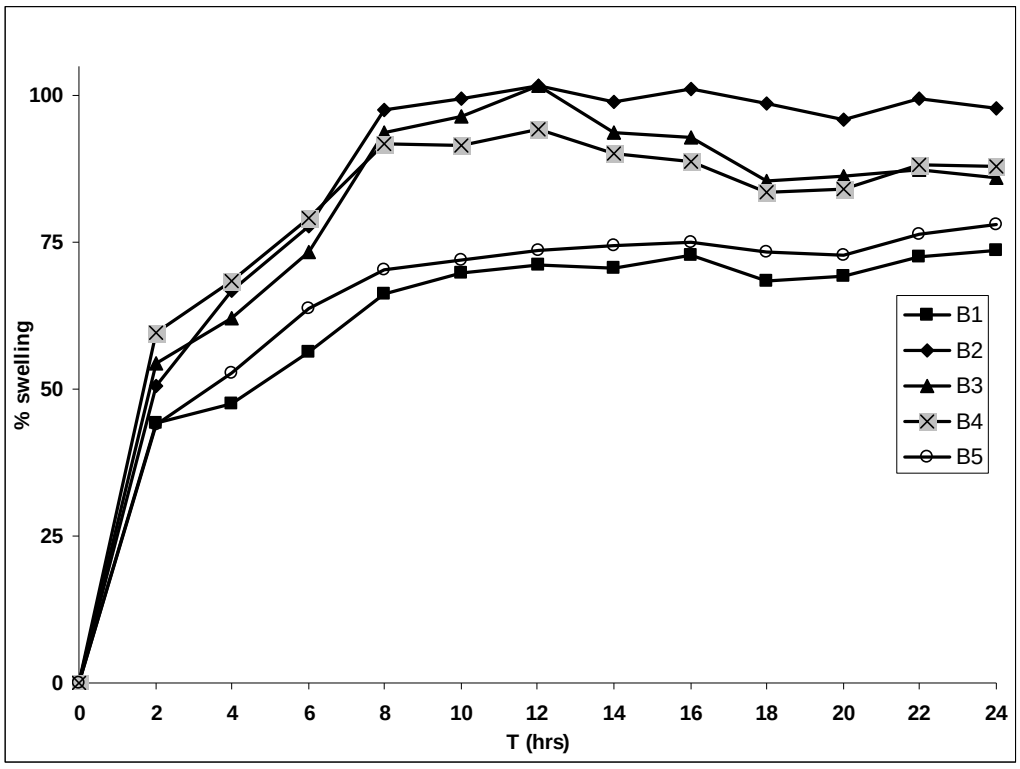

Figure 4.6: Swelling of CIP tablets prepared using Methocel K15M and series B polymers

Hence matrix tablets prepared with series B polymers exhibited faster equilibrium swelling than those prepared using series A polymers. However CIP matrix tablets did not dissolve even after 24 h and hence are not suitable for preparation of gastroretentive delivery systems.

4.3.4.2 Release and floating studies from CIP tablets prepared using Methocel K15M and series B polymers

The floating characteristics of CIP matrix tablets prepared using Methocel K15M and series B polymers are given in table 4.3.

The drug release from CIP matrix tablets prepared using Methocel K15M and series B polymers is given in figure 4.7.

Table 4.3: Floating of CIP tablets: Methocel K15M and series B polymers

Tablet code	BT	FT (h)
B1	16 sec	24
B3	25 sec	24
B4	22 sec	24
B5	21 min	24

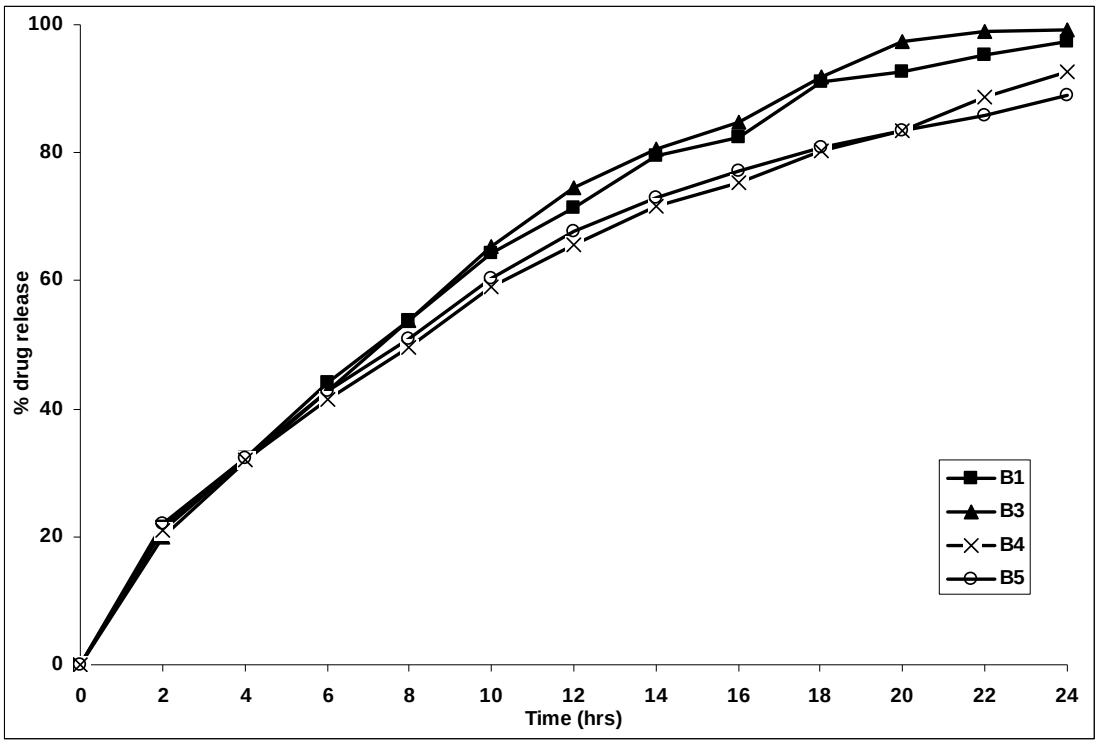

Figure 4.7: Release from CIP tablets prepared using Methocel K15M and series B polymers

The tablets based on Methocel K15M blends with polymers B1, B3 and B4 floated immediately. The tablets prepared using B5 polymer floated after 21 min. This was because the swelling of polymer B4 after 2 h was 60 % and for polymer B5 it was 9 % only. All the CIP floating matrix tablets prepared using Methocel K15M and series B polymers released 80-95 % of drug in 24 h.

The polymers of series B swelled and dissolved. When used along with Methocel K15M, these polymers enhanced the water penetration into tablets and resulted in faster drug release than that obtained with series A polymers. Although the drug

release profiles exhibited by Methocel K15M and series B polymer blends were satisfactory, the systems still did not dissolve at the end of 24 h. Thus, series B polymers did not offer any significant advantage over series A polymers. Hence, series C polymers containing 30-34 mole % VP and which dissolved without swelling were further evaluated along with Methocel K15M for the preparation of CIP floating matrix tablets.

4.3.5 CIP floating matrix tablets prepared using Methocel K15M and series C polymers

Incorporation of series C polymers with Methocel K15M based matrix tablets was expected to sustain drug release as well as dissolve tablets after release is complete as these polymers dissolve directly without swelling.

4.3.5.1 Swelling / dissolution studies of CIP tablets prepared using Methocel K15M and series C polymers

The swelling / dissolution of CIP floating tablets prepared using Methocel K15M and series C polymers is shown in figure 4.8.

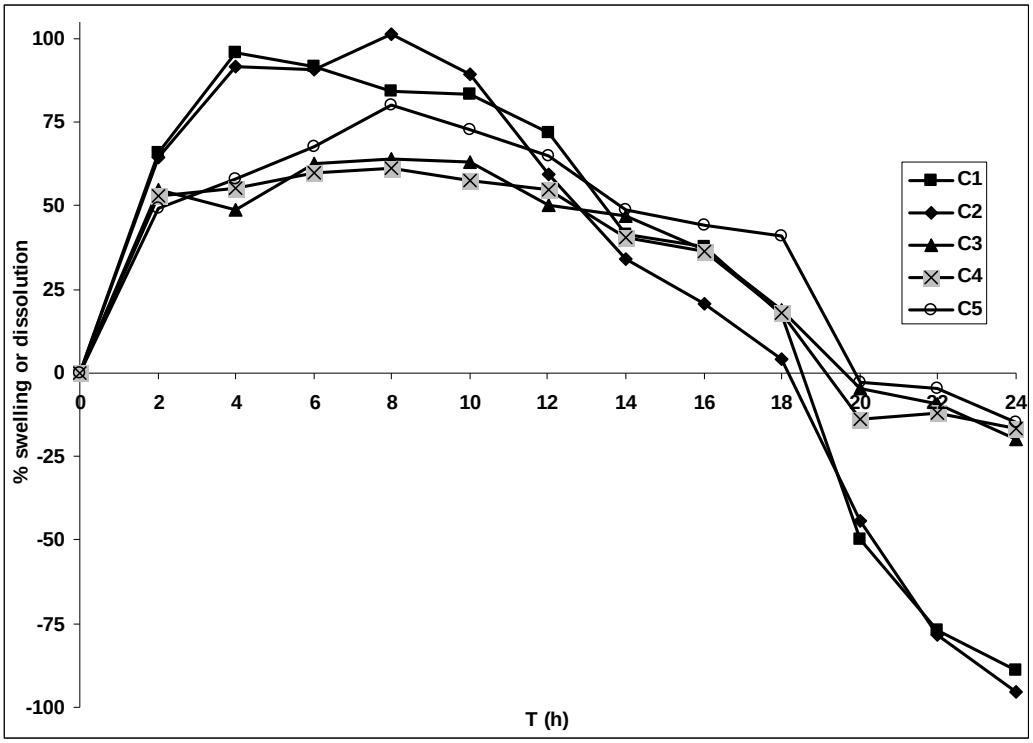

Figure 4.8: Swelling / dissolution of CIP tablets prepared using Methocel K15M and series C polymers

The polymers of series C dissolve without swelling within 1 hour and thus the CIP floating matrix tablets which erode completely over 18-24 h were obtained. Maximum swelling was achieved within 4 h in tablets prepared using series C polymers as compared to 12 h and 8 h in the case of polymer blends of series A and B.

This is because the polymers of series C dissolve without swelling. This allowed rapid water ingress into matrix tablets which subsequently resulted in erosion of the tablets. All these observations on floating tablets suggest that the pH sensitive polymers influence maximum equilibrium swelling and dissolution of gastroretentive tablets.

4.3.5.2 Release and floating studies from CIP tablets prepared using Methocel K15M and series C polymers

The floating characteristics of CIP matrix tablets prepared using Methocel K15M and series C polymers are summarized in table 4.4. The drug release profiles from CIP matrix tablets prepared using Methocel K15M and series C polymers are shown in figure 4.9. All CIP tablets prepared with Methocel K15M and series C polymers floated within 15 min and remained floated for 24 h. Although there was an increase in BT, it is much lower than that observed in case of Eudragit EPO (44 min).

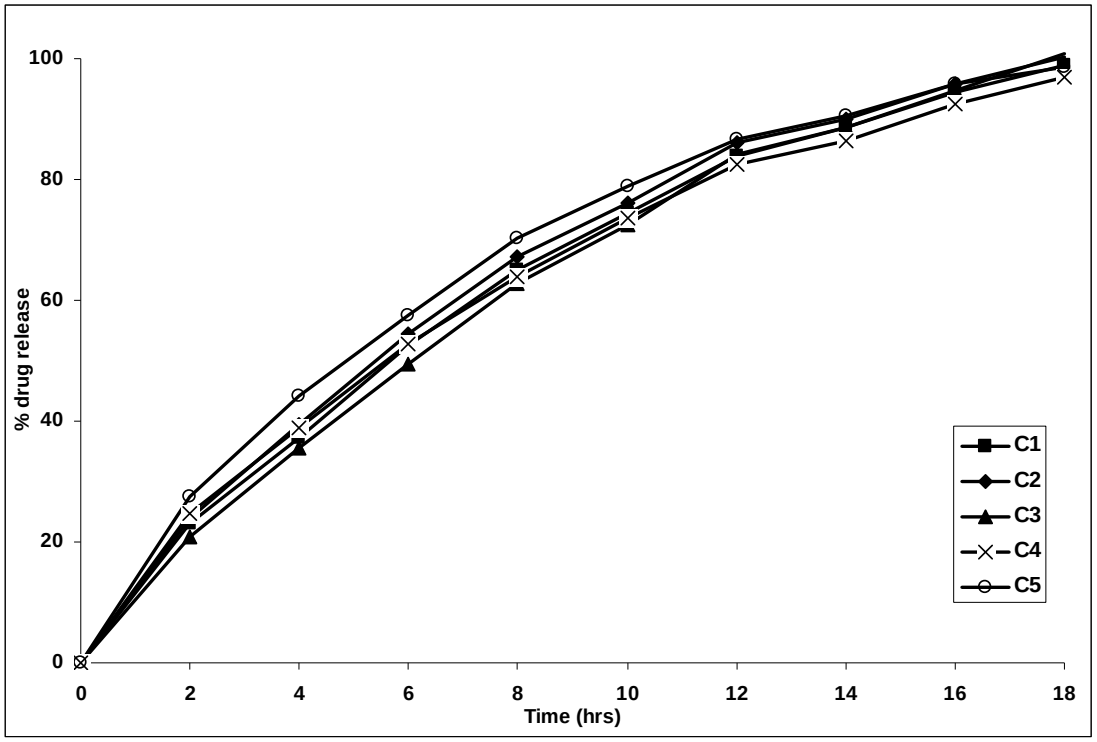

Figure 4.9: Release from CIP tablets prepared using Methocel K15M and series C polymers

CIP floating matrices resulted in sustained release of CIP over 18 h in all series C polymer blends with Methocel K15M and dissolved completely after the drug release was over. Such systems are ideal for the preparation of floating matrix tablets.

The series C polymers dissolve without swelling whereas PEO used in Depomed patent swells and dissolves. As a result, dissolution of the tablets based on PEO may be delayed and also subsequently delay its exit from the stomach. While Depomed used a special oval shaped geometry for preparation of floating tablets, no such geometric modifications were required in the present case.

In case of Propranolol HCl floating matrix tablets described by Jagdale et al (2009), incorporation of additional two polymers HPC and MCC was needed to enhance swelling and drug release from tablets, the same effect could be achieved using a single pH sensitive polymer in the present case.

Arza et al (2009) described CIP floating matrix tablets using Methocel K100M, sodium bicarbonate and superdisintegrants. Methocel K100M was used because incorporation of superdisintegrants into matrix tablets based on Methocel K15M exhibited poor tablet integrity due to weaker gel formation using Methocel K15M than that with Methocel K100M.

Table 4.4: Floating of CIP tablets: Methocel K15M and series C polymers

Tablet code	BT (min)	FT (h)
C1	14	24
C2	15	24
C3	11	24
C4	12	24
C5	9	24

These systems could sustain drug release for 8 h in a better manner than marketed formulation, Cifran OD® which showed about 80 % drug release at 3 h and remainder over next 5 h. However, we could prepare CIP floating matrix tablets using Methocel K15M and pH sensitive polymer and sustained release over a period of 18-24 h.

The wide range of swelling and dissolution behavior of pH sensitive polymers of the series A-C offers broader latitude in terms of swelling and dissolution as well as drug release profiles when pH sensitive polymer is used along with Methocel K15M than the systems reported earlier.

4.3.6 Interaction of Methocel K15M and series C polymer

The polymer-polymer interactions play a critical role in governing miscibility and release from polymer blends. A systematic investigation of polymer-polymer interaction and its implication on drug release was reported by Menjoge and Kulkarni (2007). We investigated interactions between Methocel K15M and a pH sensitive polymer C4 using FTIR spectroscopy. In case of covalent interactions, additional peak for particular functional group emerges whereas in case of non covalent interactions, there is slight shift or reduction in the peak intensity depending on the type and extent of interaction. The IR spectra of Methocel K15M, pH sensitive polymer C4 and their blend are shown in figure 4.10.

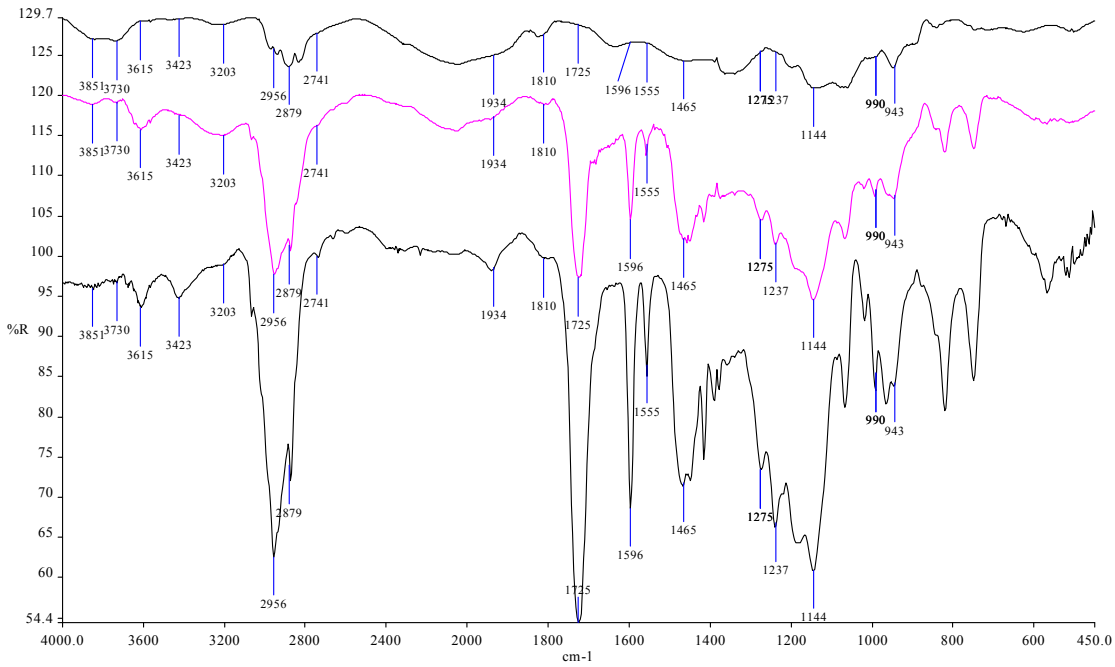

Figure 4.10: FTIR spectra of Methocel K15M (upper spectrum), C4 polymer (lower spectrum) and their blend (middle spectrum)

The FTIR spectra of these three polymers exhibited peaks for respective functional groups. There was no shift of major peaks or emergence of new peaks. The carbonyl peak at 1725 cm^{-1} exhibited a shoulder at 1635 cm^{-1} which was absent in neat C4 polymer. This indicated a weaker interaction between hydroxyl groups of Methocel K15M and carbonyl region of MMA and BMA. The peaks at 1549 cm^{-1} and 1594 cm^{-1} were unaltered and indicated lack of interaction between pyridine nitrogen and hydroxyl of C4 polymer. Thus, it can be concluded that there is a weak interaction

between Methocel K15M and C4 polymer which results in the formation of transparent films.

4.3.7 Effect of drug type on floating and release

The effect of drug type was investigated to evaluate the performance of floating matrices using series C polymers as these polymers resulted in matrix tablets which ultimately dissolved after the drug release was over. CIP and ACP were chosen to investigate the effect of drug type because of differences in their solubilities and molecular weights. The floating characteristics of ACP floating matrix tablets are summarized in table 4.5 and ACP and CIP release profiles are shown in figure 4.11. The floating characteristics of CIP floating matrix tablets prepared using series C polymers are summarized in table 4.4.

The buoyancy times of floating matrix tablets containing CIP and ACP using polymers C1, C3 and C5 were within 15 min and are acceptable for floating tablets. There was only marginal difference in buoyancy behavior of the tablets prepared using CIP and ACP.

The drug characteristics such as solubility and molecular weight affect the diffusion of drug through hydrophilic matrix tablets. CIP is more soluble than ACP. Also CIP molecular weight (385) is higher than that of ACP (151) and hence ACP would have higher diffusivity than CIP through the matrix.

Table 4.5: Floating of ACP tablets

Tablet code	BT (min)	FT (h)
C1	12	12
C3	13	12
C5	13	12

As a result, ACP showed faster release rates than CIP from floating matrices prepared using series C polymers. Also it was observed that the floating matrices practically dissolved after the drug was released. The floating times of tablets containing ACP were shorter than those containing CIP. Therefore, series C polymers containing 30-34 mole % VP are suitable for preparation of floating matrices which could sustain the drug release over a period of 12-18 h. Also the tablets dissolved completely after the release was over. This demonstrates that the incorporation of pH sensitive polymer into Methocel K15M matrix is useful for preparation of floating matrix tablets.

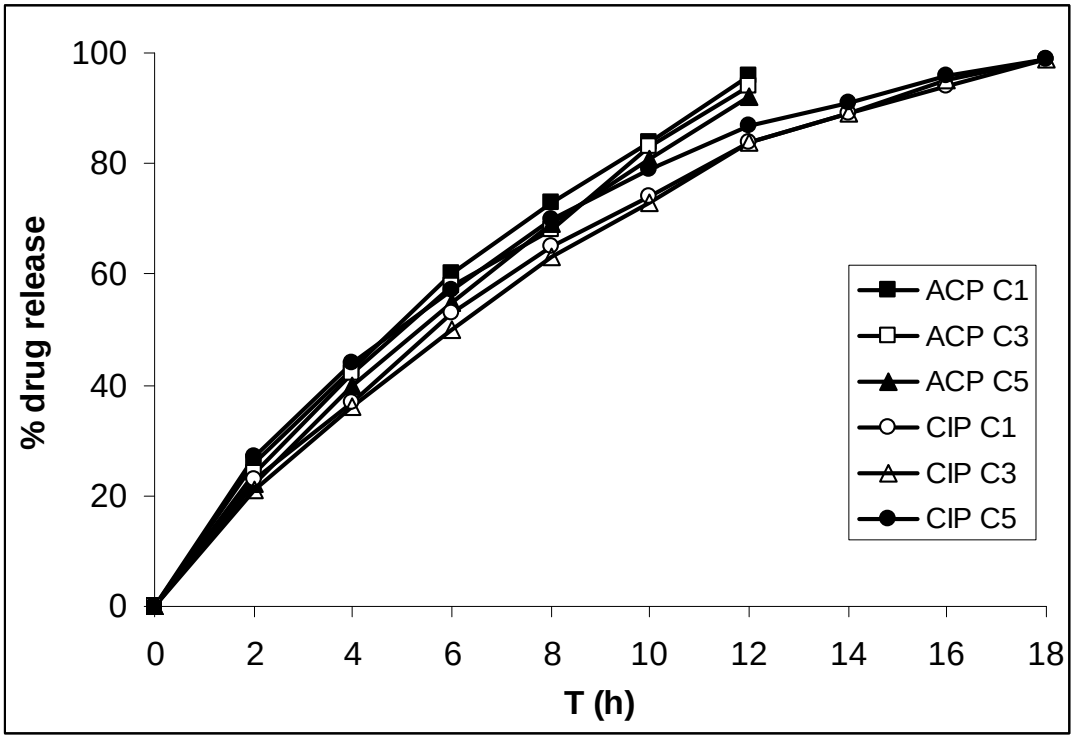

Figure 4.11: Effect of drug type on release from matrix tablets

4.4 Conclusions

We report basic pH sensitive polymers containing MMA, BMA and VP which exhibit a wide range of swelling / dissolution characteristics for preparation of floating matrix tablets along with Methocel K15M and gas generating agent. pH sensitive polymers modified swelling / dissolution of floating matrix tablets and drug release. The swelling / dissolution characteristics of matrices were governed by the properties of pH sensitive polymers. CIP matrix tablets based on Methocel K15M alone resulted in incomplete drug release and these tablets did not dissolve after 24 h. Incorporation of Eudragit EPO resulted in delayed buoyancy time and faster drug release.

The polymers which swelled (series A) or swelled and dissolved (series B) exhibited sustained release but were not suitable since the matrices did not dissolve after the drug release was over. The polymers which dissolved without swelling (seris C) led to matrices from which the release was sustained over a period of 18 h and the matrix was dissolved thereafter. Such systems are therefore more desirable. Also, weak interaction between Methocel K15M and basic pH sensitive polymers as confirmed using FTIR study resulted in formation of transparent film from their blends.

4.5 References

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Chapter 5

Gastroretentive sustained release systems using basic pH sensitive polymers

5.1 Introduction

Drugs exhibit restricted absorption window due to pH dependent solubility, instability in gastrointestinal tract which results in low bioavailability and hence are formulated using gastroretentive systems (GRS) in order to increase residence time in stomach and the bioavailability. The gastric retention is achieved using mechanisms based on floating systems, expandable systems, high density systems and bioadhesive systems (Singh and Kim, 2000). Cheuh et al (1995) suggested that systems based on floating mechanism suffer from disadvantage that they are effective only when sufficient fluid level is available in the stomach. The buoyancy of the dosage form may be affected by gastric emptying. Varshosaz et al (2009) described ciprofloxacin hydrochloride floating matrix type bioadhesive tablets composed of sodium carboxymethylcellulose, Methocel K4M and effervescent mixture for maximizing absorption of CIP at its absorption site. Thus a gastroretentive system exploiting combination of mechanisms is advantageous for the delivery of drugs which exhibit restricted absorption window.

Verapamil hydrochloride (VER) belongs to the group of calcium channel blockers and is used for the management of hypertension. It is well absorbed after oral administration but is metabolized extensively by liver and exhibits high first pass metabolism. This results in poor bioavailability of orally administered dose $\underline{\sim}$ 20 to 35 %. VER solubility is 150, 2.71 and 0.75 mg/ml at pH 1.2, 6.8 and 7.4 respectively (Streubel et al, 2000). The preparation of floating pellets was used to enhance absorption of VER to exploit higher solubility of drug in the stomach than that in the lower gastrointestinal tract. Clinical studies revealed that the floating formulation of VER exhibited higher bioavailability than immediate release product (Sawicki, 2002).

5.1.1 Approaches to gastroretentive sustained delivery of VER

Different gastroretentive systems developed hitherto for sustained release of VER are based on matrix and reservoir approaches and are discussed below in brief. Streubel et al (2002) described floating microparticles of VER using polypropylene foam powder in combination with polymers such as ethyl cellulose, poly (methyl methacrylate) and Eudragit RS at 10 % drug loading. EC and Eudragit RS based microparticles showed burst release of 40-50 % within 1 h and yet did not release drug completely in 8 h whereas poly (methyl methacrylate) based systems exhibited sustained release for 8 h. VER loading was only 10 % w/w in these microparticles which were prone to rapid gastric emptying from pylorus of gastrointestinal tract due to smaller size.

Londhe et al (2010) reported bilayer tablets for VER using high viscosity HPMC and Carbopol 971P. These tablets were based on an immediate release layer and a floating sustained release layer. The tablets floated within 20 seconds and released drug over a period of 12 h. These tablets had only 25 % w/w drug loading and exhibited burst release of 40 % within 1 h.

Patel et al (2009) described floating matrices of VER using blend of Methocel K4M, and xanthan gum in 3:2 ratio, which floated within a minute and resulted in sustained drug release over a period of 24 h. Polymer loading of 32 % w/w resulted in first order release profile. The drug loading was 38 % w/w.

In order to increase the drug loading and to achieve better control on drug release, a reservoir system which uses a polymeric coating surrounding the drug core containing entrapped carbon dioxide is expected to be more effective than the matrix system. Conventional reservoir systems often lead to linear drug release profile (Kallstrand and Ekman, 1983).

Floating reservoir systems for VER investigated in the past are summarized below. Sawicki and Glod (2004) investigated acrylic polymers Eudragit NE30D, Eudragit L30D55 and Eudragit RL as coatings for the preparation of floating sustained release VER pellets. Due to high permeability of VER through Eudragit NE30D and Eudragit RL, it was rapidly released. VER pellets coated with a 1:1 blend of Eudragit NE30D and Eudragit L30D55 resulted in BT of 3 min and sustained the release over a period of 6 h, attributed to presence of Eudragit L30D55 in the blend which remained collapsed in acidic pH resulted in lowered porosity of the coating and diffusion of VER. Hence a blend of polymers had to be used for preparation of floating sustained release pellets of VER.

Lunio and Sawicki (2006) also reported that Eudragit RL coated VER pellets, floated immediately but released 80 % VER within 1 h. VER pellets coated with Eudragit RS resulted in buoyancy time of 70 min and released less than 3 % drug in 4 h. Hence Eudragit RL and Eudragit RS were not suitable for reservoir floating system for VER. VER pellets coated with a blend of Eudragit RL and Eudragit RS in the ratio 1:1, resulted in buoyancy time of 5 min but released 80 % VER within 1 h. Coating VER pellets with a blend of Eudragit RL and Eudragit RS in the ratio 1:4 resulted in BT of 22 min and released drug over a period of 6 h after a lag time of 1 h. To ensure VER release during lag phase, 20 % by weight of uncoated VER pellets had to be

incorporated in the VER pellets coated with blend. The manufacture of such systems used multiple components and multiple steps.

5.1.2 Limitations of existing approaches to gastroretentive sustained delivery of VER

Floating reservoir systems for VER required a blend of polymers as coating and could sustain VER release over a period of 6 h (Sawicki and Glod, 2004 and Lunio and Sawicki, 2006). Therefore there exists a need to develop new polymers which could be used as a coating for preparation of VER floating system which exhibit shorter buoyancy time and sustain drug release over a prolonged period.

5.1.3 Performance requirements of polymers for reservoir type gastroretentive sustained release systems

Characteristics of ideal polymers for fabrication of reservoir type floating systems were discussed by Krogel and Bodmeier (1999). These include high permeability to dissolution medium, high swelling and high flexibility both in dry and wet state. High permeability to medium is required to initiate rapid CO_2 formation and high flexibility is required to withstand internal pressure generated by CO_2 gas. The polymer should not dissolve so as to maintain system integrity and also should sustain drug release.

5.1.4 Our approach to gastroretentive sustained release systems

We designed pH sensitive polymers containing MMA, BMA and VP which could provide buoyancy as well as sustained drug release. Polymers which exhibit different sorption characteristics were prepared by using MMA/BMA ratios in the range 3 to 0. BMA was used to impart hydrophobicity and high flexibility to polymers so that the coated system does not burst because of high internal pressure as a result of gas generation. The pH sensitive monomer, VP was used to impart swelling to the polymer. The swelling was required so that the coating withstood the expansion of tablet after gas generation and maintained system integrity. We evaluated a series of basic pH sensitive polymers which swelled but did not dissolve as described in chapter 3, as polymeric coatings for effervescent VER cores.

5.2 Experimental section

5.2.1 Materials

Magnesium stearate, sodium bicarbonate, anhydrous citric acid and dichloromethane were purchased from Merck Chemicals, India. Lactose and Microcrystalline cellulose (MCC) were purchased from S D Fine chemicals Ltd, India. Acetaminophen (ACP) and Verapamil HCl (VER) were gift samples from Lupin Laboratories Ltd., India.

Synthesis and characterization of MMA, BMA and VP polymers has already been described in discussed in chapter 3.

5.2.2 Methods

5.2.2.1 Preparation of VER tablets using basic pH sensitive polymer

5.2.2.1.1 Preparation of VER tablets

VER tablets were prepared by direct compression using pneumatic press using 13 mm die. A mixture of gas generating agent i.e. sodium bicarbonate and anhydrous citric acid was used. Magnesium stearate was used as lubricant. Diluents such as lactose and microcrystalline cellulose were also evaluated.

5.2.2.1.2 Coating of VER tablets

The drug tablets were coated by dip coating method using 10 % w/v solution of pH sensitive polymer in dichloromethane and drying the tablets at room temperature to achieve required polymer loading.

5.2.2.2 Release and floating studies from tablets

The release from floating tablets was carried out using dissolution apparatus, USP Type II, 50 rpm at 37 ± 0.5 ºC in 900 ml of 0.1 N HCl. 5 milliliters aliquots were withdrawn at predetermined time intervals. The medium was replenished with fresh medium. The samples were filtered and analyzed by UV spectrophotometer at 278 nm and 244 nm for VER and ACP respectively. The floating behavior of the VER tablets was monitored during the drug release study. The time required to float the tablet in the dissolution medium was taken as buoyancy time (BT) and total floating time in dissolution medium was taken as floating time (FT). The duration over which the drug was released was taken as release time (RT).

5.2.2.3 Mechanism of drug release from VER tablets

To investigate the mechanism of drug release, we carried out scanning electron microscopy (Leica, model) of the polymer films. The polymer films were prepared by solvent casting method and films of 200 ± 20 μ were prepared. The films were treated with 0.1 N HCl at 37.5 ºC upto 24 h and samples were collected periodically, gently wiped with tissue paper and dried. The scanning electron microscopy was carried out on the dried samples.

5.3 Results and discussion

Floating matrix tablets for VER reported earlier could incorporate 25-38 % by weight of drug and 11-32 % w/w polymers of the total dosage form (Londhe et al, 2010 and

Patel et al, 2009). To increase the drug loading in the tablets, a polymer coating can be used instead of a gel forming polymer both to entrap generated carbon dioxide gas and sustain the drug release. The reservoir systems developed for VER by Lunio and Sawicki (2006) used 20 % uncoated drug pellets and 80 % drug pellets coated with a blend of Eudragit RS and Eudragit RL in ratio of 4:1 to achieve sustained release over a period of 6 h. Sawicki and Glod (2004) used blend of Eudragit NE30D and Eudragit L30D55 to achieve sustained release of VER over a period of 5 h.

Floating systems for VER reported earlier comprised multiple polymers and low drug loading. Hence, there exists a need to develop a new polymer which could be useful for the preparation of VER floating tablets which float rapidly and also sustain the drug release over a prolonged period.

Eudragit EPO dissolves in acidic pH and hence is not suitable for the present application as it would not be able to maintain system integrity. A nontoxic terpolymer, new reverse enteric polymer (NREP) was reported as polymeric coating for taste masking of bitter drugs which met *in vitro* and *in vivo* biological reactivity tests as per USP (Menjoge and Kulkarni, 2007). NREP was composed of MMA, HEMA and VP. It dissolves rapidly in acidic environment and hence the water soluble monomer, HEMA in NREP was replaced by hydrophobic monomer BMA for the present application so that the polymer swells but does not dissolve. We synthesized polymers containing MMA, BMA and VP. The monomers MMA and BMA are present in Eudragit EPO which is already approved by USFDA for drug delivery applications. MMA/BMA ratios in the range 3 to 0 were used to synthesize polymers exhibiting varying sorption properties. BMA was used to impart hydrophobicity and high flexibility to polymer which would ensure expansion of coating and help retain system integrity. VP was used to impart pH dependent swelling characteristic to the polymer so as to allow faster penetration of dissolution medium and to initiate gas generation and eventually cause floating of system. We used basic pH sensitive polymers which swelled but did not dissolve for the present application. The drug tablets containing effervescent mixture were coated with the pH sensitive polymers and their performance on floating and drug release characteristics was evaluated. Mixture of sodium bicarbonate and anhydrous citric acid was used as gas generating agent (GGA) in core tablets in ratio 1:0.76 (Anderson et al, 1982). 13 mm diameter VER tablets were prepared in order to provide size exclusion effect through pylorus in addition to floating mechanism (Khosla and Davis, 1990).

5.3.1 Optimization of VER tablets

5.3.1.1 Effect of GGA concentration on floating and drug release

Krogel and Bodmeier (1999) and Meka et al (2009) emphasized that polymer should be flexible both in dry and wet state and should swell to initiate the gas generation for fabrication of reservoir type floating system. It was also suggested that polymer swelling should be low for sustaining the drug release as coating of highly swelling polymer Eudragit RL resulted in rapid release of Chlorpheniramine maleate. Polymer A8 exhibiting T_g of 35 ºC and composed of BMA:VP in 89:11 mole % is in a rubbery state at physiological temperature of 37 ± 0.5 ºC. The polymer has low equilibrium swelling of 25 % and hence was chosen as coating material for the development of gastroretentive sustained release tablet for VER. VER tablet cores with GGA concentration in the range 0-35 % w/w were prepared and coated using procedure given in section 5.2.2.1 and compositions are described in table 5.1. The floating and release studies were carried out using procedure described in section 5.2.2.2.

Table 5.1: Composition of VER tablets: Effect of GGA content

No	Ingredient					
1	VER	495	420	370	345	320
2	Sodium bicarbonate	0	43	71	85	100
3	Citric acid	0	32	54	65	75
4	Magnesium stearate	5	5	5	5	5
	Total	500	500	500	500	500
5	Polymer A8	20	20	20	20	20
	GGA conc. (%)	0	15	25	30	35

All quantities are in “mg”

The effect of gas generating agent concentration on floating characteristics of coated VER tablets is summarized in table 5.2, and its effect on drug release is shown in figure 5.1.

The tablet cores containing different GGA concentration disintegrated immediately in the dissolution medium and did not float. The core drug tablets dissolved and resulted in rapid drug release. The core tablets dissolved without floating and this necessitated a polymeric membrane to achieve floating and control drug release.

Increase in GGA content in the tablet core caused rapid gas generation and lowered buoyancy time. This was because of entrapment of gas into polymeric coating. VER tablets sans GGA system exhibited longer buoyancy time of 92 min.

Table 5.2: Floating of VER tablets: Effect of GGA content

GGA content (%)	BT (min)	FT (h)	RT (h)
0	92	4	4
15	45	> 10	> 10
25	29	10	10
30	9	5	5
35	1	5	5

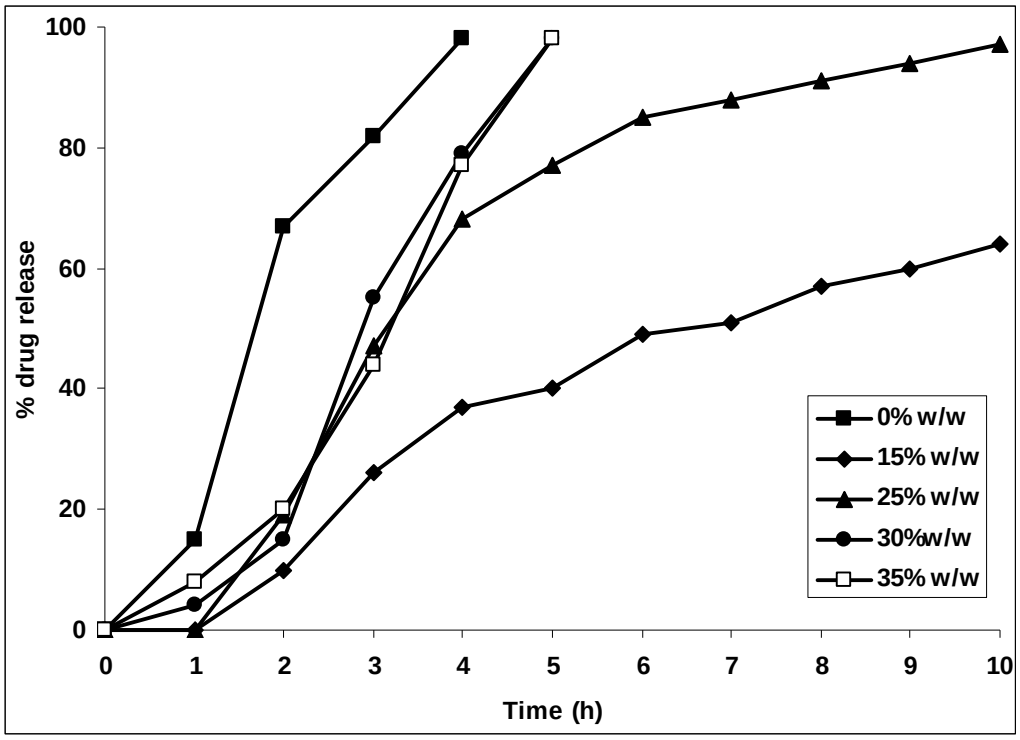

Figure 5.1: Effect of GGA content in tablet on VER release

Increase in GGA content in the VER tablet core resulted in higher gas generation and led to high internal pressure inside tablet and accelerated the diffusion of drug through polymeric coating as well as permeation of the gas resulting in shorter buoyancy time. GGA content of 30 % w/w in the tablet core resulted in immediate floating as well as sustained release of drug over a period of 5 h and hence this GGA concentration was chosen for further development of VER floating tablets.

Krogel and Bodmeier (1999) described effect of gas generating agent concentration on buoyancy time of placebo tablets coated with Eudragit NE30D. The tablet cores were prepared using 20 % w/w effervescent agent and 80 % w/w lactose. Increase in GGA content of tablet cores from 20-50 % w/w lowered buoyancy time from 3 min to less than 1 min. This was attributed to faster and higher gas generation on increase in gas generating agent content of the core tablet.

VER core tablets at 30 % w/w GGA content resulted in buoyancy time of 9 min and also sustained VER release over a period of 5 h. Thus a single polymer coating suffices to develop VER delivery system which has acceptable floating characteristics, and which sustained VER release over 5 h.

5.3.1.2 Effect of type and concentration of diluents

The effect of water soluble diluent, lactose and water insoluble diluent, MCC on floating and release of coated VER tablets was investigated at two levels i.e. 5 and 15 % w/w. VER tablets containing these diluents were prepared and coated as per procedure described in section 5.2.2.1 and compositions in table 5.3. The effect of Lactose and MCC content of tablet cores on floating characteristics of coated tablets is given in table 5.4. The floating and release was carried out using procedure discussed in section 5.2.2.2 and is shown in figure 5.2.

Table 5.3: Composition of VER tablets: Effect of diluents

S No	Ingredient		
1	VER	320	270
2	Diluent	25	75
3	Sodium bicarbonate	85	85
4	Citric acid	65	65
5	Magnesium stearate	5	5
	Total	500	500
6	Polymer A8	20	20
	Diluent conc. (%)	5	15

All quantities in “mg”

Increase in lactose concentration in the drug core caused decrease in buoyancy time of tablets but the drug release profile was practically unaffected. This was because of faster water penetration due to osmotic effects of water soluble lactose which led to faster gas generation and dissolution of VER.

MCC, although water insoluble, swelled on contact with dissolution medium. Increase in MCC content in the tablet core resulted in increase in drug release rate but the buoyancy time was unaffected. Krogel and Bodmeier (1999) described that tablet cores prepared with MCC and coated with Eudragit RL coating ruptured during drug release test and attributed the rupture of Eudragit RL coating to high internal pressure generated by swollen MCC. Incorporation of diluents i.e. Lactose or MCC could not prolong the drug release time although resulted in shorter buoyancy time. Hence it

was decided to prepare VER floating tablets without diluents for further investigations.

Table 5.4: Floating of VER tablets: Effect of diluents

Diluent conc. (%)	Lactose		MCC	
	BT (min)	FT (h)	BT (min)	FT (h)
5	7	3	10	3
15	4	3	10	3

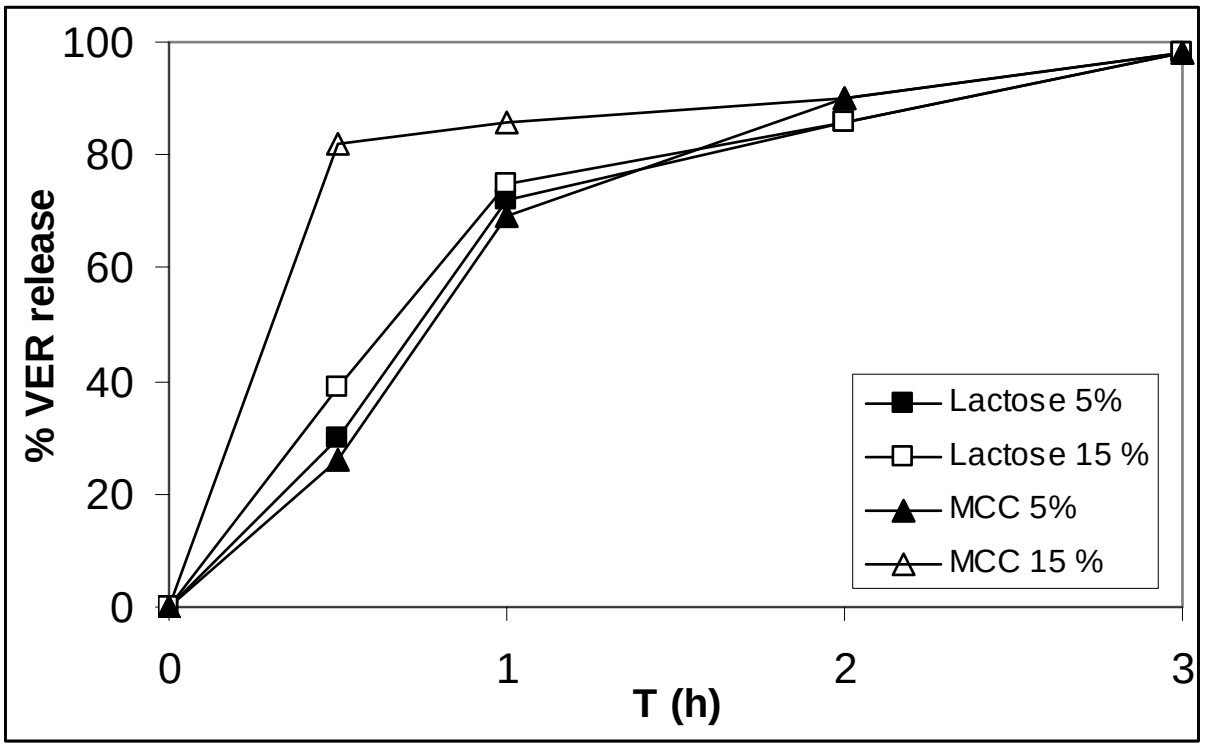

Figure 5.2: Effect of diluents on VER release

5.3.1.3 Effect of drug type on floating and drug release

To investigate the effect of drug solubility on floating and drug release of tablets, we chose two drugs with low and high solubility such as ACP (15 mg/ml) and VER (150 mg/ml) respectively. The composition of core tablets is described in table 5.5 and the tablets were prepared and coated using polymer A8 as per procedure described in section 5.2.2.1. The floating and release studies were carried out using procedure given in section 5.2.2.2.

The effect of drug solubility on floating characteristics of coated tablets is given in table 5.6. The effect of drug solubility on release from coated tablets using A8 polymer is shown in figure 5.3.

Table 5.5: Composition of tablets: Effect of drug type

S No	Ingredient	Quantity (mg)
1	Drug	345
2	Sodium bicarbonate	85
3	Citric acid	65
4	Magnesium stearate	5
	Total	500
5	Polymer A8	20

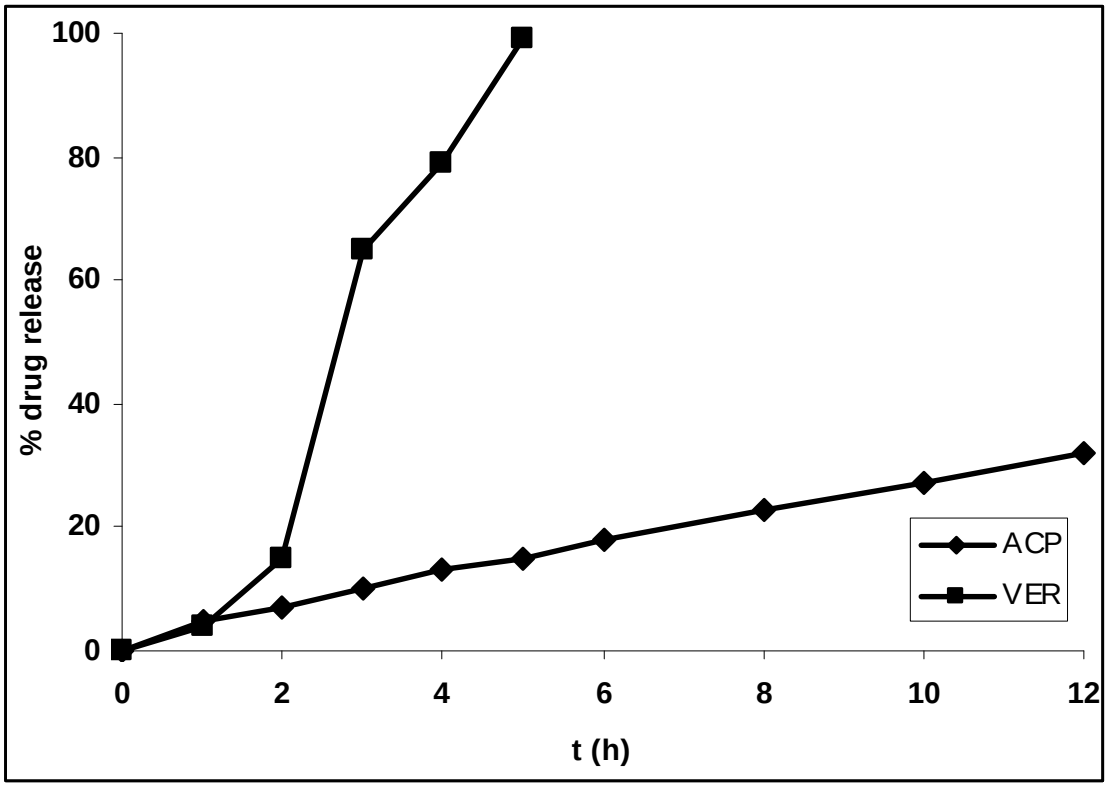

Figure 5.3: Effect of drug solubility on release

Table 5.6: Floating of tablets: Effect of drug type

Drug	BT (min)	FT (h)
VER	9	5
ACP	180	> 12

VER tablets exhibited shorter buoyancy time than ACP tablets. This was due to difference in drug solubility. VER dissolved faster than ACP, caused rapid gas generation and led to shorter buoyancy time. Being more soluble, VER permeated the coating faster than ACP which required longer time to permeate through polymeric

coating. These results suggest that the system developed in this work can be effectively used for drugs with high solubility.

5.3.2 Polymer coating optimization

5.3.2.1 Effect of polymer swelling on floating and drug release

The effect of polymer swelling on floating and drug release was investigated using pH sensitive polymers, A2, A4 and A8 exhibiting equilibrium swelling 200, 80 and 25 % respectively. VER core tablets were prepared and coated using procedure described in section 5.2.2.1 and composition in table 5.7. The floating and release from coated VER tablets using pH sensitive polymers exhibiting different equilibrium swelling was performed using procedure discussed in section 5.2.2.2 and is shown in figure 5.4. The effect on floating characteristics of coated VER tablets is given in table 5.8. VER tablet coated with A2 polymer did not float because of higher polymer swelling (200%) which resulted in escape of generated gas as well as VER. VER tablet coated with polymer A4 exhibiting equilibrium swelling value of 80 % resulted in BT of 3 min, released 75 % drug within 2 h and showed FT and RT of 4 h.

Table 5.7: Composition of VER tablets: Effect of polymer swelling

S No	Ingredient	Quantity (mg)
1	VER	345
2	Sodium bicarbonate	85
3	Citric acid	65
4	Magnesium stearate	5
	Total	500
5	Polymer coat	20

Table 5.8: Floating of VER tablets: Effect of polymer swelling

Polymer	BT (min)	FT (h)
A2	#	NA
A4	3	4
A8	9	5

The tablet did not float

VER tablet coated with the polymer A8 exhibiting lower equilibrium swelling (25 %) resulted in sustained release over a period of 5 h with no burst effect as observed with VER tablet coated with polymer A4. Thus the BT, FT and RT of VER tablets was governed by equilibrium swelling of polymers.

Krogel and Bodmeier (1999) reported that Eudragit RL exhibiting high swelling released chlorpheniramine maleate rapidly and exhibited lower buoyancy time as compared to the tablets coated with Eudragit RS exhibiting lower swelling. Lunio and Sawicki (2006) also reported that high swelling polymer Eudragit RL when coated onto VER pellets resulted in shorter buoyancy time and drug release duration than when coated with Eudragit RS. VER pellets coated with Eudragit RS exhibited BT of 70 min and could release less than 3 % drug after 4 h.

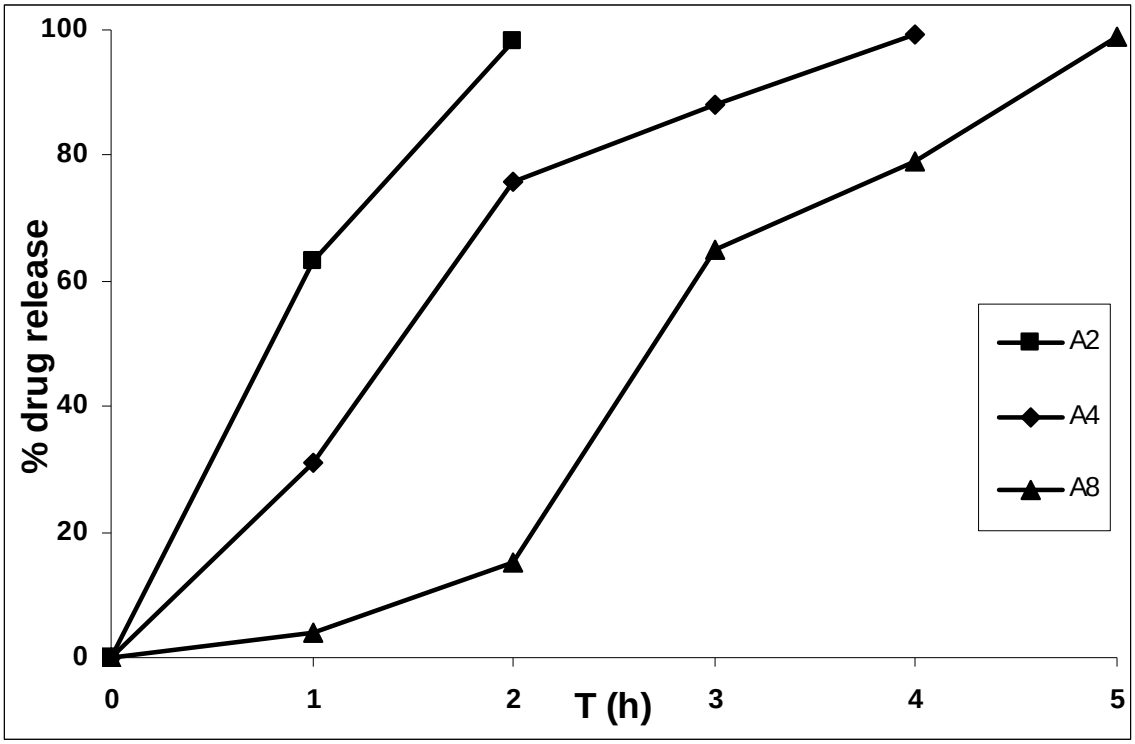

Figure 5.4: Effect of polymer swelling on VER release

5.3.2.2 Effect of polymer coating level on floating and drug release

VER core tablets as per composition in table 5.9 were prepared using procedure described in section 5.2.2.1. To investigate effect of polymer coating level on floating and drug release of VER tablets, VER drug cores were coated at coating levels of 4-8 % w/w of the drug core using polymer A8. The floating and release studies were carried out as per procedure discussed in section 5.2.2.2.

Table 5.9: Composition of VER tablets: Effect of polymer coating level

S No	Ingredient			
1	VER	345	345	345
2	Sodium bicarbonate	85	85	85
3	Citric acid	65	65	65
4	Magnesium stearate	5	5	5
	Total	500	500	500
5	Polymer A8	20	30	40
	Coating level (%)	4	6	8

All amounts in "mg"

The effect of polymer coating level on floating characteristics of coated VER tablets is given in table 5.10. The effect of coating level on drug release from coated VER tablets is shown in figure 5.5.

Increase in coating level onto tablets caused increased thickness of coating membrane and lowered the rate of swelling which resulted in increased BT, FT and RT. Sawicki and Glod (2004) reported that increase in coating thickness caused increase in duration of time over which the VER was released in the case of VER pellets coated with a 1:1 blend of Eudragit NE30D and Eudragit L30D55. Thicker coating resulted in increased diffusional path length for VER and increased the duration over which drug was released.

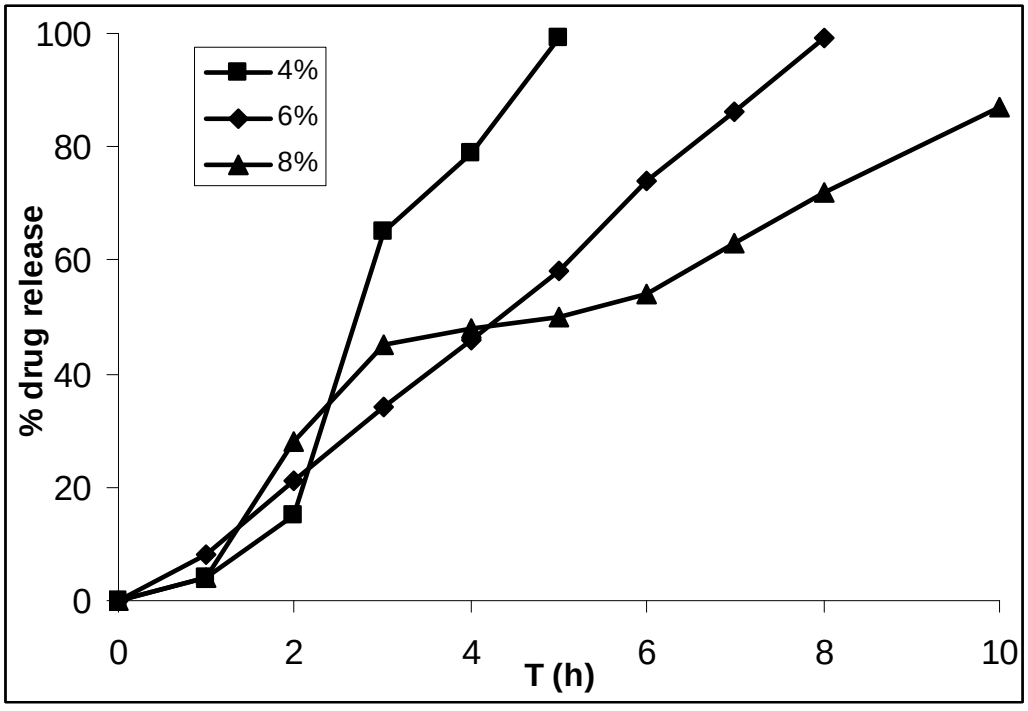

Figure 5.5: Effect of polymer coating level on VER release

Table 5.10: Floating of VER tablets: Effect of polymer coating level

Coating (% w/w)	BT (min)	FT (h)
4	9	5
6	14	8
8	19	> 10

5.3.3 Mechanism of release from tablets

The mechanism of drug release through polymeric coating was investigated by studying morphological changes in the polymer film for 24 h by treatment with 0.1 N HCl at 37 ± 0.5 ºC.

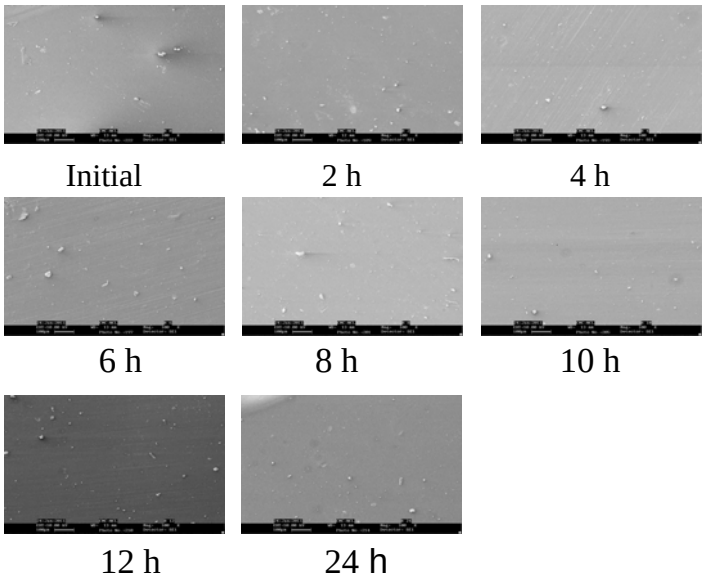

Figure 5.6: Morphological changes during polymer film swelling

The SEM pictures of polymer films treated for different time intervals with 0.1 N HCl are shown in figure 5.6. The polymer surface was smooth and was unchanged for 24 h. Thus the polymers remained intact for 24 h. We conclude that the drug release occurred by drug dissolution followed by diffusion through polymer coating membrane.

5.4 Conclusions

We synthesized pH sensitive polymers containing MMA, BMA and VP which swelled but did not dissolve at acidic pH and evaluated the same for gastroretentive sustained delivery using VER as a model drug. Rubbery polymer exhibiting low glass transition temperature of 35°C and BMA:VP 89:11 mole % was used for evaluation

so as to impart high flexibility to the polymer coating for the VER effervescent tablet cores. Buoyancy of the VER tablets was achieved by incorporation of gas generating mixture into the drug core at 30 % loading. Increase in GGA loading lowered BT, FT and RT of VER tablets. Incorporation of diluents such as lactose and MCC lowered BT, FT and RT of the VER tablets. The effect of polymer swelling on performance of coated VER tablets revealed that the tablet coated with polymer which swelled highly (200 %) did not float and caused rapid drug release. The tablet coated with polymer exhibiting equilibrium swelling of 80 % resulted in shorter BT, FT and RT of VER tablets than the tablet coated with polymer exhibiting lower equilibrium swelling value of 25 %. Increase in polymer coating level onto VER tablets resulted in higher values of BT, FT and the duration over which the drug was released. Highly soluble drugs can be effectively delivered using the pH sensitive polymer based system. The SEM pictures of the polymer films revealed that the polymer film remained intact for 24 h after treatment with 0.1 N HCl. The drug release was lowered with increase in polymer coating level onto VER tablet. Hence we conclude that the drug release occurred by diffusion of drug through polymer coating. No plasticizer was required during coating process as the polymer had lower glass transition temperature of 35°C. Thus, we demonstrate that the single pH sensitive polymer coating is useful for floating sustained delivery of VER.

5.5 References

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Chapter 6

Gastroretentive chronotherapeutic systems using basic pH sensitive polymers

6.1 Introduction

The symptom intensity of many medical conditions such as asthma, arthritis, duodenal ulcer and cardiovascular diseases exhibits precise timings. The circadian rhythm dependence of intensity necessitates chronotherapeutic delivery of drugs. Patients with allergic rhinitis and rheumatoid arthritis often report that symptoms worsen in the early hours of the morning. Oral pulsatile and delayed release systems are designed to elicit programmable lag time followed by the release of the drug to treat diseases which exhibit circadian recurrence of symptoms (Youan, 2004).

Theophylline is chemically a methylxanthine derivative and is indicated for the treatment of reversible airflow obstruction associated with chronic asthma and other lung diseases like chronic bronchitis. Understanding of the effect of circadian rhythm on bronchial asthma suggests that the symptoms are exaggerated between midnight and early morning. The symptoms of asthma occur 50-100 times more often at night than during the day (Washington and Wilson (2011). One approach to treat such conditions is to use long acting bronchodilator. However, this produces sustained high doses of drug even when none is required, thus increasing the risk of undesirable side effects. A better method of delivering drugs for diseases that display chronobiology such as asthma is to use a time delayed delivery system. The timing between administration of formulation and the release of drug has to be carefully controlled. Therefore, TPH dosage forms which release drug between midnight and early morning are desired.

6.1.1 Approaches to chronotherapeutic delivery of TPH

Approaches used for chronotherapeutic delivery of TPH include a) asymmetric dosage regimen, b) osmotic systems, c) colon targeted systems, d) floating pulsatile systems and erosion controlled systems. Each of these approaches is discussed below in brief.

a) Asymmetric dosage regimen

Wang et al (2003) described an asymmetric dosage regimen using sustained release formulation for chronotherapeutic delivery of Theophylline sodium glycerinate. The extended release delivery system was prepared using an inert matrix. This regimen was based on administering one such tablet in the morning and four tablets in the evening for six consecutive days in 10 volunteers. A lower dose in the morning could reach effective concentrations and higher dose in the evening did not result in toxic effects. This approach required higher drug dosages.

b) Osmotic systems

A controlled porosity osmotic pump tablet was described by Bi et al (2007). It was based on tablet-in-tablet (TIT) core and further coated with controlled porosity semipermeable membrane. The porous semipermeable membrane was composed of cellulose acetate: poly (ethylene glycol) 400: diethyl phthalate in the ratio 55:36:9. Inner tablet composed of TPH, polyvinylpyrrolidone, magnesium stearate and sodium phosphate, 250 mg in weight and 8 mm diameter. External layer of the tablet contained TPH, sodium chloride, polyvinylpyrrolidone and magnesium stearate, and weighed 400 mg. The core tablet (8 mm) was prepared and sandwiched between two layers of powder mixtures i.e. 160 mg below the tablet and 240 mg above the tablet followed by tablet compression to get 11 mm diameter tablet. *In vitro* drug release profile of coated tablet exhibited a dissolution profile wherein a lag time of about 6 h was followed by sustained release upto 12 h. During initial 6 h, the drug was released by osmotic pressure generated by dissolution of sodium chloride. Once sodium chloride diffused out of the system, the osmotic pressure dropped. After 8 h, dissolution of sodium phosphate caused increase in pH which accelerated the drug release. This was caused by increase in solubility of TPH at pH 11 in the tablet core. Such systems are based on complex geometry, composed of many additives and are not easily amenable to large scale manufacture.

c) Colon targeted systems

Colon targeted systems used for chronotherapy are based on systems coated with pH sensitive polymers which degrade in the colon. The colonic flora or enzymes are responsible for degradation of polymers. Colonic fluid contains bacterial flora such as bacteroides, bifidobacterium and eubacterium and also enzymes such as azo-reductase, nitroreductase, esterases, glycosidases and amidases. These systems provide a predetermined lag time which is governed by the time taken by the device to reach colon followed by drug release either by degradation of polymer by the bacteria in colon or by pH dependent dissolution of polymer such as Eudragit S. However, the time to reach colon, i.e. the lag time varies because of the variation in gastric retention time.

Patel et al (2011) described a colon targeted TPH system for chronotherapy of nocturnal asthma. The drug core composed of Methocel K4M and polyvinylpyrrolidone was coated with a polymeric blend of Eudragit S100 and Ethyl cellulose. This system provided a lag time of 5 h followed by sustained release over

24 h. This approach required multiple polymers and the product performance could be affected by its transit time in gastrointestinal tract. Soni et al (2011) described a chronotherapeutic delivery system for TPH exploiting pH dependent characteristic of the polymer and colonic degradation of polymer. TPH cores were made with guar gum and coated with a blend of Eudragit L and Eudragit S which provided a lag time of 4 h followed by TPH release upto 8 h. Eudragit polymers provided pH dependent lag time and enzymes present in the colon degraded guar gum to release the drug. This approach too required multiple polymers.

Mastiholimath et al (2007) described an oral colon specific pulsatile release device for chronotherapeutic delivery of TPH. The device consisted of an insoluble capsule body, enteric coated insoluble hard gelatin capsule containing TPH microcapsules coated with a blend of Eudragit L and Eudragit S and a swellable hydrogel plug. Enteric coat was intact for 2 h and dissolved at pH 7.4 exposing soluble cap which dissolved. The exposed hydrogel plug swelled and sustained the release and on complete wetting of hydrogel plug, the TPH microcapsules were easily ejected out of swollen hydrogel releasing the drug at colonic pH. This system resulted in a lag time of 4 h followed by sustained release for 24 h. This approach required multiple polymers and the product performance would be affected by variable gastric emptying time.

d) Floating pulsatile systems

Floating pulsatile systems are based on floating of beads in the stomach due to low density followed by transit to intestine which results in drug release as a result of increased pH.

Sharma and Pawar (2006) described a combination of floating and pH dependent solubility of the drug for chronotherapy of arthritis. Floating pulsatile beads were prepared by ionotropic gelation of Meloxicam loaded calcium silicate (Florite RE) particles and sodium alginate using calcium chloride solution. These beads provided a lag time of 2-8 h in acidic medium followed by rapid release in simulated intestinal fluid. Similarly, Sher et al (2007) described floating pulsatile beads of Ibuprofen adsorbed on low density microporous polypropylene (Accurel MP1000) which resulted in a lag time of 6 h followed by rapid release in pH 7.2 phosphate buffer.

The floating time of such systems is expected to provide lag time in real life application. As lag time of floating pulsatile systems is likely to be affected by rapid gastric emptying of beads due to their smaller size, these systems may not be useful in

real life situation and there exists a need to develop systems with better mechanisms for providing floating and pulsatile release.

e) Erosion controlled systems

Polymers which swell and erode provide lag time followed by drug release. This principle is used to provide pulsatile delivery. Fukui et al (2000) described hydroxypropylcellulose (HPC) as dry coating material to prepare timed release Diltiazem HCl tablets. Drug tablets were coated with HPC by press coating which resulted in a lag time of 7 h followed by rapid drug release in pH 6.8 phosphate buffer. Cao et al (2004) described high viscosity hydroxypropyl methylcellulose (100, 000 cps) as coating material for chronotherapeutic delivery of nifedipine. The photo-imaging analysis revealed that the lag time could be attributed to the swelling of HPMC for initial 5 h without disintegration. The disintegration of the dosage form occurred after 7 h and caused drug release. This approach had to use very dilute solutions of HPMC (4 % w/w) and ethanol: water mixture as a solvent since concentrated solutions exhibited high viscosity which could not be used for coating. Coating with very dilute polymer solutions requires longer processing times to achieve desired polymer loading. Therefore such an approach is not viable for industrial use.

Zou et al (2008) described a floating pulsatile release bilayer tablet for verapamil HCl. The pulsatile release tablet was tablet-in-tablet produced using immediate release core and was dry coated using hydrophilic erodible polymer Methocel E15 (260 mg) which formed the external layer. The second layer was used to provide buoyancy and composed of Methocel K4M, Carbopol 934P and sodium bicarbonate. Drug core, 6 mm in diameter was composed of polyvinylpyrrolidone and magnesium stearate. This tablet was press coated by placing 130 mg of Methocel E15 in the die, the tablet and another 130 mg of Methocel E15 and compressed into a 10 mm diameter tablet to achieve pulsatile release. Powder mixture of buoyant layer was filled in the die above pulsatile release tablet and compressed to form a floating pulsatile release tablet. This tablet floated immediately and released drug after a lag time of 5 h. The lag time was attributed to erosion of Methocel E15 and floating was achieved by buoyant layer. Although floating pulsatile tablets may improve the effectiveness of the pulsatile systems, these are difficult to manufacture and simpler approach for floating pulsatile drug delivery is desirable.

6.1.2 Limitations of existing approaches to chronotherapeutic delivery of TPH

In all these systems reported above, the lag time of dosage forms can not be precisely controlled because of highly variable residence time of formulation due to presence or absence of food, and in the former case, the calorie value of the meal. Gastric emptying of formulations is the most critical factor which affects residence time. Zou et al (2008) recommended floating pulsatile tablets since the highly variable nature of gastric emptying process can result in *in-vivo* variability and bioavailability problems with conventional pulsatile release dosage forms.

6.1.3 Our approach to gastroretentive chronotherapeutic delivery of TPH

We propose gastroretentive chronotherapeutic delivery for TPH tablet coated with a basic pH sensitive polymer which swells and dissolves as discussed in chapter 3. The tablets prepared using this approach would stay in the stomach and result in predetermined lag time followed by drug release. The drug released would enter intestine and be absorbed. We evaluated a series of pH sensitive polymers containing MMA, BMA and VP which swell and dissolve over 24 h for gastroretentive chronotherapeutic delivery using Theophylline as a model drug.

6.2 Experimental section

6.2.1 Materials

Magnesium stearate, sodium bicarbonate, anhydrous citric acid and dichloromethane were purchased from Merck Chemicals, India. Lactose and Microcrystalline cellulose (MCC) were purchased from S D Fine Chemicals Ltd, India. Theophylline (TPH) and Verapamil HCl (VER) were gift samples from Lupin Laboratories Ltd., India.

Synthesis and characterization of polymers containing MMA, BMA and VP has already been described in chapter 3.

6.2.2 Methods

6.2.2.1 Preparation of TPH tablets using basic pH sensitive polymers

6.2.2.1.1 Preparation of TPH tablets

The core TPH tablets were prepared by direct compression using pneumatic press. All ingredients as per composition were weighed and mixed using mortar and pestle. The powder mixture was compressed into 13 mm die tablets.

6.2.2.1.2 Coating of TPH tablets

The core TPH tablets were coated by dipping the tablet in 10 % w/v solution of pH sensitive polymers in dichloromethane and repeating the same coating procedure to

achieve required weight gain. The synthesis and characterization of pH sensitive polymers is described in chapter 3.

6.2.2.2 Release and floating studies from tablets

The drug release from coated tablets was carried out using dissolution apparatus, USP Type II, 50 rpm at 37 ± 0.5 ºC in 900 ml of 0.1 N HCl. 5 ml aliquots were withdrawn at predetermined time intervals. The medium was replenished. The samples were filtered and analyzed by UV spectrophotometer at 270 and 278 nm for TPH and VER respectively. The floating behavior of the tablets was monitored during the drug release study. The time required for the tablet to float in the dissolution medium was taken as buoyancy time (BT) and duration for which the tablet floated was noted as floating time (FT). The time to release 10 % drug was taken as lag time (T_{lag}). The duration over which drug was release was noted as release time (RT).

6.2.2.3 Morphological changes during polymer film swelling / dissolution

The morphology of B5 polymer films was studied using scanning electron microscope (Leica, 440 model). The polymer films were prepared by solvent casting method and films 200 ± 20 μ thickness were prepared. The films were treated with 0.1 N HCl at 37.5 ºC upto 24 h and samples were removed periodically, gently wiped with tissue paper and dried. The scanning electron microscopy was carried out for the dried samples.

6.3 Results and discussion

Gastroretentive drug delivery systems developed in the past to provide sustained release of drugs have been discussed in the previous chapters. In this chapter we report gastroretentive systems for chronotherapeutic delivery. A series of pH sensitive polymers which swell and dissolve were evaluated for gastroretentive chronotherapeutic delivery using theophylline as a model drug.

We developed a series of pH sensitive polymers containing MMA, BMA and VP. VP was used to provide pH dependent swelling / dissolution. The polymers which swelled 200-700 % followed by dissolution depending on MMA/BMA ratios as described in chapter 3 were evaluated for gastroretentive chronotherapeutic delivery of TPH. Effervescent agents were used to impart buoyancy to coated tablets by entrapment of carbon dioxide gas in the tablets and provide low density (Krogel and Bodmeier, 1999). Mixture of sodium bicarbonate and anhydrous citric acid was used as gas generating agent (GGA) in core tablets. 13 mm diameter tablets were prepared

which enables gastric retention because of the size in addition to floating mechanism (Khosla and Davis, 1990).

6.3.1 Optimization of TPH tablets

6.3.1.1 Effect of GGA concentration on floating and drug release

The core TPH tablets were prepared and coated with the terpolymer composed of 15:67:18 mole % of MMA:BMA:VP respectively to achieve 15 % w/w polymer loading using procedure described in section 6.2.2.1 as per composition given in table 6.1. This polymer was chosen because of slowest hydration rate and longer time needed to reach equilibrium swelling. The effect of gas generating agent concentration on floating characteristics of coated TPH tablets is summarized in table 6.2. The drug release from coated TPH tablets is shown in figure 6.1.

Table 6.1: Composition of TPH tablets: Effect of GGA content

S No	Ingredient				
1	TPH	420	370	320	270
2	Sodium bicarbonate	43	71	100	129
3	Citric acid	32	54	75	96
4	Magnesium stearate	5	5	5	5
	Total	500	500	500	500
5	Polymer B6	75	75	75	75
	GGA conc. (%)	15	25	35	45

All amounts in ‘mg’

Table 6.2: Floating of TPH tablets: Effect of GGA content

GGA conc. (%)	15	25	35	45
BT (h)	#	#	5.75	7.75
FT (h)	NA	NA	9	15
T_{lag} (h)	8	8	7	7
RT (h)	15	15	14	15

The tablets did not float.

The TPH tablets did not float until 25 % GGA was present. At 35 % GGA content, the tablet floated after 5.75 h but settled after 9 h. This could be attributed to inadequate GGA level. At 45 % GGA loading, the BT of TPH tablet was 7.75 h and it floated throughout the duration of drug release. The GGA level of 35 % was chosen for further evaluation to explore whether incorporation of additive would enhance the buoyancy and floating at this GGA loading.

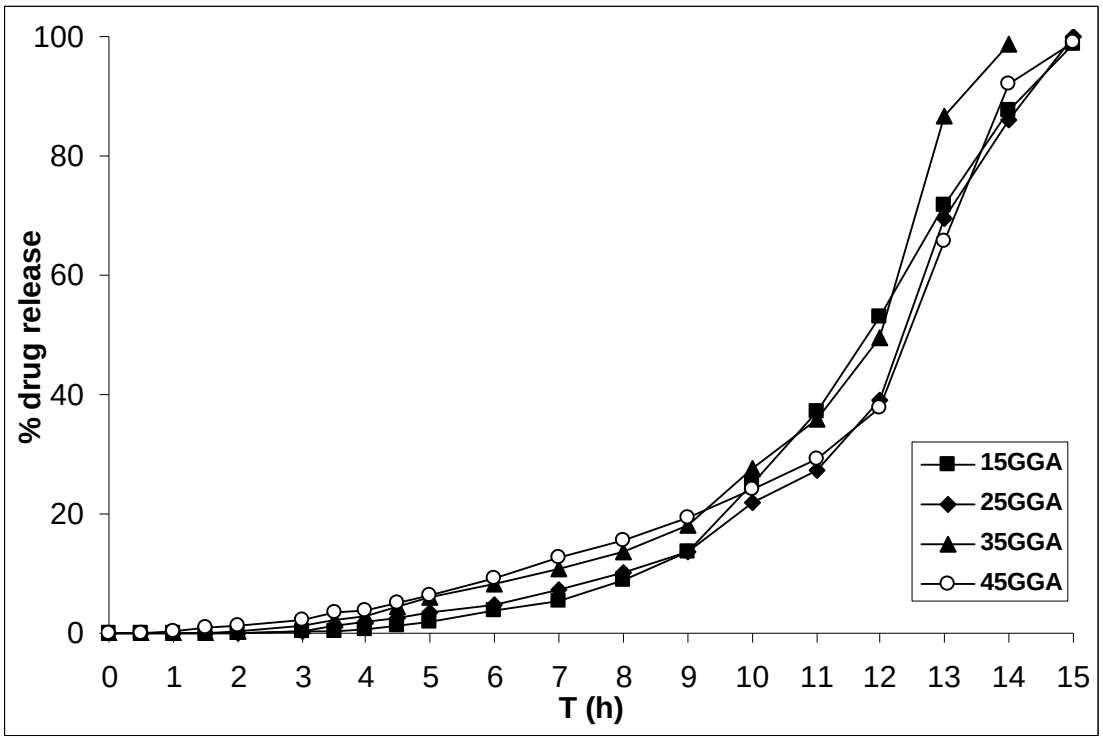

Figure 6.1: Effect of GGA content in tablet on TPH release

The T_{lag} for drug release was 8 h for 15-25 % GGA level and reduced to 7 h at 35-45 % level. Increase in GGA concentration caused increased release rate initially upto 9 h and sustained release over next 6 h.

6.3.1.2 Effect of type of diluent on floating and drug release

TPH tablets as per composition in table 6.3 were prepared and coated with B6 polymer to achieve 15 % w/w polymer loading as described in section 6.2.2.1. The effect of water soluble, Lactose and insoluble microcrystalline cellulose (MCC) was investigated as diluents in drug core at 14 % w/w level on floating and drug release of coated TPH tablets. The drug release from coated TPH tablets containing lactose or MCC as diluents is shown in figure 6.2 and the floating characteristics for coated TPH tablets are given in table 6.4.

Table 6.3: Composition of TPH tablets: Effect of diluent type

S No	Ingredient	Amount (mg)
1	TPH	250
2	Diluent	70
3	Sodium bicarbonate	100
4	Citric acid	75
5	Magnesium stearate	5
	Total	500
6	Polymer B6	75

Table 6.4: Floating of TPH tablets: Effect of diluent type

Diluent	BT (h)	FT (h)	T_{lag} (h)	RT (h)
Lactose	2.5	11	5	11
MCC	3.5	13	5	13

The incorporation of diluents in the drug core at 14 % w/w lowered BT and RT. Tablets based on lactose, because of its water solubility exhibited lower BT and RT than those based on MCC. Krogel and Bodmeier (1999) also described that incorporation of lactose lowered the BT and RT of CPM tablets coated with Eudragit RS/ATBC coating. MCC based drug cores coated with Ethyl cellulose resulted in rapid drug release after a predetermined lag time. This was because of disintegrant properties of MCC. In the present case, incorporation of MCC could not convert sustained release after lag time into rapid pulse after a predetermined lag time because of flexibility of polymer B6 as it has higher BMA content. Lactose was chosen as diluent for further trials as it resulted in lower BT and lag time followed by faster drug release than MCC.

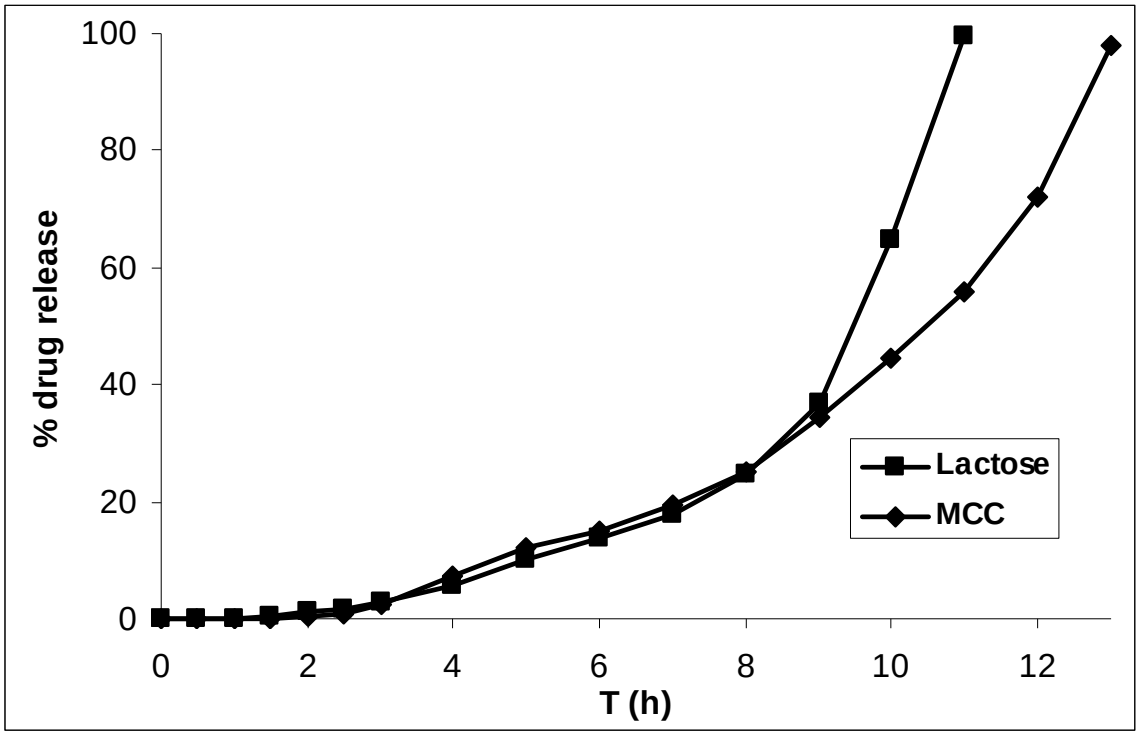

Figure 6.2: Effect of diluent type on TPH release

6.3.1.3 Effect of drug type on floating and drug release

Two drugs with varying solubilities i.e. TPH (12 mg/ml) and Verapamil HCl (VER) (150 mg/ml) were selected to investigate the effect of drug type on floating and drug release. The core tablets containing drug were prepared and coated with B6 polymer to achieve 15 % w/w polymer loading using procedure described in section 6.2.2.1 as per composition in table 6.5.

Table 6.5: Composition of tablets: Effect of drug type

S No	Ingredient	Amount (mg)
1	Drug	250
2	Lactose	70
3	Sodium bicarbonate	100
4	Citric acid	75
5	Magnesium stearate	5
	Total	500
6	Polymer B6	75

The effect of drug type on release is shown in figure 6.3 and the floating characteristics are summarized in table 6.6.

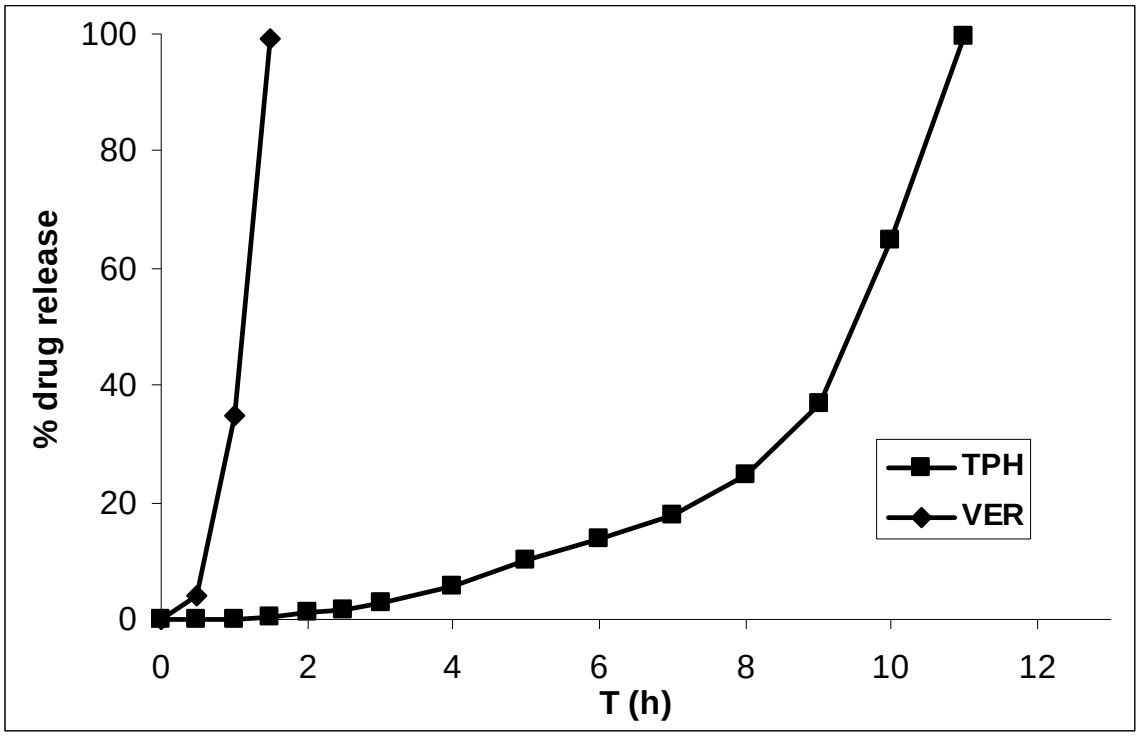

Figure 6.3: Effect of drug solubility on release

Table 6.6: Floating of tablets: Effect of drug type

Drug	BT (h)	FT (h)	T_{lag} (h)	RT (h)
TPH	2.5	11	5	11
VER	0.25	1.5	0.5	1.5

The BT and RT were governed by the solubility of drugs. VER being more soluble dissolved and diffused out faster than TPH from the swollen tablet coating and resulted in shorter BT and RT as compared to TPH based systems. Therefore, the drugs which have limited solubility in the stomach and high solubility in the intestine such as Dichlofenac sodium and Indomethacin can be delivered using this approach.

6.3.2 Optimization of polymer coating

6.3.2.1 Effect of polymer swelling / dissolution on floating and drug release

The TPH tablets as per table 6.7 were prepared and coated with polymers exhibiting different equilibrium swelling and dissolution properties at 15 % w/w polymer loading as per procedure given in 6.2.2.1.

The polymers B1-B6 varying in extent of swelling (200-700 %) and dissolution behavior were used for tablet coating to investigate the effect of polymer swelling and dissolution on floating and drug release. The drug release from coated TPH tablets using polymers having different equilibrium swelling is shown in figure 6.4. The effect of polymer swelling and dissolution on floating characteristics for coated TPH tablets is summarized in table 6.8. The tablets coated with polymer B1 did not float due to rapid swelling of coating which caused rapid water ingress and resulted in increased density and also escape of generated gas through highly swollen coating followed by dissolution of polymer coating and rapid drug release.

BT and RT of TPH tablets increased with reduction in swelling of polymer films. This was because higher swelling caused rapid water ingress and gas generation followed by drug diffusion. Lag time for drug release was also dependent on polymer swelling rate. Thus BT, RT and T_{lag} of TPH tablets were governed by hydrophobicity (BMA content) of the polymer. Low swelling of polymer resulted in higher lag time as it took longer time for the medium to reach the drug core, which results in dissolution and diffusion of the drug through swollen polymer layer, which may also undergo dissolution. This was evident from the SEM pictures of polymer B5 which revealed that the polymer film swelled initially and dissolved over a period of 24 h. The SEM pictures are shown in figure 6.5. For small change in BT of TPH tablets in

the range 2-2.5 h, a wide variation in T_{lag} i.e. 1.5-5 h of tablets was achieved by selection of polymer.

Table 6.7: Composition of TPH tablets: Effect of polymer swelling / dissolution

S No	Ingredient	Amount (mg)
1	TPH	250
2	Lactose	70
3	Sodium bicarbonate	100
4	Citric acid	75
5	Magnesium stearate	5
	Total	500
6	Polymer	75

Table 6.8: Floating of TPH tablets: Effect of polymer swelling / dissolution

Polymer	BT	FT (h)	T_{lag} (h)	RT (h)
B1	#	NA	1.5	3
B2	2 h	7	2	7
B3	2 h 8 min	7	3	7
B4	2 h 17 min	11	4	11
B5	2 h 28 min	11	4	11
B6	2 h 30 min	11	5	11

Tablet did not float

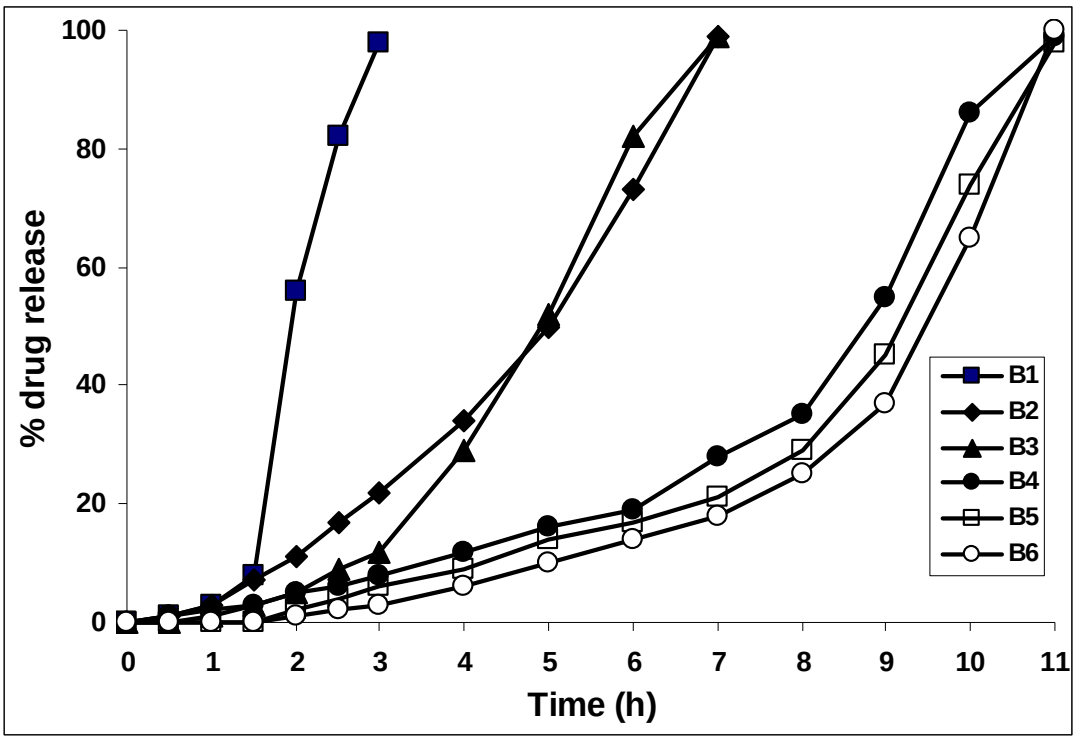

Figure 6.4: Effect of polymer swelling / dissolution on TPH release

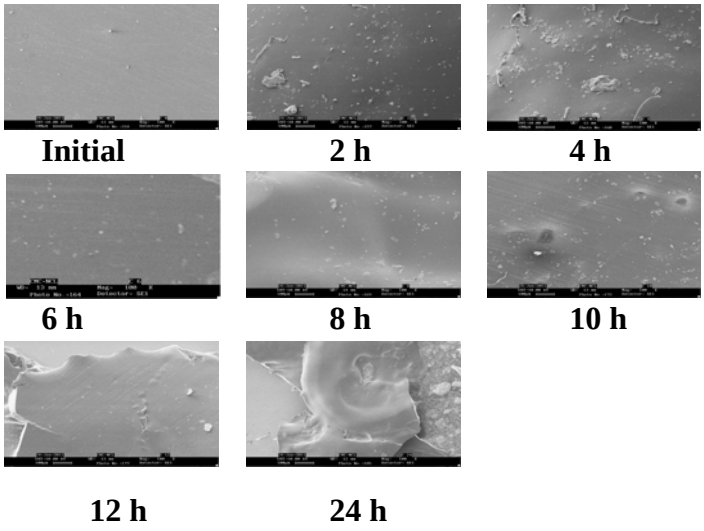

Figure 6.5: Morphological changes during polymer film swelling / dissolution

6.3.2.2 Effect of polymer coating level on floating and drug release

The TPH cores were prepared and coated at 10-20 % w/w polymer coating levels with polymer B6 as described in section 6.2.2.1. The composition of TPH tablets is shown in table 6.9. The effect of polymer coating level on floating characteristics for coated TPH tablets is summarized in table 6.10. The effect of coating level on TPH release is shown in figure 6.6.

Table 6.9: Composition of TPH tablets: Effect of polymer coating level

S No	Ingredient			
1	TPH	250	250	250
2	Lactose	70	70	70
3	Sodium bicarbonate	100	100	100
4	Citric acid	75	75	75
5	Magnesium stearate	5	5	5
	Total	500	500	500
6	Polymer B6	50	75	100
	Coating level (%)	10	15	20

All the amounts in ‘mg’

Table 6.10: Floating of TPH tablets: Effect of polymer coating level

Coating level (%)	BT (h)	FT (h)	RT (h)	T_{lag} (h)
10	2.25	10	10	4
15	2.5	11	11	5
20	4.5	14	14	7

Increase in polymer coating level resulted in higher BT, RT, FT and T_{lag} values. Krogel and Bodmeier (1999) also reported that increase in the coating level from 15.8 % to 21.8 % doubled the lag time from 4 h to 8 h for CPM tablets coated with Eudragit RS. The drug release becomes slower with increase in coating level due to increased barrier for drug to diffuse out of the core.

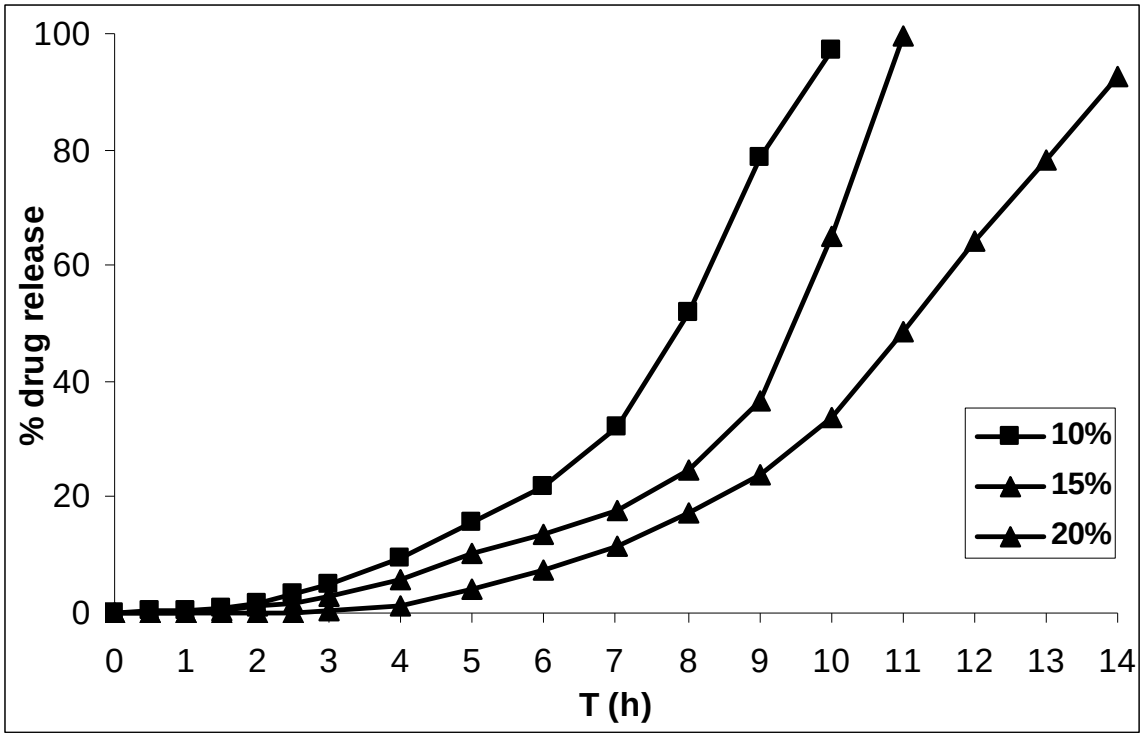

Figure 6.6: Effect of polymer coating level on TPH release

6.4 Conclusions

We synthesized pH sensitive polymers which swelled and dissolved over 24 h and evaluated the same for gastroretentive chronotherapeutic delivery using TPH as a model drug. Incorporation of GGA at 35 % level caused tablets to float after 5.75 h. Further, incorporation of lactose caused reduction in BT to 2.5 h. The performance of present gastroretentive chronotherapeutic system was dependent on drug solubility. Drugs with limited solubility at acidic pH and higher solubility at neutral pH such as Diclofenac sodium and Indomethacin can be delivered more effectively using this approach. The effect of polymer swelling and dissolution properties on performance of TPH coated tablets revealed that tablets coated with polymer which swelled faster exhibited shorter BT and RT than those which swelled slowly. The drug release was governed by swelling and dissolution of the basic pH sensitive polymers. The

hydrophobic polymers which swelled slowly exhibited longer buoyancy time, lag time and duration over which drug was released. Also increase in polymer coating level delayed BT and RT values of coated TPH tablets. The SEM study for polymer films prepared with B5 polymer revealed that polymer swelled and dissolved over 24 h. The lag time of TPH tablets was governed by polymer swelling and drug was released from the tablet core as the polymers swelled extensively and dissolved. The large size (13mm) of the tablets, buoyancy time of 2.25 h as well as the floating time of 10 h provided a means for gastroretentive system to deliver the drug following a predetermined lag time for chronotherapeutic delivery.

6.5 References

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Chapter 7

Gastroretentive multiple pulsed delivery using basic pH sensitive polymers

7.1 Introduction

Ciprofloxacin hydrochloride (CIP) is a fluoroquinolone antibacterial agent for the treatment of urinary and respiratory tract infections. Neuhouser et al (2003) reported that the overall susceptibility to ciprofloxacin decreased steadily from 86 % in 1994 to 76 % in 2000 and was significantly associated with increased use of fluoroquinolones and suggested that more innovative use of fluoroquinolones was required to tackle susceptibility changes. Occurrence of ciprofloxacin resistance in strains of pseudomonas aerugenosa and streptococcus pneumoniae reviewed by Zhanel et al (2004) suggested necessity for optimal dosing strategies to eradicate the causative pathogen before a resistant efflux mutant could emerge.

7.1.1 Rationale for gastroretentive multiple pulsed delivery

Multiple pulsed delivery of antimicrobial drugs such as ciprofloxacin is likely to avoid development of resistance in bacteria and would have better effectiveness due to its higher absorption from stomach. Advancis Pharmaceutical Corp developed Pulsys^{TM} technology for multiple pulsed antimicrobial formulations to avoid development of resistance against antimicrobial agents.

Pulsys^{TM} exploited the principle that bacteria exposed to initial dose, sequential bursts or pulses were killed more efficiently and effectively than when exposed to standard sustained dosage regimens. When sustained release antibacterial formulation was administered, the bacteria responded to it by going into a dormant stage. The administration of pulsatile system in such a case was more effective because the pulsed release did not allow the defense system of the bacteria to go into dormant stage.

The patent application WO2007/079082 by Advancis Pharmaceutical Corp. highlighted the need for better pulsatile delivery mechanism for oral delivery methodologies which would extend the time available for absorption of an active ingredient having poor absorption in the lower GI tract.

7.1.2 Gastroretentive multiple pulsed delivery: Prior efforts

Gastric release pulsed delivery system disclosed in patent application WO2007/079082 was based on a product which had at least three distinguishable C_{max} and T_{max} in a pharmacokinetic plasma profile. This patent revealed that there is a need for improved pulsatile delivery of active ingredients, such as an immediate onset of release to achieve desired C_{max} and separation between multiple $C_{max.}$ This patent demonstrated first rapid release pulse from immediate release fraction, second pulse

after a lag time from timed release coating and third sustained release pulse after a lag time which was achieved by the use of a rupturable coating. The extent of coating rupture was controlled using different ratios of soluble to insoluble film former or additives and thus the lag time and duration of drug release after the lag was manipulated. Time dependent rupturable coating (Ethyl cellulose) was prepared using swellable polymer to aid film rupture. Swellable polymer used was superdisintegrant such as Crosscarmellose sodium (Ac-di-sol). Third pulse was also based on time dependent rupturable coating as described above. Additionally a mucoadhesive coat was applied to provide gastric retention.

7.1.3 Limitations of existing gastroretentive multiple pulsed delivery systems

The product disclosed in patent application WO2007/079082 used mucoadhesive coating to achieve temporary gastric retention. The patent disclosed release of drug in lower part of GI tract also and thus it was not purely multiple pulsed system for release of drug in stomach. The consecutive pulses in release profile overlapped with each other and hence there was no clear separation between pulses. It was desired that these pulses should be well separated which was achieved partially. However, distinguishable C_{max} and T_{max} were demonstrated.

7.1.4 Our approach to gastroretentive multiple pulsed delivery

In view of the pulsatile release strategy recommended to avoid drug resistance and the limitations of the results presented in above patent application, we propose a new approach for multiple pulsed delivery using CIP as model drug in stomach which would improve effectiveness of the therapy and bioavailability. Our approach is based on the use of basic pH sensitive polymers which swell and dissolve at different rate and extent to achieve gastroretentive multiple pulsed release.

7.2 Experimental section

7.2.1 Materials

Magnesium stearate, sodium bicarbonate, anhydrous citric acid and dichloromethane (DCM) were procured from Merck Chemicals Ltd, India. Lactose was purchased from S D Fine Chemicals Ltd., India. CIP was a gift sample from Lupin Laboratories Ltd., India.

The synthesis and characterization of pH sensitive polymers is described in chapter 3.

7.2.2 Methods

7.2.2.1 Preparation of CIP floating tablets

7.2.2.1.1 Preparation of CIP tablets using basic pH sensitive polymers

The core CIP tablets were prepared by direct compression using pneumatic press. All ingredients as per composition were weighed and mixed together in mortar and pestle. The powder mixture was compressed into 13 mm diameter tablets.

7.2.2.1.2 Coating of CIP tablets

The CIP core tablets were coated by dipping the tablet in 10 % w/v solution of pH sensitive polymer solution in dichloromethane and drying the tablets at room temperature and repeating the same procedure to achieve required weight gain.

7.2.2.2 Release and floating studies from CIP tablets

The release of CIP tablets was carried out using Electrolab dissolution apparatus, USP Type II, 50 rpm at 37 ± 0.5 ºC in 900 ml of 0.1 N HCl. 5 ml aliquots were withdrawn at predetermined time intervals. The dissolution medium was replenished with fresh medium. The samples were filtered and analyzed by UV spectrophotometer at 277 nm. The floating behavior of the CIP tablets was monitored during the dissolution test. The time required to float the tablet was taken as buoyancy time (BT) and floating period (FT) was the time the tablet remained floated in the medium. The time to release about 10 % drug was taken as lag time (T_{lag}). The duration over which drug was release was taken as drug release time (RT).

7.2.2.3 Preparation of CIP multiple pulsed delivery systems

Based on the results of drug release profiles obtained, three tablets were selected to prepare CIP multiple pulsed delivery systems. Two CIP multiple pulsed delivery systems were designed and evaluated.

7.3 Results and discussion

Research on time control and temporal control of drug delivery systems is receiving a major impetus for the development of new and/or improved drug therapies. Pulsatile release is defined as the rapid and transient release of drug within a short time period immediately after predetermined lag time. Many biological functions in the body are regulated by the temporal and pulsatile release of biochemicals. Thus it may be necessary to administer drugs in a manner which more closely follows circadian rhythm in the body (Cleland and Langer, 1994). Pulsatile systems are of mainly two types' i.e. site specific systems and pulsatile release which release the drug in stomach

as well as in the intestine. While the pulsatile release in the stomach as well as in the intestine has been extensively investigated (US 6544555 and US 5837284), there is very little information on the pulsed delivery in the stomach.

Pulsatile release systems that release drug throughout gastrointestinal tract are disclosed by Pulsys™ technology (US 6544555). These are based on once a day antibiotic product consisting of first immediate release fraction of drug, second and third delayed release fractions wherein each of these fractions initiate release at different times. Pulsys™ technology utilized enteric polymers which resulted in release of drugs at different pH and released drug in stomach, proximal intestine and lower intestine.

US patent 5837284 disclosed a dosage form for administration of methylphenidate which provided an immediate dose of methylphenidate followed by another dose at a predetermined time from particles containing drug and Eudragit RS and Eudragit RL.

From the foregoing, it is obvious that multiple pulsatile delivery of CIP in the stomach would improve effectiveness of therapy and bioavailability. We synthesized a series of pH sensitive polymers containing MMA, BMA and VP which exhibit a variety of swelling and dissolution properties. The pH sensitive polymers which swell followed by dissolution were evaluated. Effervescent agents were used to provide buoyancy to coated tablets by entrapment of carbon dioxide gas. The tablets were 13 mm diameter which also enabled size based gastric retention in addition to floating (Khosla and Davis, 1990). Thus the present multiple pulsed CIP tablets have dual mechanism for gastric retention.

7.3.1 Optimization of CIP tablets

7.3.1.1 Effect of GGA concentration in the core on floating and release

The CIP core tablets were prepared with GGA concentrations in the range 20-45 % as shown in table 7.1 and procedure described in section 7.2.2.1. These tablets were further coated with a pH sensitive polymer composed of 27:54:19 mole % MMA, BMA and VP respectively to achieve 15 % w/w polymer loading. The polymer has slow hydration rate and time to reach equilibrium swelling was 9 h. Therefore, it was chosen for evaluation of effect of gas generating concentration on performance of CIP tablets. Krogel and Bodmeier (1999) suggested use of low swelling polymers for preparation of pulsatile systems wherein Chlorpheniramine maleate (CPM) tablet cores coated with highly swelling polymer Eudragit RL resulted in rapid release, and hence polymers with lower swelling such as Eudragit RS and Ethyl cellulose were

chosen which yielded pulsatile systems. Lactose, a water soluble diluent was used for drug core preparation to increase the rate of water penetration into the core tablets.

Increase in GGA concentration caused increase in BT and T_{lag} of CIP tablets. This was due to increase in pH of drug core after increasing GGA concentration. CIP has lower solubility at higher pH. With increase in GGA concentration in the tablet the drug loading in the core was lowered which delayed medium penetration into tablet core and led to increased BT and RT of the tablets. This was confirmed by checking pH of CIP tablet cores. Chavanpatil et al (2006) reported effect of GGA concentration on release of floating Ofloxacin tablets. Increase in GGA concentration caused decrease in Ofloxacin release for the floating tablets prepared using Psyllium husk, Methocel K100M, crosspovidone and β-cyclodextrin. This was attributed to reduction in solubility due to sodium bicarbonate

Table 7.1: Composition of CIP tablets: Effect of GGA content

S No	Ingredient						
1	CIP	325	300	275	250	225	200
2	Lactose	70	70	70	70	70	70
3	Sodium bicarbonate	55	70	85	100	115	130
4	Citric acid	45	55	65	75	85	95
5	Magnesium stearate	5	5	5	5	5	5
	Total	500	500	500	500	500	500
6	Polymer B4	75	75	75	75	75	75
	GGA concentration (%)	20	25	30	35	40	45

All the amounts in ‘mg’

The results of gas generating agent concentration on floating characteristics and drug release from CIP tablets are summarized in table 7.2 and figure 7.1 respectively.

CIP exhibits reduced solubility at neutral pH (Firestone et al, 1998) and thus the drug release was slowed down with increase in gas generating agent concentration. GGA concentration of 35 % w/w was selected for subsequent studies because at this concentration, lag time of 2.5 h was obtained and BT was 47 min. Also by increase in GGA concentration to 45 % w/w, we could increase T_{lag} of tablets upto 3.5 h followed by drug release.

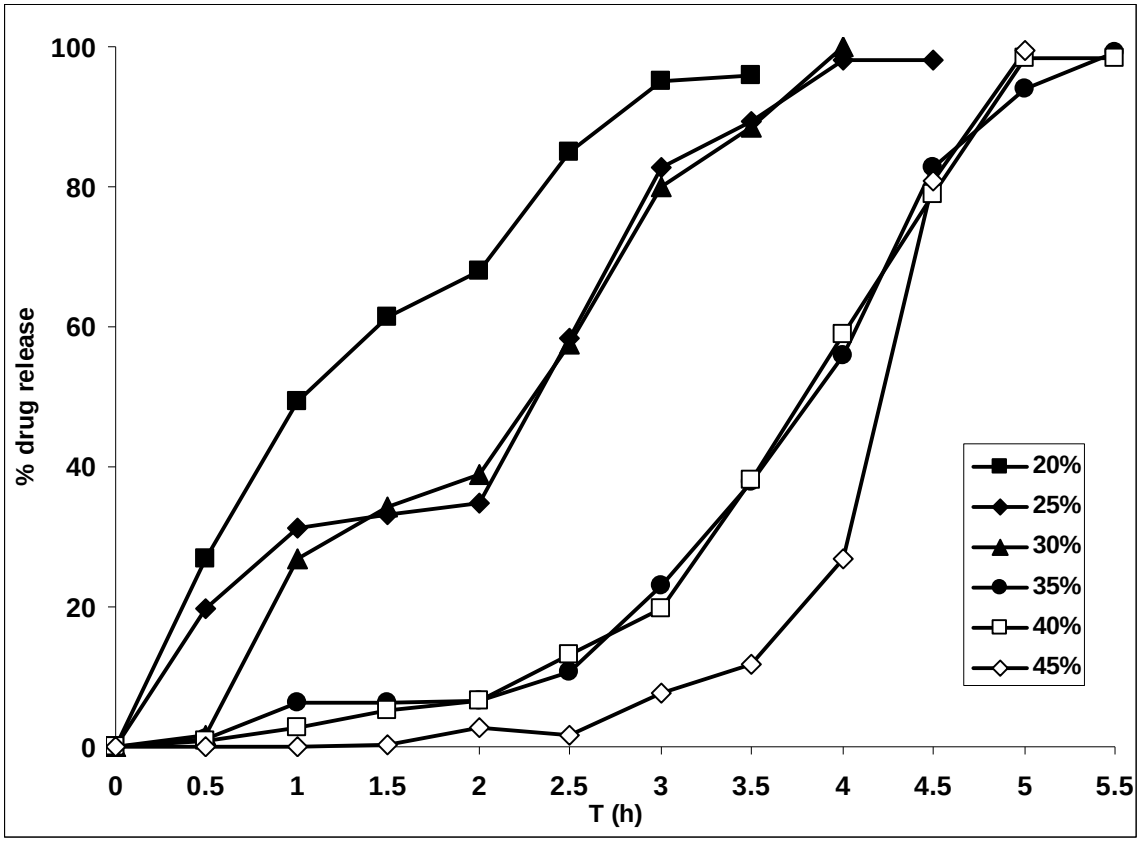

Figure 7.1: Effect of GGA content in tablet on CIP release

Table 7.2: Floating of CIP tablets: Effect of GGA content

GGA content (% w/w)	BT (min)	FT (h)	Lag time (h)	RT (h)
20	23	3	< 0.5	3
25	30	4	< 0.5	4
30	40	4	< 0.5	4
35	47	5	2.5	5.5
40	75	5	2.5	5
45	90	5	3.5	5

7.3.2 Optimization of polymer coating

7.3.2.1 Effect of polymer swelling / dissolution on floating and release

The CIP tablets were prepared using compositions in table 7.3 and coated as per procedure given in 7.2.2.1 for evaluation of effect of polymer swelling / dissolution on floating and drug release. The polymers B1-B6 which exhibited varying degree of swelling (200-700 %) and dissolution behavior were used for tablet coating to investigate the effect of polymer swelling and dissolution on floating and drug release. The tablets were coated with polymers at 15 % w/w polymer loading.

Table 7.3: Composition of CIP tablets: Effect of polymer swelling / dissolution

S No	Ingredient	Amount (mg)
1	CIP	250
2	Lactose	70
3	Sodium bicarbonate	100
4	Citric acid	75
5	Magnesium stearate	5
	Total	500
6	Polymer	75

The CIP release from coated tablets using polymers exhibiting different equilibrium swelling is shown in figure 7.2. The effect of polymer swelling / dissolution on floating characteristics for coated CIP tablets is summarized in table 7.4.

The BT and T_{lag} of tablets were governed by swelling rate and dissolution of polymers. Polymers which swelled slowly required longer time to float and because of delayed penetration of medium, the duration over which the drug released and T_{lag} was increased.

Table 7.4: Floating of CIP tablets: Effect of polymer swelling / dissolution

Tablet code	BT (min)	FT (h)	T_{lag} (h)	RT (h)
B1	18	3	1	2.5
B2	31	5	1.5	5
B3	38	5	2	5
B4	47	5	3	5
B5	56	12	6	12
B6	135	>12	7	>12

The drug release after lag time was governed by the polymer swelling / dissolution. With increase in BMA content, the polymers become more hydrophobic and their swelling rate was reduced. Thus hydrophobicity governed penetration of dissolution medium into the core tablet, swelling and dissolution of polymers. Thus, BT, FT, T_{lag} and RT values of coated CIP tablets were influenced by swelling and dissolution of polymer used for coating.

B5 polymer swelled more and dissolved faster than B6 since the latter contained more BMA. Thus BT, FT, T_{lag} and RT of CIP tablets coated with B5 polymer were shorter than those coated with B6 polymer. The SEM pictures taken for B5 polymer films as a function time treated with 0.1 N HCl are shown in figure 7.3. The SEM study revealed that the polymer swelled initially followed by dissolution over 24 h. The

slower hydration of drug core due to low polymer swelling delayed penetration of medium within the drug core and also slower gas generation led to longer BT. Hydration of the core tablet resulted in the dissolution of the drug and its release through the swollen / dissolved polymer film. Hence the lag time and duration of drug release from tablets coated with pH sensitive polymers was governed by polymer swelling / dissolution.

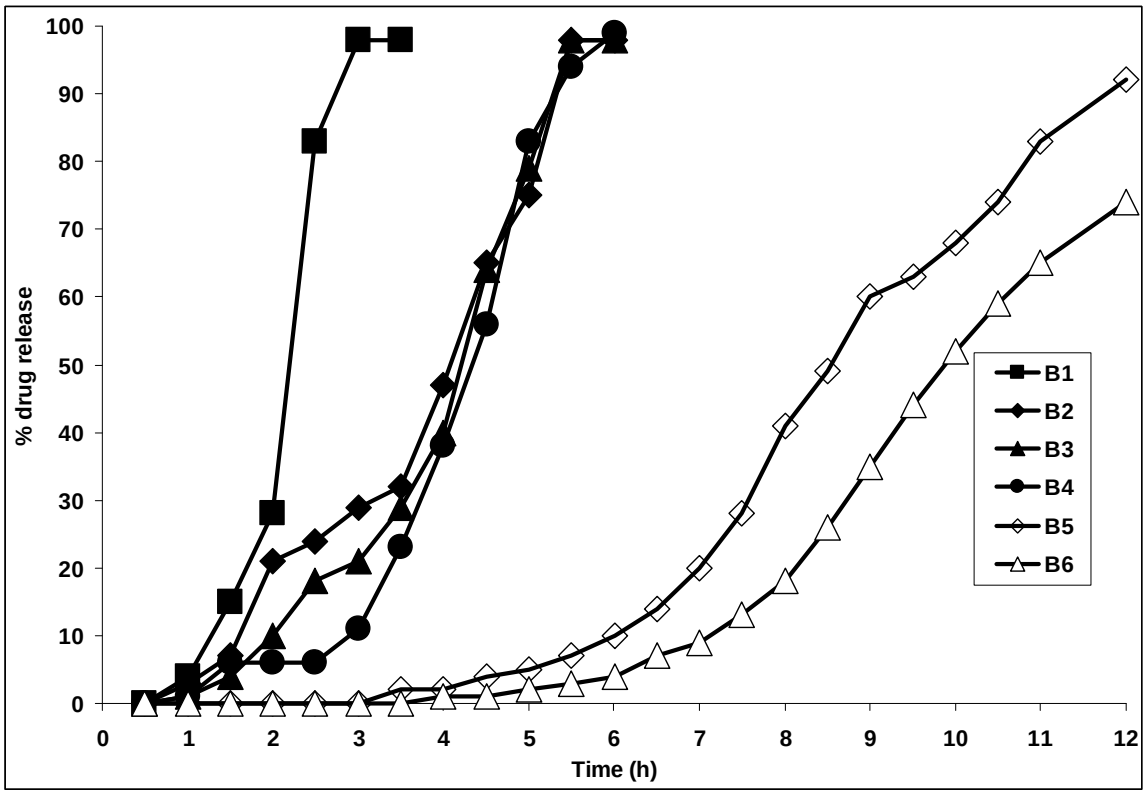

Figure 7.2: Effect of polymer swelling / dissolution on CIP release

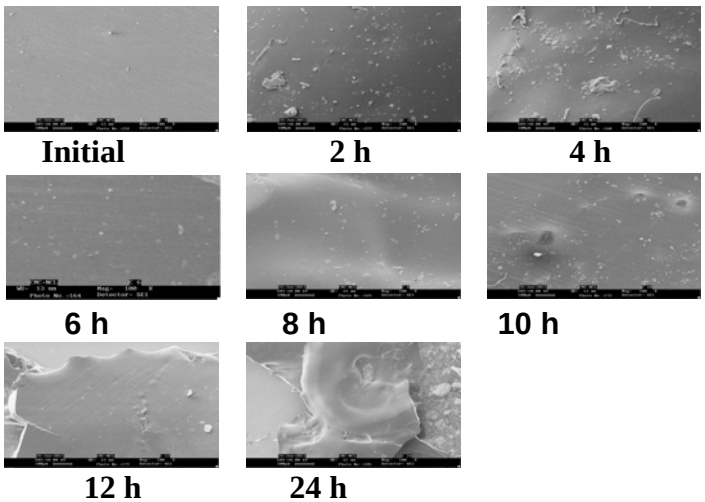

Figure 7.3: Morphological changes during polymer film swelling / dissolution

The drug release profiles of CIP tablets coated with polymers B1, B4 and B5 can be exploited to prepare multiple pulsed CIP formulation as the drug release of tablet coated with B4 polymer started after complete release of drug from tablet coated with B1 polymer and drug release from tablet coated with B5 polymer started after complete release from tablet coated with B4 polymer and continued further.

The release profile exhibited by CIP tablets coated with polymers B5 and B6 could also be useful for chronotherapeutic drug delivery systems which require drug release after a predetermined lag time. These chronotherapeutic systems are useful for the treatment of diseases which exhibit circadian rhythm based intensity of symptoms.

7.3.2.2 Effect of polymer coating level on floating and release

The CIP drug cores were prepared and coated at 5-20 % w/w coating levels with polymer B5 as described in section 7.2.2.1. The composition of CIP tablets is shown in table 7.5. The drug release from coated CIP tablets using B5 polymer with different coating levels such as 5-20 % is shown in figure 7.4. The effect of polymer coating level on floating characteristics for coated CIP tablets is shown in table 7.6.

Table 7.5: Composition of CIP tablets: Effect of polymer coating level

S No	Ingredient				
1	CIP	250	250	250	250
2	Lactose	70	70	70	70
3	Sodium bicarbonate	100	100	100	100
4	Citric acid	75	75	75	75
5	Magnesium stearate	5	5	5	5
	Total	500	500	500	500
6	Polymer B5	25	50	75	100
	Coating level (%)	5	10	15	20

All the amounts in ‘mg’

Table 7.6: Floating of CIP tablets: Effect of polymer coating level

Coating (%)	BT (min)	FT (h)	T_{lag} (h)	RT (h)
5	42	2	1	7
10	55	12	2	10
15	63	12	6	12
20	135	12	7	11

The drug cores disintegrated and dissolved within 2 minutes without floating, which revealed that a polymeric coating was required to make the tablet buoyant and sustain the release. Increase in polymer coating level caused delay in penetration of

dissolution medium into the core tablets and prolonged time for gas generation which caused increase in BT and RT values of tablets. Increase in coating level from 10 to 15 % w/w resulted in small change in BT of CIP tablets but the lag time was substantially increased from 2 h to 6 h. This behavior could be useful in the design of CIP multiple pulsed systems.

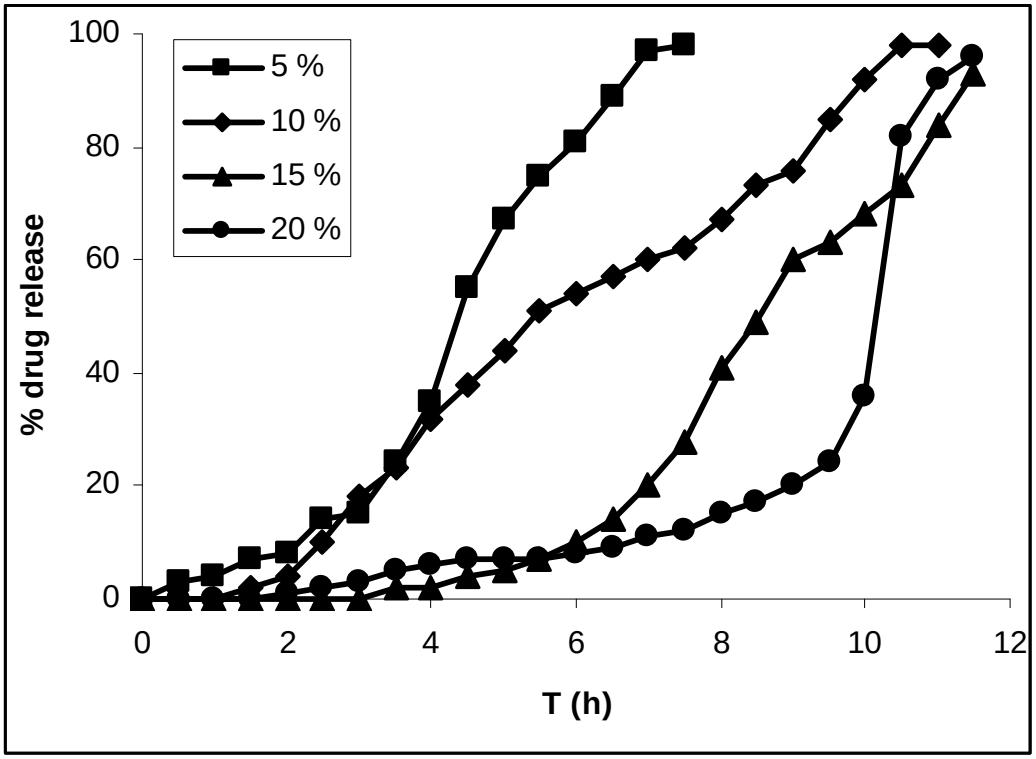

Figure 7.4: Effect of polymer coating level on CIP release

Krogel and Bodmeier (1999) also reported that increase in coating level caused increase in the buoyancy time of placebo cores coated with Eudragit NE30D.

7.3.2 Preparation of CIP multiple pulsed delivery systems

Based on the release from CIP tablets coated with different polymers as described in section 7.3.1, two multiple pulsed CIP systems X and Y were prepared. Multiple pulsed system X was prepared by preparing three tablets, A, B and C and taking together. CIP system X was designed so that the CIP pulses occur one after another and give clear separation among three pulses. The procedure for the preparation of CIP tablet cores and coating was same as shown in section 7.2.2.1. The systems of CIP tablets A, B and C for preparation of system X are given in table 7.7. The floating

characteristics of system X are given in table 7.8. The cumulative CIP release and CIP release rate profiles of system X are shown in figures 7.5-7.6 respectively.

The pulses were obtained at 0 h, 2 h and 4 h for system X prepared using CIP tablets A, B and C. The system X exhibited clear separation among three pulses and is advantageous over the system disclosed in patent application WO2007/079082 by Advancis Pharmaceutical Corporation.

Table 7.7: Composition of CIP multiple pulsed delivery system X

		Tablet A	Tablet B	Tablet C
S No	Ingredient			
1	CIP	250	250	200
2	Lactose	70	70	70
3	Sodium bicarbonate	100	100	130
4	Citric acid	75	75	95
5	Magnesium stearate	5	5	5
	Total	500	500	500
6	Polymer coating	NA	B1	B4
7	Coating level	0	75	75

All amounts are in ‘mg’

The separation of pulses was achieved because the drug release of tablet B started after complete drug release from tablet A and drug release from tablet C started after complete drug release from tablet B.

Multiple pulsed system Y was prepared by preparing tablets P, Q and R and taking together. The procedure for the preparation of CIP tablet cores and coating was same as described in section 7.2.2.1. The compositions of CIP tablets P, Q and R used for the preparation of system Y are shown in table 7.9.

Table 7.8: Floating of system X

Tablets	BT (min)	FT (h)
Tablet A	#	NA
Tablet B	21	3
Tablet C	98	5

Tablet did not float

The floating characteristics for the system Y are summarized in table 7.10. The cumulative CIP release and CIP release rate profiles of system Y are shown in figure 7.7-7.8 respectively. The first tablet ‘P’ coated with polymer B1 released drug

completely within 2.5 h after a lag time of 1 h, the second tablet 'Q' coated with polymer B4 released drug completely within 5 h after a lag time of 3 h and third tablet 'R' coated with polymer B5 had lag time of 6 h and then released the drug in sustained manner for 12 h.

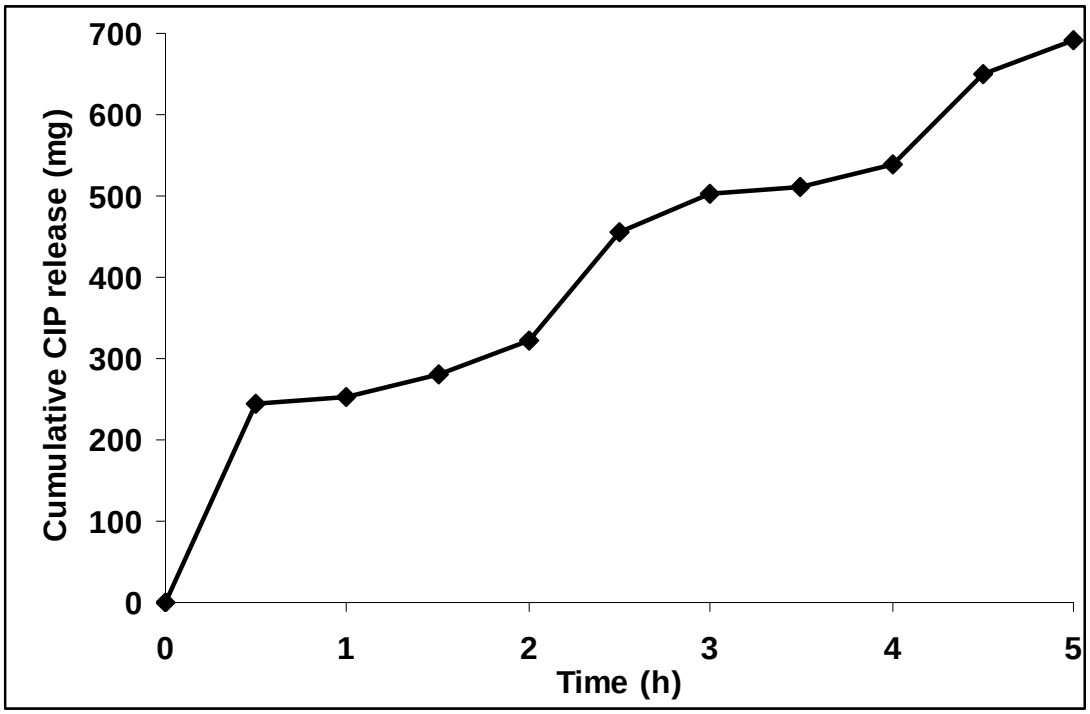

Figure 7.5: Cumulative CIP release profile from system X

Table 7.9: Composition of CIP multiple pulsed delivery system Y

		Tablet P	Tablet Q	Tablet R
S No	Ingredient			
1	CIP	250	250	250
2	Lactose	70	70	70
3	Sodium bicarbonate	100	100	100
4	Citric acid	75	75	75
5	Magnesium stearate	5	5	5
	Total	500	500	500
6	Polymer	B1	B4	B5
7	Coating level	75	75	75

All amounts in 'mg'

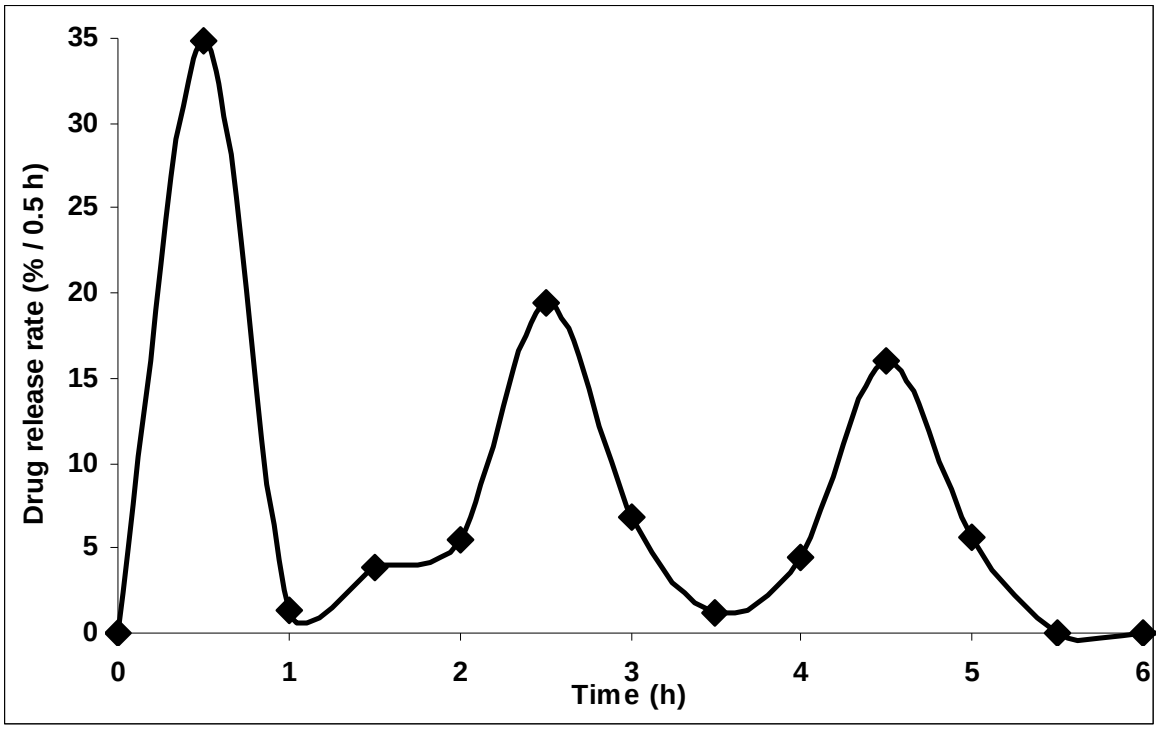

Figure 7.6: CIP release rate profile from system X

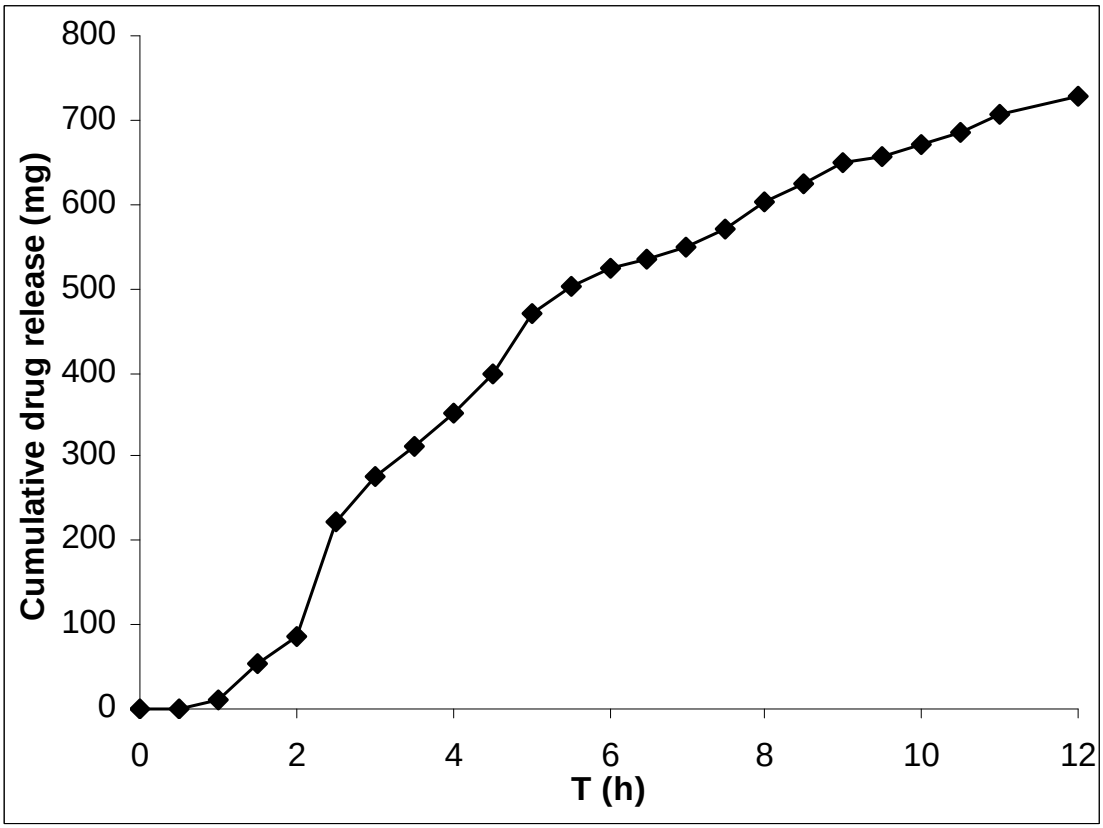

Figure 7.7: Cumulative CIP release profile from system Y

Table 7.10: Floating of system Y

Tablet	BT (min)	FT (h)
Tablet P	16	2.5
Tablet Q	52	5
Tablet R	62	12

The pulses were obtained at 1, 2, 4 and 7. Hence system Y is useful for twice a day product in addition to improved effectiveness against bacteria.

The tablets have size of 13 mm and are not expected to be cleared from the stomach during gastric emptying rapidly. Khosla and Davis (1990) described that large dosage forms such as 13 mm diameter tablets of non-disintegrating type were retained in stomach for 171 ± 29 min after a light breakfast of 360 Kcal. In addition to large size, the tablets also have floating properties which would further enhance gastric retention. So these systems have dual mechanism for gastric retention.

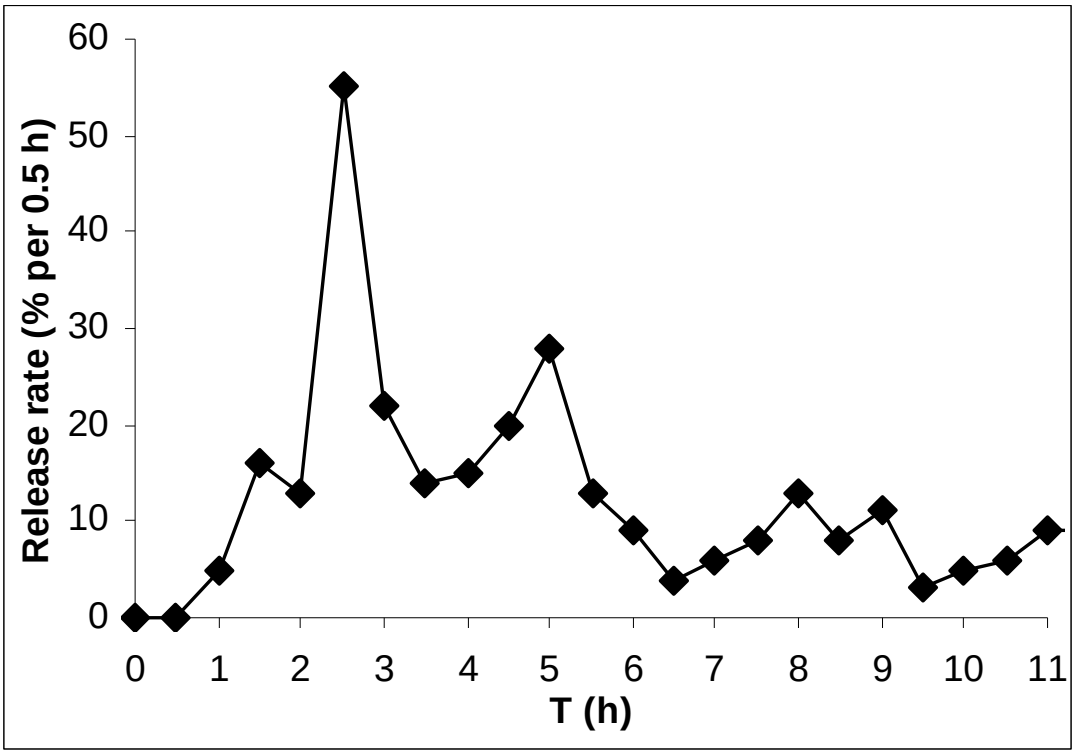

Figure 7.8: CIP release rate profile from system Y

7.4 Conclusions

The pH sensitive polymers containing MMA, BMA and VP synthesized and characterized earlier which swelled and dissolved over 24 h were evaluated for

gastroretentive multiple pulsed delivery using CIP as model drug. Increase in GGA concentration in the core tablets caused increase in values of BT, FT, RT and T_{lag}. The floating and release studies of CIP tablets coated with basic pH sensitive polymers revealed that polymers with lower swelling rate and longer dissolution time resulted in longer BT, FT, T_{lag} and RT of tablets. The lag time was governed by polymer swelling rate as tablets coated with polymer with lowest swelling rate exhibited longest lag time, which was due to its higher hydrophobicity. The drug release was governed by swelling and dissolution of polymers. The SEM study also revealed that polymer swelled initially followed by dissolution and this supported above observations on lag time and release control. The lag time and drug release was influenced by BMA content of polymers which imparted hydrophobicity to these polymers. The floating time and drug release duration increased with increase in polymer coating level onto tablets. Thus by choosing appropriate GGA concentration in the drug core, choice of polymer and polymer coating level, gastroretentive multiple pulsed release systems with clear separation among pulses were developed. The systems of present approach have dual mechanism for gastric retention i.e. due to large of size (13 mm) and buoyancy.

7.5 References

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Chapter 8

Methacrylic acid copolymers for sustained release at intestinal pH

8.1 Introduction

DLT is a calcium channel blocker used to treat hypertension. It has high solubility along the pH range 2-7 and molecular weight of 414. NDDS have been utilized to extend life cycle of this drug. Its NCE patent expired in 1986. The product life cycle was extended by introduction of newer forms of NDDS such as Cardizem CD, Cardizem LA, Tiazac, etc. Conventional enteric polymers Eudragit L100 and Eudragit S100 are insoluble at acidic pH and dissolve at intestinal pH. Copolymers of methacrylic acid and hydrophobic macromonomer resulted in copolymers which exhibit a diverse swelling / dissolution characteristics at intestinal pH (WO2010/103366 assigned to CSIR, India). These polymers were used to achieve sustained release under simulated intestinal conditions.

8.1.1 Approaches to DLT sustained release at intestinal pH

Approaches used for Diltiazem HCl (DLT) sustained release are based on a) drug-polymer interaction (Sousa et al, 2005), b) osmotic systems (Prabhakaran et al, 2003), c) coated systems (US 5288505) and d) modified geometries (Wilding et al, 1995 and Kim 1999). Of these, modified geometries and coated systems have been commercialized successfully. Systems based on drug polymer interaction for sustained release of DLT include polymers like carboxyalkyl methacrylate (Cornejo-Bravo et al, 2005), poly (methacrylic acid-graft-ethylene glycol) (Sipahigil et al, 2006) and Poly (N-isopropylacrylamide-co-methacrylic acid) (Sousa et al, 2005). In these systems, the drug loading was low as imbibition method was used for drug loading. Further, drug was released for 12 h only. Systems based on unmodified and modified polyacrylamide grafted guar gum sustained DLT release over a period of 8 and 12 h respectively. This method used freeze drying process for the preparation of drug loaded particles (Toti and Aminabhavi, 2004). Also saponified polyacrylamide grafted guar gum containing free carboxyl acid groups was evaluated for DLT release but could release DLT only upto 3h (Soppimath et al, 2002). Since acrylamide monomer is carcinogenic, unreacted monomer must be removed completely. Also regulatory approvals would be a concern.

DLT microparticles prepared using Eudragit RL/RS could sustain DLT release only upto 3 h. DLT is freely soluble in water and released by diffusion (Kritsmundsottir et al, 1996). DLT osmotic pumps were investigated by Prabhakaran et al (2003). Since release rates from osmotic pumps were high, systems based on hydrophilic polymeric additives like HPMC and Na CMC were investigated. The osmotic pumps containing

DLT and hydrophilic polymer exhibited sustained release for 18 h. Osmotic systems are technology intensive as the fabrication requires laser drilling onto coated tablet surface. Coated donut shaped tablets (CDST) were prepared for sustained release of DLT. The CDST could sustain the release for 5-20 h based on drug loading level and diameter of hole. Such tablets with hole are not readily amenable for large scale manufacture (Kim, 1999).

Dilacor XR was the first sustained release product for DLT in US market based on Geomatrix® technology developed by Jagotec AG (US patent 5422123). Geomatrix® system for DLT was based on multilayered tablet. The drug core was sandwiched between two high viscosity grade hydroxypropyl methylcellulose (HPMC) layers applied by dry coating. These systems released DLT for a period of 24 h and were suitable for once a day dosage form. Geomatrix® system requires large polymer loadings (Wilding et al, 1995). Cardizem CD which is covered by US patents 5286497, 5439689, 5470584 and 5364620, is a combination of two fractions, i.e. a sustained release fraction and a delayed release fraction to achieve release over 24 h. The drug cores were coated with drug permeable membranes made of Eudragit RL /RS. Cardizem LA disclosed by US patents 5288505, 5529791 and 7108866 is based on drug cores coated with rate controlling microporous polymer, Eudragit NE 30 D.

8.1.2 Limitations of existing approaches to DLT sustained release at intestinal pH

All commercial products for the sustained release of DLT except Dilacor XR are based on coatings and therefore need longer processing time. The DLT matrix system based on Geomatrix® technology contains 30-90 % w/w of high molecular weight HPMC and its manufacture involves multiple steps. Thus there is a need for polymers which could be used for the preparation of matrix system for sustained release of DLT.

8.1.3 Our approach to DLT sustained release at intestinal pH

We report simple matrix system for sustained release of DLT using PLAMAMA copolymers. Conventional enteric polymer such as Eudragit L100 (copolymer of MMA and MAA in ratio 1:1) is insoluble at acidic pH and dissolve at pH > 6. Increase in the hydrophobic content (MMA) resulted in just shift of threshold pH value at which the polymer dissolve to pH 6.5 in case of EudragitS100 (copolymer of MMA:MAA in ratio 2:1). Copolymers of MAA and hydrophobic macromonomer are reported which are insoluble at acidic pH and exhibit a wide variety of swelling /

dissolution characteristics at near neutral pH (WO2010/103366). Following a similar approach we proposed that copolymers of MAA and oligolactide methacrylate would result in polymers with diverse swelling / dissolution characteristics at near neutral pH and remain collapsed at acidic pH. These MAA copolymers could be useful for preparation of simple matrix systems to achieve sustained release of DLT at intestinal pH.

8.2 Experimental section

8.2.1 Materials

DLT was obtained as gift sample from Lupin Lab Ltd, India.

L-lactide [(3S)-cis-3, 6-Dimethyl-1, 4-dioxan-2, 5-dion, 98 %] (LA), iron acetate (II), 99.99 %, Methacrylic acid (MAA), 99 %, deuteriated chloroform ($CDCl_3$), deuteriated dimethyl sulfoxide (DMSO d6) and HPLC grade chloroform ($CHCl_3$) were purchased from Aldrich, India. Triethyl amine (TEA), N, N', dimethyl formamide GR (DMF), diethyl ether (stabilized) and solvents such as tetrahydrofuran were procured from Merck Ltd, India. Indomethacin (IND) was purchased from Fluka Chemicals. 1, 4 butanediol (BD), 99% was purchased from Sigma-Aldrich, India. 2, 2' azobis-(isobutyronitrile) (AIBN) was purchased from local supplier.

8.2.2 Methods

8.2.2.1 Synthesis of PLAMAMA copolymers

8.2.2.1.1 PLAMA macromonomer synthesis

PLAMA was prepared by forming L-lactide diol by melt polymerization of BD and LA followed by methacryloylation of LA diol. To evaluate the effect of the Lactide chain length, two ratios of LA to BD (50:15 and 50:8) were chosen and 0.05 % w/w iron (II) acetate was used as catalyst. The sealed glass ampoules were kept in fluidized sand bath at 210 ºC for 8 h. The molecular weight of LA diols was determined by vapor pressure osmometer (VPO).

Vinyl groups were introduced onto LA diols by condensation with methacryloyl chloride (MC) in presence of TEA in THF and constant stirring at 0 to 5 ºC. The reaction mixture was added slowly into 800 ml deionized (DI) water to remove traces of iron (II) acetate, TEA. The slightly yellowish viscous liquid was obtained which was dried at room temperature (RT) for 2 to 3 days.

8.2.2.1.2 Synthesis of copolymers

Free radical polymerization of PLAMA with MAA in different ratios was carried out in DMF using 2 mole % AIBN as free radical initiator at 65 ºC for 24 h. The

copolymers were precipitated in DI water followed by vacuum drying for 12 h at RT. The copolymers prepared using PLAMA of mol. wts 638 and 1233 are referred to as series P and series Q respectively.

8.2.2.2 Characterization of PLAMAMA copolymers

8.2.2.2.1 Proton NMR analysis of copolymers

Proton NMR spectra were recorded using Brucker AC instrument at 200 MHz.

8.2.2.2.2 Acid values of copolymers

Acid base titration was used to determine acid values of all PLAMAMA copolymers. The copolymer was dissolved in DMF and the solution was titrated against standardized 0.05 N sodium hydroxide solution using alcoholic phenolphthalein solution as an indicator.

8.2.2.2.3 Molecular weights of copolymers

The molecular weights of PLAMA macromonomer and PLAMAMA copolymers were determined using vapor pressure osmometer (VPO) Model K 7000, Knauer, Germany. HPLC grade $CHCl_3$ was used for molecular weight determination by VPO. VPO measurements were carried out at 32 ºC. The instrument was calibrated using benzil in $CHCl_3$. 15 mg/ml polymer solution was made in $CHCl_3$. Three dilutions of sample were prepared in $CHCl_3$ subsequently.

8.2.2.2.4 Glass transition temperatures of copolymers

Differential scanning calorimeter (DSC), TA, model Q10 was used to determine T_g of polymers at heating rate of 10 ºC/min from -80 ºC to 250 ºC.

8.2.2.3 Swelling / dissolution behavior of copolymer films

Swelling / dissolution studies of PLAMAMA polymers of series P and Q were performed using copolymer films of 200 μm thick made by solvent casting. The swelling / dissolution study was carried out in 0.1 N HCl and pH 6.8 phosphate buffer at 37±0.5 °C. The weights of copolymer films were taken periodically after removing excess of medium gently with tissue paper. The % swelling was determined using following formula:

$$\% \text{ swelling} = [(W_s - W_d)/W_d] \times 100$$

Where, W_s and W_d are weights of swollen polymer and Wd are weight of dry polymer.

Polymer dissolution was calculated using following formula:

$$\% \text{ polymer dissolved} = [(W_d - W_t)/W_d] \times 100$$

Where, W_t is the weight of polymer at respective time, t.

8.2.2.4 Evaluation of PLAMAMA copolymers for sustained release

8.2.2.4.1 Preparation of drug loaded copolymer films

15 % w/w DLT loaded copolymer films approx. 200 μm thick were prepared from both P and Q series PLAMAMA copolymers by solvent casting method. Weighed quantities of drug and copolymer were dissolved in solvent and poured onto plain surface and dried at RT.

8.2.2.4.2 Release studies from drug loaded copolymer films

Release studies from drug loaded copolymer films were performed using USP Type I apparatus, (Electrolab, Model TDT 8L, India) at 100 rpm in 900 ml of pH 6.8 phosphate buffer solution at 37 ± 0.5 ºC. 5 ml samples were withdrawn periodically at predetermined time intervals and filtered. The drug content was analyzed using UV spectrophotometer (Shimadzu, Germany) at 237 and 320 nm respectively for DLT and IND. 5 ml buffer solution was replenished to maintain sink condition.

8.2.2.4.3 Drug polymer interactions

The interactions between DLT and IND with PLAMAMA copolymer were characterized by FTIR spectroscopy (Perkin Elmer Spectrometer) using diffused reflectance mode. 3 mg sample and 100 mg potassium bromide were mixed thoroughly in mortar with pestle and small quantity was placed in sample holder and scanned in the region 4000 cm^{-1} to 400 cm^{-1}.

8.3 Results and discussion

The objective of the present investigation was to synthesize and evaluate PLAMAMA copolymers for sustained delivery of DLT. The use of lactide macromer based enteric polymer is reported by Suvarnapathaki, (2007). In the present investigation the compositions have been modified so as to achieve swelling / dissolution characteristic suitable for sustained release of DLT.

The polymers are prepared from monomers that are already approved by USFDA for use in drug delivery systems. Poly (D/L Lactic acid) is biodegradable and

biocompatible polymer and Methacrylic acid (MAA) is a component in commercially available enteric polymer Eudragit L.

8.3.1 Synthesis of PLAMAMA copolymers

Effect of molar feed ratio of LA to BD on molecular weight of LA diol is shown in table 8.1. The LA diols were synthesized by the ring opening polymerization of LA using BD in the presence of catalyst, iron (II) acetate. The molecular weights of LA diols were determined using VPO.

The variation in chain length of LA diol can be used to control the polymer swelling / dissolution. With increase in molar ratio of LA to BD, mol. wt of LA diol was increased. Similar behavior was observed using 2-hydroxyethyl methacrylate (HEMA) in presence of stannous octoate (Lim, 2000).

Table 8.1: Effect of LA to BD ratio on molecular weight of LA diol

S No.	LA: BD (Mole ratio)	Mol .Wt (Mn)
1	50:15	570
2	50:8	1165

8.3.2 Characterization of PLAMAMA copolymers

8.3.2.1 Proton NMR analysis of copolymers

The presence of vinyl group in PLAMA is shown in ^{1}H NMR spectrum. The NMR of PLAMA showed vinyl peaks at δ values of 5.6 and 6.2 ppm as shown in figure 8.1.

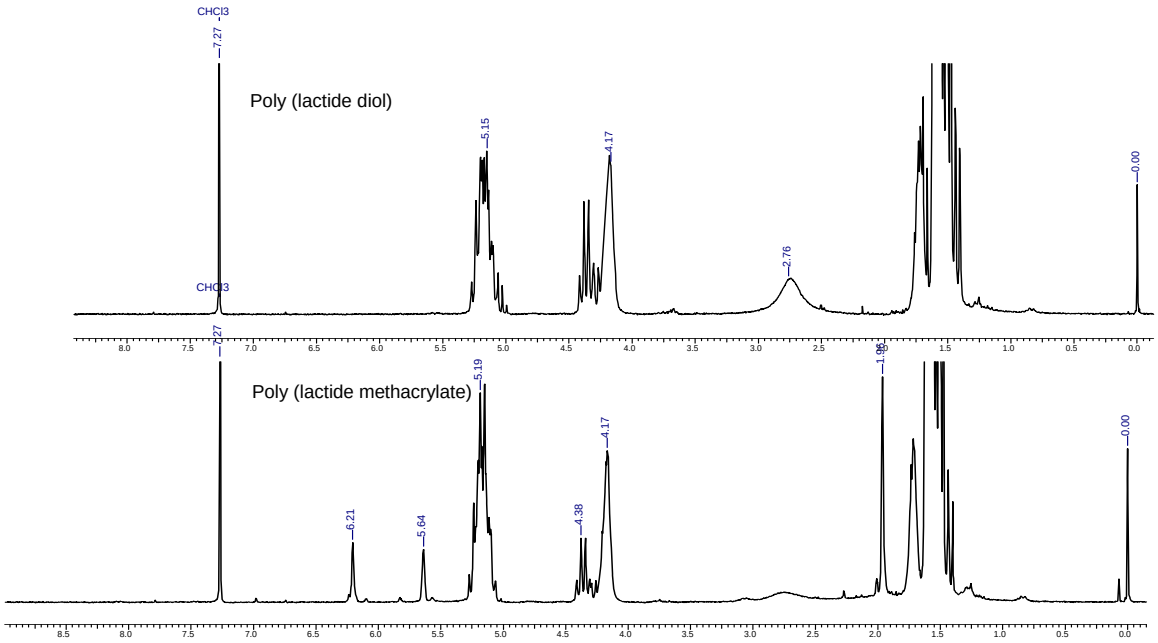

Figure 8.1: ^{1}H NMR spectra of LA diol and PLAMA macromonomer

8.3.2.2 Acid values of copolymers

The compositions of polymers were determined by acidimetric titration. The MAA content in PLAMAMA copolymers synthesized from PLAMA of molecular weights 638 and 1233 is shown in tables 8.2 and 8.3 respectively. Copolymer codes are based on PLAMA molecular weight and MAA content. Symbols P and Q are used for copolymers based on PLAMA of molecular weights 638 and 1233 respectively followed by number indicating actual MAA content in the polymer. From tables 8.2-8.3, it is apparent that MAA content in the product is greater than that in the feed. This is because PLAMA used is a mixture of the monomethacrylate and the unreacted diol. The crude mixture had to be used since it was not possible to separate the two components. During polymerization, only the monomethacrylate derivative polymerized with MAA and the unreacted diol was eliminated during the work up.

Table 8.2: Compositions of P series copolymers

S No.	Code	MAA:PLAMA (Feed wt %)	MAA:PLAMA (Actual wt %)
1	P16	3:97	16:84
2	P22	6:94	22:78
3	P28	8:92	28:72
4	P37	10:90	37:63
5	P40	12:88	40:60
6	P52	24:76	52:48

Table 8.3: Compositions of Q series copolymers

S No.	Code	MAA:PLAMA (Feed wt %)	MAA:PLAMA (Actual wt %)
1	Q12	2:98	12:88
2	Q15	3:97	15:85
3	Q26	4:96	26:74
4	Q32	6:94	32:68
5	Q36	7:93	36:64
6	Q47	14:86	47:53

8.3.2.3 Molecular weights of copolymers

The molecular weights of series P and Q copolymers are shown in table 8.4 and 8.5 respectively. P series has molecular weights in range of 7292 to 9989 while Q series has molecular weights in range 3162 to 8106.

Table 8.4: Molecular weights of P series copolymers

S No.	Code	Molecular weight (by VPO)
1	P16	9580
2	P22	9989
3	P28	7292
4	P37	9194
5	P40	9480

Table 8.5: Molecular weights of Q series copolymers

S No.	Code	Molecular weight (by VPO)
1	Q12	3559
2	Q15	4293
3	Q26	4762
4	Q32	3162
5	Q36	8106

8.3.2.4 Glass transition temperatures of copolymers

Differential scanning calorimetry (DSC), TA, model Q10 was used to determine T_g of copolymers at heating rate of 10 ºC/min from -80 ºC to 250 ºC. The T_g values of series P and Q copolymers are summarized in table 8.6 and 8.7 respectively. PLAMAMA copolymer was synthesized from PLAMA macromonomer and MAA. PLAMA has T_g value of -22 °C and Poly (methacrylic acid) has Tg of 228 °C. These polymers exhibited two T_g values, one due to PLAMA macromonomer and second T_g value due to MAA portion of polymer. In P40 and P52 polymers, only first T_g appeared while the second T_g was not seen due to anhydride formation between carboxylic acid groups of polymer backbone as second T_g was merged with exothermic peak of anhydride formation between adjacent carboxylic acid groups (Grant and Grassie, 1960).

Table 8.6: T_g values of P series copolymers

Polymer	T_g (º C)	
P16	14	129
P22	41	147
P28	32	141
P37	34	160
P40	16	-
P52	19	-

Table 8.7: T_g values of Q series copolymers

Polymer	T_g (° C)	
Q12	19	151
Q15	22	158
Q26	20	159
Q32	22	159
Q36	23	155
Q47	30	161

8.3.3 Swelling / dissolution studies of copolymer films

Swelling / dissolution studies of copolymers were carried out to quantify the swelling rate and extent of swelling as a function of MAA content of PLAMAMA copolymer. For sustaining the drug release, we need PLAMAMA copolymers that swell to different extents and remain swollen over extended period of time in pH 6.8 phosphate buffer. The copolymer dissolution in pH 6.8 phosphate buffer solution depends upon MAA content of polymers. The results are shown in figures 8.3 – 8.4. Copolymers with acid content of 40-52 % w/w (P40 and P52) dissolved without swelling whereas the one with 37 % w/w acid content (P37) swelled followed by dissolution and those with acid content 16-28 % w/w (P16, P22 and P28) swelled but did not dissolve.

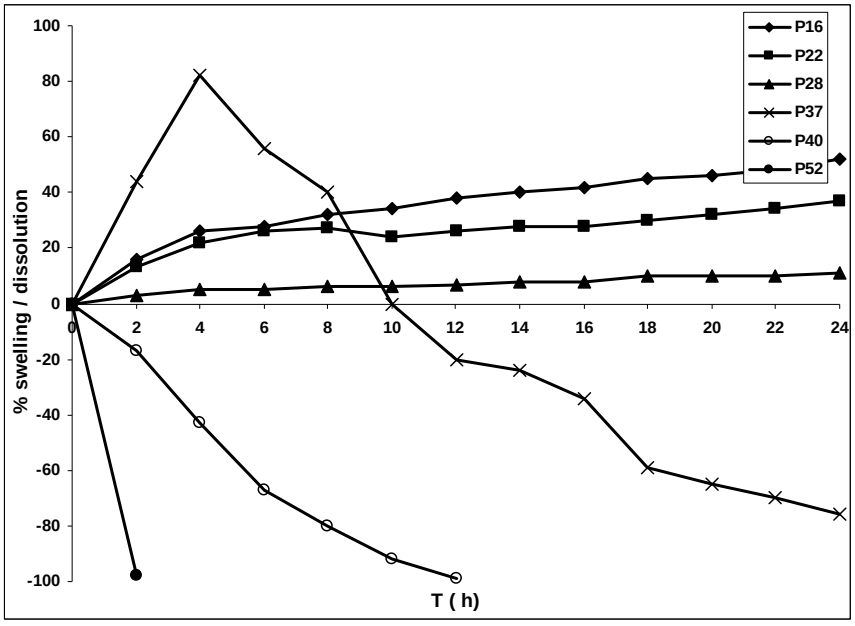

Figure 8.2: Swelling / dissolution of series P copolymers

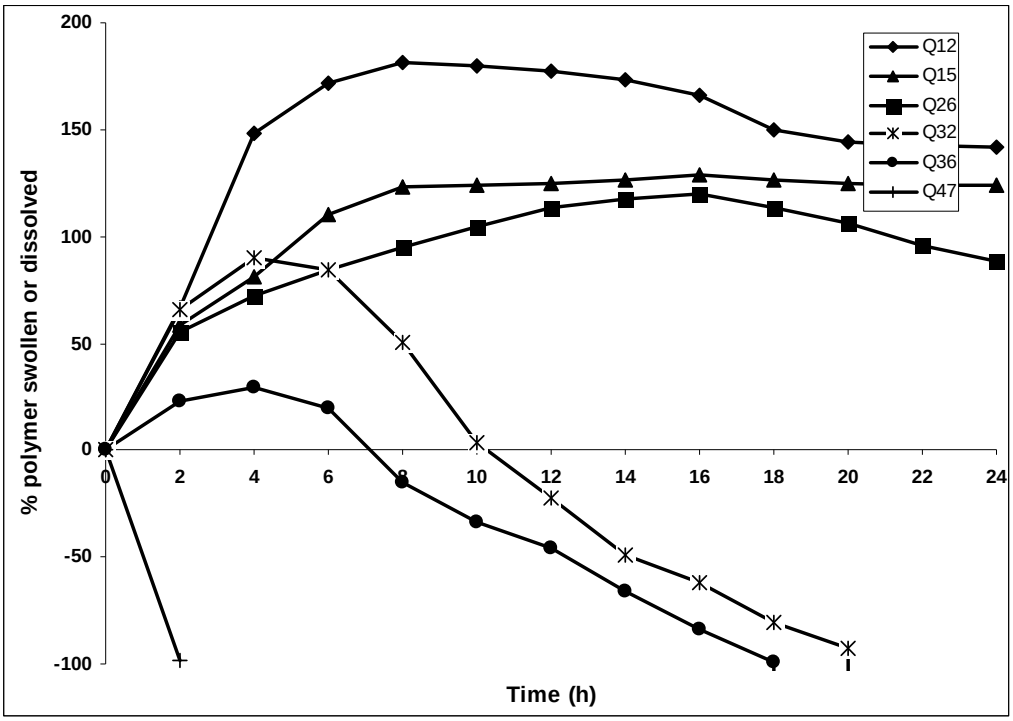

Figure 8.3: Swelling / dissolution of series Q copolymers

At comparable MAA content, the copolymers of series Q swelled more than those of series P. Thus swelling characteristics of copolymers could be manipulated by the choice of the molecular weight of the macromonomer.

8.3.4 Release studies from drug loaded copolymer films

8.3.4.1 Effect of PLAMAMA composition on release

DLT loaded polymer films using PLAMAMA copolymers of series P were prepared as described in section 8.2.2.4.1 using polymers P16, P22, P37, P40 and P52 having MAA content 16–52 % w/w. The drug release study was carried out as described in section 8.2.2.4.2. The DLT release as a function of copolymer compositions is shown in figure 8.4.

Copolymers P16 and P22 showed only about 20 % drug release as the equilibrium swelling of the copolymer was low (28 and 43 % respectively) which lowered drug diffusion. DLT release from P37 showed sustained release for 16 h as the copolymer exhibited swelling followed by dissolution over a period of 24 h. P40 released DLT for a period of 6 h whereas P52 exhibited immediate release. This was consistent with the dissolution behavior of P40 and P52; P40 dissolved over 12 h whereas P52 copolymer films dissolved within 2 h.

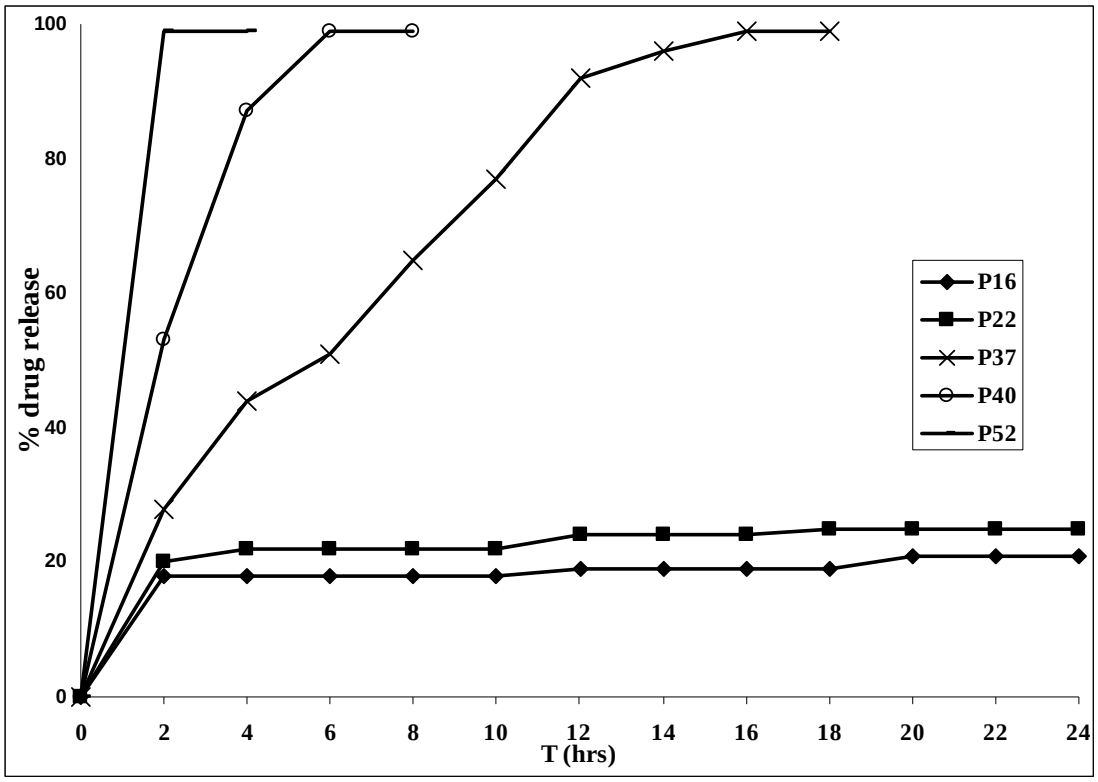

Figure 8.4: Effect of copolymer composition on DLT release

8.3.4.2 Effect of drug loading on release behavior

Effect of DLT loading levels (15–45 % w/w) on the release using Q36 copolymer was investigated. Film preparation, drug loading and release were monitored as described in section 8.2.2.4 (figure 8.5).

Decrease in DLT loading resulted in lowering in release from 45-25 % w/w whereas at 15 % w/w DLT loading, the release was accelerated. This could be attributed to interactions between cationic DLT and anionic PLAMAMA. At 25 % w/w loading level, the drug polymer interaction was sufficient to sustain the drug release whereas above this level, some amount of drug was interacted with polymer and remaining was present as free drug. The free drug was released faster and remaining drug was released slowly as shown in case of 35 % w/w drug loading. At 45 % w/w drug loading, the quantity of free DLT further increased and showed burst release of free drug followed by sustained release.

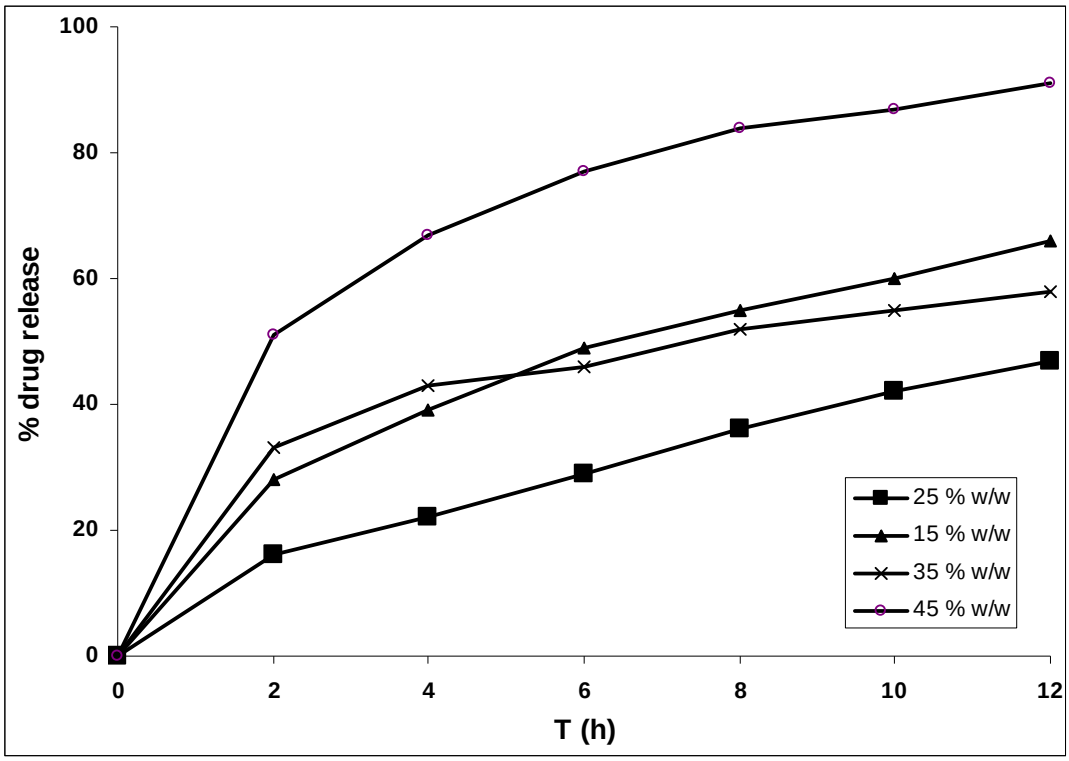

Figure 8.5: Effect of DLT loading on release

8.3.4.3 Effect of drug type on release

Effect of drug type on its release from PLAMAMA copolymers Q15, Q26 and Q36 which exhibited 120, 100 and 30 % equilibrium swelling respectively was investigated to determine utility of PLAMAMA copolymers. Q 15 and Q26 did not dissolve whereas Q36 swelled and dissolved over 18 h. Acidic drug IND was selected to compare release with basic drug DLT. Drug loaded films (15 % w/w) were prepared as per method described in section 8.2.2.4.1. The drug release was carried out using method described in section 8.2.2.4.2.

The choice of drug influenced the drug release profiles from PLAMAMA copolymers. The release profiles of DLT and IND from PLAMAMA compositions are shown in figure 8.6.

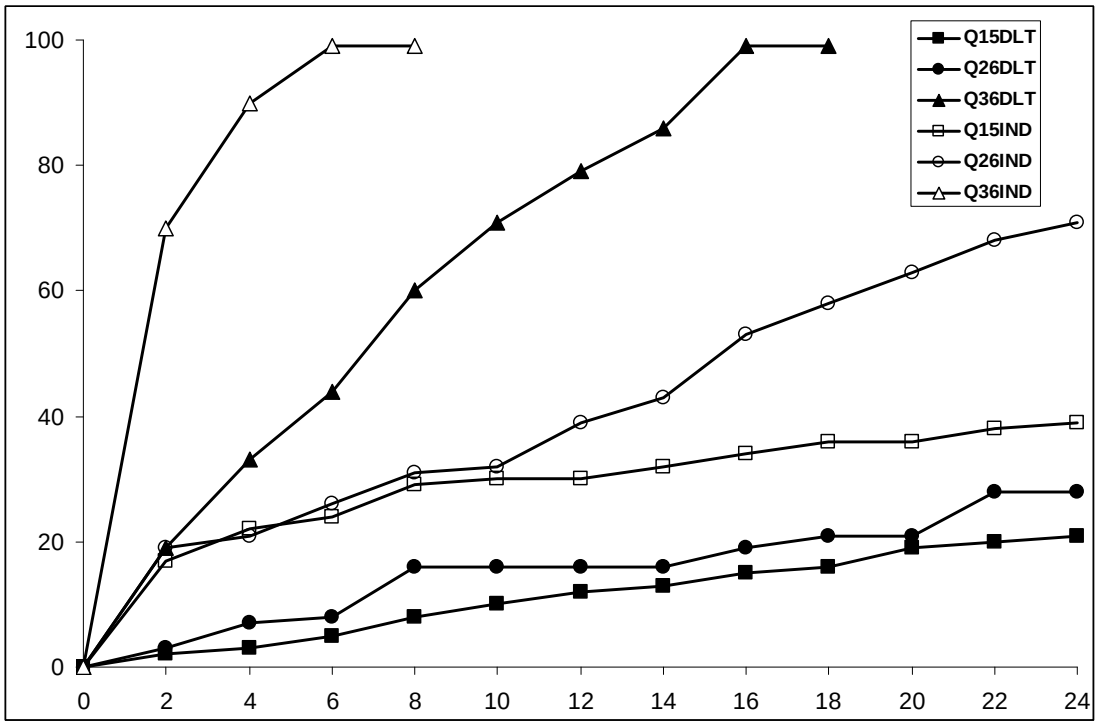

Figure 8.6: Effect of drug type on release

At comparable acid content, release was sustained for longer duration in case of DLT than with IND which was due to a) DLT (mol. wt. 414) is bulkier and rigid molecule than IND (mol. wt 357) and b) drug polymer interactions. DLT being cationic and PLAMAMA anionic could exhibit interaction whereas IND being acidic would not have interactions with the polymer. The drug polymer interactions are discussed in subsequent section.

8.3.5 Drug polymer interactions

The FTIR spectra of DLT, P37 (P) and their blends at DLT loading levels of 15, 35 and 45 % w/w are shown in figure 8.7 and the lactam carbonyl frequency shifts of DLT are summarized in table 8.8.

DLT exhibited hydrogen bonding interactions with PLAMAMA as described by results of FTIR study.

The copolymer P37 showed intense broad peak at 1751 cm^{-1} due to ester carbonyl of polymer with small shoulder at 1700 cm^{-1}. The peak at 1700 cm^{-1} was due to carboxylic acid carbonyl of polymer and was merged with intense broad ester carbonyl peak of copolymer. The shoulder at 1700 cm^{-1} was absent in drug polymer blends at 35 and 45 % w/w DLT loading, indicating formation of carboxylate ion due to interaction with tertiary amine of DLT. This indicated that intramolecular

interaction between ester carbonyl and acid carbonyl of the polymer was suppressed in drug polymer blends and acid carbonyl had interacted with tertiary amine of DLT leaving ester carbonyl free.

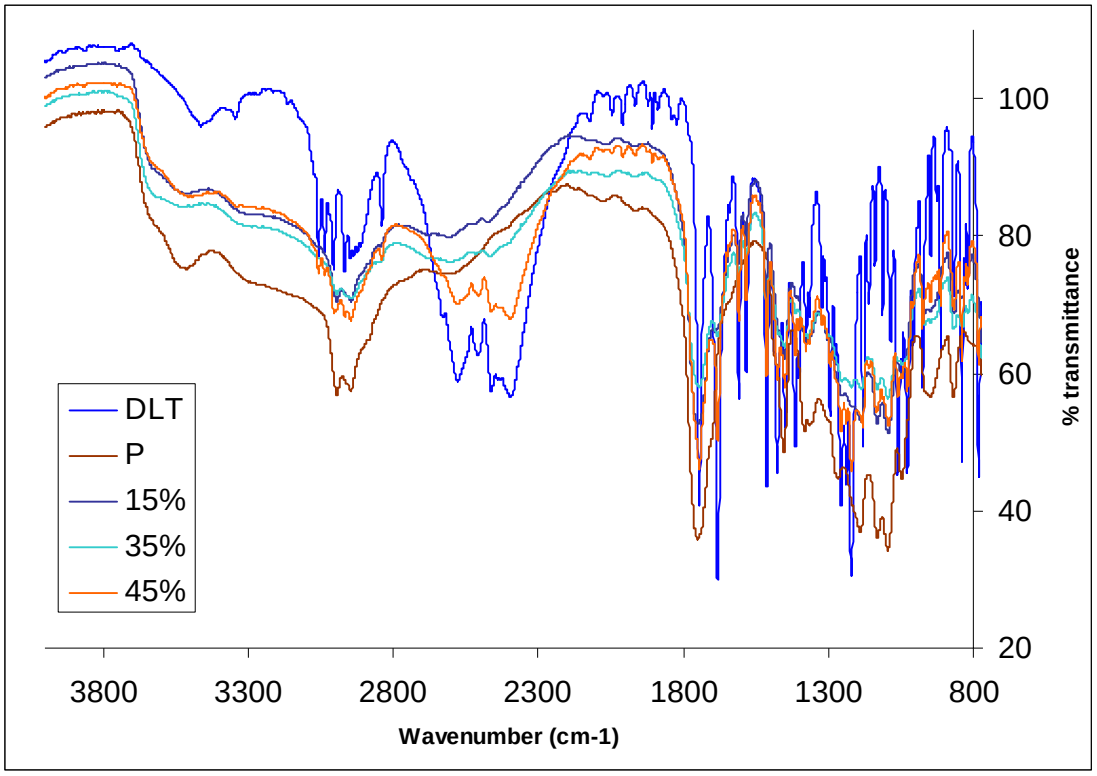

Figure 8.7: FTIR spectra of DLT, P37 and blends

Due to inadequate amount of DLT present in the blend at 15 % w/w drug loading, this intramolecular interaction in the copolymer could not be suppressed which indicated lower interaction at this loading. Similar findings were reported by for methacrylic acid and vinyl pyridine groups by Lee et al, (1988). This could be further supported by presence of new carboxylate peak in the range 1610-1550 cm^{-1}. Presence of sharp peaks between regions 1592 -1572 cm^{-1} and 1614-1594 cm^{-1} in DLT made it difficult to interpret for presence of carboxylate ions as these peaks are also present in the drug polymer blends.

The lactam carbonyl peak at 1681 cm^{-1} was shifted to lower wavenumber as DLT loading was decreased from 45 to 35 % w/w and the peak disappeared at 15 % w/w DLT loading in the blend. The wavenumber shifts due to lactam carbonyl of DLT in DLT and P37 blends are shown in table 8.8. This trend in interactions between polymer and DLT explained the effect of drug loading on its release. The interaction

of lactam carbonyl group was lowered as drug loading was increased from 15 to 45 % w/w. The tertiary amine C-N stretching in DLT occur in region the range 1250 to 1020 cm^{-1}. These two peaks of lactam carbonyl and tertiary amine stretching of DLT showed decrease in the intensity and peak broadening in drug polymer blends suggesting interactions.

Table 8.8: Lactam carbonyl stretching shifts in DLT and P37 blends

Sample	Wavenumber (cm^{-1})
DLT	1681
45 %	1680
35 %	1675
15 %	Absent
P37	Absent

Although at 15 % w/w DLT loading, lactam carbonyl in DLT exhibited greater interaction with –COOH than that for 35 and 45 % w/w drug loading, the release was relatively faster at 15 % w/w DLT loading. This can be attributed to the fact that the DLT and polymer interaction due to carbonyl of carboxylic acid of PLAMAMA and tertiary amine in DLT has predominant effect in sustaining the release than that exhibited between lactam carbonyl of DLT and carbonyl of polymer.

IND is carboxylic acid derivative and exists as cyclic dimer due to intermolecular hydrogen bonding. FTIR spectra of IND, P37 (P) and their blend are shown in figure 8.8.

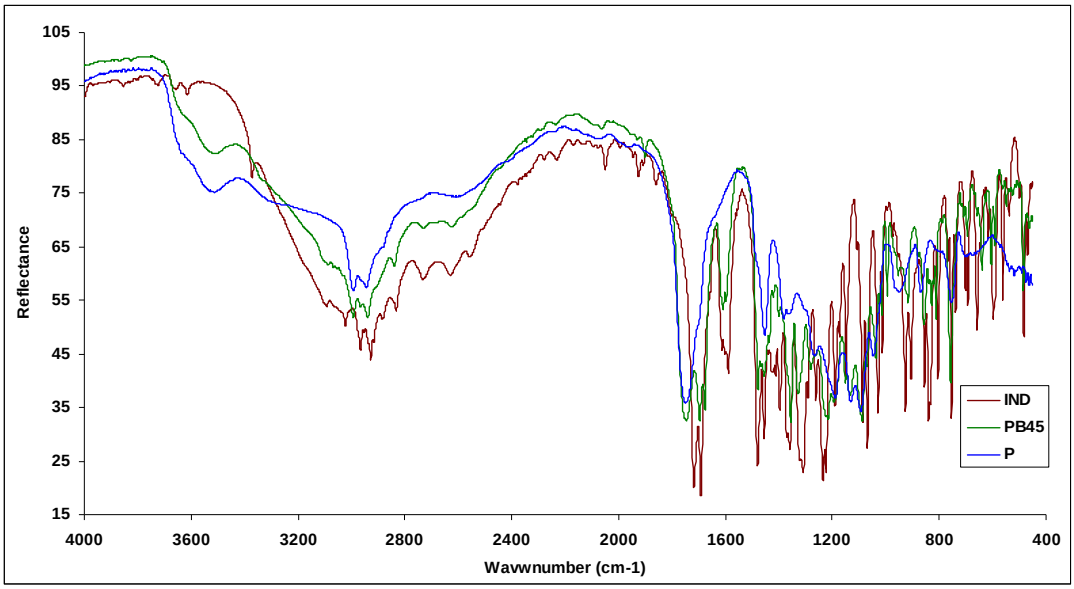

Figure 8.8: FTIR spectra for IND, P37 and blend

The ester carbonyl of copolymer occurred at 1751 cm^{-1} which was unaffected in drug polymer blend. IND exhibited carbonyl stretching bands of acid carbonyl and chloro-benzyl carbonyl at 1716 cm^{-1} and 1695 cm^{-1} respectively. The results indicated no interaction between IND and PLAMAMA.

8.3.6 Mechanism of drug release

The Peppas equation was used for predicting the mechanism of drug release from polymers.

$$Mt/ M\infty = kt^n$$

Where Mt and M∞ represent the fraction of drug released at time t and infinite time. k is a constant incorporating structural and geometric characteristic of device, and n is the release exponent, indicative of the mechanism of drug release. This equation has two distinct physical realistic meanings in the two special cases n =0.5 (indicating diffusion controlled drug release) and n = 1 (indicating swelling controlled drug release). Values of 'n' between 0.5 and 1 indicate anomalous transport (Siepmann and Peppas, 2001).

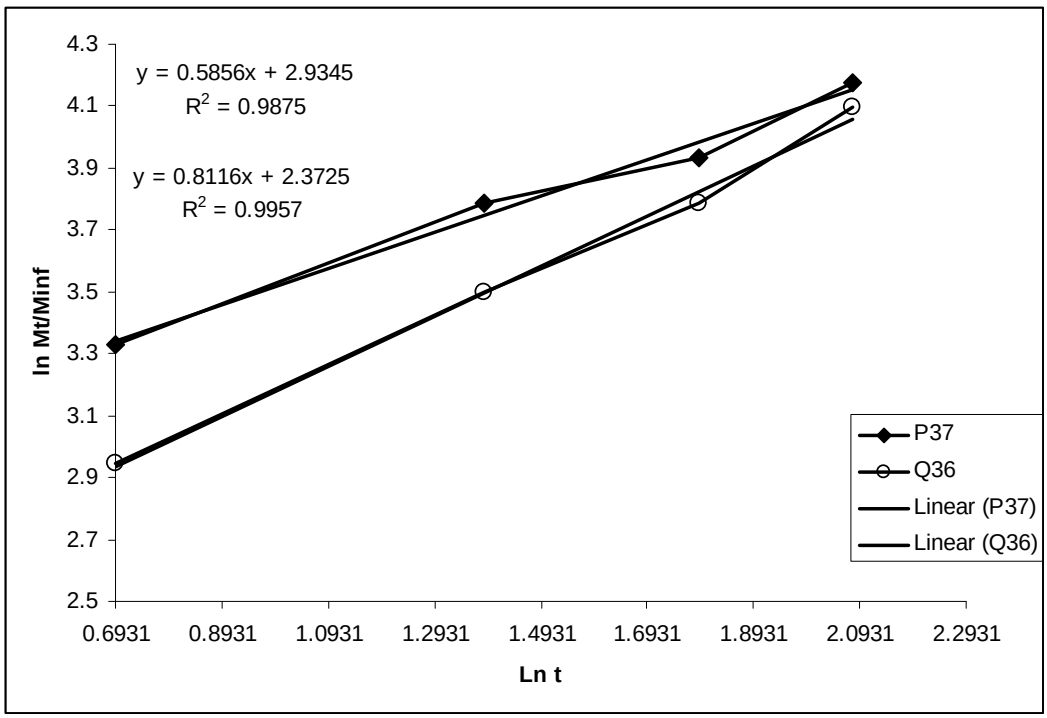

Figure 8.9: Plot for Peppas equation for DLT release

The DLT release data from copolymer films P37 and Q 36 upto 60 % was analyzed in the framework of Peppas equation by plotting ln Mt/M∞ versus ln t and the slope of the resultant line was reported as release exponent 'n'. The results are summarized in table 8.9 and are shown in figure 8.9. The values of n are between 0.5 to 1 indicating anomalous diffusion mechanisms.

Table 8.9: Peppas equation parameters

Polymer	N	Y intercept	R	Comment
P37	0.5856	2.9	0.99	Anomalous transport
Q36	0.8116	2.3	0.99	Anomalous transport

8.4 Conclusions

We report synthesis and evaluation of poly (methacrylic acid-g-lactide methacrylate) polymers (PLAMAMA) for extended release of DLT and IND from matrix systems. The copolymers are based on copolymerization of lactide methacrylate macromonomer (PLAMA) with methacrylic acid. The PLAMAMA copolymers exhibited different extents of swelling / dissolution characteristics based on their acid content and molecular weight of macromonomer. The drug release from matrix films was controlled by polymer swelling / dissolution characteristics as well as the drug-polymer interactions. Drug polymer interactions study using FTIR spectroscopy revealed that DLT exhibited interaction with PLAMAMA and its release was sustained as compared to that of IND. The swelling / dissolution characteristics of polymer which affect drug release were its MAA content and drug loading level. The PLAMAMA copolymers would be useful for preparation of extended release product suitable for once a day dosage regimen.

8.5 References

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Chapter 9

Conclusions and suggestions for future work

This investigation was undertaken to design, synthesize, characterize and evaluate pH sensitive polymers for NDDS for oral route. The basic pH sensitive polymers synthesized exhibited a wide variety of swelling / dissolution characteristics. During the course of this work, we demonstrated utility of basic pH sensitive polymers for 1) release modulation, and in the development of 2) floating sustained drug delivery, 3) floating chronotherapeutic delivery and 4) floating multiple pulsed delivery. *In vitro* floating and drug release performance of these systems and effect of formulation parameters on performance was investigated.

Acidic copolymers with tunable swelling / dissolution characteristics at neutral pH were evaluated for sustained release at the intestinal pH. Effect of polymer composition, molecular weight of PLAMA, drug loading and drug choice on *in vitro* release was investigated. Drug polymer interactions were investigated to get an insight into effect of these interactions on *in vitro* release behavior.

This chapter summarizes the conclusions arrived at from the investigation undertaken and suggestions for future work based on the results obtained.

Conclusions

1. A series of basic pH sensitive polymers which exhibited a wide variety of swelling / dissolution characteristics at acidic pH was synthesized. The polymers were characterized for physicochemical, thermal and pH dependent swelling / dissolution characteristics.

At 11-12 mole % VP content, polymers containing different MMA / BMA ratios exhibited T_g in the range 35 to 101 °C.

VP content and MMA / BMA ratio in basic pH sensitive polymers governed the swelling / dissolution characteristics and degree of swelling as well as dissolution time of the polymers.

a) Polymers containing 11-12 mole % VP swelled but did not dissolve.
b) Polymers containing 18-19 mole % VP swelled followed by dissolution.
c) Polymers containing 30-34 mole % VP dissolved without swelling.

2. The basic pH sensitive polymers were used as additive with Methocel K15M for preparation of matrix tablets using CIP and ACP as model drugs. The role of pH sensitive polymers on swelling / dissolution characteristics of matrix tablets and floating and drug release behavior was investigated.

a) Matrix tablets composed of Methocel K15M alone exhibited acceptable buoyancy and floating characteristics but did not release the drug completely within 24 h, nor did the tablets dissolve after the release.
b) Matrix tablets composed of Methocel K15M and Eudragit EPO exhibited delayed buoyancy time and sustained the drug release for 10 h with burst release of 60 % after 2 h.
c) Incorporation of polymers which swelled or swelled and dissolved exhibited acceptable buoyancy and floating characteristics and also sustained the release for 24 h but were not suitable since the tablets did not dissolve after the drug release was over.
d) Incorporation of polymers which dissolved without swelling led to matrix tablets with acceptable buoyancy and floating characteristics and sustained the drug release upto 12-18 h.
e) Matrix tablets prepared with polymers which dissolved without swelling and Methocel K15M were ideal for preparation of floating matrix tablets since these dissolved completely after the drug release was over.
f) The matrix tablets exhibited faster drug release for ACP than CIP which could be attributed to higher diffusivity of the former.
g) The FTIR study revealed that polymers exhibited a weak interaction with Methocel K15M which resulted in miscible blends.

3. The basic pH sensitive polymers which swelled but did not dissolve were used as coatings for effervescent VER tablets. The role of drug core and polymer coating parameters on floating and drug release behavior of these tablets was investigated.

a) The tablet cores without GGA floated after 92 min. Rapid buoyancy was achieved by incorporation of GGA at 30 % w/w in the tablet core.
b) Increase in GGA content in the tablet core resulted in higher pressure inside the tablet and subsequent lowering in BT, FT and RT values.
c) Incorporation of soluble or swellable diluents in the drug core caused rapid release of drug although it resulted in lower BT values and hence these diluents were not suitable for real life applications.
d) No plasticizer was required during tablet coating process as the polymer glass transition temperature was 35 °C.

e) Effect of polymer swelling on performance of tablets showed that ideal polymer for floating reservoir sustained release system has to have low equilibrium swelling since highly swelling polymers can not sustain the drug release for an extended period.

f) Increase in coating level onto tablet cores resulted in increased BT, FT and RT values.

g) The SEM study revealed that the polymer remained intact for 24 h after exposure to 0.1 N HCl.

h) The drug release from swollen polymeric coating occurred by diffusion

4. The basic pH sensitive polymers which swelled and dissolved were used as coatings for effervescent TPH tablets. The role of drug core and polymer coating parameters on floating and drug release behavior of these tablets was investigated.

a) The tablet cores did not float until 25 % by weight of the GGA was incorporated in the core.

b) Incorporation of soluble or swellable diluents in the tablet core resulted in reduction of BT, FT, RT and T_{lag} values of the coated tablets. Since lactose containing tablets exhibited rapid drug release after lag time than that observed in case of MCC, Lactose was used for subsequent development.

c) Drugs which exhibit limited solubility in the stomach and high solubility in intestine such as Diclofenac sodium and Indomethacin could be delivered using this approach.

i) Hydrophobic polymers were ideal for floating chronotherapeutic system.

j) Increase in coating level onto tablet cores resulted in increased BT, FT, T_{lag} and RT values.

k) The polymer swelled and dissolved as evidenced by the SEM pictures.

l) The polymer swelling governed the lag time and the drug release occurred as the polymer swelled extensively and dissolved.

m) The large size (13 mm) of the tablet, BT of 2.25 h as well as the FT of 10 h provided a means for floating chronotherapeutic delivery of drugs.

5. The basic pH sensitive polymers which swelled and dissolved were used as coatings to develop multiple pulsed release system for CIP. The role of drug core and polymer coating parameters on floating and drug release behavior of these tablets was investigated.

a) Increase in GGA concentration in the tablet core caused increase in BT, FT, T_{lag} and RT values of tablets as the CIP solubility decreased at higher pH by incorporation of GGA.
b) The BT, FT, T_{lag} and RT values increased with decrease in polymer swelling.
c) Increase in coating level caused increase in BT, FT, T_{lag} and RT values of coated CIP tablets.
d) The polymer swelling governed the lag time of tablets and the drug release occurred as the polymer swelled extensively and dissolved.
e) The multiple pulsed release system which exhibited separation between consecutive pulses was developed by choosing appropriate GGA concentration in the tablet, choice of polymers and polymer coating level.
f) The floating multiple pulsed tablet has dual mechanism for gastric retention i.e. large size of tablets (13 mm) and buoyancy.

6. The acidic pH sensitive copolymers poly [methacrylic acid-co-oligo (lactide methacrylate)] which exhibited a wide variety of swelling / dissolution characteristics were synthesized, characterized and evaluated for sustained release from drug loaded polymer films at the intestinal pH using DLT and IND as model drugs. Physicochemical, thermal and swelling and dissolution characteristics of these polymers were determined. The role of polymer composition, drug choice, drug loading level and drug polymer interactions on release was investigated at pH 6.8 phosphate buffer.

a) The copolymers exhibited two T_g values due to main chain and pendant chain.
b) The copolymers exhibited diverse swelling / dissolution characteristics depending on their acid content and molecular weight of the macromonomer used in polymer synthesis.
c) The copolymer swelling / dissolution characteristics sustained DLT release over a period of 24 h.
d) The drug release was sustained over longer duration in case of DLT than in case of IND since DLT exhibited hydrogen bonding interaction with the copolymer as shown by FTIR study whereas IND did not exhibit any interaction.

e) The release data fitted in Peppas equation gave ‘n’ between 0.5 and 1 indicating that the drug release occurred by anomalous diffusion from polymer films.
f) The copolymers could be further optimized for the preparation of once a day DLT dosage form.

We have demonstrated in principle the feasibility of developing both matrix and reservoir type gastroretentive delivery system for sustained and pulsatile release of CIP, TPH and VER. Similarly, sustained release of DLT which can be tailored for once a day dosage form has been demonstrated. However, no investigations of this kind can address all the issues, especially those arising during the course of investigation. These present opportunities for future investigations in this area.

Suggestions for future work

Suggestions for further work have been summarized below.

a) The pH sensitive polymers developed were evaluated mainly for drug release characteristics *in vitro.* As these are new excipients, their cytotoxicity evaluation needs to be undertaken before undertaking *in vivo* evaluation.
b) *In vitro* and *in vivo* performance correlation needs to be established.
c) The basic pH sensitive polymers have been evaluated for different floating type NDDS *in vitro*. The floating behavior of these systems needs to be investigated using gamma scintigraphy to determine the gastric retention time under real life conditions.
d) Development of gastroretentive systems for drugs which have restricted absorption window is expected to result in increased bioavailability. The enhancement in bioavailability can be established by undertaking clinical trials.
e) The basic pH sensitive polymers which dissolve at acidic pH can be investigated as polymeric coatings to develop moisture resistant coatings.
f) Methacrylic acid copolymers could be further optimized for development of DLT once a day dosage form.

Synthesis and Evaluation of Polymers for Novel Drug Delivery Systems

Synopsis

For the Degree of Doctor of Philosophy

(Technology)

In

Chemical Engineering

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M. S. (Pharmaceutics)

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SYNOPSIS OF THE THESIS TO BE SUBMITTED TO THE UNIVERSITY OF MUMBAI FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (TECHNOLOGY) IN CHEMICAL ENGINEERING

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Synopsis

Introduction

Oral drug delivery constitutes more than 50 % of the total drug delivery market share and the pharmaceutical companies are continuously looking for differentiated products using novel oral drug delivery systems (NDDS) which improve the drug safety and efficacy and are useful to extend the life cycle of the drugs.

Polymers play an important role in controlling the drug release in sustained and delayed release systems. The development of systems which release drug at constant rate was the major focus in the early eighties. However, the realization that drug absorption is affected by physicochemical and physiological factors such as pH dependent solubility, instability, gastrointestinal transit time, regional pH, surface area, enzymatic activity and colonic microflora has necessitated the development of site specific and chronotherapeutic delivery systems (Dressman et al, 1993). Drugs having restricted absorption window are delivered using site specific systems that release the drug along the GI tract where the absorption is maximum so as to enhance the drug bioavailability and reduce adverse effects. Gastroretentive drug delivery systems (GRS) improve bioavailability and safety profile for drugs like ciprofloxacin HCl (CIP) (Harder et al, 1990), Verapamil HCl (VER) (Streubel et al, 2000), Riboflavin (Kagan et al, 2006), Valacyclovir (Kagan and Hoffman, 2008) and Metformin (Marathe et al, 2000). Transit time in small intestine seems to be affected neither by food intake nor by the nature of dosage form (Davis et al, 1986). Thus, systems are formulated which release drug in sustained manner in the intestine to enhance bioavailability of drugs. Present investigation involves design, synthesis, characterization and evaluation of new polymers for site specific oral drug delivery systems and is presented in nine chapters as outlined below.

Chapter 1: Literature review

This chapter provides an introduction to current status of polymers used in oral drug delivery systems. It covers an overview of the systems used for site specific drug delivery systems. The use of existing polymers for the development of site specific systems for stomach as well as intestine, and their advantages and limitations for the development of NDDS are discussed. The current approaches to achieve sustained and pulsatile release using gastroretentive systems and their limitations are highlighted. The survey reveals the need for new polymers which can provide sustained or pulsatile drug release using gastroretentive systems as well as need to

avoid use of multiple polymers. The chapter reviews in particular the systems developed for Diltiazem HCl (DLT) sustained release and their limitations, and the need for new polymers which can sustain DLT release and avoid need for multiple polymers.

Chapter 2: Objectives and scope of investigation

This chapter focuses on present gaps and possible options to overcome the limitations of existing site specific NDDS. Major objectives and scope of the investigation are highlighted below.

1. Design and synthesize basic pH sensitive polymers which exhibit a wide variety of swelling / dissolution characteristics at acidic pH. Polymers with characteristics mentioned below would be synthesized.

- Polymers which swell but do not dissolve
- Polymers which swell and dissolve
- Polymers which dissolve directly without swelling

2. Characterize pH sensitive polymers for composition, molecular weight, glass transition temperature and swelling / dissolution behavior.

3. Evaluate pH sensitive polymers as modulator of swelling / dissolution characteristics and drug release from gastroretentive matrices based on HPMC.

4. Evaluate pH sensitive polymers which swell but do not dissolve for floating reservoir type sustained drug delivery.

5. Evaluate pH sensitive polymers which swell followed by dissolution over an extended period at acidic pH for gastroretentive chronotherapeutic delivery.

6. Evaluate pH sensitive polymers which swell followed by dissolution over an extended period at acidic pH for gastroretentive multiple pulsed delivery.

7. Develop and evaluate multiple pulsed release systems based on above results.

8. Investigate factors influencing the performance of gastroretentive reservoir systems. These include gas generating agent concentration in the tablet cores, amount and type of diluents, drug choice, polymer swelling / dissolution characteristics and coating level.

9. Monitor morphological changes during swelling / dissolution of polymer films by SEM.

10. Synthesize different compositions of poly (methacrylic acid-g-lactide methacrylate) (PLAMAMA) copolymers and characterize the same for acid content, glass transition temperature and swelling / dissolution behavior at neutral pH.

11. Evaluate PLAMAMA polymers for sustained release at simulated intestinal conditions.

12. Elucidate the drug release mechanism for drug loaded copolymer films.

Chapter 3: Basic pH sensitive polymers: Synthesis and characterization

This chapter describes design, synthesis and characterization of basic pH sensitive polymers containing methyl methacrylate (MMA), n-butyl methacrylate (BMA) and 4-vinyl pyridine (VP). The polymers are designed in order to achieve tunable swelling / dissolution characteristics which could be exploited for the development of gastroretentive systems to achieve a variety of drug release profiles. Polymer characteristics including structure, composition, molecular weight and glass transition temperature were investigated using ^{1}H NMR, FTIR, GPC and DSC. The swelling / dissolution characteristics of these basic pH sensitive polymers were investigated at acidic pH. Depending on VP content and MMA: BMA ratios in the polymer, these polymers exhibited a variety of swelling / dissolution characteristics. The polymers exhibited T_g values in the range 35-101 ºC.

Chapter 4: Modulation of properties of floating matrix tablets using basic pH sensitive polymers

The current floating matrix tablets available in market use a combination of HPMC and PEO (US patent 672340, Depomed Inc.); in order to achieve sustained release of drugs and dissolution of tablets after the drug release is over. Since PEO swells and dissolves, the release profiles which can be obtained when used along with HPMC are limited. pH sensitive polymers which exhibit a wide variety of swelling / dissolution characteristics would offer advantages for the design of floating matrix tablets as compared to PEO.

Floating matrices containing HPMC alone released the drug over 24 h but the systems did not dissolve at the end of release. Eudragit EPO incorporation could sustain the drug release for 12 h and exhibited buoyancy time of 44 min. Incorporation of polymers developed in the chapter 3 provided a latitude to manipulate swelling / dissolution of systems as well as release profiles. Also we demonstrated the use of these pH sensitive polymers for matrix tablets which exhibited rapid buoyancy, sustained the release over 18 h as well as dissolved after the drug release was over.

Chapter 5: Gastroretentive sustained release systems using basic pH sensitive polymers

Gastroretentive reservoir systems designed to achieve sustained release of highly soluble drugs used multiple polymers (Krogel and Bodmeier, 1999, Lunio and Sawicki, 2006, Sawicki and Glod, 2004). The gastroretentive matrix systems for these drugs resulted in a burst release followed by sustained release for 24 h (Londhe et al, 2010 and Patel et al, 2009). It was suggested that reservoir systems be developed for highly soluble drugs in order to ensure better control over the drug release. Gastroretentive systems prepared using Eudragit RL30D and Eudragit NE30D coatings which have high permeability for dissolution medium resulted in rapid release. Eudragit RS30D based system had a buoyancy time of 70 min and also released only 4 % VER in 4 h. Thus, these polymers when used as blend could not sustain the VER release for a prolonged period. Hence there is a need to develop a new polymer which when used as a coating, provides acceptable floating characteristics as well as sustains the drug release over an extended period. This could be achieved by encapsulation of effervescent drug cores using a pH sensitive polymer which swelled but did not dissolve and had low equilibrium swelling.

Basic pH sensitive polymer coating was evaluated using VER as model drug. No plasticizer was required as the polymer had T_g value of 35 °C. The results of *in vitro* release from coated tablets showed sustained release and rapid floating characteristics. The sustained release of drug was attributed to swelling characteristics of the polymer. Increase in gas generating agent (GGA) concentration lowered buoyancy time. No diluents were needed in the core and the sustained release could be obtained using basic pH sensitive polymer coating. The drug release was governed by coating level.

Chapter 6: Gastroretentive chronotherapeutic systems using basic pH sensitive polymers

Gastroretentive chronotherapeutic systems reported in the past are based on combination of floating and pulsatile release mechanisms. These systems are based on drug adsorption onto highly porous material. The release profile exhibited a lag time so long as the device floated in the stomach followed by a rapid release at near neutral pH in the intestine (Sharma and Pawar, 2006 and Sher et al, 2007). Zou et al (2008) described a floating pulsatile release bilayer tablet for VER based on tablet- in-tablet

approach and also recommended floating pulsatile tablets since the highly variable nature of gastric emptying can result in *in-vivo* variability and lower bioavailability problems with conventional pulsatile release dosage forms. To overcome the problem we proposed a tablet containing Theophylline (TPH) as a model drug; coated with a basic pH sensitive polymer which swelled followed by dissolution. The tablets prepared using this approach would stay in stomach and result in predetermined lag time followed by release.

13 mm diameter tablets coated with basic pH sensitive polymer exhibited a lag time of 5 h followed by TPH release over 6 h. Buoyancy time of 2.25 h as well as floating and release time over 10 h provided a means for gastroretentive chronotherapeutic delivery. The lag time was governed by polymer swelling and the release occurred as polymer swelled extensively followed by dissolution as evident from scanning electron microscopy.

Chapter 7: Gastroretentive multiple pulsed delivery using basic pH sensitive polymers

Gastroretentive multiple pulsed delivery system disclosed in WO2007/079082 by Advancis Pharm Inc. was based on mechanism used in Pulsys™ system which exploited the principle that bacteria when exposed to initial dose followed by sequential pulses were killed more efficiently and effectively than when exposed to standard sustained dosage regimen. The product disclosed by this patent exhibited at least three distinguishable C_{max} and T_{max} in pharmacokinetic profile but the pulses overlapped. Gastroretentive multiple release systems were recommended for drugs which exhibited restricted absorption in lower GI tract. Thus, basic pH sensitive polymers which swelled and dissolved were evaluated as coatings for effervescent tablet core using CIP as model drug. The coated tablets exhibited predetermined lag time followed by release depending on core and polymer compositions. Gastroretentive multiple pulsed systems which exhibited clear separation between consecutive pulses were developed.

Chapter 8: Methacrylic acid copolymers for sustained release at intestinal pH

Sustained release at intestinal pH could be achieved using multiple polymers (Biju et al, (2004) and using dosage forms of complex geometric shapes (Wilding et al, 1995 and Kim, 1999). These systems used a combination of enteric and swellable polymers. Lactide macromonomer based polymers as enteric polymer was reported by

Suvarnapathaki, 2007. In the present investigation PLAMAMA copolymers have been modified so as to achieve swelling / dissolution characteristics suitable for sustained release at intestinal pH. The polymers were synthesized and characterized for physicochemical characteristics including polymer composition, molecular weight, T_g and swelling / dissolution under simulated intestinal conditions. Diltiazem HCl (DLT) was loaded in PLAMAMA copolymer films and release profiles were monitored at simulated intestinal pH. The *in vitro* release studies showed sustained release for 18 to 24 h. The drug release is governed by polymer swelling and drug polymer interaction. PLAMAMA copolymers would be useful for preparation of once a day extended release product.

Chapter 9: Conclusions and suggestions for future work

This investigation was undertaken to design, synthesize, characterize and evaluate pH sensitive polymers for NDDS for oral route. Basic pH sensitive polymers synthesized exhibited a wide variety of swelling / dissolution characteristics. During the course of this investigation, we demonstrated the utility of basic pH sensitive polymers for 1) modification of swelling / dissolution characteristics of floating matrix systems as well as release modulation and in the development of 2) gastroretentive sustained drug delivery, 3) gastroretentive chronotherapeutic drug delivery and 4) gastroretentive multiple pulsed drug delivery. *In vitro* floating and drug release performance of these systems was evaluated and effect of formulation parameters was investigated.

Acidic graft copolymers with tunable swelling / dissolution characteristics at neutral pH were evaluated for sustained delivery at intestinal pH. Effect of polymer composition, drug loading and drug choice on *in vitro* release was investigated. Drug polymer interactions were investigated to get an insight into effect of these interactions on *in vitro* release performance. This chapter summarizes the conclusions arrived at from the present investigation and suggestions for future work.

Conclusions

1. A series of basic pH sensitive polymers which exhibited a wide variety of swelling / dissolution characteristics at acidic pH was synthesized. At 11-12 mole % VP content, polymers with different MMA / BMA ratio exhibited T_g in the range 35 to 101 °C. VP content and MMA/BMA ratio governed the swelling / dissolution characteristics of the polymers.

2. The role of basic pH sensitive polymers for modulation of swelling / dissolution characteristics of matrix tablets, floating and drug release behavior was investigated.

a) Matrix tablets composed of Methocel K15M alone exhibited acceptable buoyancy and floating characteristics but did not release CIP completely within 24 h.
b) Matrix tablets composed of Methocel K15M and Eudragit EPO exhibited delayed buoyancy time and sustained the drug release for 10 h with burst release of 60 % in 2 h.
c) Incorporation of polymers which swelled or swelled and dissolved exhibited acceptable buoyancy and floating characteristics and also sustained the release over 24 h. However, these polymers were not suitable since the tablets did not dissolve after the drug release was over.
d) Incorporation of polymers which dissolved without swelling led to matrix tablets which exhibited acceptable buoyancy and floating characteristics and sustained the CIP release upto 18 h.
e) Matrix tablets prepared with a blend of basic pH sensitive polymer which dissolved without swelling and Methocel K15M are ideal for floating matrix tablets since these dissolved completely after the drug release was over.
f) The matrix tablets exhibited faster drug release for Acetaminophen (ACP) than CIP which could be attributed to higher diffusivity of the former.
g) The FTIR study revealed that polymers exhibited a weak interaction with Methocel K15M which is useful for preparing a miscible blend.

3. The basic pH sensitive polymers which swelled but did not dissolve were used as coatings for effervescent VER tablets. The role of drug core and polymer coating parameters on floating and release behavior of these tablets was investigated.

a) The tablet cores without GGA floated after 92 min. This was reduced to 9 min by incorporation of GGA at 30 % w/w of the tablet core.
b) Increase in GGA content in the core resulted in higher pressure inside the tablet on contact with dissolution medium and consequently lowered buoyancy, floating and release times.
c) Incorporation of soluble or swellable diluents in the drug core caused rapid release of drug although it resulted in lowered buoyancy times and hence these diluents are not useful.

d) No plasticizer was required during tablet coating process as the polymer glass transition temperature was 35 °C.
e) Ideal polymer for gastroretentive reservoir system to achieve sustained release should have low equilibrium swelling.
f) Increase in coating level onto tablet cores resulted in increased buoyancy, floating and drug release times.
g) The SEM study revealed that the polymer remained intact for 24 h when exposed to 0.1 N HCl.
h) The drug release from swollen polymeric coating occurs by diffusion.

4. The basic pH sensitive polymers of series B which swelled and dissolved were used as coatings for effervescent TPH tablets. The role of drug core and polymer coating parameters on floating and drug release behavior of these tablets was investigated.

a) The tablet cores did not float until 25 % by weight of the core of GGA was incorporated.
b) Incorporation of soluble or swellable diluents in the tablet core resulted in lowered buoyancy, floating, drug release and lag times of the coated tablets. Since lactose containing tablets exhibited faster buoyancy than MCC, the former was used for subsequent development.
c) Drugs which have limited solubility in the stomach and high solubility in intestine could be delivered using this approach.
i) Hydrophobic polymers were ideal for floating chronotherapeutic system.
j) Increase in coating level onto tablet cores resulted in increased buoyancy, floating, drug release and lag times.
k) The polymer swelling governed the lag time and the drug release occurred as the polymer swelled extensively followed by dissolution.
l) The large size (13 mm) of the tablet, buoyancy time of 2.25 h as well as the floating and release time of 10 h provided a means for floating chronotherapeutic delivery of drugs.

5. The basic pH sensitive polymers which swelled and dissolved were used as coatings for effervescent CIP tablets. The role of drug core and polymer coating parameters on floating and drug release behavior of these tablets was investigated.

a) Increase in GGA concentration in the core caused increase in buoyancy, floating, drug release and lag times of tablets as the drug solubility decreased at neutral pH by incorporation of GGA.
b) The effect of polymer swelling / dissolution showed that buoyancy, floating, drug release and lag times increased with decrease in polymer swelling.
c) Increase in coating level caused increase in values of buoyancy, floating, drug release and lag times from coated CIP tablets.
d) The polymer swelling governed the lag time of tablets and the drug release occurred as the polymer swelled extensively followed by dissolution.
e) The multiple pulsed release system which exhibited separation between consecutive pulses was developed by choosing appropriate GGA concentration in the tablet, choice of polymers and polymer coating level.
f) 13 mm diameter CIP tablet coated with pH sensitive polymer with floating characteristics have provided dual mechanism for gastric retention.

6. The acidic pH sensitive PLAMAMA copolymers which exhibited a wide variety of swelling / dissolution behavior were synthesized, characterized and evaluated for sustained release at the intestinal pH using Diltiazem HCl (DLT) and Indomethacin (IND) as model drugs from drug loaded polymer films. The role of polymer composition, drug choice, drug loading level and drug polymer interactions on release was investigated at pH 6.8 phosphate buffer.

a) The acidic copolymers exhibited two T_g values due to main chain and pendant chain.
b) The acidic copolymers exhibited a wide variety of swelling / dissolution characteristics depending on their acid content and molecular weight of the PLAMA macromonomer used in polymer synthesis.
c) The polymer swelling / dissolution characteristics governed the drug release and sustained the release over a period of 24 h.
d) The drug release was sustained over longer duration for DLT than IND since DLT is bulky and rigid molecule and exhibited hydrogen bonding interaction with PLAMAMA as revealed by FTIR study whereas IND is smaller molecule than DLT and did not exhibit interaction with PLAMAMA copolymer.

e) The release data fitted in Peppas equation gave ‘n’ between 0.5 and 1 indicating that the drug release occurred by anomalous diffusion.

f) The PLAMAMA copolymers could be used for preparation of once a day DLT product.

Suggestions for future work

This work has demonstrated in principle the utility of pH sensitive polymers developed at gastric and intestinal pH. To exploit these results in order to develop practical dosage forms, a series of additional investigations will have to be undertaken to ensure that the regulatory requirements are met. Suggestions to undertake some of these investigations are summarized below.

a) These polymers are new excipients, thus their cytotoxicity evaluation needs to be undertaken before undertaking *in vivo* evaluation.

b) *In vitro* and *in vivo* performance correlation needs to be established.

c) The basic pH sensitive polymers have been evaluated for different floating type NDDS *in vitro.* The floating characteristics of these systems can be investigated using gamma scintigraphy to determine the gastric retention time.

d) Development of gastroretentive systems for drugs which exhibit restricted absorption window is expected to result in increased bioavailability. The enhancement in bioavailability needs to be established by undertaking clinical trials.

e) The basic pH sensitive polymers which dissolved at acidic pH can be investigated as polymeric coatings to develop moisture resistant coating and taste masking of bitter drugs.

f) PLAMAMA copolymers can be further optimized for once a day DLT delivery system.

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List of publications / posters

Publications

1. Kolhe U D and Kulkarni M G, Gastroretentive sustained or pulsatile drug delivery systems, Indian patent application No. 2854/DEL/2011.

Posters

1. Kolhe U D and Kulkarni M G, “Lactide based pH sensitive polymers for sustained release in the intestine”

Poster presented at 10^{th} international symposium of Controlled Release Society, Indian chapter, Mumbai, India, February 17-18, 2010.