Synthesis and Evaluation of Stimuli Sensitive Polymers for Pharmaceutical Applications

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by

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STATEMENT BY THE CANDIDATE

As required by the University ordinances 770, I wish to state that the work embodied in this thesis titled **"Synthesis and Evaluation of Stimuli Sensitive Polymers for Pharmaceutical Applications"** forms my own contribution to the research work carried out under the guidance of **Dr. M.G. Kulkarni,** at 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 other, it has been clearly indicated as such and included in the Bibliography.

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Ramesh M.

Table of Content

List of Figures

List of Tables

Abbreviations

A	Allyl glycidyl ether
(A)	Adipic acid
AIBN	Azobisisobutyronitrile
B	1, 4 Butane diol
(B)	Bis (2-hydroxyethyl terephthalate)
C	1, 4 Cyclohexane dimethanol
CA	Citric acid
$CHCl_3$	Chloroform
$CDCl_3$	Deuterated chloroform
CH_3OH	Methanol
CIPFN	Ciprofloxacin hydrochloride
CEPLN	Cephalexin monohydrate
D	Dodecandioic acid
DH	Diltiazem hydrochloride
DBP	n-Dibutyl phthalate
DMF	Dimethyl formamide
DSC	Differential scanning colorimetry
DMSO-d_6	Deuterated dimethyl sulfoxide
ESEM	Environmental scanning electron microscope
F	Fumaric acid
FTIR	Fourier transform infrared spectroscopy
FITC-dextran	Fluorescein isothiocyanate-dextran
G	Glycidyl methacrylate
HCl	Hydrochloric acid
HPMC	Hydroxypropyl methylcellulose
I	Itaconic acid
M_n	Number average molecular weight
M_w	Weight average molecular weight
min.	Minutes
MS	Magnesium stearate
MAA	Methacrylic acid

NMR	Nuclear magnetic resonance spectroscopy
NaOH	Sodium hydroxide
$NaHCO_3$	Sodium bicarbonate
OFN	Ofloxacin
PA	Paracetamol
RFP	Riboflavin 5' - phosphate sodium
S	Succinic acid
(S)	Sebacic acid
T	Trimethylolpropane methacrylate
T_g	Glass transition temperature
TEA	Triethylamine
THF	Tetrahydrofuran
TMP	Trimethylolpropane
UV	Ultraviolet
USP	United states pharmacopeia
VH	Verapamil hydrochloride
4VP	4-Vinylpyrridine
WAXD	Wide angle X-ray diffraction

Chapter 1

Literature Review

1.1 Introduction

Polymers are an integral part of pharmaceutical formulations and they have been used as binder, protective film coating, stabilizer and release modifier for drugs. Polymers of natural, semi-synthetic and synthetic origins are routinely used for oral delivery of drugs. They also have been used for parenteral drug administration to sustain and / or target the delivery of drugs. Polymers offer a wide range of possibilities to modify their structure and composition to achieve desired properties. The flexibility in tailoring the polymer architecture and composition makes them suitable for variety of applications in the field of pharmaceutics (Uchegbu and Schatzlein, 2006).

This chapter presents an overview of various polymers and their role in oral controlled release drug delivery systems. Particularly, the novelty of polymers which undergo reversible phase transformation in response to change in environmental conditions has been reviewed. General aspects of pH sensitive polymers including their swelling / dissolution behavior in relation to their structure have been discussed. A brief introduction to various types of controlled drug delivery systems and their limitations arising from limited role of polymers has been given. The importance of designing of new pH sensitive polymers with controlled architecture for sustaining and / or targeting the release of drugs has been discussed. The treatment is illustrative rather than encyclopedia.

1.2 Polymers in pharmaceutics

The polymers which have been used in pharmaceutical formulations can be classified based on their origin such as natural, modified natural (semi-synthetic) and synthetic polymers. The role of these polymers in drug delivery systems has been discussed below.

1.2.1 Natural polymers

Protein based polymers, such as collagen, albumin and gelatin have been investigated for the development of absorbable sutures, wound dressing matrices and drug delivery systems. Similarly, the polysaccharides and their derivatives which include alginates, carrageenan, starch, guar gum, xanthan gum, chitosan and dextran have been investigated as matrices for the sustained delivery of drugs. However, the utility of natural polymers is limited by their poor resistance to the

attack of microorganisms and poor film forming and mechanical properties. The structural complexity of natural polymers often renders difficulties in modification and purification and hence there is no reproducible production method. Significant variations among the different batches were found since they are produced from living organisms by biopreparation method (Martín del Valle et al., 2009).

1.2.2 Semi-synthetic polymers

The natural polymers are often modified to alter their physico-chemical properties. For example, cellulose is a linear polymer of β-anhydro glucose and each glucose unit contains three hydroxyl groups. The etherification of hydroxyl groups using appropriate moieties yields a variety of cellulose ethers. The degree of modification as well as the molecular weight of polymer determines hydration rate and subsequent dissolution in the aqueous medium. The cellulose ethers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, sodium carboxymethyl cellulose, methylcellulose and ethylcellulose are the most widely used polymers for the development of oral drug delivery systems (Bhardwaj et al., 2000).

Apart from functional group modifications, the cellulosic polymers have been tailored to yield various viscosity grades. For example, HPMC is available in various viscosity grades, *viz*., 4000, 15000 and 100000 cPs under the trade name Methocel K4M, K15M and K100M respectively. The rate of hydration and subsequent dissolution of polymer is slowed as the viscosity increases from 4000 to 100000 cPs. HPMC is directly compressible along with drug and other ingredients to form tablets. The ingress of aqueous medium into the tablet leads to dissolution of drug within the tablet. The dissolved drug diffuses out from the tablet due to the difference in concentration gradients. The release of insoluble drugs from HPMC matrices is poor since they can not diffuse out (Rao et al., 2001). The role of cellulosic polymers in the development of oral controlled release systems has been reviewed by Salsa et al., 1997.

The cellulosic polymers such as methyl cellulose and ethyl cellulose are hydrophobic and they do not dissolve or swell in the aqueous medium, but they are permeable. Ethyl cellulose is more often used for film coating of drugs to form reservoir systems. The film coating facilitates the swallowing of dosage forms,

protects the drug from moisture during storage and controls the release of drug (Siepmann et al., 2007).

1.2.3 Synthetic polymers

In recent years, the synthetic polymers have drawn much attention of researchers involved in the development of pharmaceutical formulations. The role of polymers becomes crucial due to the requirement of precise release profile of drugs. Therefore, new polymers have been developed and evaluated for controlled drug delivery systems. New polymers can be tailored to obtain definite structure, composition and functional groups using appropriate monomers and polymerization methods. Synthetic polymers can be classified into two categories based on their response to the aqueous medium and they are stimuli independent and stimuli sensitive polymers.

1.2.3.1 Stimuli independent polymers

The stimuli independent polymers undergo swelling, erosion and dissolution in the aqueous medium irrespective of stimulus like pH, temperature and ionic strength. One of the most widely used polymers is poly (ethylene oxide) which is available in various molecular weights. This polymer is used as a matrix for sustained delivery of drugs which exhibit a wide range of solubility. The swelling as well as erosion of poly (ethylene oxide) in the aqueous medium makes it suitable for water insoluble drugs. However, this polymer can not be used in large quantities due to toxicity concerns (Gusler et al., 2004). Poly (meth)acrylates have been developed by Evonik industries and marketed under the trade name Eudragit® NE 40D, Eudragit® NE 30D, Eudragit® NM 30D, Eudragit® RL 30D and Eudragit® RS 30D. These polymers have been used for coating of dosage form to achieve sustained delivery of drugs.

1.2.3.2 Stimuli sensitive polymers

Stimuli sensitive polymers are extensively investigated for pharmaceutical applications. These polymers undergo reversible phase transformation from one state to another in response to external stimuli such as pH, temperature, ionic strength, light and magnetic field. The stimuli sensitive polymers have been investigated for wide variety of applications which include membrane for bio-separation, biosensors, artificial muscles, chemical valves and drug delivery systems

(Peppas, 1991). These polymers can be classified based on the environmental conditions to which they respond, *viz.,* temperature, ionic strength, pH, electric and magnetic field. The schematic representation of stimuli induced swelling and collapsing of polymer is shown in Figure 1.1. The various types of stimuli and response of polymers are summarized in Table 1.1.

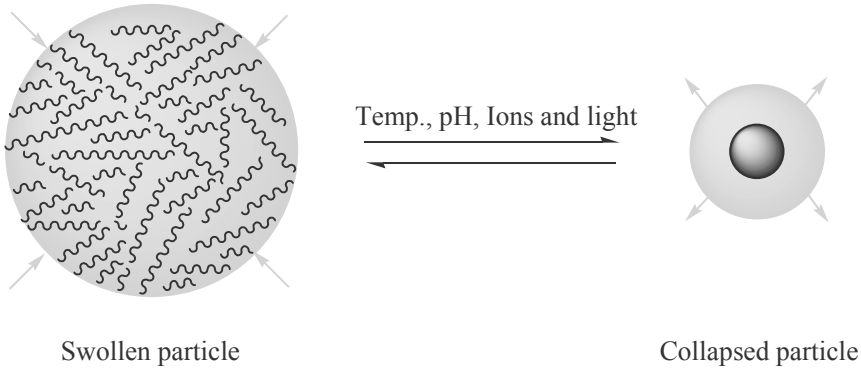


Figure 1.1. Stimuli induced swelling and collape of polymer particle

Table 1.1. Stimuli responsive smart polymers

Types of stimuli	**Responsive polymers**
pH	Poly (propyl acrylic acid)
	Poly (ethacrylic acid)
	Eudragit L100
	Eudragit S100
	Eudragit E100
	Hydroxypropyl methylcellulose phthalate
	Cellulose acetate phthalate
	PMAA-co-PEG copolymer
Ca^{2+}	Sodium alginate
Temperature	Poly (N-isopropyl acrylamide)
Magnetic field	Poly (N-isopropyl acrylamide-co-acrylamide) containing ferromagnetic material
Electric potential	Polythiophen gel

Temperature sensitive polymers

Temperature sensitive polymers reversibly swell or collapse with respect to temperature of the aqueous medium. These polymers can be classified as positive or negative temperature sensitive systems. A positive temperature sensitive polymer has an upper critical solution temperature that contracts upon cooling. Negative temperature sensitive polymer has a lower critical solution temperature that contracts upon heating. In the field of pharmaceutics, one of the most frequently investigated temperature sensitive polymer is poly (N-isopropyl acrylamide) (NIPA) and its copolymers (Schild, 1992). The homopolymer of NIPA exhibits the lower critical solution temperature at 32 ^{o}C which increases on copolymerization with hydrophilic monomers. The copolymerization of NIPA with acidic monomers such as acrylic acid and methacrylic acid results in polymers which respond to both temperature and pH. The phase transformation is sharper in graft copolymers than in random copolymers (Chen and Hoffman, 1995).

Ion sensitive polymers

Ion sensitive polymers undergo reversible phase transition in presence of various ions. Many polysaccharides show ion sensitive gelling behavior. For example, k-carrageenan forms rigid, brittle gel in the presence of K^+ and i-carrageenan forms elastic gel in the presence of Ca^{2+} ion. Similarly, the gellan gum is an anionic polysaccharide that undergoes gelation in the presence of mono and divalent cations including Ca^{2+}, Mg^{2+}, K^+ and Na^+. Likewise, alginic acid undergoes gelation in the presence of divalent / polyvalent cations (Guo et al., 1998 and Bhardwaj et al., 2000).

pH sensitive polymers

The pH sensitive polymers contain ionizable groups and they can accept or donate protons in response to change in environmental pH. The degree of ionization of polymer abruptly changes at a specific pH which is referred as pK_a. The rapid change in net charge of ionizable groups causes a change in hydrodynamic volume of polymer chains. The transition of polymers from collapsed state to swollen state occurs due to the osmotic pressure exerted by mobile counter-ions which neutralize the network charges (Tonge and Tighe, 2001). The polymers containing ionizable groups form polyelectrolyte in the aqueous solution. The polyelectrolytes can be

classified as weak polyacids and weak polybases. The acidic and basic monomers used for the preparation of polyelectrolytes are shown in Figure 1.2.

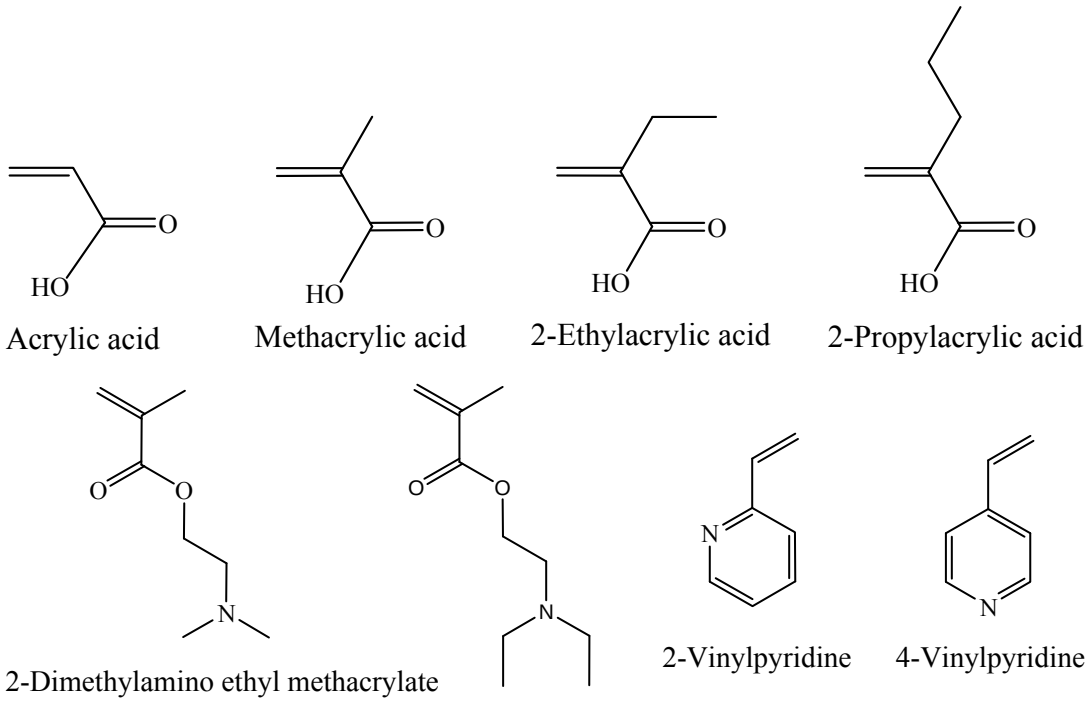


Figure 1.2. Acidic and basic monomers used for the preparation of pH sensitive polymers

The weak polyacids accept protons at low pH and release the same at neutral and basic pH (Philippova et al., 1997). On the contrary, the polybases are positively ionized at low pH (Pinkrah et al., 2003). Complete ionization of polyelectrolytes is difficult due to the electrostatic effects exerted by adjacent ionized groups. This makes the apparent dissociation constant (K_a) different from that of the corresponding monoacid or monobase. The pH range in which the reversible phase transformation occurs can be varied by tailoring the polymer composition. The most widely used strategy involves the selection of ionizable monomer with a pK_a matching the desired pH range. Therefore, the selection of monoacid and monobase is critical in the design of pH dependent polymers. Another approach involves the copolymerization of ionizable monomer with hydrophobic monomer(s). When the ionizable groups are not charged, the electrostatic repulsion forces disappear and the hydrophobic interactions dominate. The incorporation of highly hydrophobic monomer results in compact conformation of polymer chains and hence sharper

phase transition. The reversible ionization and protonation of polyacid and polybase is represented in Figure 1.3.

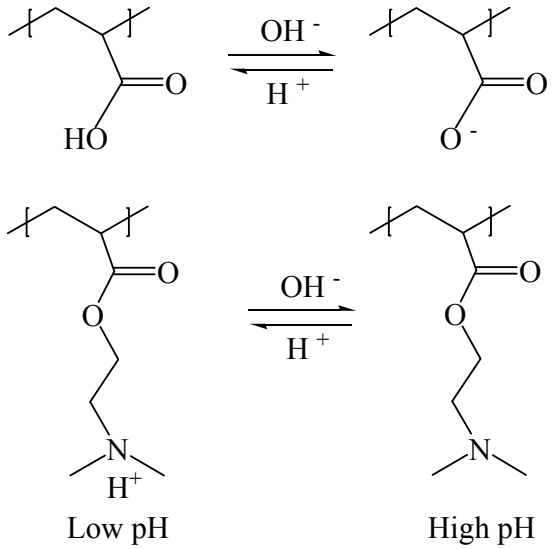


Figure 1.3. Reversible ionization and protonation of polymers

Polyacids

Polyacids which contain carboxyl groups exhibit pK_a in the range 4 to 6. Among the polyacids, poly (acrylic acid), poly (methacrylic acid) and their copolymers have been extensively investigated for pH dependent delivery of drugs (Philippova et al., 1997 and Torres-Lugo and Peppas, 1999). The ionization of carboxyl groups at the near neutral and basic pH results in swelling and / or dissolution of polymer. At acidic pH, the polymer precipitates or shrinks due to the hydrophobic interaction between the polymer chains. While the poly (methacrylic acid) exhibits an abrupt phase transition, poly (acrylic acid) undergoes relatively continuous phase transition. This is due to the α - methyl groups of poly (methacrylic acid) which induce stronger hydrophobic interaction and hence the aggregation of the polymer. Similarly, poly (2-ethylacrylic acid) and poly (2-propylacrylic acid) are more hydrophobic and form more compact conformational structure at low pH (Murthy et al., 1999 and Tonge and Tighe, 2001).

Polybases

Polybases contain amino groups which accept protons under acidic conditions and release the same under neutral and basic pH conditions. Poly (2-dimethylaminoethyl methacrylate) and poly (2-diethylaminoethyl methacrylate) are the examples for

polybases. These polymers undergo phase transition at pH 3 and 7.5 respectively. Similarly, the heterocyclic polybases such as poly (2-vinylpyridine) and poly (4-vinylpyridine) undergo phase transition at pH ~ 5 as a result of protonation and deprotonation of pyridine groups (Gohy et al., 2002 and Pinkrah et al., 2003). Poly (vinyl imidazole) is another polybase bearing the imidazole group (Sutton et al., 1988).

1.3 pH sensitive polymers in pharmaceutics

1.3.1 Enteric polymers

The enteric polymers contain carboxyl groups which undergo reversible protonation and ionization with respect to pH of the aqueous medium. These polymers do not dissolve in medium at acidic pH and dissolve rapidly in medium at near neutral and basic pH (Davis et al., 1986 and Silva et al., 2006). The enteric polymers presently marketed and the threshold pH at which they dissolve are summarized in Table 1.2.

Table 1.2. Marketed enteric polymers

Enteric Polymers	Trade Name	Threshold pH
Methacrylic acid - Methyl methacrylate copolymer (1:1)	Eudragit® L100	≥ 6.0
Methacrylic acid - Methyl methacrylate copolymer (1:2)	Eudragit® S100	≥ 7.0
Methacrylic acid - Ethyl acrylate copolymer (1:1), Dispersion 30 %	Eudragit® L30D-55	≥ 5.5
Methacrylic acid - Methyl methacrylate-Ethyl acrylate copolymer (Ratio between carboxyl and ester groups is 1:10), Dispersion 30 %	Eudragit® FS30D	≥ 7.0
Methacrylic acid - Ethyl acrylate copolymer (1:1)	Eudragit® L100-55	≥ 5.5
Polyvinyl acetate phthalate	Coateric™	5.0
Hydroxypropyl methylcellulose phthalate	Hypromellose Phthalate (HP50®)	≥ 5.0
Cellulose acetate phthalate	Aquateric®	6.0

(Singh, 2007 and Evonik product data sheet)

The enteric polymers have been used as film coating for pharmaceutical dosage forms to suppress the release of drugs under the acidic pH conditions prevalent in the stomach (Guo et al., 2002, Toorisaka et al., 2005 and Cerea et al., 2008). Among the enteric polymers, Eudragit® L100 and Eudragit® S100 are the polymers extensively used due to their better storage stability. These are the random copolymers of methyl methacrylate and methacrylic acid in the ratio of 1:1 and 2:1 respectively.

1.3.2 Reverse enteric polymers

The reverse enteric polymers contain basic groups which undergo protonation at acidic pH and deprotonation at near neutral and basic pH. These polymers dissolve rapidly at acidic pH, and remain in collapsed state at near neutral and basic pH. Presently marketed reverse enteric polymer Eudragit® E100 is a random copolymer of methyl methacrylate, butyl methacrylate and 2-dimethylaminoethyl methacrylate. This polymer has been used as a protective film coating for pharmaceutical dosage forms (Bley et al., 2009).

1.4 Methods of polymer synthesis

Among the various methods of polymer synthesis, the condensation and addition polymerization are frequently used. They have been briefly described below.

1.4.1 Condensation polymerization

Polyesters are synthesized by condensation polymerization of diol and diacid monomers. In the first step, the reaction between diol and diacid monomers yields dimer and a water molecule. The dimer then forms trimer by reacting with diol monomer or diacid monomer. The polymerization proceeds in this stepwise manner and the molecular weight of polymer continuously increases with time.

The condensation polymerization falls into two categories depending upon the type of monomer used. The schematic representation of polyesterification is shown in Figure 1.4. In the first type, the reaction occurs between two different bifunctional monomers wherein each monomer contains only one type of functional groups. In the second type, the reaction occurs between the same types of monomers which contain two different functional groups.

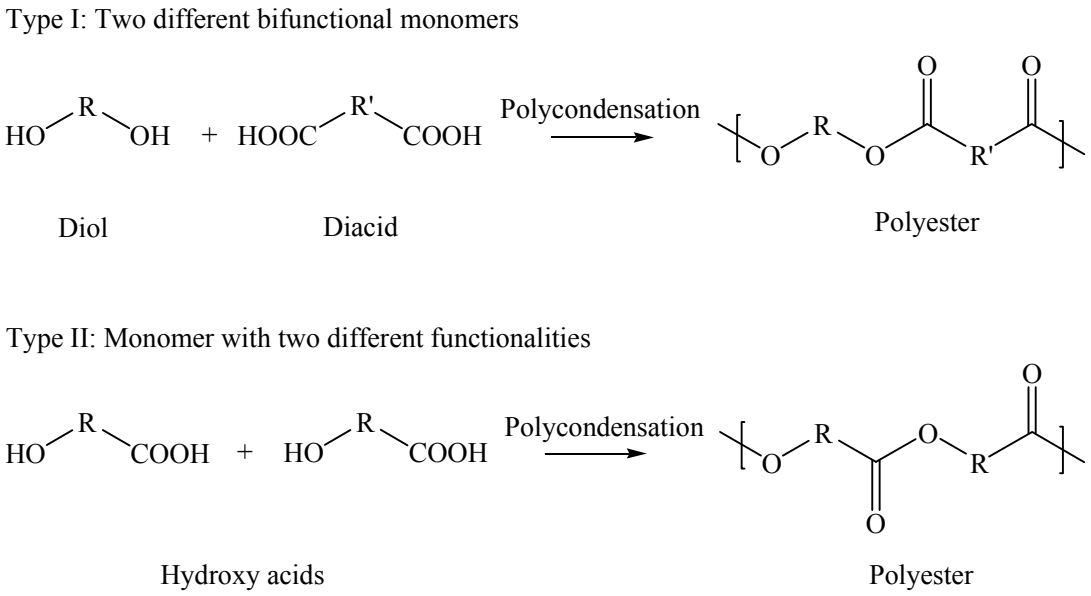


Figure 1.4. The schematic representation of polyesterification

Melt polycondensation

Condensation polymerization is not exothermic and heat dissipation is not problem hence the bulk polymerization is an excellent method for the synthesis of polyesters. This technique is used for the polymerization of monomers which do not decompose around their melting point. The monomers should be pure and stoichiometric amount is required to obtain high molecular weight polymer. To displace the reaction equilibrium towards the direction of polymer formation, the condensed water must be distilled off from the reaction mixture by employing suitable temperature with reduced pressure. Since the temperature involves in the melt polycondensation is very high, the reaction has to be carried out at inert atmosphere to avoid the side reactions, *viz*., oxidation, decarboxylation, degradation etc. Since the bulk polymerization involves only the monomers and catalyst, the separation of polymer is easy and it is free from impurities.

Solution polycondensation

In the solution polycondensation technique, the monomers are dissolved in a suitable inert solvent. The reaction is carried out at suitable temperature, the heat and mass transfer is easy due to the presence of solvent. Since the exact stoichiometry is needed to obtain high molecular weight polymer, the solvent must be free from impurities that might react with monomers. High boiling aromatic hydrocarbon is normally used as a solvent that forms an azeotrope with reaction byproduct which

can be removed easily. However, the presence of solvent makes the polymer chain growth slow which leads to reduced reaction rate and low degree of polymerization (Odian G., 2004).

1.4.2 Addition polymerization

The addition polymerization involves self-addition of monomer molecules to each other very rapidly through a chain reaction and yields the polymer. The elemental composition of polymer is same as monomer and there is no byproduct formation. In general, the addition polymerization can be classified into three types depending upon the nature of initiator or catalyst used. They include free radical, ionic and coordination polymerizations. Among these methods, the free radical polymerization is most widely used for the polymerization of vinyl monomers. The free radical polymerization of vinyl monomers is brought about by free radical initiators. These initiators are thermally unstable and they decompose into two free radicals of equal reactivity in response to applied heat energy. The free radical polymerization reaction involves in three steps which include initiation, propagation and termination.

In initiation step, the highly reactive free radials attack the double bond of vinyl monomer and yields monomer radical. In propagation step, the monomer radical attacks the double bond of another monomer molecule. As a result, the second monomer unit gets linked with first monomer unit and the free radical site of first monomer is transferred to second monomer unit. This process continues until some compound which reacts with the growing chain radical and inhibits its activity or till there is no monomer molecule left for reaction.

The decomposition of initiator molecules produces many free radicals, each one of them capable of initiating and propagating the polymer chains at same time. The collision of two growing chains leads to their termination. When the two growing chains unite by the coupling of their radical sites, the growth is stopped. Since this process involves the coupling of two radicals, this kind of termination is called termination by coupling.

The chain termination by disproportion occurs, when a growing chain radical abstracts a hydrogen from other growing chain and get stabilized. The chain which

donated the hydrogen gets stabilized by the formation of double bond. The growing polymer chains also can get terminated by chain transfer reactions. In this case, the growth of one polymer chain is inhibited and simultaneously a new free radical is generated which is capable of initiating a fresh chain. The chain transfer reaction occur, when a growing chain radical abstract hydrogen from a dead polymer molecule, monomer or chain transfer agent.

Addition polymerization techniques

The addition polymerization of vinyl monomers can be carried out by bulk, solution, suspension and emulsion polymerization techniques. Among these techniques, bulk and solution polymerization are most widely used due to their simplicity. The other two techniques are used only for specific applications wherein the polymer is required in the form beads or aqueous coating (Odian, 2004).

(1) Bulk polymerization

In bulk polymerization, the initiator is dissolved in monomer and resultant mixture is heated to initiate polymerization. The increase in viscosity as polymerization reaction proceeds leads to the polymer with broad molecular weight distribution. The disadvantage of bulk polymerization is that the increase in viscosity of the reaction mixture, reduces the chain diffusivity and hence termination. This leads to increase in the rate of polymerization which is exothermic in nature and may cause explosion.

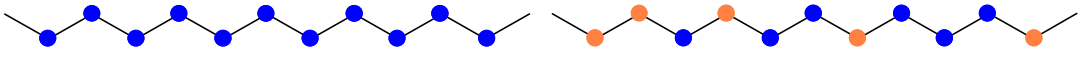
(2) Solution polymerization

Solution polymerization is carried out by dissolving the monomer and initiator in suitable solvent wherein, the monomer and resultant polymer is soluble. Since the polymer formed is dissolved in solvent, the stirring is possible and hence the heat dissipation. The polymer formed can be isolated by precipitating the reaction mixture in suitable non solvent.

1.5 Architecture of polymers

The physico-chemical, thermal and mechanical properties of polymers depend upon their structure and composition. One can select the monomer and polymerization technique to design the polymer for desired applications. Based on the elemental composition, the polymer can be classified as homopolymer and copolymer. The

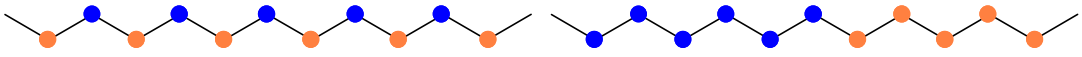
homopolymer contains only one type of repeat unit throughout the chain. In the case of copolymer, the chain contains more than one type of repeat unit (Figure 1.5).



Homopolymer Random copolymer

Figure 1.5. Arrangement of repeat units in homopolymers and random copolymers

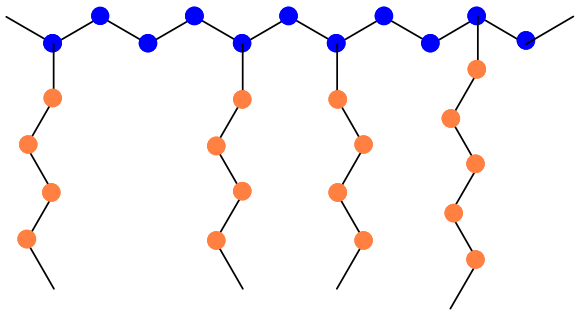
Depending upon the arrangement of repeat unit, the copolymers are classified as follows. When the two repeat units are randomly placed on the chain, the polymer is called as random copolymer (Figure 1.5). The random copolymers form, when both the monomers exhibit nearly equal reactivity towards one another. The composition of random copolymer depends upon the concentration of monomers in the reaction feed. The copolymer chain which contains two repeat units alternatively is called as alternate copolymer (Figure 1.6). In this case, one repeat unit will react with only second repeat unit and vice-versa. As a result, the copolymer formed will have equal number of both the monomeric units irrespective of their feed composition.



Alternate copolymer Block copolymer

Figure 1.6. Arrangement of repeat units in alternate and block copolymers

Block copolymer contains a block of one repeat unit followed by a block of another repeat unit (Figure 1.6). The block copolymers are synthesized by variety of techniques either in one step or by multiple steps. One of the ways to synthesize block copolymer is linking of two different blocks through their end group functionalities. The block copolymers can also be synthesized by living anionic polymerization which involves a sequential addition of multiple monomers. Graft copolymers contain a backbone of one repeat unit on which another repeat unit chains are attached (Figure 1.7). The graft copolymer can be tailored with hydrophobic backbone and hydrophilic graft chains and vice-versa. The unique behavior of graft copolymers and various methods of synthesis are discussed in subsequent sections.



Graft copolymer

Figure 1.7. Arrangement of repeat units in graft copolymers

1.6 Properties of graft copolymers and their significance

The graft copolymers exhibit unique properties compared with their linear analog of similar compositions. The graft copolymerization technique offers flexibility to designer for tailoring the structure and composition of polymers to meet the desired properties. The properties of graft copolymers depend not only on the nature of monomer used but also the grafting level and distribution of graft chains on the backbone. The graft copolymers comprising hydrophobic backbone and hydrophilic graft chains and vice-versa are capable of forming micelles and they are extensively investigated as drug carrier (Mendichi et al., 2003 and Lo et al., 2005). The graft copolymerization techniques allow the modification of polymers to alter their physico-chemical properties. For example, the grafting of poly (D, L - lactide) and poly (D, L - lactide -co- glycolide) on the hydrophilic dextran changes their degradation behavior and hence the rate of drug release (Li et al., 1998). Also the crystallinity of poly (ε-caprolactone) and poly (L-lactic acid) can be suppressed by grafting them on the backbone of hydroxypropyl cellulose and methyl methacrylate (Avella et al., 2000 and Wang et al., 2003).

The biocompatibility of hydrophobic polymers can be improved by grafting with hydrophilic monomer. For example, poly (styrene-butadiene-styrene) has been grafted with 4-vinylpyridine to enhance its blood compatibility (Yang and Hsiue, 1996). The grafting of natural polymers such as guar gum and maleoyl chitosan with acrylic acid results in pH sensitive graft copolymers. These polymers have been investigated for sustained delivery of drugs (Soppimath et al., 2001, Toti and Aminabhavi, 2004 and Huang et al., 2006). These reports reveal the importance of graft copolymerization technique in the design of polymers for particular applications.

1.7 Methods of graft copolymer synthesis

The graft copolymers are synthesized by various methods and they can be broadly classified into two categories. The first method involves the free radical copolymerization of monomer and macromer. In the second method, the functional groups of preformed or natural polymers are utilized as grafting sites and on which the graft chains are anchored.

1.7.1 Copolymerization of macromer

The free radical polymerization of vinyl monomers in the presence of functional chain transfer agent provides oligomer with end group functionality. For example, the chain transfer agents such as mercapto ethanol, mercapto propionic acid and 2-aminoethanethiol provide hydroxyl, carboxyl and amino end group to the oligomer respectively. The functionalized oligomer can be reacted with appropriate vinyl monomer to obtain macromer. Free radical copolymerization of macromer with monomer yields the graft copolymer. For example, the graft copolymer of poly (styrene) backbone and methacrylic acid graft chains has been prepared by this method (Riza et al., 1995). Similarly, numerous graft copolymers containing hydrophobic backbone and hydrophilic graft chains have been developed and evaluated for oral delivery of proteins (sakuma et al., 1997).

1.7.2 Modification of natural polymers

Natural and semi-synthetic polymers such as starch, dextran, ethylcellulose, guar gum, hydroxypropylmethyl cellulose and carboxymethyl chitosan are often modified to alter their physico-chemical properties. These polymers have been modified by grafting with vinyl monomers such as (meth)acrylic acid, ethyl acrylate, acrylamide etc., The grafting reaction involves the introduction of free radical sites on the polymer backbone followed by grafting of vinyl monomer by free radical polymerization. Initiators which include benzoyl peroxide, potassium persulfate, ammonium persulfate, ceric ion and redox initiation systems have been used for grafting reaction (Hebeish et al., 1998). Grafting of acidic or basic monomers on the natural polymer results in pH sensitive graft copolymers (Toti and Aminabhavi, 2004).

1.8 Routes of drug administration

The drug delivery systems can be classified based on the route through which a drug is administered into the body. The routes of drug administration include oral, pulmonary, intravenous / intraarterial, intramuscular / subcutaneous, transdermal, buccal / sublingual, ocular, nasal, rectal and vaginal. The various routes of drug administration and their market share are shown in Figure 1.8.

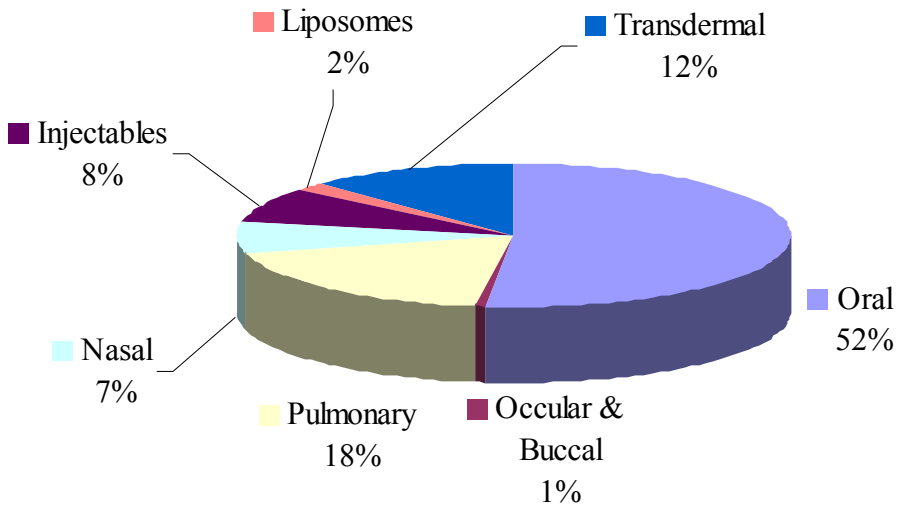


Figure 1.8. The routes of drug administration and their market share

1. Oral

Oral delivery systems are most attractive and widely used for administration of drugs. In the oral route, a dosage form is taken by mouth into the gastrointestinal tract wherein drug would be absorbed. This mode of delivery is a convenient and noninvasive method of administering drugs and offers better patient compliance. The intestinal epithelium offers an ideal target for drug absorption since it has a total surface area about 200 m^2 (Martín del Valle et al., 2009).

2. Pulmonary

Pulmonary delivery of drugs is used for the treatment of asthma, chronic obstructive pulmonary disease and cystic fibrosis. In this method, the drug is administrated by inhalation which gives the direct access of drug to the lungs. The pulmonary delivery of drugs gives rapid response with minimum side effect. The required dose is low, since the drug is delivered directly to the lungs. The lung offers large surface area of 80-100 m^2 and it is highly permeable membrane which helps for the drug absorption and transportation to the blood. Protein molecules which are susceptible

to degrade under the acidic conditions and / or the enzymatic attack in the intestinal region can be administrated through the pulmonary route (Martín del Valle et al., 2009).

3. Parenteral

Injection is the most widely used method for delivery of drugs which are not suitable for oral administration (Robinson and Lee, 1987). The parenteral route of drug administration can be classified as intravenous and intramuscular injections.

(A) Intravenous

The intravenous route of drug delivery gives an immediate biological response as the drug is directly placed in the blood. The major challenge associated with the intravenous route of drug administration is sustaining drug delivery. It needs frequent dose administration to maintain the therapeutic level of drug in the blood for extended period of time. To overcome this limitation, various strategies are being investigated which include viscous vehicles, suspension and biodegradable microspheres.

(B) Intramuscular

Intramuscular route is preferred, when the disease state does not call for oral dose or when prolonged drug action is required. The sustained delivery of drug can be achieved by reducing drug solubility, gelling of the oily vehicles, biodegradable delivery systems and / or implants. Both intravenous and intramuscular injection methods have several draw backs which include pain to patient, rapid release of drugs, needle phobia, risk of infections and the need of physician for dose administration.

4. Transdermal

The delivery of drugs across the skin is gaining increasing attention as it is non-invasive and easy to administrate. Transdermal delivery system offers sustained drug release, reduced systemic side effects, avoids degradation of drugs which normally occurs when dose is administered through oral. However, the skin normally acts as a barrier to foreign substances and prevents the penetration of majority of drugs.

5. Buccal / Sublingual

In this route, the drug is absorbed by oral cavity through the mucosa under the tongue (sublingual) and between the cheek and gingiva (buccal). The absorption of drug is rapid when it is administered through buccal / sublingual route due to thin mucous membrane and high blood supply. This route is preferred over oral route when the rapid action of drug is required.

6. Ocular

Topical instillation of drugs is required for the treatment of diseases which affect the anterior segment of the eye. However, topical application of drug to the eye is impeded by drainage and the permeability of drug through the corneal membrane is low. Therefore, only 3 % or less than that of administered dose penetrates into the humor following the topical instillation of aqueous solution.

7. Nasal

Nasal route is used primarily for local action on the nasal mucosa. This is considered as an alternate route for drugs those are poorly absorbed by oral route. It becomes an attractive route for drug delivery because of rapid drug absorption and relatively easy to administrate the dose. Variety of drugs including propranolol, testosterone, naloxone cromolyn sodium have been shown to be absorbed nasally in humans.

1.9 Gastrointestinal tract: Anatomical considerations

The gastrointestinal tract (GI tract) starts from mouth and ends in anus. The schematic representation of GI tract is shown in Figure 1.9. It is a long passage through which food is broken apart, digested and the nutrients are absorbed into the body. The chewed food in the mouth passes through the esophagus into the stomach wherein, the food is subjected to digestion in the presence of acidic fluid and enzymes. The stomach is connected with small intestine through a valve, pylorus sphincter which opens and draws the food materials from stomach and passes to the small intestine. The small intestine contains three sections namely, duodenum, jejunum and ileum.

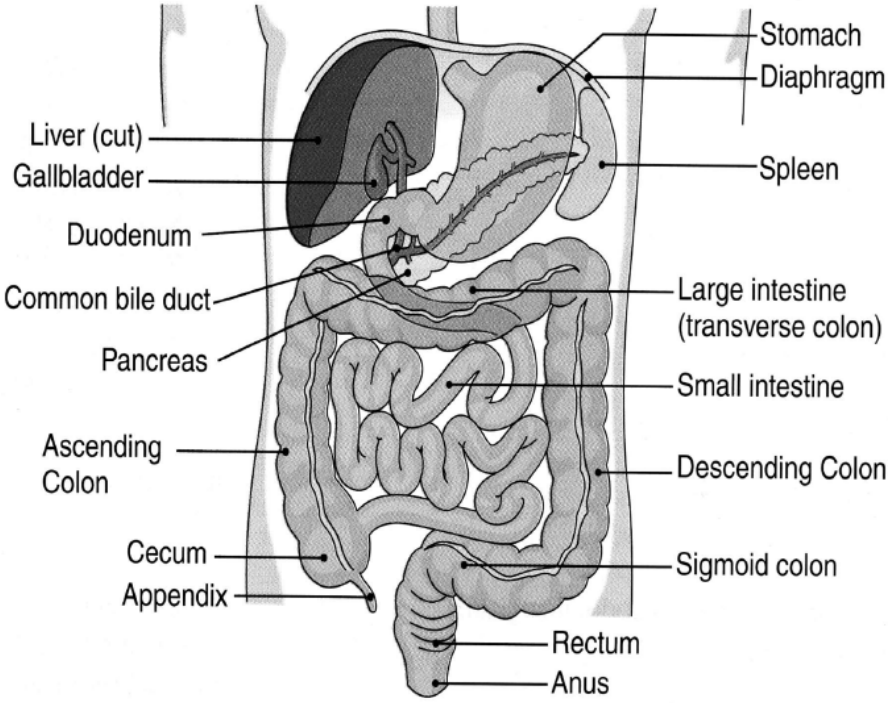


Figure 1.9. Schematic representation of the GI tract

In duodenum, fats, carbohydrates and proteins are digested in the presence of bile and pancreatic juice. The digested materials are absorbed by jejunum and ileum. The remaining undigested materials pass into the large intestine (colon). The main function of colon is to dry out the remaining food materials to form stool. The stool contains undigested and indigestible materials which are emptied by anus.

Oral administration of drug commences with ingestion of dosage form through the mouth. The residence time of dosage form in mouth is only few seconds and it reaches stomach through esophagus. Immediate release dosage form dissolves rapidly in the stomach and release the drug. On the other hand, the sustained release dosage form releases the drug over an extended period of time throughout the GI tract. New drug delivery systems have been developed to deliver the drugs at specific site in the GI tract at the time of requirement. The site specific delivery of drugs has been achieved by exploiting the variation of pH along the GI tract.

The pH of fluids present in various segments of GI tract is summarized in Table 1.3. The drug release can be targeted to the small intestine by enteric coating the immediate / sustained release dosage forms (Farinha et al., 2000 and Kovacs-Nolan and Mine, 2005). Similarly, the colon specific delivery of drugs can be achieved by

coating the dosage form using the polymer which dissolves at pH prevalent in the ileo-colonic junction (Ibekwe et al., 2006 and Schellekens et al., 2008).

Table 1.3. pH of fluids in the various segments of GI tract

Segments	pH
Stomach	1.0 – 3.0
Duodenum and Jejunum	6.5 – 7.0
Ileum	7.0 – 8.0
Colon	6.0 – 6.8

Azopolymers have been extensively investigated for colon specific delivery of drugs. For example, Kopeček et al., 1995 have developed a colon specific delivery system based on hydrogel which comprised azo bonds. The release of drug occurred as a result of microbial degradation of hydrogel through the cleavage of azobonds. However, the degradation of azopolymers is slow due to their hydrophobic nature (Yeh et al., 1995). Another disadvantage of azopolymer based delivery systems is their toxicity and hence they are not suitable for long term use (Singh, 2007).

1.10 Preparation of drug delivery dosage forms

The tablets are most commonly used solid dosage form for oral administration of drugs (Rasenack and Muller, 2002). They offer the advantages of relatively ease of manufacturing, convenient to patients for administration, accurate dosing, better stability than liquids and better tamper resistance compared to capsules. The techniques of wet granulation, roller compaction and direct compression are frequently used for manufacturing tablets. Among these techniques, the direct compression of active pharmaceutical ingredient (API) and excipients is the most widely used (Shangraw and Demarest, 1993).

The direct compression is defined as the process by which tablets are compressed directly from the powder blend of API and excipients. This process does not involve the pre-treatment of the powder blends by wet or dry granulation. The various processes involve in direct compression, dry granulation and wet granulation is summarized in Table 1.4. Some of the pharmaceutical ingredients can not be compressed directly to form a tablet due to the lack of flow, cohesion and

lubricating properties. The physical modification and incorporation of processing aid(s) enhances the compressibility of such ingredients.

Table 1.4. Comparison of major steps involved in the tablet preparation

Process steps	Direct compression	Dry granulation	Wet granulation
1.	Mixing / blending of API and adjuvants	Mixing / blending of API and adjuvants	Mixing / blending of API and adjuvants
2.	Compression	Compression into slugs	Preparation binder solution
3.		Size reduction and screening	Massing of binder solution with the mixture of step 1
4.		Mixing of granules with pharmaceutical aid(s)	Wet screening of damp mass
5.		Compression	Drying of wet granules
6.			Blending with pharmaceutical aid(s)
7.			Compression

(Gohel et al., 2005)

The directly compressible adjuvants can be prepared by various methods which include chemical modification, physical modification, grinding and / or sieving, spray drying and granulation / agglomeration. Among these methods, the spray drying offers spherical and uniform microparticles of adjuvant(s). The spray dried microparticles are better for the preparation of tablets by direct compression. Spray drying also helps to co-process the adjuvants or the API and adjuvant to achieve intimate mixing among them. For example, the co-processing of API and polymer by spray drying results in microparticles wherein, the API and polymer molecules are intimately mixed. These microparticles can be formulated with other adjuvants and compressed directly to form a tablet.

Spray drying is a method by which a dry powder can be produced from liquid or suspension by rapidly drying them using hot air. Typical spray drying equipment is shown in Figure 1.10. This process is preferred for the preparation of microparticles

containing thermally sensitive API. Hot air is normally used for drying the solution or suspension to obtain drug encapsulated polymer microparticles. The spray drying process involves continuous introduction of the solution of polymer and drug prepared from volatile solvent into a drying chamber through a spraying gun in the form of droplets. These droplets are rapidly dried by the aspirated hot compressed air within the drying chamber. This leads to the formation of film over the droplets followed by evaporation of solvent from the core renders solid microparticles. So formed particles are aspirated into subsequent chamber wherein they are allowed to settle by cyclone technique in a collection flask.

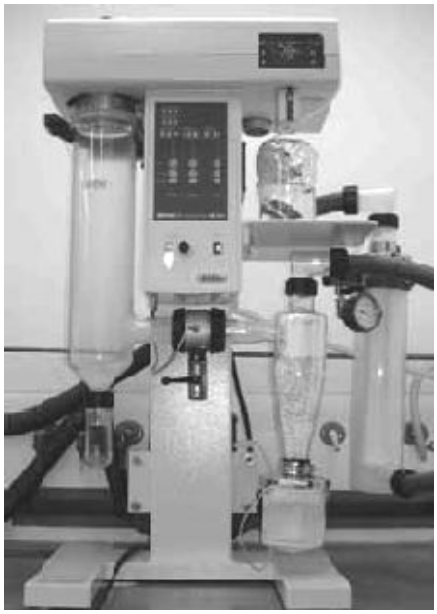


Figure 1.10. Spray drier for the preparation of drug loaded polymer microparticles

Advantages of direct compression process

The direct compression process is economical compared to the wet granulation as it requires fewer unit operations. Direct compression is more suitable for APIs which are sensitive to moisture and heat since it does not involve wetting and drying process. The release behavior of drug from the tablet that made by direct compression method is less likely to change on storage than that made by wet granulation technique (Shangraw, 1988). The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression method. The materials are under processing for a

shorter period of time and hence the chance for contamination is less (Rubinstein, 1998).

1.11 Controlled release technology: Oral route

The controlled drug delivery systems reduce the frequency of dosing, dose requirement and drug related toxicity and enhance the patient compliance (Ravi Kumar and Neeraj Kumar, 2001). Sustained release dosage forms deliver the drug for extended time period. On the other hand, the controlled release dosage forms maintain therapeutic level of drug over an extended period of time.

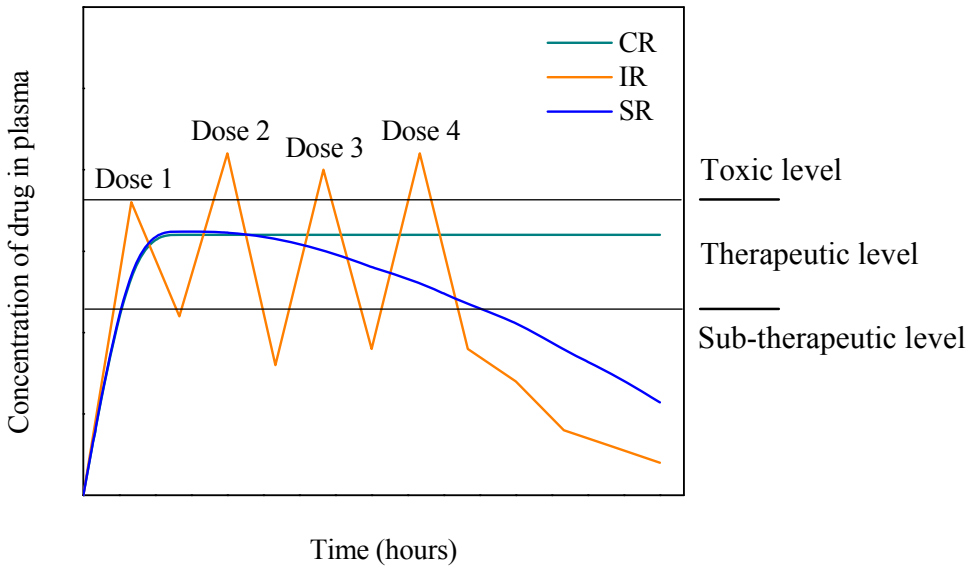


Figure 1.11. Profiles: Plasma concentration of drug by controlled (CR), immediate (IR) and sustained (SR) release dosage forms

The plasma concentration of drug results from various types of delivery systems is shown in Figure 1.11. In the case of immediate release dosage form, the concentration of drug in blood fluctuates when a dose is administered. The patient has to administer multiple doses in a day to maintain the drug in blood for extended time period. Sustained release dosage forms maintain the therapeutic level of drug only for certain period of time and thereafter the drug concentration declines. Therefore, the controlled drug delivery systems which release the drug at constant have gained much attention. Such delivery systems maintain the therapeutic level of drug for longer time period when patient administrate a single dose.

Controlled release drug delivery systems: Advantages

1. Reduced dosing frequency
2. Less fluctuation of drug concentration in plasma
3. Lesser dose requirement
4. Minimum side effect
5. More uniform effect of drug
6. Better patient compliance

1.12 Mechanisms of drug delivery

(1) Diffusion controlled release

Diffusion controlled systems do not swell in the aqueous medium. The release takes place by diffusion of dissolved drug through the channels of polymer matrix. These systems can be fabricated in the form of reservoir and matrix devices. The schematic representation of drug diffusion from matrix and reservoir devices is shown in Figure 1.12.

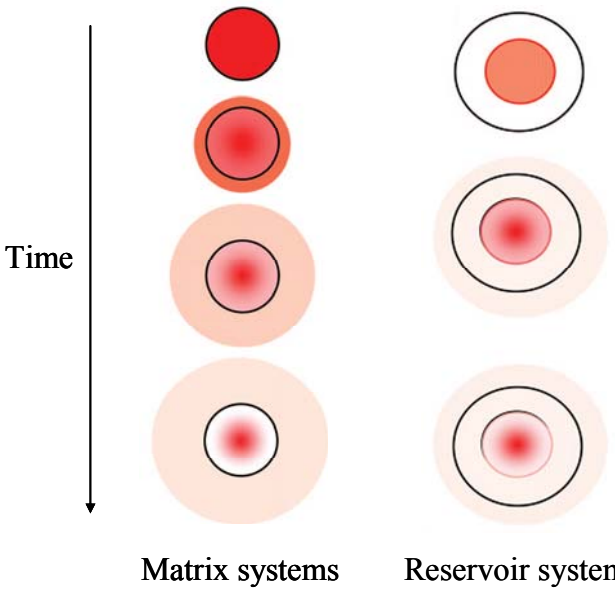


Figure 1.12. Drug diffusion from matrix and reservoir devices
(Martín del Valle et al., 2009)

(a) Reservoir devices

Reservoir device consists of drug core on which the polymeric membrane has been coated. Ingress of aqueous medium results in diffusion of dissolved drug to the external environment through the membrane. The nature of polymer membrane

including the thickness and permeability to the aqueous medium and molecular weight of the drug determines the rate of drug release. Since the polymeric membrane remains intact for longer time period, the diffusion rate of drug can be fairly constant throughout the lifetime of device. The major drawback with reservoir device is dose dumping which results from the premature rupturing of polymeric membrane.

(b) Matrix devices

Matrix devices are the most widely used oral solid dosage form for controlled delivery of drugs. They are relatively easy to fabricate compared to reservoir devices. In this device, drug is present uniformly throughout the polymer matrix. There is no danger of dose dumping unlike in the case of reservoir devices. The matrix devices are prepared by compressing either dry blend of drug and polymer or spray dried microparticles obtained from solution blending of drug and polymer. In the case of dry blend compressed matrix, the drug is present in the state of dispersion. On the other hand, the drug is present in dissolved state in microparticles compressed matrix. The microparticles compressed matrices are known to release the drug for longer time compared with matrices made from dry blend compression.

The penetration of dissolution medium into the matrix results in diffusion of dissolved drug to the external environment through the polymer network. The rate of drug release decreases with time, since the drug has to travel progressively longer distance to diffuse out. The duration of drug release from the matrix devices depends upon the drug solubility, drug loading, drug molecular weight and tortuosity of the matrix.

(2) Dissolution and erosion controlled release

The dissolution and erosion controlled release systems contain the polymer which dissolves or erodes in the aqueous medium. The rate of drug release depends on the rate of dissolution or erosion of the polymer matrix. The drug release occurs at constant rate when the polymer matrix undergoes dissolution or erosion at constant rate.

(3) Swelling controlled release

The swelling controlled systems contain the polymer which swells in the aqueous medium. The release occurs by the diffusion of the drug through the tortuous path of swollen polymer network. Most of the swelling controlled devices are based on hydrogel which is a crosslinked polymeric network. The hydrogels are capable of holding a large amount of water without dissolution (Yoshada et al., 1992 and 1994 and Abraham et al., 2005).

The extent of swelling of hydrogel and the drug release rate can be varied by tailoring the polymer architecture using appropriate monomer(s) and crosslinker. It is possible to design a hydrogel which reversibly swells and shrinks depending upon the environmental conditions such as pH, temperature and ionic strength. pH sensitive hydrogels are much relevant for oral delivery of drugs. For example, an anionic hydrogel capable of suppressing the release of drug at acidic pH prevalent in the stomach and releases the same at near neutral pH prevalent in the intestinal region. Since the hydrogels do not dissolve in solvents, the drug loading has to be performed by immersing them in drug solution. However, the drug loading achievable by imbibition method is very low.

Another method of drug loading involves the incorporation of drug during the hydrogel preparation. However, the solubility of drug within the monomer mixture, the drug stability, the possible reaction between drug and reactive monomers during the polymerization and removal of unreacted monomers from the drug loaded device limits the utility of hydrogels in oral delivery of drugs.

(4) Osmotically driven release

Osmotic delivery systems consist of drug core encapsulated within a semi-permeable membrane. The membrane contains an orifice through which drug is released. The device imbibes the aqueous medium which generates osmotic pressure within the core due to the dissolution of drug and / or osmotic agent. As a result, the drug is released through the orifice at controlled rate. Sodium chloride, sodium carbonate, potassium chloride, sodium carboxymethyl cellulose and HPMC are used as osmotic agent. Since the membrane is permeable only to water and impermeable to drug and osmotic agent, the drug release occurs only through the orifice.

1.13 Types of controlled release delivery systems

Controlled drug delivery systems can be classified based on the manner in which the delivery of drug occurs. The release of drug governed by the nature of excipients incorporated in the formulation, design of dosage form and pH of physiological medium. Among the excipients, polymer plays a vital role in sustaining and / or targeting the release of drugs. The behavior of polymers in the aqueous medium such as swelling, dissolution and erosion governs the drug release kinetics. The various types of oral drug delivery systems are briefly described below.

1.13.1 Delayed release delivery systems

Delayed release dosage form consists of drug core which is coated with an enteric polymer. This dosage form suppresses the release of drug in stomach since the enteric coat does not swell or dissolve at acidic pH. Once the dosage form reaches the upper intestine, the enteric coat dissolves and releases the drug rapidly. The delay period depends on the gastric residence time of dosage form. Enteric coated dosage forms have been used to deliver drugs and other active materials which are susceptible to undergo degradation under acidic pH conditions of stomach (Farinha et. al., 2000, Sánchez-Lafuente et al., 2002 and Kovacs-Nolan and Mine, 2005). Such dosage forms are also used to avoid gastric inflammation (Torres et al., 1995), nausea and vomiting (Min and Heon, 2007).

1.13.2 Sustained release delivery systems

Sustained release systems deliver drug throughout the GI tract over an extended period of time. The monolithic sustained release matrices are easy to manufacture and are cost competitive. Hydrophilic gellable polymers, *viz*., hydroxypropylmethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose and polyethylene oxide are frequently investigated as sustained release matrix. However, these polymers do not offer much control over the release of highly water soluble drugs. For example, diltiazem hydrochloride is a highly water soluble drug used to treat hypertension and angina pectoris. Because of its shorter half-life, multiple doses in a day have to be administered to maintain the therapeutic level for longer time period (Kim and Fassihi, 1997 and Altaf et al., 1998). Most of the formulations presently available are able to deliver the drug over 12 hours. Therefore, it is necessary to administrate the dose at least twice in a day (Khan, 1995).

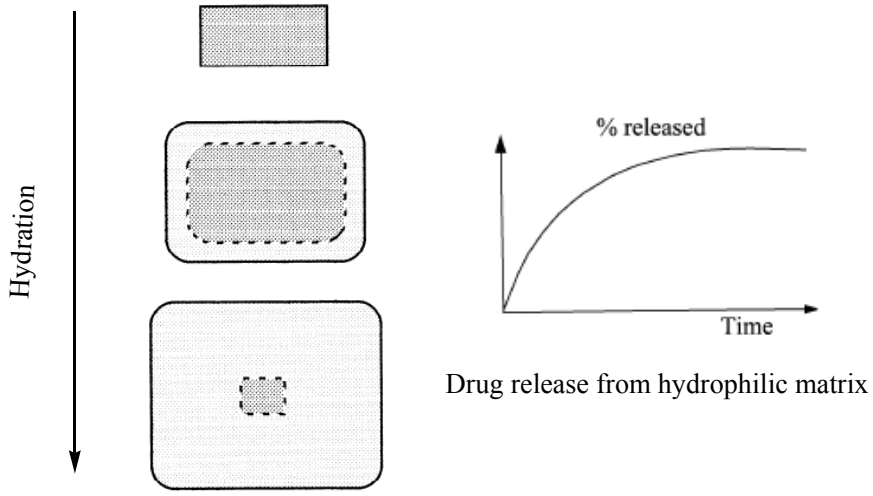


Figure 1.13. Hydration of conventional hydrophilic matrix and its drug release behavior (Conte and Maggi, 2000)

The release of drugs from hydrophilic monolithic matrix follows nearly first order kinetics. The release occurs rapidly at initial stage due to the dissolution of drug on the surface. The initial burst release is not desirable since it would lead to toxic level of drug in the blood. After the initial burst release, the polymer matrix hydrates and swells which results in sustained release of drug. The release rate decreases with time as result of increase in diffusion path length of drug progressively (Conte and Maggi, 2000 and Abdul and Poddar, 2004). The hydration of conventional hydrophilic tablet and its drug release behavior is shown in Figure 1.13.

Over the years, considerable efforts have been made to design delivery systems which release the drug at constant rate for extended time period. Particularly the matrices of various geometries which include spherical, donut shape, cylindrical, biconvex, biconcave and multi-layered tablets have been investigated (Abdul and Poddar, 2004). The constant release rate is desirable especially for drugs which have narrow therapeutic index.

Multilayered tablet: Geomatrix® technology

Geomatrix® technology involves construction of tablets in multilayered structure. The core layer contains hydrophilic gellable polymer along with drug. One or more barrier layers of impermeable or semi-permeable polymer cover the core layer. The barrier layers can be applied directly on the core layer during the tablet preparation.

These layers reduce the surface area available for the ingress of dissolution medium. Therefore, the drug release occurs exclusively from the uncovered area of core. The hydration behavior of triple layered tablet is shown in Figure 1.14. Numerous investigations have been undertaken to optimize the composition of barrier layer to obtain constant release rate of drugs. Similarly, the drugs differing in solubility have been incorporated and studied for their release behavior (Conte and Maggi, 1996).

The first extended release product based on Geomatrix® technology was introduced in the US market in 1992, under the trade name Dilacor XR™ which delivers diltiazem hydrochloride over an extended time period. It has been used for the treatment of hypertension and angina pectoris. Dilacor XR™ contains 3 to 4 triple layered tablets in a gelatin capsule and each of the tablets contains 60 mg of drug (Wilding et al., 1995). The tablet has been modified for sparingly soluble drugs by incorporating erodible polymer as barrier layers. These layers undergo steady erosion on the progression of drug release which leads to increase in surface area with time. Therefore, the release of sparingly soluble drug occurs at constant rate for prolonged period of time (Conte and Maggi et al., 1996).

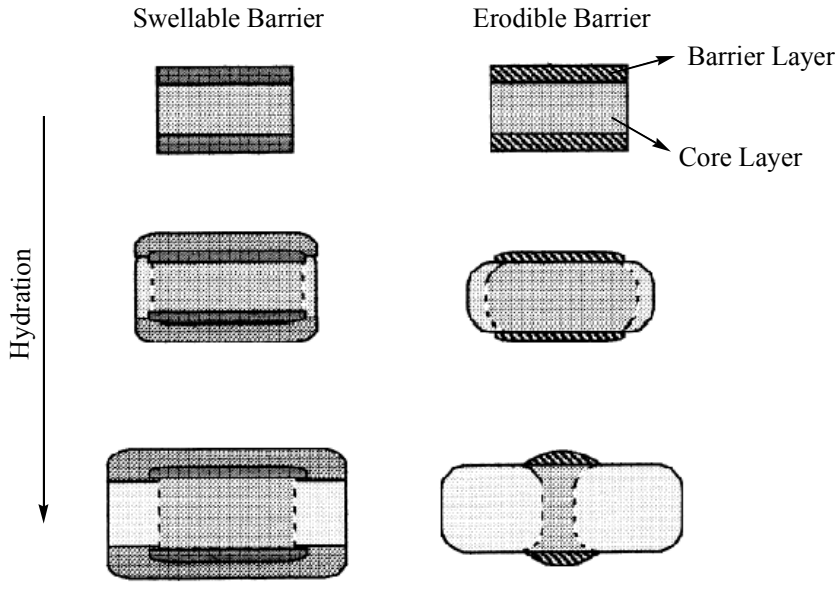


Figure 1.14. Hydration of multilayered tablets comprising swellable and erodible barrier (Conte and Maggi, 2000)

The fabrication of multilayered tablets is a complex process and needs special tabletting equipments. Therefore, considerable attempts have been made to develop

a simple matrix tablet for sustained delivery of highly water soluble drugs. Kim et al., 1997 have developed a ternary polymeric matrix system for controlled release of diltiazem hydrochloride. They blended pectin, hydroxypropyl methylcellulose and gelatin and fabricated to form matrix tablets. *In vitro* release study showed, at lower drug loading 12 %, the release was sustained and the rate of release was constant. At higher loading level of drug 24 %, the release was rapid (50 % in 6 hours) and showed anomalous release behavior.

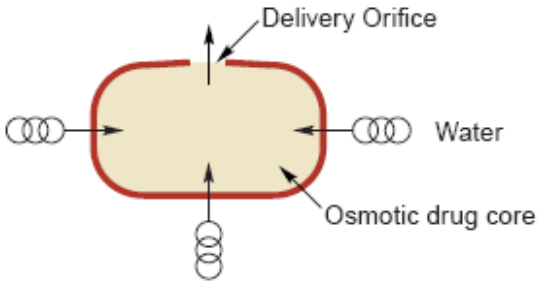
Another approach to achieve constant rate of drug release involves complexation of drug and polymer. The primary requirement for this approach is the polymer and drug should be oppositely charged. Kim et al., 1999 have prepared the complex of poly (acrylamido-2-methyl-1-propanesulfonate sodium -co- methyl methacrylate) and various cationic drugs, *viz.,* labetalol hydrochloride, propranolol hydrochloride, verapamil hydrochloride, diltiazem hydrochloride and oxprenolol hydrochloride. The tablets prepared from these complexes showed sustained release of drug over 24 hours at constant rate. The release of drug occurred via ion exchange mechanism and hence the release rate was dependent on the ionic strength of release medium. Similarly, the polyelectrolytes like λ-carrageenan and poly (carboxyalkyl methacrylates) were investigated for sustained delivery of cationic drugs (Bonferoni et al., 2000 and Cornejo-Bravo et al., 2005).

Osmotic drug delivery systems

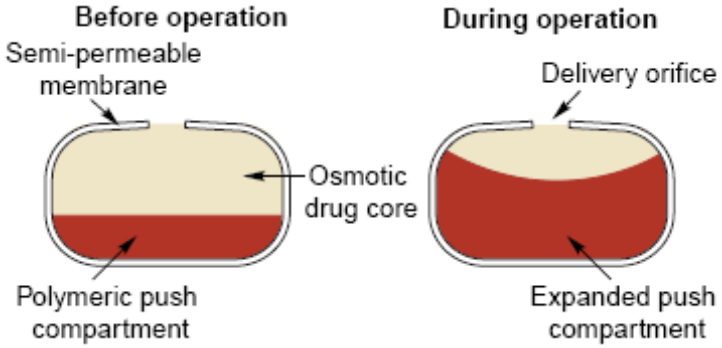
Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. The osmotic system contains a core of water soluble drug and an osmotic agent encapsulated within a semi permeable membrane. The membrane allows the penetration of aqueous medium into the core, but resists the permeation of drug. The delivery orifice in the membrane is created by laser drilling technique. The penetration of aqueous medium into the core generates osmotic pressure. As a result, the drug released through the orifice over longer period of time. This device is known as elementary osmotic pump developed by Alza corporation (USA).

The limitation of elementary osmotic pumps is that they do not deliver poorly soluble drugs completely. Therefore, a number of modified osmotic devices were developed. One such device is push-pull™ osmotic pump, which is a bi-layer tablet coated with a semi permeable membrane. The upper layer consists of drug and

osmotic agent and lower layer is made from a swellable polymer. The penetration of aqueous medium causes swelling of polymer which pushes the drug out through the orifice. The elementary osmotic system and push-pull osmotic pump are shown in Figure 1.15.



Elemetry Osmotic Pump



Push-Pull^{TM} Osmotic Pump

Figure 1.15. Osmotic drug delivery systems developed by Alza Corporation, USA (Verma and Garg, 2001)

The release of drugs from osmotic systems is pH independent and other physiological conditions. It is possible to modulate the release characteristics by optimizing the composition and design of system. Particularly, the rate of drug release can be varied by selecting appropriate semi permeable membrane and its wall thickness and pore forming agents. The osmotic devices exhibit zero order release over an extended period of time. However, these systems suffer from the draw back of complex processing steps in the preparation of dosage form. The accidental rupture of membrane would lead to dose dumping and sudden rise in drug level in the blood. In some cases the osmotic adjuvant is unable to imbibe sufficient aqueous medium so as to push out the drug completely (Khan, 1995).

1.13.3 Modified release delivery systems

The sustained release dosage forms maintain the prolonged action of drug in the body compared to immediate release dosage forms. However, sustained release dosage forms are not suitable for the drugs which undergo metabolic degradation as well as for the treatment of chronic diseases. Therefore, the modified release dosage forms are being increasingly investigated. These dosage forms are capable of delivering the drug at right time and site. Most of the body functions are follow a circadian rhythm and their activity changes with time. For example, the concentration of hormones like rennin, aldosterone and cortisol fluctuates in the blood with respect to time / day. Therefore, the delivery of drugs at the time of requirement would be more effective. One of the modified release systems has been designed to achieve pulsed delivery of drugs after a predetermined lag time. The conditions those demand for pulsatile delivery of drugs are briefly summarized below.

Chronotherapeutic drug delivery

Bronchial asthma, myocardial infarction, angina pectoris, rheumatic arthritis, ulcer and hypertension attacks are more pronounced at particular time period in a day. For example, asthmatic attack, rheumatic arthritis and heart attack are likely to occur early morning hours (Lemmer, 1991, 2004). A pulsatile release dosage form that administered at bed time, but delivers the drug at early morning hours would be preferable for effective treatment.

Drugs which exhibit biological tolerance

These drugs should not be delivered at constant rate, since their effect decreases with time. Therefore, the pulsatile release dosage form would be preferable (Chang et al., 1999).

Reducing toxicity

The drugs which exhibit toxicity when they are being held for longer time in the body require pulsatile release formulation. For example, sustained release dosage form of sulfonylurea damages the pancreas earlier than the corresponding immediate release dosage form (Survase and Kumar, 2007).

Avoiding the delivery of drugs in stomach

The drugs which undergo degradation under acidic conditions of stomach, drugs which induce gastric inflammation, nausea and vomiting have to be delivered after a lag time period (Farinha et. al., 2000, Torres et al., 1995 and Min and Heon, 2007).

Delivering the drug at desired site

Proteins and peptides are well absorbed in the colonic region (Rubinstein et al., 1997). Similarly, colon specific delivery of drugs is needed for the treatment of inflammatory bowel diseases (Friend et al., 2005 and Sinha et al., 2006). The pulsatile release dosage form which delivers the active agents after reaching the colonic region would be desirable.

Enhancing bioavailability

The continuous release of drugs which exhibit extensive first pass metabolism leads to their degradation. In this case, the pulsatile release dosage forms are suitable since they can minimize the degradation of such drugs (Survase and Kumar, 2007).

In all these cases, the dosage form which releases the drug rapidly at the time of requirement and / or at desired site would be preferable. Therefore, the pulsatile release dosage forms have been investigated by several researchers. These dosage forms can be classified into two categories, *viz*., time and site controlled release systems. The time controlled systems release the drug after lag time irrespective of its location in the GI tract. On the other hand, the site controlled systems release the drug only when they are placed at particular site in the GI tract. Various types of time and site controlled release systems have been developed and reviewed in the literature (Anal, 1997a and b).

1.13.3.1 Time controlled release delivery systems

Time controlled release systems have been used for chronotherapeutic applications. Chronopharmaceutics is a branch of pharmaceutics which involves the design of drug delivery systems which release the drug in a rhythm which matches the biological requirement. The chronotherapeutic drug delivery systems are more effective and provide reliable therapeutic effect. The ideal chronotherapeutic systems should be non-toxic, easy to manufacture, low cost and easy to administrate. However, such ideal system is not yet available in the market (Youan, 2004). Some of the time controlled pulsatile release systems have been discussed below.

Pulsatile release systems with barrier coating

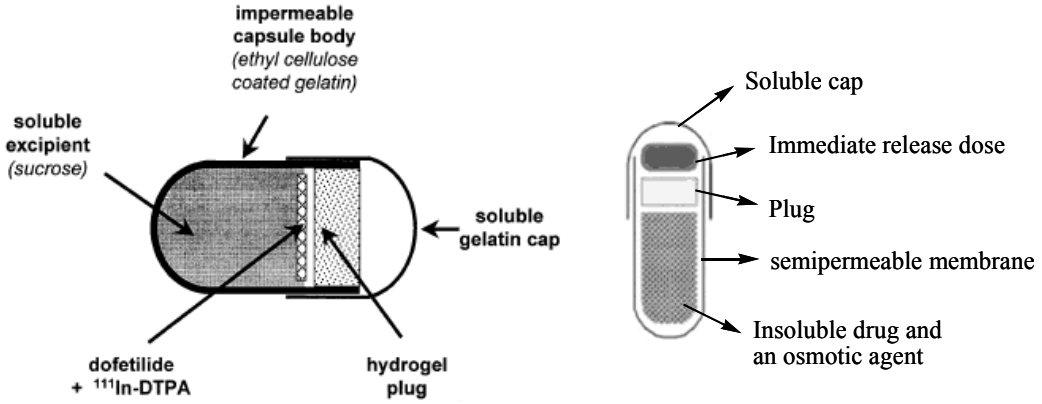
The conventional pulsatile release dosage forms are reservoir devices comprising a barrier coat. The coating collapses after a lag time by erosion or dissolution of polymer and results in pulsed release of drug. The lag time of release is controlled by thickness of the barrier coating. Time Clock® system consists of drug core coated with lipidic materials such as carnauba wax and bees wax along with a surfactant like polyoxyethylene sorbitan monooleate. The release of drug occurs after a lag time as result of erosion of coating in the aqueous medium (Pozzi et al., 1994). Since the erosion occurs irrespective of pH, the release would occur either in stomach or in intestinal region. One of the limitations of this dosage form is the premature release of drug. Similarly, the failure of coat to undergo complete erosion would result in sustained release of drug after lag time. Chronotropic® system contains a drug core coated with hydroxypropyl methylcellulose as a barrier. The erosion or dissolution of the coat triggers the pulsed release of drug. The lag time of release is controlled by viscosity of the polymer and coating thickness (Sangalli et al., 2001).

Pulsatile release system with rupturable coating

Rupturable dosage form contains a core of drug and swelling agent coated with polymeric membrane. The ingress of aqueous medium causes swelling of core and generation osmotic pressure. As a result, the coating ruptures and drug releases rapidly after a lag time (Sungthongjeen et al., 2004). The polymers which include croscarmellose sodium, crospovidone and sodium starch glycollate have been used as swelling agents. Water insoluble but permeable ethylcellulose is most frequently investigated polymer as a rupturable membrane. The ethylcellulose film is mechanically weak and ruptures easily in response to pressure exerted by swollen core. The lag time of release increases with the coating thickness of ethylcellulose. The mechanical properties of polymeric membrane play a vital role in the performance of rupturable systems. Bussemer et al., 2003 have done detailed investigation on various polymers to find their suitability as a rupturable film coat. They concluded that the polymers which remain weak and brittle under dry as well as wet conditions are suitable.

Capsular systems

The capsular system consists of an insoluble capsule body containing drug and polymer as a plug in mouth of the capsule. The detachment of plug as a result of swelling, erosion or dissolution after a lag time leads to pulsed delivery of drug. Pulsincap® is an example for such system which comprises a capsule body filled with drug. The mouth of the capsule is closed with a swellable or erodible hydrogel as a plug. Upon contacting with aqueous medium the plug swells and gets ejected from the capsule followed by pulsed release of drug occurs (Krögel and Bodmeier, 1998 and 1999). The lag time of pulsed release is controlled by composition, dimension and position of plug material. The swellable polymethacrylates and erodible polymers such as hydroxypropyl methylcellulose, polyvinyl alcohol, polyethylene oxide, enzymatically erodible pectin have been investigated as plug materials. The components of capsular systems are shown in Figure 1.16.



Pulsincap® System Port® System

Figure 1.16. Components of capsular pulsatile release systems
(Stevens et al., 2002 and Crison et al., 1995)

The Port® system comprises a semipermeable capsule wherein the drug, osmotic agent and other ingredients are placed as a bottom layer. Above this layer, the polymer plug and an immediate release dose unit are placed. The mouth of the capsule is closed with a soluble cap. The dissolution of the cap in the aqueous medium results in rapid release of drug as a first pulse from immediate release dose unit. The permeation of aqueous medium into the capsule generates osmotic pressure. As a result, the polymer plug gets ejected from the capsule after a lag time

and releases the drug rapidly as a second pulse. The lag time of release is controlled by the thickness of semipermeable membrane (Crison et al., 1995). Since the preparation of capsular systems involves complex processing steps and requires special equipments the cost of dosage form is high.

1.13.3.2 Site controlled release delivery systems

The site specific delivery system is useful to deliver the drugs at desired site in the GI tract. The colon specific delivery systems are designed such that they prevent the release of drug in stomach and upper intestine and release the same in colonic region. The delivery of drugs in colonic region is needed for the treatment of inflammatory bowel diseases, irritable bowel syndrome and colon cancer (Friend et al., 2005 and Sinha et al., 2006). The bioavailability of proteins and peptides can be enhanced by delivering them in colonic region. This is because the enzymatic degradation of proteins and peptides is low in the colon (Rubinstein et al., 1997).

The time controlled pulsatile release systems have been investigated for colon specific delivery of drugs (Pozzi et al., 1994, Niwa et al., 1995 and Fukui et al., 2000). In these systems, the site at which the delivery occurs is decided by transit time of dosage form in stomach. However, the gastric residence time of dosage form is not predictable and it varies largely among the humans (Davis et al., 1984). Therefore, the colon arrival of time controlled release systems can not be predicted accurately. To overcome this limitation, the time controlled release systems have to be enteric coated (Sangalli et al., 2001).

The site controlled release systems rely on the variation of pH along the GI tract. In healthy humans, the pH varies from stomach (pH = 1-3), upper intestine (duodenum and jejunum, pH = 6-7 and Ileum, pH = 7-8) and colon (pH = 6-6.8). Therefore, the pH dependent polymers which dissolve at pH 7-8 prevalent in the ileo-colonic junction are extensively investigated for coating the dosage form. Most widely investigated polymer is the copolymer of methyl methacrylate and methacrylic acid (2:1) which dissolves at pH $\geq$ 7.5. However, this polymer coated dosage forms release the drug in upper intestine or not at all (Ashford et al., 1993 and Schellekens et al., 2007). For example, mesalazine tablet coated with the above polymer is marketed under the trade name of Asacol® in many countries. There have been

instances when the coating failed to undergo dissolution and resulted in evacuation of intact tablet (Schroeder et al., 1987).

1.13.4 Gastroretentive delivery systems

All drugs can not be absorbed uniformly through out the GI tract due to variation in physico-chemical properties and physiological and biological factors. The drug should be in dissolved form to cross the biological membrane. The dissolved drug would expose to acidic, neutral and basic pH conditions when it passes through the GI tract. The solubility of ionizable drugs dramatically varies depending on the pH. For example, the basic drugs are soluble at acidic pH prevalent in the stomach and the solubility declines at near neutral and basic pH prevalent in the intestinal region. Hence, these drugs are poorly absorbed in intestinal region. Similarly, the presence of enzymes in the GI tract cause regional variation in the absorption of drugs (Chungi et al., 1979). Therefore, some of the drugs are absorbed only in particular segment of GI tract and / or the extent of absorption are different.

The absorption window is defined as the site at which a drug absorbed exclusively / extensively. Drugs with narrow absorption window have to be delivered at right site for better bioavailability (Davis, 2005). For example, the drugs which have absorption window in stomach and upper intestine have to be delivered in stomach (Streubel et al., 2006). Some of such drugs are summarized in Table 1.5.

Table 1.5. Drugs absorbed in stomach

Acyclovir	Metformin
Alendronate	Minocyclin
Atenolol	Riboflavin
Captopril	Sotalol
Ciprofloxacin	Amoxycillin trihydrate
Furosemide	Verapamil hydrochloride
Ganciclovir	Diazepam
Ketoprofen	Ranitidine hydrochloride
Levodopa	Cephalexin monohydrate
Melatonin	Ofloxacin

(Patil et al., 2006)

Gastrointestinal motility

Two different patterns of gastrointestinal motility and secretions take place depending on the fasted and fed states of the stomach. The stomach contains saliva, mucus, and cellular debris. In fasted state, a cyclic contractile events occur which known as Migrating Myoelectric Complex (MMC). Liquid materials pass through the partially constricted pylorus sphincter. On the contrary, the large undigested materials are retained by an 'antral-sieveing' process and stomach remains in the fed state. The gastric contractions move the solid food towards the antrum and the pyloric sphincter. A series of interdigestive events take place in the stomach. However, feeding disrupts this cycle and cause irregular contractile pattern (Fell, 1996). There are four consecutive phases of activity in the MMC (Sarna, 1985) which are given below.

Phase I: It is a quiescent period lasting from 30 to 60 minutes with no contractions.

Phase II: It consists of intermittent contractions which gradually increase in intensity with time, and it lasts about 20 to 40 minutes. The fluid and very small particles are discharged from the stomach in this phase.

Phase III: This is a short period of intense distal and proximal gastric contractions (4-5 contractions per minute) lasting about 10 to 20 minutes. These contractions are known as 'house-keeper wave'. This wave sweeps off solid food and pass to the small intestine.

Phase IV: This is a short transitory period 0 to 5 minutes between the last part of phase III and phase I.

Transit time of dosage forms

The average time required for a dosage form to traverse the gastric and small intestine is 3-4 hours and slightly varies among various dosage forms. Therefore, the conventional sustained release dosage forms would stay in stomach only for shorter duration and hence they are not suitable for gastroretentive delivery of drugs. The transit time of various dosage forms is summarized in Table 1.6.

Table 1.6. Transit time of dosage forms

Dosage form	Stomach	Small Intestine	Total (hours)
Tablets	2.7 ± 1.5	3.1 ± 0.4	5.8
Pellets	1.2 ± 1.3	3.4 ± 1.0	4.6
Capsules	0.8 ± 1.2	3.2 ± 0.8	4.0
Solution	0.3 ± 0.07	4.1 ± 0.5	4.4

(Chawla et al., 2003)

In order to extend the delivery of drugs in gastric region, the gastroretentive dosage forms are extensively investigated (Talukder and Fassihi, 2004). The conditions which necessitate gastroretentive dosage forms are highlighted below.

- Treatment of gastric diseases;
- Drugs better absorbed in stomach;
- Drugs poorly soluble at neutral pH of intestinal region; and
- Drugs degraded by enzymes in intestinal region.

Three major approaches have been followed to achieve gastroretentive delivery of drugs which include mucoadhesive microparticles, expandable or unfolding devices and floatable tablets.

Mucoadhesive dosage forms

The polymers which bind with gastric mucosal membrane have been investigated for the development of mucoadhesive dosage forms. Particularly, chitosan and its derivatives and acrylic acid based polymers are investigated (Lehr et al., 1992, He et al., 1998 and Gåserød et al., 1998). *In vitro* evaluation of chitosan based particles has shown good adhesion on the mucin layer (Säkkinen et al., 2002). However, *in vivo* evaluation showed no evidence for gastric retention of particles. For example, gastric retention behavior of furosemide containing chitosan and microcrystalline chitosan has been evaluated in human subjects. The result showed that the particles were not retained in the stomach. The adhesion of particles on gastric mucosa occurred only in one third of the cases and the results were not reproducible (Säkkinen et al., 2003 and 2004).

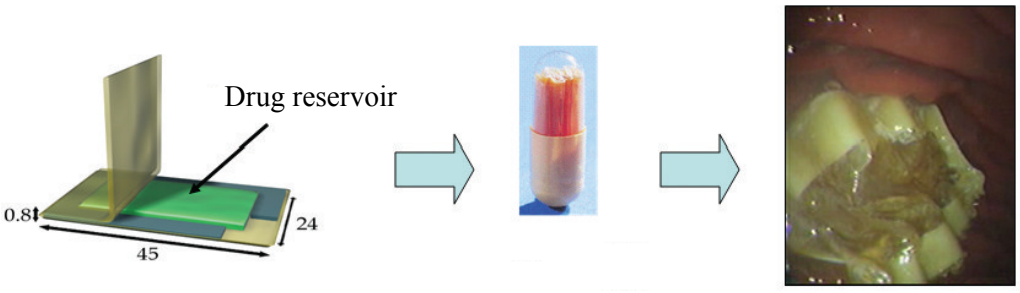
Similarly, the polymers which are known to be mucoadhesive, *viz.,* carbopol 934P and polycarbophil did not show significant gastric retention (Harris et al., 1990). For example, Cuña et al., 2001 developed mucoadhesive formulation which comprised the complex of amoxicillin and ion-exchange resin. The complex particles were prepared by dispersing the resin in the aqueous medium containing the drug. The complex formed was suspended in a dispersion of bioadhesive polymer, crosslinked polyacrylic acid and then emulsified in liquid paraffin. Gastric retention of these particles was evaluated in rats and the results showed that almost all the particles left the stomach within 2-3 hours. The authors concluded that the mucoadhesive polymer would not enhance the gastric residence time of dosage form. The unreliable performance of mucoadhesive formulations is mainly due to the non specific adhesion of dosage form and the influence of stomach content on the adhesion behavior of polymer.

Expanding devices

The expandable devices are initially small enough to swallow and they expand upon reaching the stomach. The device can be inserted in gelatin capsule under folded condition. Dissolution of the capsule in the aqueous medium results in unfolding of device to large size. Since the diameter of opened pylorus is ~15 mm, the expanded device greater than this size would be retained in the stomach (Klausner et al., 2003). These devices have been developed in various geometries (Caldwell et al., 1988 and Cargill et al., 1988).

Caldwell et al., 1988 have developed an expandable device using a blend of erodible and non-erodible polymers. The size and shape of the device has been designed in such way that it would not pass through the opened pylorus. The device containing the drug was inserted into the capsule in the folded form. When the capsule was placed in the aqueous medium, the device expanded to retain its original size and shape. The authors reported that the device was capable of staying in the stomach upto one year and released the drug. Similarly, Pogany et al., 1993 have developed an expandable device based on crosslinked poly (orthoester), and reported that the device would stay in stomach for extended time period and release the drug. The degradation of polymer would facilitate the evacuation of device from the stomach.

Recently, a gastroretentive device comprising multilayered sheets pasted one over another has been reported (Hoffman et al., 2004 and Kagan et al., 2006). The sheet containing riboflavin 5′ - phosphate sodium was prepared by solution casting of shellac and the drug. The sheet obtained was sandwiched within the intermediate layers prepared by mixing the enzymatically hydrolysable gelatin, methyl methacrylate-methacrylic acid copolymer (2:1) and glycerine followed by crosslinking using glutaraldehyde. The surface of the intermediate layers was coated with microcrystalline cellulose and the entire assembly was framed with strips of polylactide and ethylcellulose blend. The device has been prepared in rectangular shape which then folded in the shape of "accordion" and inserted in capsule (Figure 1.17). *In vivo* study of this dosage form in beagle dog showed gastric retention upto 24 hours. The dosage form has been developed by Intec Pharma and named as "accordion pill™".



Laminated structure of device Folded device in capsule Unfolded device in stomach

Figure 1.17. The 'Accordion pill™' developed by Intec Pharma (Afargan and Lapidot, 2006)

Although, numerous expandable dosage forms have been developed for gastroretentive delivery of drugs, their safety is still a matter of concern. If the dosage form is caught in esophagus during swallowing, the premature expansion of device would lead to esophagus obstruction. On the other hand, if the device fails to expand within short time, it would be emptied from stomach. This would lead to obstruction and injuries in the intestinal tract (Waterman, 2007). The resilience of device may reduce during the storage which would affect rapid unfolding in the gastric fluid. The construction of expandable devices is difficult and needs special equipments as they involve assembling of multiple components.

Floating dosage forms

Floating drug delivery systems have bulk density less than gastric fluid and hence they are buoyant. While the system is floating, the drug release occurs in the gastric fluid. These systems contain a drug, hydrophilic gellable polymer, gas generating system (e.g., sodium bicarbonate and citric acid) and other ingredients. Ingress of gastric fluid into the dosage form, followed by the reaction between sodium bicarbonate and gastric fluid leads to liberation of carbon dioxide. The gas formed gets trapped within the gelled polymer matrix and results in decrease of density of dosage form below that of gastric fluid. When the density becomes < 1.0, the dosage form attains buoyancy. Under the fed condition of stomach, the pH would be higher (pH ~ 3). In this condition, citric acid reacts with sodium bicarbonate and generates carbon dioxide.

Most frequently investigated polymer for the development of floating tablet is hydroxypropyl methylcellulose. This polymer undergoes hydration and forms gel in the aqueous medium. The gelling behavior of this polymer facilitates the entrapment of carbon dioxide. Other polymers like guar gum, polyethylene oxide and sodium carboxymethyl cellulose are often mixed with hydroxypropyl methylcellulose in order to modify the release behavior of drugs (Baumgartner et al., 2000 and Dave et al., 2004). For example, Chavanpatil et al., 2005 developed a floating dosage form which comprised ofloxacin, psyllium husk, hydroxypropyl methylcellulose, crosspovidone and gas generating agent. *In vitro* release showed an initial burst of drug ~ 35 % within 2 hours followed by sustained release over 22 hours.

Floating microcapsules have been developed for gastroretentive delivery of drugs (Atyabi et al., 1996). The microcapsules were based on ion-exchange resin comprising sodium bicarbonate and sodium pertechnetate as a model drug. The capsules were coated with Eudragit RS for retaining carbon dioxide. The microcapsules were evaluated in human volunteers and the uncoated microcapsules were used as control. The gastric retention of coated and uncoated microcapsules was compared and the results showed that the coated capsules could float on gastric fluid for longer duration than uncoated microcapsules.

A bilayered dosage form has been reported by Lohray et al., 2006. The dosage form comprised a spatial control layer and temporal control layer which helped for

floating and sustained release of drugs. The spatial control layer is based on low density polymer like ethylcellulose and other excipients. The drug was incorporated in the temporal layer of hydroxypropyl methylcellulose and other excipients. The incorporation of spatial layer reduced overall density of the dosage form and promoted floating.

The limitation of floating dosage form is the requirement of sufficient fluid in the stomach for longer time period. At the time of gastric emptying, the dosage form would pass through the opened pylorus along with food. Therefore, the fed state of stomach has to be maintained for longer time period. Also the patient has to maintain upright position during the treatment. These limitations call for new gastroretentive delivery systems which would perform better.

The pharmaceutical industry is one of the technology intensive industries wherein the products protected by patents are highly valued. A patent is a property right granted by a sovereign state to the inventor of a novel, non-obvious and useful invention. The owner of a patent has the right to exclude others from making, using, offering for sale, or selling his or her invention for a period of 20 years from the filing of the patent application. In the field of pharmaceutics, a product can be easily replicated by competitors with little investment. Since the investment in R & D is very high, the patenting of invention is the only way to get return on the investment. In the field of pharmaceutics, the patents have been filed to protect new drugs, polymers, composition of delivery systems, process, design of dosage forms, method of treating diseases etc. The patents owned by various pharmaceutical industries in the development of sustained, pulsatile and gastroretentive delivery systems are summarized in Table 1.7-1.9. The data summarized are illustrative rather than exhaustive.

Table 1.7. Patents in sustained release delivery systems

Patent Number	Title	Inventor(s)	Assignee
US 4,863,744	Intestine drug delivery	Hohn and Felix, 1989	Alza Corporation
US 4,968,508	Sustained release matrix	Peter and Werner, 1990	Eli Lilly and Company
US 5,422,123	Tablets with controlled-rate release of active substances	Ubaldo et al., 1995	Jagotec
WO 97/48386	Enteric coated diltiazem once-a-day formulation	Chen, 1997	Andrx Pharmaceuticals
US 5,945,125	Controlled release tablet	Kim, 1999	Temple University
US 6,274,173 B1	Oral pharmaceutical composition with delayed release of active ingredient for pantoprazole	George and Rango, 2001	BYK Gulden Lomberg Chemische Fabrik GmbH
WO 02/34240 A2	Delayed and sustained release formulations and method of use thereof	Mehta, 2002	-
EP 1043 976 B1	Oral pharmaceutical extended release dosage form	Karehill and Lundberg, 2005	Astra Zeneca
US 6,893,661 B1	Controlled release formulations using intelligent polymers	Isa and Amina, 2005	Biovail Corporation
WO 2007/052877 A1	An enteric coated sustained- release tablet comprising paroxetine	Kim and Song, 2007	GL Pharmtech Corporation

Table 1.8. Patents in pulsatile release delivery systems

Patent Number	Title	Inventor(s)	Assignee
US 5,017,381	Multi-unit pulsatile delivery system	Maruyama and Cortese, 1991	Alza Corporation
US 5,260,069	Pulsatile particles drug delivery system	Chih-Ming, 1993	Anda SR Pharmaceuticals Inc.
US 5318558	Osmotically driven delivery device with expandable orifice for pulsatile delivery effect	Linkwitz et al., 1994	Alza Corporation
US 5840329	Pulsatile drug delivery system	Bai, 1998	BioAdvances LLC
US 6217904 B1	Pharmaceutical dosage form for pulsatile delivery of d-threo-methylphenidate and a second CNS stimulant	Midha and Teicher, 2001	Pharmaquest Ltd.
US 6372254 B1	Press coated, pulsatile drug delivery system suitable for oral administration	Ting and Hsiao, 2002	Impax Pharmaceuticals Inc.
EP 0701437 B1	Multiparticulate pulsatile drug delivery system	Chih-Ming, 2002	Andrx Pharmaceuticals Inc.
US 6,632,451	Delayed total release two pulse gastrointestinal drug delivery system	Adel et al., 2003	Dexcel Pharma Technologies Ltd.
US 7048945 B2	Timed pulsatile drug delivery systems	Percel et al., 2006	Eurand Pharamaceuticals, Ltd.

Table 1.9. Patents in gastroretentive delivery systems

Patent Number	Title	Inventor(s)	Assignee
US 5002772	Gastric retention system for controlled drug release	Curatolo and Lo, 1991	Pfizer Inc.
US 5217712	Bioerodible thermoset elastomers	Pogany and Zentner, 1993	Merck & Co., Inc.
US 5582837	Alkyl-substituted cellulose-based sustained-release oral drug dosage forms	Shell, 1996	Depomed, Inc.
WO 0015198A1	Orally administered controlled drug delivery system providing temporal and spatial control	Talwar et al., 2000	Ranbaxy Laboratories Ltd.
US 6207197	Gastroretentive controlled release microspheres for improved drug delivery	Illum and Ping, 2001	West Pharmaceuticals…
US 6548083	Prolonged release active agent dosage form adapted for gastric retention	Wong et al. 2003	Alza Corporation
WO 2007093999A1	A gastro-retentive system for the delivery of macromolecules	Lapidot et al., 2007	Intec Pharma Ltd.
WO 2007089876A2	Preparation for gastric buoyant sustained drug release dosage form	Jiang, 2007	Anabolic Laboratories Inc.
WO 2007072495A2	Coated tablets having prolonged gastric retention	Dharmadhikari and Zala, 2007	Sun Pharmaceutical Industries Ltd.

1.14 Concluding remarks

The literature review presents the current efforts on the development of oral drug delivery systems. It revealed the need of designing new pH sensitive polymers for sustaining and / or targeting the delivery of drugs. The presently available enteric and reverse enteric polymers are random copolymers and dissolve rapidly at near neutral and acidic pH respectively. Hence, the utility of these polymers is limited in the development of sustained, pulsatile and gastroretentive dosage forms. Therefore, pH sensitive polymers of new architecture are needed.

In the present research work, we developed a new family of acidic and basic graft copolymers which swell and / or dissolve in the aqueous medium depending on the pH. The synthetic methodology has been chosen to control the structure and composition and hence the swelling / dissolution of polymers. The acidic graft copolymers have been formulated with drugs differing in solubility and other ingredients and fabricated to monolithic matrix and reservoir systems. *In vitro* release study of these dosage forms exhibited sustained and pulsatile release of drugs respectively. Similarly, the basic graft copolymers have been formulated with drugs those absorption limited to stomach and upper intestine along with other ingredients and fabricated to matrix tablets. *In vitro* release study of these tablets showed rapid swelling after floating. The release of drug occurred over an extended period of time from the tablets on floating. The influence of structure and composition of polymers and formulation variations on the release behavior of drugs has been investigated.

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Chapter 2

Objectives and Scope of Work

2.0 Objectives and scope of work

The present work focuses on the design, synthesis and evaluation of pH dependent graft copolymers for gastrointestinal delivery of drugs. The pH dependent random copolymers presently available dissolve rapidly and release the drugs. On the other hand, the pH sensitive hydrogels do not dissolve in solvents and hence they have limited processability. The graft copolymers exhibit unique behavior of swelling before they undergo dissolution in the aqueous medium. Such behavior can be exploited for the development of oral controlled release delivery systems. The present investigation has been undertaken with following objectives:

1. To synthesize acidic graft copolymers which swell / dissolve over an extended time period at near neutral pH while remaining in collapsed state at acidic pH. Such polymers would ensure minimal or no release of drugs at acidic pH prevalent in the stomach and release the same at near neutral pH prevalent in the intestinal region. This involves,

i. Synthesis of aliphatic unsaturated polyesters followed by grafting with acidic monomer at various levels. This approach would provide a wide range of possibilities to vary the structure and composition of graft copolymers.

ii. Screening of various unsaturated monomers for the preparation of unsaturated polyesters which would react better towards the acidic monomer. Optimization of reaction conditions to obtain better grafting efficiency.

iii. Physico-chemical and thermal characterization of polymers which include structure, composition, molecular weight, morphology and glass transition temperature by ^{1}H NMR and FTIR spectroscopy, Acid value estimation, GPC, XRD and DSC. This would help to screen the polymers for the preparation of drug delivery dosage forms.

iv. Analysis of pH dependent swelling / dissolution as well as change in morphology of the polymer. This would help to choose the polymer to achieve desired release profile.

2. To evaluate the acidic graft copolymers for sustained delivery of drugs differing in solubility. Sustained release dosage forms would reduce the frequency of dose administration, drug related toxicity and enhance the patient compliance. This involves,

i. The preparation of drug loaded polymer microparticles by spray drying technique. Spray dried microparticles are suitable to fabricate matrix tablets by direct compression method.

ii. Analysis of spray dried microparticles for drug-polymer interaction before and after treating with release medium. This would provide an insight to the stability of dosage form as well as release behavior of drug.

iii. Investigation of factors influencing the drug release which include the composition of polymer, drug loading, drug solubility and dimension of dosage form. This would help to design the formulation to achieve desired release profile.

iv. Understanding mechanism of drug release which would help to fine tune the release profiles and to explore the polymers for wide variety of drugs.

3. To evaluate the acidic graft copolymers for pulsatile delivery of drugs by fabricating the dosage form as a reservoir system. The pulsatile release dosage forms would be useful for the treatment of diseases which follow circadian rhythm and colon specific delivery of drugs. This involves,

i. Investigation of mechanical properties of polymer films under dry as well as wet conditions which would help to find the suitability of polymers as a rupturable film coat.

ii. Preparation of pulsatile release dosage form by film coating the tablets comprising drug and other ingredients.

iii. Investigation of factors influencing the drug release which include the composition of polymer, coating thickness, plasticizer content and the physico-chemical properties of drugs, *viz*., solubility and molecular weight

on the lag time of pulsatile release. This would help to design the formulation to achieve desired lag time of release.

iv. Understanding mechanism of pulsatile release by observing the film coated tablets on release by ESEM. This would help to extend the application of polymers for wide variety of drugs.

4. To synthesis basic graft copolymers which swell rapidly at acidic pH while remaining in collapsed state at near neutral pH. The rapid swelling of polymers would be exploited for the development of swellable floating tablets. Such tablets would remain in stomach for longer time period and release the drugs. This involves,

i. Synthesis of aliphatic unsaturated polyesters followed by grafting with basic monomer. Screening of basic monomers to obtain graft copolymers which would not absorb moisture during formulation and / or storage of dosage form.

ii. Characterization of polymers which includes structure, composition, molecular weight and glass transition temperature by ^{1}H NMR and FTIR spectroscopy, GPC and DSC. This would help to evaluate the suitability of polymers for the development of swellable floating tablets.

iii. Investigation of swelling / dissolution behavior of the polymers under acidic pH conditions. Ensuring of hydrophobicity of the polymers under near neutral pH conditions. This would help to screen the polymers for the development of swellable floating tablets.

5. To evaluate the basic graft copolymers for the development of swellable floating tablets. Such tablets would be retained in stomach for longer time and release the drug. This involves,

i. The preparation of tablets by incorporating drugs for which absorption limited to stomach and upper intestine.

ii. *In vitro* evaluation of tablets for floating, swelling and drug release behavior.

iii. Investigation of factors influencing the drug release which include the composition of polymer, the loading level and solubility of drugs. This would help to design the formulation to achieve desired release profile.

iv. Understanding mechanism of drug release from the swellable floating tablets.

Chapter 3

Acidic Graft Copolymers: Synthesis and Characterization

3.1 Introduction

Polymers play a vital role in the development of oral drug delivery systems. They have been used to sustain and / or target the delivery of drugs. The pH independent cellulosic polymers, poly (ethylene oxide) and poly (meth)acrylates are mostly investigated to modify the release of drugs (Apicella et al., 1993, Salsa et al., 1997 and Khan et al., 1999). These polymers undergo pH independent dissolution or erosion in the aqueous medium and release the drug throughout the gastrointestinal tract.

The introduction of new drugs and improved understanding of the pharmacokinetics of existing drugs has necessitated tailoring more precise release profiles. For example, the release of drugs should be suppressed in stomach either to protect the drug from acidic environment of stomach (Farinha et al., 2000, Sánchez-Lafuente et al., 2002 and Kovacs-Nolan and Mine, 2005) or to protect the stomach from drug induced inflammation (Torres et al., 1995). These drugs have been formulated by encapsulating them in enteric polymers.

Enteric polymers presently available are Eudragit® L100, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methyl cellulose acetate succinate and polyvinyl acetate phthalate. Although, these polymers are preventing the release of drug under acidic pH of stomach, they dissolve and release rapidly at near neutral pH of proximal intestine (Guo et al., 2002, Toorisaka et al., 2005, Silva et al., 2006 and Cerea et al., 2008). This behavior limits their utility in the development of controlled release dosage forms.

Enteric polymers have been evaluated as sustained release matrices in the past. The results showed that they could sustain the drug release when the drug and polymer ratio was 1:8 (Palmieri et al., 2000). Similarly, the enteric coated dosage forms do not delay the drug release beyond their gastric residence time and hence their utility in the development of pulsatile release dosage forms is limited. These reports reveal the requirement of new enteric polymers which sustain and / or delay the drug release in the intestinal region.

Acidic random copolymers dissolve rapidly at near neutral and basic pH. Reducing the content of acidic groups did not vary their dissolution rate. Instead, the critical pH at which the polymer dissolves shifts to a higher value. For example, Eudragit® L100 and Eudragit® S100 are the random copolymers of methyl methacrylate and methacrylic acid comprising 1:1 and 2:1 ratios respectively. While the Eudragit® L100 dissolves at pH ≥ 6.0, Eudragit® S100 dissolves at pH ≥ 7.0. Similarly, the methylation of carboxyl groups in Eudragit® S100 leads to increase in the critical pH at which the polymer dissolves (Peeters and Kinget, 1993). This shows that the enteric polymer with new architecture is required to achieve controlled swelling / dissolution at near neutral pH.

Graft copolymers exhibit different dissolution behavior compared with their linear analogs of similar composition. These polymers comprise a backbone on which graft chains are anchored. Hydrophilic chains can be anchored on hydrophobic backbone and vice versa. We synthesized a series of copolymers which comprise hydrophobic polyester backbone and methacrylic acid graft chains. The synthesis and characterization of acidic graft copolymers has been described in this chapter. The synthesis of graft copolymers involved in two steps. In the first step, the polyesters differing in unsaturation frequency were synthesized. In the second step, the unsaturated polyesters were grafted with methacrylic acid at various levels. The rationale behind the selection of this approach is that provides a route to vary, not only the methacrylic acid content but also the grafting frequency. This would help to modify the swelling / dissolution behavior of polymers at near neutral pH.

Polyesters were synthesized using four different unsaturated monomers, *viz*., fumaric acid, itaconic acid, allyl glycidyl ether and glycidyl methacrylate. The conversion of unsaturations as well as the incorporation of methacrylic acid was compared. The polyester comprising pendent vinyl groups showed better reactivity towards methacrylic acid and yielded the graft copolymers without free unsaturations. The synthesized polymers were characterized for structure, composition, molecular level interactions, glass transition temperature and swelling / dissolution behavior.

3.2 Experimental

3.2.1 Materials

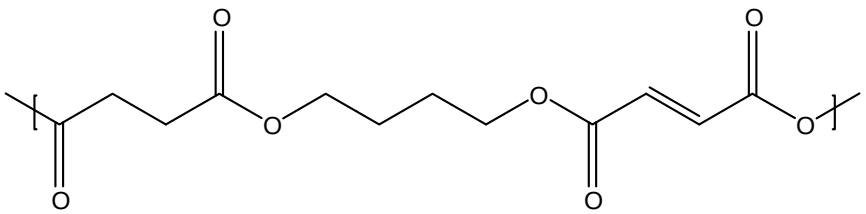
1,4 Butane diol (B), 1,4 Cyclohexane dimethanol (C), Bis (2-hydroxyethyl terephthalate) [(B)], Succinic acid (S), Adipic acid [(A)], Sebacic acid [(S)], Dodecandioic acid (D), Fumaric acid (F), Itaconic acid (I), Allyl glycidyl ether (A), Glycidyl methacrylate (G), Titanium (IV) butoxide and Methacrylic acid (MAA) were purchased from Sigma-Aldrich, St Louis, USA. Dimethyl formamide (DMF), Chloroform ($CHCl_3$), Methanol (CH_3OH) and Sodium hydroxide (NaOH) were purchased from Merck, India. Hydroquinone was purchased from s.d.fine-chem Ltd., India. Azobisisobutyronitrile (AIBN) was purchased from a local supplier.

3.2.2 Synthesis of unsaturated polyesters

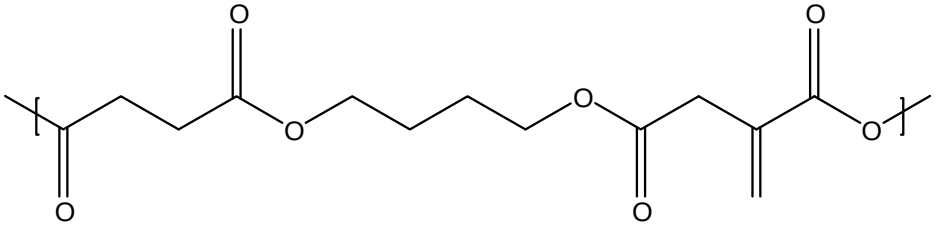
Unsaturated polyesters were synthesized by the bulk polymerization of diol, dicarboxylic acid and an unsaturated monomer. The reaction was carried out in a two neck round-bottom flask equipped with a nitrogen containing bladder and a water cooled condenser. The flask was charged with diol, dicarboxylic acid and an unsaturated monomer and then 1 wt. % of hydroquinone was added as an inhibitor to avoid the free radical polymerization of unsaturated monomer. The condensation polymerization was carried out at 165-170 ^oC using 0.1 wt % of titanium (IV) butoxide as a catalyst. The formed water during the reaction was distilled off continuously. After 6 hours, vacuum was applied for about 15 minutes in order to remove the trapped water from reaction mixture and the reaction was continued for further 4 hours. The polyester obtained was dissolved in chloroform and precipitated into cold methanol. The precipitate was filtered and washed with methanol repeatedly and was finally air dried at room temperature.

Structural representation

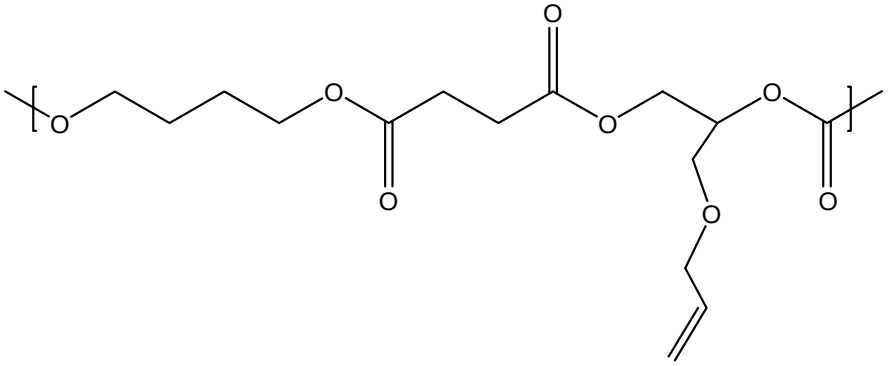
(A) Unsaturated polyesters comprising various types of unsaturation units



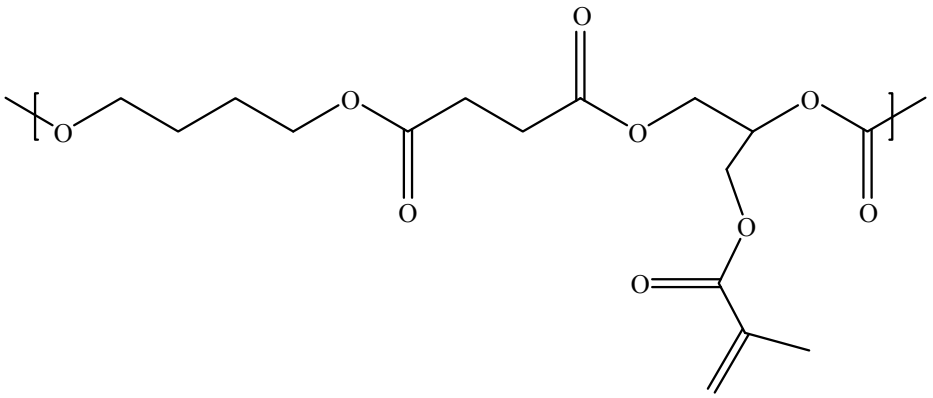
Poly (1,4 Butanediol - Succinic acid - Fumaric acid) (BSF)



Poly (1,4 Butanediol - Succinic acid - Itaconic acid) (BSI)

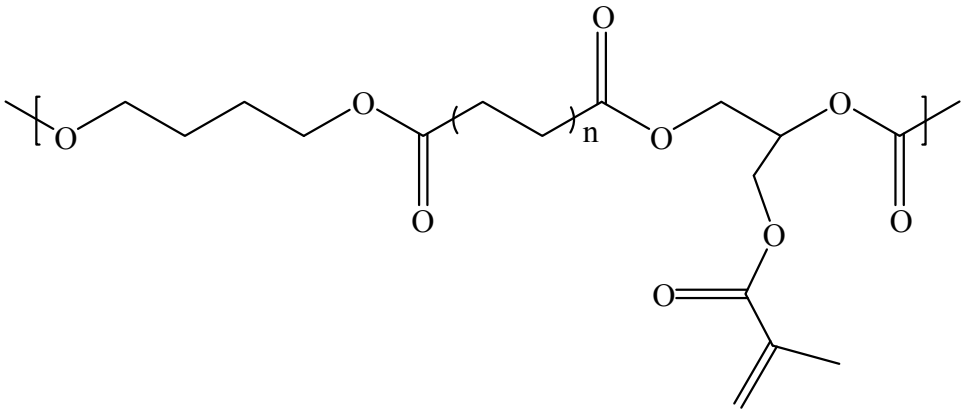


Poly (1,4 Butanediol - Succinic acid - Allyl glycidyl ether) (BSA)



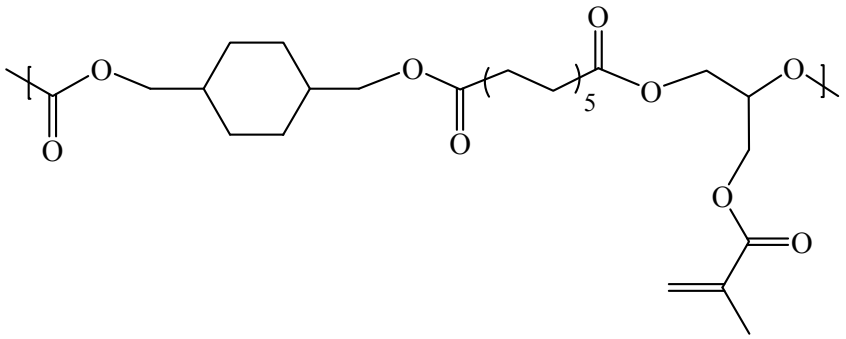
Poly (1,4 Butanediol - Succinic acid - Glycidyl methacrylate) (BSG)

(B) Unsaturated polyesters comprising various diols and dicarboxylic acids

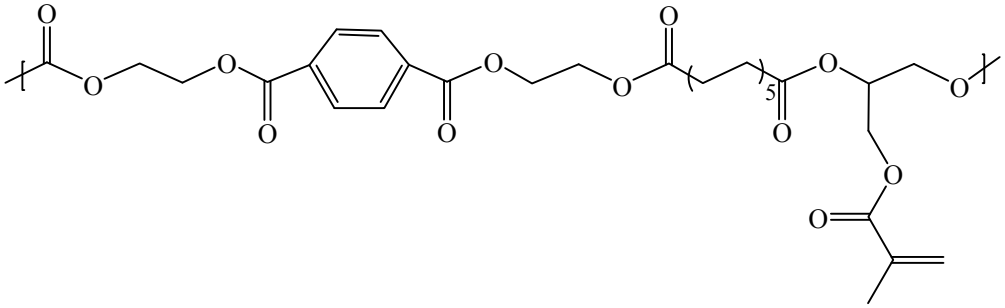


n = 1, Succinic acid (BSG); n = 2, Adipic acid [B(A)G];

n = 4, Sebacic acid [B(S)G] and n = 5, Dodecanedioic acid (BDG)



Poly (1, 4 Cyclohexane dimethanol- Dodecanedioic acid - Glycidyl methacrylate) (CDG)



Poly [Bis-(2- hydroxyethyl) terephthalate - Dodecanedioic acid - Glycidyl methacrylate] [(B)DG]

3.2.3 Synthesis of MAA grafted polyesters

MAA was grafted onto the unsaturated polyesters by free radical copolymerization. Typically, 1.0 g of unsaturated polyester and MAA were dissolved in 40 ml of DMF and purged with nitrogen gas for 15 minutes. The polymerization was carried out using 1 wt. % AIBN as a free radical initiator at 65 ^{o}C for 20 hours. The solvent was partially removed by rotary evaporator and then precipitated into cold water. The polymer obtained was reprecipitated from DMF into cold water to remove the unreacted monomer and MAA homopolymer. The purified polymers were dried under vacuum for 4 days at room temperature.

3.2.4 Characterization of unsaturated polyesters and graft copolymers

^{1}H NMR spectra were recorded on Bruker AV200 (200 MHZ) spectrometer, using $CDCl_3$ and DMSO-d_6 as solvents for unsaturated polyesters and graft copolymers respectively. Fourier Transform Infrared Spectra (FTIR) were recorded on Perkin-Elmer Spectrum One instrument in diffuse reflectance mode. Spectra were collected in the range 4000-400 cm^{-1} by cumulating 10 scans at a resolution of 4 cm^{-1}. The scan speed was set at 0.5 cm/s. Baseline correction was made for all spectra using Perkin-Elmer spectrum software. The molecular weight of unsaturated polyesters

was determined by Gel Permeation Chromatography (Thermo separation products, Spectra series AS300) using Styragel column and $CHCl_3$ as an eluting solvent at the rate of 1ml / min. Polystyrene (Polyscience) was used as standards.

Glass transition temperature of unsaturated polyesters and their graft copolymers was recorded on TA instruments DSC Q10 equipment using nitrogen as a purging gas. Sealed aluminium pan containing ~5 mg of sample was scanned from -80 to 180 ^oC at 10 ^oC / min. The wide angle X-ray diffraction (WAXD) pattern of representative unsaturated polyester and its graft copolymers were recorded on X-ray diffractometer (Rigaku Dmax 2500) equipped with copper target and a diffracted beam monochromator. The generator was operated at 40 kV and 100 mA. The samples were ground into fine powder and used for the measurements. The samples were scanned in 2θ range 5 to 50°.

3.2.5 Determination of grafting parameters

The MAA content of the graft copolymers was determined by acid value estimation. 0.050 g of polymer was dissolved in 20 ml of DMF and titrated against 0.1 N NaOH using phenolphthalein as an indicator. The MAA content of the graft copolymer was calculated using the following equation,

$$\text{Carboxyl group (MAA) content (moles / gram)} = [V \times N_{NaOH}] / [W \times 1000]$$

Where, V, N_{NaOH} and W represent the volume of NaOH consumed, the normality of NaOH solution and the weight of graft copolymer respectively. The grafting parameters, *viz*., weight percentage of MAA in the graft copolymer and grafting efficiency were calculated as follows.

$$\text{MAA in the graft copolymer (wt. \%)} = [(W_1 - W_0) / W_1] \times 100$$

$$\text{Grafting efficiency } (G_{E\,\%}) = [(W_1 - W_0) / W_2] \times 100$$

Where, W_0, W_1, and W_2 are the weight of unsaturated polyester, weight of graft copolymer and the weight of MAA in the feed respectively.

3.2.6 Preparation of polymer films

The polymer films were prepared by solution casting. The polymer solution was prepared by dissolving 0.200 g of polymer in 2 ml of $CHCl_3$ and CH_3OH mixture (7:3 v / v). The polymer solution obtained was poured in a petri dish and the solvent was evaporated. The resulting films were dried under vacuum for 3 to 4 days at room temperature. The thickness and diameter of the films were 200 μm and 2 cm respectively.

3.2.7 Determination of degree of swelling

The degree of swelling of polymer films was determined by placing them in phosphate buffer, pH 6.8. At regular interval the swollen films were removed and blotted with tissue paper to remove excess water in the surface and weighed. The degree of swelling (DS) of the films was calculated as follows.

$DS = [(W_s - W_d) / W_d] \times 100$

Where, W_s, W_d are the swollen and dry weight of the polymer films respectively.

3.2.8 Analysis of molecular interaction within the graft copolymer

The interaction between the polyester backbone and MAA graft chains was analyzed using FTIR spectroscopy. The unsaturated polyester, graft copolymer and the sodium salt of graft copolymer were characterized and the results compared. The sodium salt of graft copolymer was prepared by treating the polymer with 0.1 N NaOH. The volume of NaOH taken was such that the molar ratio between the carboxyl groups of graft copolymer and NaOH was 1:1. The solution of sodium salt of graft copolymer was freeze dried. The stability of polyester backbone in the sodium salt of graft copolymer was confirmed by ^1H NMR spectroscopy.

3.2.9 Morphology of polymer films

The surface morphology of polymer films was observed using environmental scanning electron microscope (ESEM, Quanta 200 3D, FEI). The films were immersed in 0.1 N HCl for the first 2 hours followed by phosphate buffer, pH 6.8. The films were withdrawn from the medium at predetermined interval and their surface morphology was observed by ESEM.

3.3 Results and discussion

Traditionally, the grafting of acrylic and methacrylic acid on natural polymers has been performed using benzoyl peroxide, potassium persulfate, ceric ion, redox initiators, γ-ray, electron beam irradiation and photolysis (Hebeish et al., 1998 and Toti and Aminabhavi, 2004). The grafting of monomer occurred randomly on the backbone and hence there was no control over the polymer architecture. The graft copolymer comprising hydrophilic backbone would swell in the acidic pH medium as well. Such graft copolymer is not suitable for enteric coating of dosage form to suppress the release of drugs under acidic pH conditions prevalent in the stomach.

We synthesized, a series of acidic copolymers comprising polyester backbone and methacrylic acid graft chains. The polyesters varying in unsaturation frequency were synthesized in the first step. This was achieved by keeping the diol constant and varying the chain length of dicarboxylic acid. Succinic acid, adipic acid, sebacic acid and dodecanedioic acid were used for this purpose. Also the hydrophobicity of the polyesters was varied by using aliphatic, cycloaliphatic and aromatic diol. The unsaturated polyesters synthesized were grafted with methacrylic acid at various levels. In the following sections, the choice of the polymer backbone, the effect of grafting on the physicochemical properties of the polymer, pH dependent swelling of the polymer and the morphological changes accompanying swelling of the polymers has been discussed.

3.3.1 Synthesis of unsaturated polyesters

Polyesters have been chosen as backbone of graft copolymer since they are known to be biocompatible. For instance, dibutyl sebacate is widely used as a plasticizer (Krogel and Bodmeier, 1999). Fumaric acid, itaconic acid, allyl glycidyl ether and glycidyl methacrylate were used to introduce unsaturation. The degree of unsaturation was limited to 6 to 7 mole percent to ensure that the polymers do not crosslink. As will be seen later, this level of unsaturation was adequate to ensure the desired level of grafting of MAA. ^{1}H NMR spectrum of representative unsaturated polyester BSG is shown in Figure 3.1.

Peaks at 6.11 and 5.61 ppm correspond to the unsaturation of glycidyl methacrylate. Peaks at 4.1 and 4.3 ppm correspond to methylene protons adjacent to the hydroxyl groups in 1, 4 butanediol (–O–C$\underline{H}_2$–CH_2–CH_2–C$\underline{H}_2$–O–) and ring opened glycidyl

methacrylate [–O–C<u>H</u>$_2$–CH(CH$_2$)–O–] respectively. Peak at 1.7 ppm corresponds to methylene protons of 1, 4 butanediol (–O–CH$_2$–C<u>H</u>$_2$–C<u>H</u>$_2$–CH$_2$–O–). Methylene protons of succinic acid [–(O=C) C<u>H</u>$_2$–C<u>H</u>$_2$ (C=O)–] appeared at 2.6 ppm. Peak at 5.3 ppm corresponds to the methine group of ring opened glycidyl methacrylate [–O–CH$_2$–C<u>H</u>(CH$_2$)–O–]. This confirms the incorporation of glycidyl methacrylate units in the polymer chain.

Esterification of diol and dicarboxylic acid liberated water. This induced the ring opening of epoxy group to form diol which then participated in esterification. The ratio between the peak integral value of vinyl protons (g, g′) and α-methyl protons (h) is 2:3, which confirmed that the unsaturation in glycidyl methacrylate did not undergo free radical polymerization during the synthesis of polyester. These results show that glycidyl methacrylate can be used to obtain polyesters containing pendent vinyl groups. As will be seen later, these groups are more effective in grafting of methacrylic acid as compared to vinyl groups in the main chain and allyl groups as pendent.

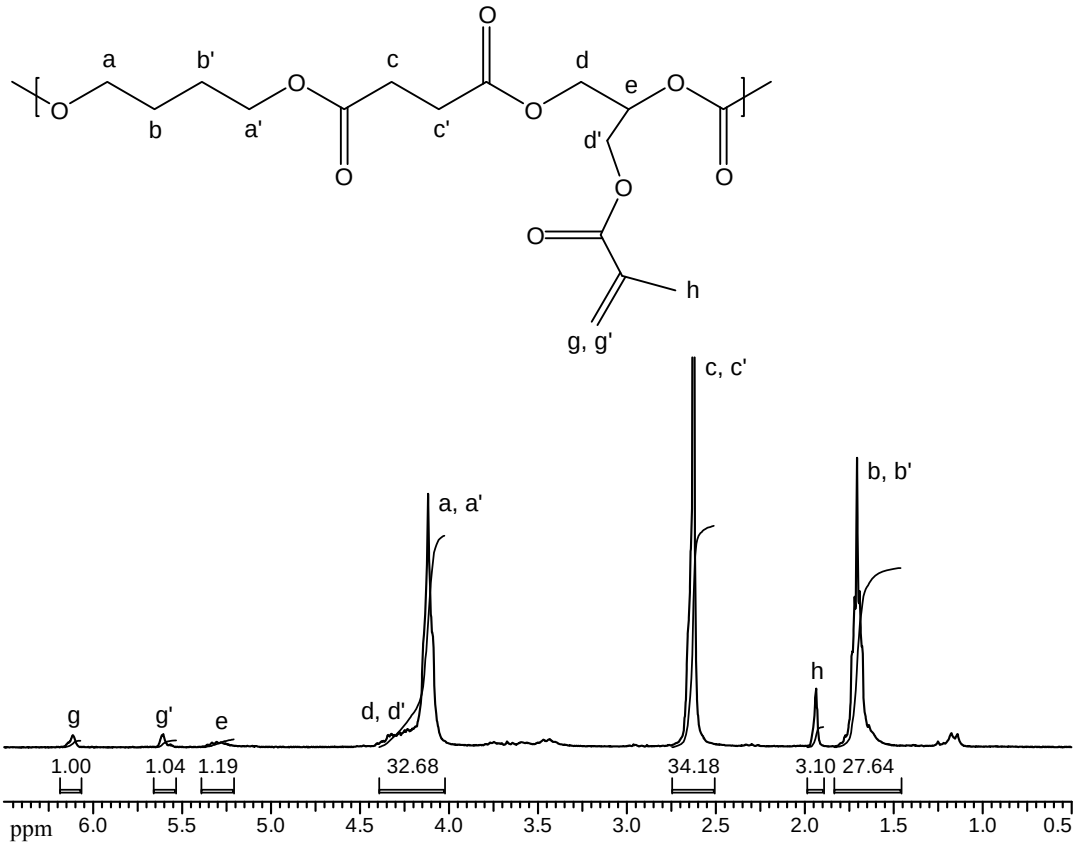


Figure 3.1. ^{1}H NMR spectrum of unsaturated polyester BSG

The molar composition of diol, dicarboxylic acid and unsaturated monomer in the polyesters was determined by peak integral value of ^{1}H NMR spectrum and the results are shown in Table 3.1. The molecular weight of unsaturated polyesters was determined by Gel Permeation Chromatography and was in the range 8500 - 12800 and the polydispersity index was 1.39 - 1.84 (Table 3.1).

Table 3.1. Composition, molecular weight and polydispersity of unsaturated polyesters

Polymers	Feed Composition (Mole ratio)	Polymer Composition (Mole Ratio)	M_w (g mol^{-1})	M_n (g mol^{-1})	M_w / M_n
BSF	50:43:07	48:46:06	8486	4658	1.82
BSI	50:40:10	49:45:06	9636	6338	1.52
BSA	41:50:09	45:49:06	10446	7462	1.39
BSG	38:50:12	42:52:06	9462	5840	1.62
B(A)G	37:50:13	45:49:06	10760	6467	1.66
B(S)G	35:50:15	40:53:07	9335	6112	1.52
BDG	35:50:15	41:52:07	10968	6834	1.60
CDG	35:50:15	42:51:07	12852	7650	1.68
(B)DG	38:50:12	41:52:07	11784	6382	1.84

3.3.2 Graft copolymerization of methacrylic acid

The graft copolymerization was carried out in DMF varying ratios of unsaturated polyesters and MAA in the feed. The polyester concentration was maintained at 1g / 20 ml. At higher concentrations the polymer gelled. The graft copolymers were characterized by ^{1}H NMR spectroscopy to estimate the conversion of unsaturation resulting from incorporation of fumaric acid, itaconic acid, allyl glycidyl ether and glycidyl methacrylate. The ^{1}H NMR Spectra of MAA grafted polyesters BSF, BSI,

BSA and BSG are shown in Figure 3.2. 50 weight % of MAA was used in the feed in all the cases.

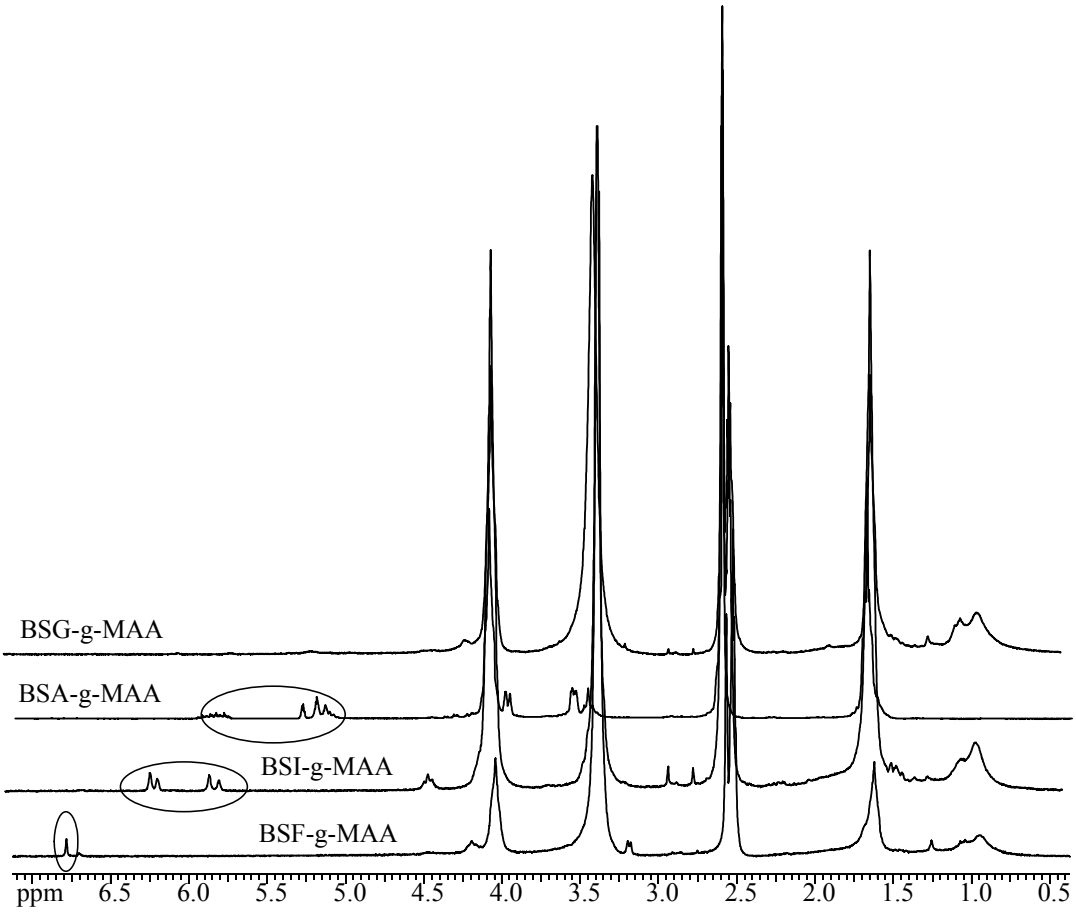


Figure 3.2. ^{1}H NMR Spectra of MAA grafted polyesters BSF, BSI, BSA and BSG

The unsaturations in polyesters containing fumaric acid, itaconic acid and allyl glycidyl ether were not completely utilized during the grafting of MAA. In the case of the polyester containing glycidyl methacrylate, the pendant vinyl unsaturation was completely utilized as evident from the ^{1}H NMR spectrum of MAA grafted BSG wherein the peaks corresponding to the unsaturations in the region 5.5 to 6.5 ppm were absent. Conversion of unsaturation for various polyesters during grafting of MAA at four levels is shown in Figure 3.3. In the range investigated the composition of MAA in feed did not influence the conversion of unsaturation significantly.

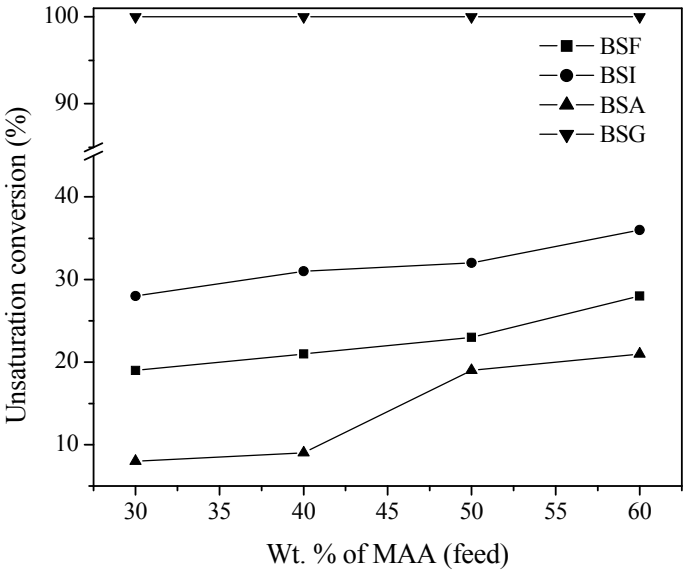


Figure 3.3. Effect of MAA content on the conversion of unsaturation

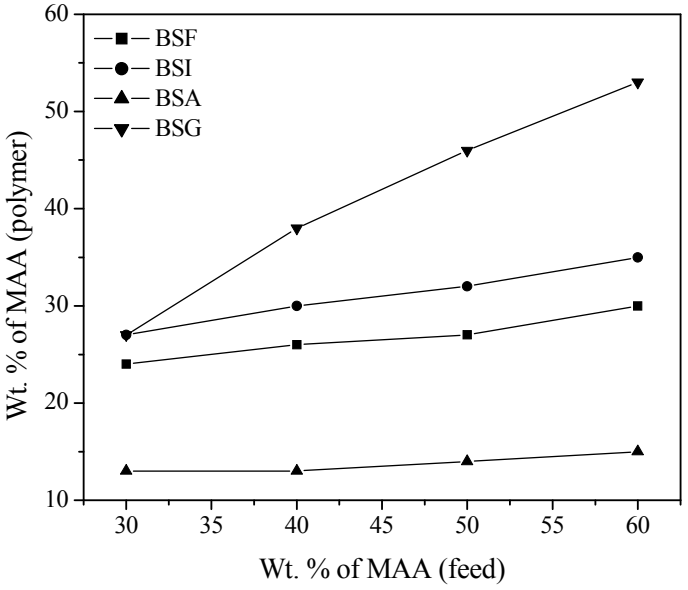


Figure 3.4. Effect of MAA wt. % in the feed on its level of grafting

The graft copolymers were analyzed for their MAA content. In the case of BSI, BSF and BSA the MAA content in feed did not influence wt. % in the graft copolymer significantly. However in the case of BSG, MAA wt. % in the graft copolymer increased steadily with its content in the feed (Figure 3.4).

Thus grafting on unsaturated polyesters BSF, BSI and BSA resulted in graft copolymers containing unreacted unsaturations and limited level of grafting of MAA. On the other hand, polyester comprising pendent vinyl groups as in BSG effectively reacted with MAA and yielded graft copolymers containing higher MAA content. Hence, subsequent investigations were carried out using the unsaturated polyesters comprising glycidyl methacrylate. Two serieses of unsaturated polyesters were prepared. In the first series the frequency of unsaturation along the polyester chain was varied. This was achieved by keeping the diol constant and varying the chain length of the dicarboxylic acid.

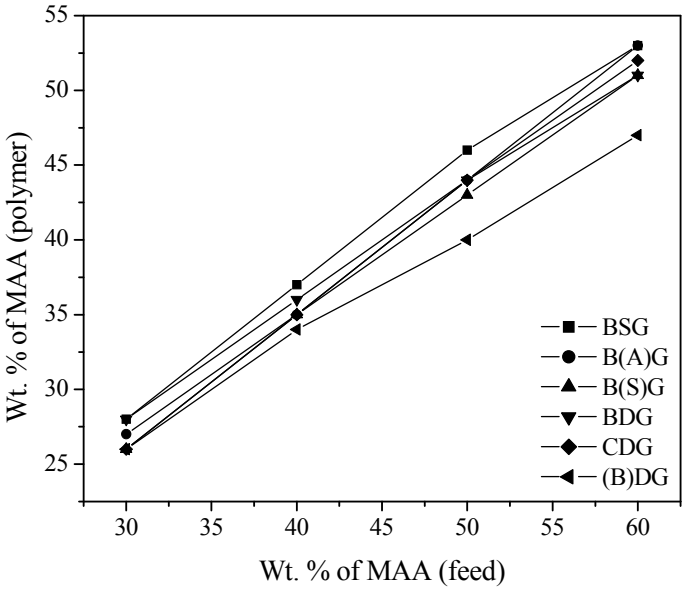


Figure 3.5. Weight % of MAA in feed and graft copolymers

In the second series the dicarboxylic acid was kept constant and a serious of hydrophobic diols was incorporated. The unsaturated polyesters so synthesized were grafted with MAA at various levels. The MAA content of graft copolymers was determined from acid value. The incorporation in the graft copolymers as function of feed composition is shown in Figure 3.5.

The effects of MAA wt. % in feed and the unsaturation content of polyester on the MAA grafting efficiency were studied. The polyester BDG comprising 7 mole % unsaturation was grafted in the presence of four different levels of MAA. The grafting efficiency decreased steadily with increasing MAA wt. % in feed. This can be attributed to increasing tendency to homopolymerization of MAA as the

availability of unsaturated groups in the polyester relative to MAA decreases (Figure 3.6a).

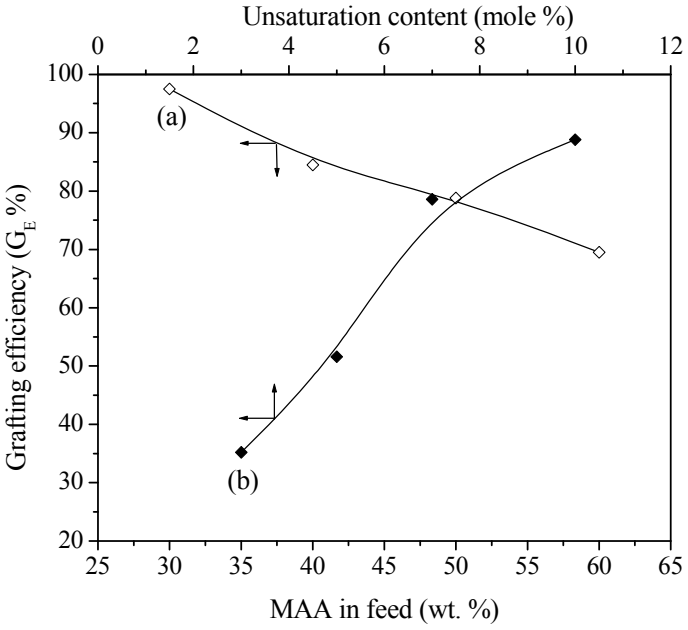


Figure 3.6. Factors influencing MAA grafting efficiency

Unsaturated polyesters of series BDG containing 3, 5, 10 mole % unsaturation were synthesized. These were grafted in the presence of 50 wt. % of MAA. The grafting efficiency increased with increasing unsaturation content of the polyester (Figure 3.6b). Thus higher grafting efficiency can be achieved by selecting the polyester containing higher level of unsaturation as well as MAA wt. % in the feed.

3.3.3 Molecular interactions in the graft copolymers: FTIR analysis

The FTIR spectra of unsaturated polyester BSG and its graft copolymers containing 28, 37, 46 and 53 wt. % MAA are shown in Figure 3.7. The bands at 1724 cm^{-1} and 1640 cm^{-1} correspond to the ester carbonyls and unsaturations in the polyester respectively. The disappearance of the band at 1640 cm^{-1} in the spectra of all graft copolymers of this series confirms complete utilization of unsaturation during grafting. The band at 1724 cm^{-1} shifted to 1717 cm^{-1} when MAA grafting exceeded 28 wt. %.

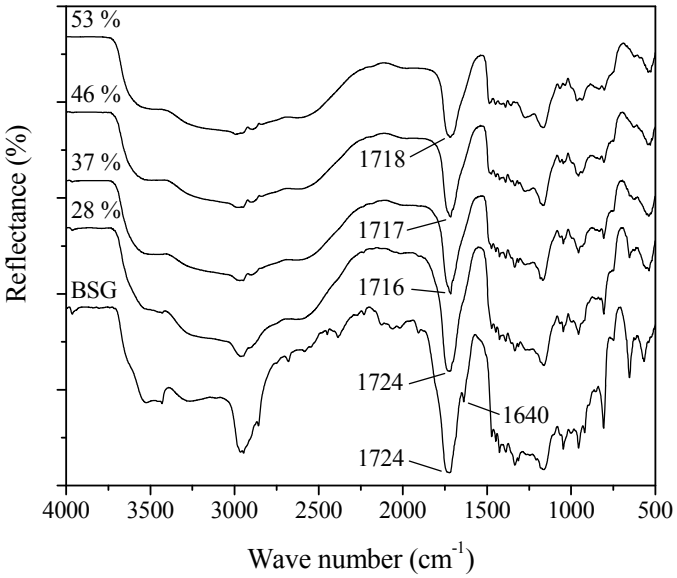


Figure 3.7. FTIR spectra of unsaturated polyester BSG and graft copolymers

The scale expanded spectra of these polymers are shown in Figure 3.8 which reveal the coexistence of three bands at 1736, 1717 (±1) and 1700 cm^{-1} attributed to the ester carbonyls of polyester, liberated and hydrogen bonded carbonyl groups in the MAA graft chains respectively. This indicates the destabilization of hydrogen bonded dimeric carboxylic acid groups within the graft chains and the formation of hydrogen bonds with carbonyls of polyester.

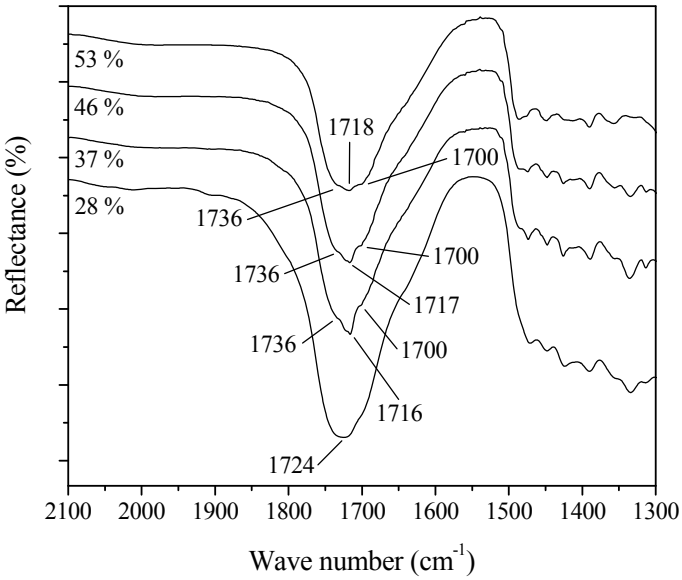


Figure 3.8. Scale expanded spectra of graft copolymers

The graft copolymer containing 28 wt. % of MAA retained the band position at 1724 cm^{-1}. This leads to the conclusion that the hydrogen bonding between the carboxyl groups of MAA graft chains and the ester carbonyls of polyester backbone does not occur below a critical MAA content in the graft copolymer. The mode of interaction between carboxyl and carbonyl groups has been reported in the past for the blend of styrene-co-methacrylic acid and styrene-co-vinyl pyrrolidone (Motzer et al., 2001). The hydrogen bonding interactions between the ester carbonyls and carboxylic acid groups have been reported in the past for copolymers of methyl methacrylate and methacrylic acid and its blend of stearic acid (Lin et al., 1995 and Sari et al., 2006).

The shift of ester carbonyl band of polyester from 1724 to 1736 cm^{-1} for the graft copolymers reveals the transformation of polyester from crystalline to amorphous phase on grafting with MAA. However the graft copolymer containing 28 wt. % MAA showed carbonyl band at 1724 cm^{-1} indicating that the crystallinity was retained. Similar observations have been reported in the past for poly (ε-caprolactone) which lost the crystallinity on the addition of tannic acid as a result of hydrogen bonding interactions between them (Yen et al., 2006).

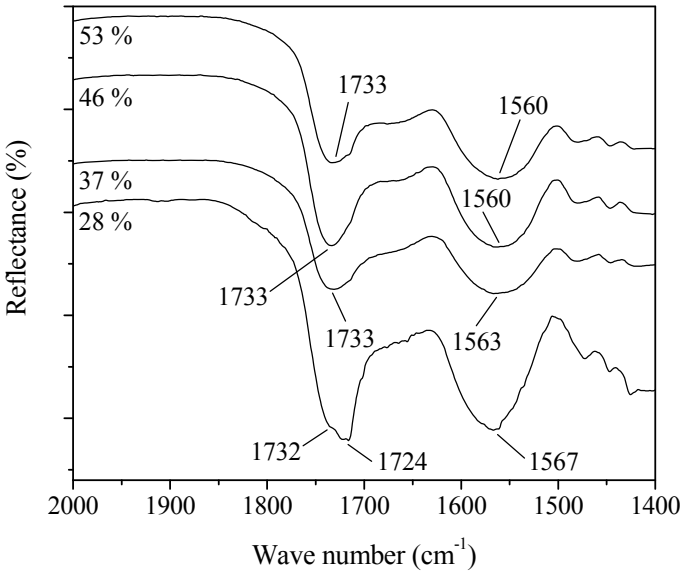


Figure 3.9. Scale expanded spectra of sodium salt of graft copolymers

The IR spectra of graft copolymers in their sodium salt form are shown in Figure 3.9. The bands which correspond to the liberated and hydrogen bonded carbonyls of

MAA graft chains at 1717 (±1) cm^{-1} and 1700 cm^{-1}, disappeared. The sodium carboxylate band appeared in the region 1560 cm^{-1} to 1567 cm^{-1}. In the case of graft copolymers containing 37-53 wt. % MAA, a single band for the ester carbonyls of polyester appeared at 1733 cm^{-1} which confirms the existence of only amorphous phase. As expected, the graft copolymer which contained 28 wt. % of MAA showed the band at 1724 cm^{-1} with a shoulder at 1733 cm^{-1} indicating the coexistence of crystalline and amorphous phase.

3.3.4 Wide angle X-ray diffraction analysis (WAXD)

X-ray diffraction analysis is frequently used to find the crystallinity of the polymers. It is known in the literature that the grafting of vinyl monomers on natural polymers resulted in decrease in the crystallinity. For instance, the crystallinity of maleoylchitosan reduced as a result of grafting of acrylic acid (Huang et al., 2006). Therefore, the change in crystallinity of unsaturated polyesters on grafting with MAA was studied. Diffractograms of unsaturated polyester BSG and MAA graft copolymers are shown in Figure 3.10.

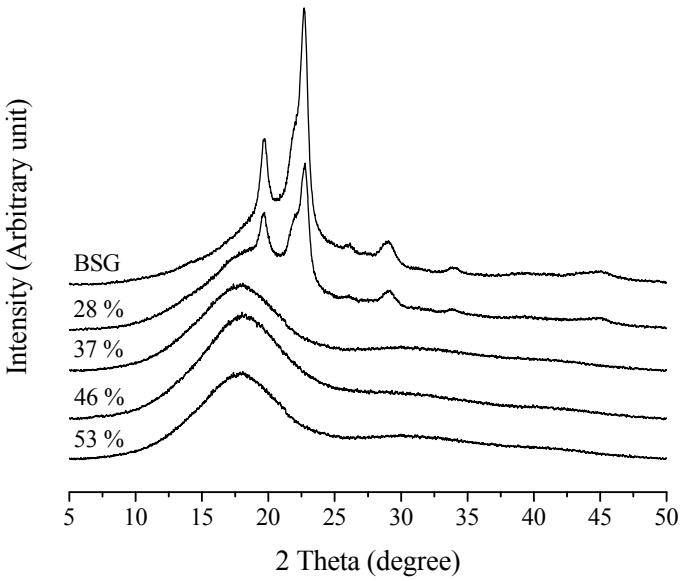


Figure 3.10. X-ray diffractograms of unsaturated polyester BSG and graft copolymers

The characteristic peaks appeared at 2θ values 19.73, 21.99 and 22.69 for (020), (021) and (110) plane respectively. These results are similar to those reported for poly (butylene-co-succinate) which has a monoclinic crystal lattice (Yoo and Im,

1999). Thus the pendent unsaturations in the polyester BSG did not influence the formation of monoclinic crystal structure. The diffractograms of graft copolymers containing more than 37 wt. % MAA indicate the absence of crystalline phase. However, the graft copolymer containing 28 wt. % of MAA exhibits the peaks at the same 2θ values as the unsaturated polyester BSG. This confirms that at lower level of MAA grafting the polyester retains its crystallinity and beyond a critical level turned amorphous. These findings substantiate the results derived from the FTIR analysis of polymers.

3.3.5 T_g of unsaturated polyesters and graft copolymers

The glassy polymers are suitable for the preparation of pharmaceutical formulations as they can be processed easily. The film forming property of polymers strongly depends on their T_g. Therefore, the unsaturated polyesters and graft copolymers were analyzed using differential scanning calorimetry. Thermograms of unsaturated polyester BSG and MAA graft copolymers are depicted in Figure 3.11.

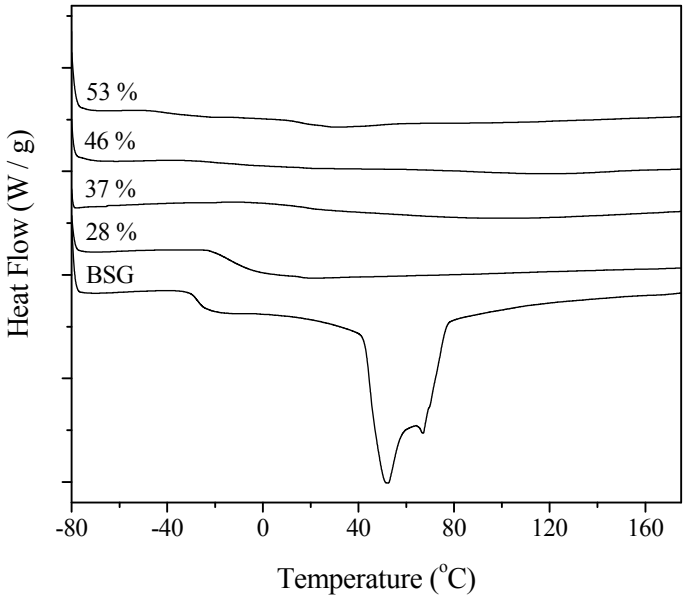


Figure 3.11. Thermograms of unsaturated polyester BSG and graft copolymers

The T_g value for BSG and graft copolymers containing 28 wt. % MAA were -27.7 and -14.72 ^oC respectively. On the other hand the graft copolymers containing higher levels of MAA did not show T_g upto 180 ^oC. Similar results were obtained for all the graft copolymers as shown in Table 3.2. As a result of hydrogen bonding the segmental motion responsible for T_g of polyester backbone was suppressed.

Heating was not continued beyond 180 ^{o}C as the carboxyl groups of poly (methacrylic acid) graft chains may undergo dehydration to form anhydride.

Table 3.2. T_g of unsaturated polyesters and their graft copolymers

Unsaturated Polyester	T_g (^{o}C)	Graft copolymers		Increase in T_g (^{o}C)
		MAA Content (wt. %)	T_g (^{o}C)	
BSG	- 27.70	28	- 14.72	12.98
B(A)G	- 32.61	27	- 23.61	8.72
B(S)G	- 10.02	26	0.42	10.44
BDG	- 27.56	28	- 22.54	5.02
CDG	- 34.93	26	- 25.37	9.56
(B)DG	- 22.45	26	- 14.42	8.03

3.3.6 Degree of swelling of graft copolymers

The random copolymers of methacrylic acid such as Eudragit® L100 and Eudragit® S100 dissolve rapidly under neutral and basic pH conditions without swelling. The hydrogels comprising methacrylic acid are crosslinked, glassy polymer networks. When exposed to the medium of neutral pH, these hydrogels swell as a result of the penetration of the medium and consequent ionization of carboxyl groups. The glassy phase turns to swollen rubbery phase through which the solute molecule diffuses out. Case II transport controlled release of solutes at constant rate has been well documented in the literature. As the medium penetrates, the glassy graft copolymer swells and then erodes or dissolves depending on the polymer composition.

To investigate the swelling behavior, the films of graft copolymers 2 mm in diameter and ~ 200 μm in thickness were prepared and exposed to phosphate buffer, pH 6.8. The ionization of carboxyl groups in the graft chains led to swelling followed by erosion or dissolution. The influence of grafting frequency on the swelling of the graft copolymers containing 35 ± 2 wt. % MAA is shown in Figure 3.12a. The rate of swelling of the polymers decreased with decrease in grafting frequency of MAA chains along the polyester backbone. The rate of swelling

increased with MAA content (Figure 3.12b). This could be attributed to the ionization of the MAA graft in the near neutral pH medium.

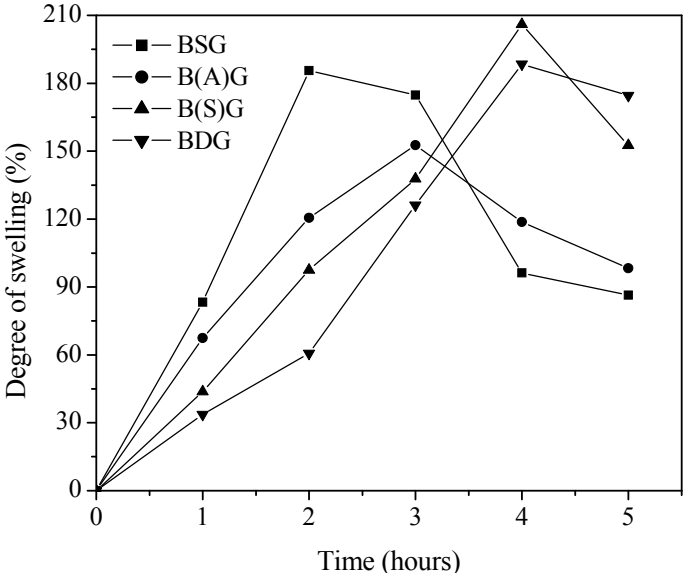


Figure 3.12a. Effect of grafting frequency on degree of swelling of graft copolymers

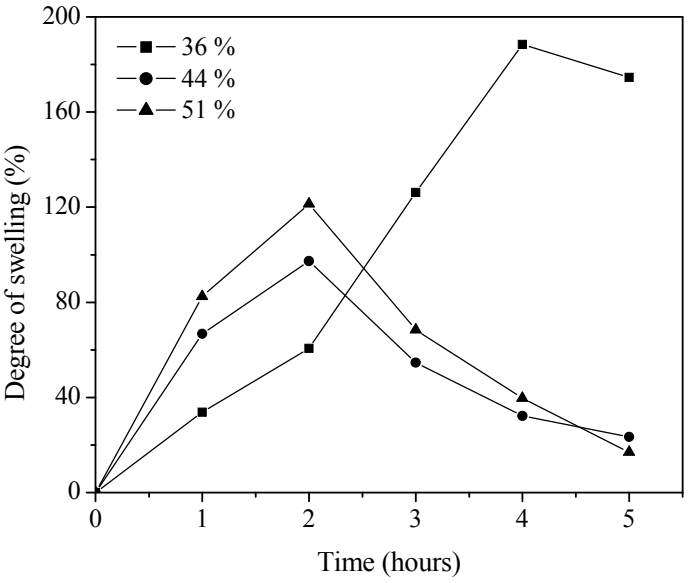


Figure 3.12b. Effect of MAA content on degree of swelling of graft copolymers

The penetration of medium into polymers bearing lower grafting frequency, *viz*., B(S)G-g-MAA and BDG-g-MAA, results in two moving boundaries. As the medium penetrates, the boundary separating the glassy and swollen layer moves inward and leaves behind the swollen layer, which may erode or dissolve depending on the hydrophobicity of the polymer backbone and the MAA content. Initially, the rate of penetration of medium is higher than the rate of erosion of polymer. Hence,

the degree of swelling increases with time. However, as the erosion proceeds, degree of swelling as measured by weight gain decreases with time.

In the case of polymers such as BSG-g-MAA and BAG-g-MAA, the penetration velocity of the medium was higher and the polymers attained maximum swelling within 2 to 3 hours. However, this rapid swelling was followed by the dissolution of the swollen layer. As a result, the maximum swelling attained was lower than the value for the hydrophobic polymers cited above. Unlike in the case of hydrogels, the maximum swelling was not the equilibrium swelling. This was also true for BDG-g-MAA polymers containing 44 and 51 % MAA.

3.3.7 Morphological changes during swelling / dissolution of polymers

Random copolymers of MAA such as Eudragit® L100 and Eudragit® S100 undergo ionization and immediate dissolution at pH > 5.5. The graft copolymers can be tailored as to undergo swelling / dissolution over an extended time period (Figures 3.12a and b) Thus in principle, the polymers could be used as enteric coating and also release the drug over extended time period. The swelling of the polymers also revealed disintegration prior to dissolution which might also have a bearing on the release characteristics of these polymers. We therefore examined swelling in more detail using ESEM.

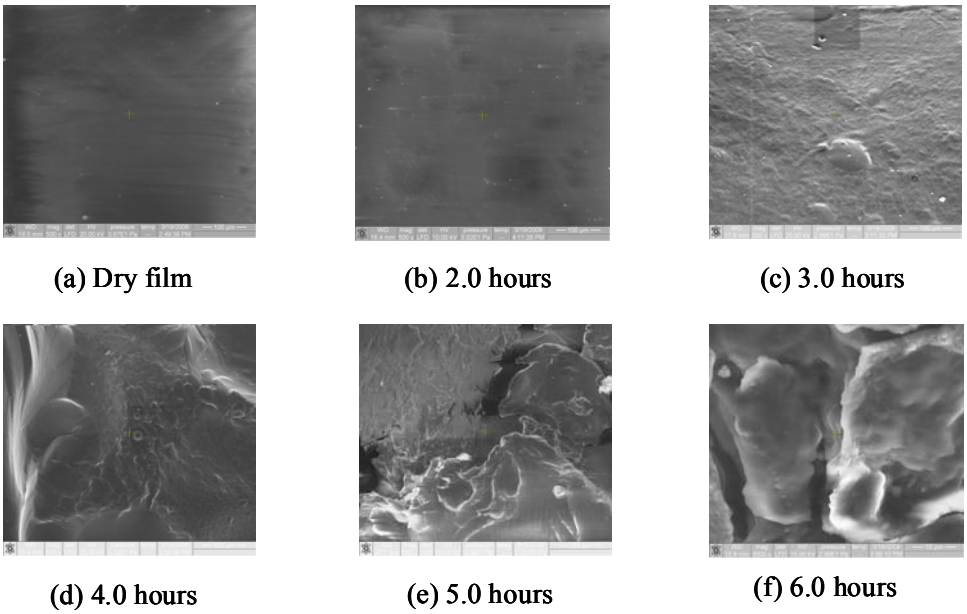


Figure 3.13. Surface morphology of the graft copolymer films: In 0.1 N HCl for 2 hours followed by phosphate buffer, pH 6.8

The morphological changes accompanying swelling of the graft copolymer BDG containing 37 wt. % MAA are shown in Figure 3.13. It is observed that during exposure to 0.1 N HCl there is no change in the surface morphology of the polymer film. On exposure to the phosphate buffer of pH 6.8, swelling of the polymer film is initiated as seen by the formation of uneven surface. With increasing time of exposure, the formation of cracks leading to rupture was noted.

It has been shown in the past that film coatings which exhibit crack formation and rupture can be exploited for the pulsatile delivery of drugs (Krögel and Bodmeier 1993, Bussemer et al., 2003 and Sungthongjeen et al., 2004). We therefore investigated the release of (a) highly water soluble drug diltiazem hydrochloride, (b) water insoluble drug indomethacin and (c) a macromolecular marker, *viz*., FITC - dextran 4000 from the graft copolymer coated reservoir tablets. The results are discussed in chapter 5.

3.4 Conclusions

A series of pH sensitive polyester-g-methacrylic acid polymers have been synthesized and characterized. Among the various unsaturated polyesters, the one which comprised pendent vinyl groups was suitable for the preparation of graft copolymers. The graft copolymers swelled and / or dissolved under near neutral pH conditions prevalent in the intestinal region and remained in collapsed state under acidic pH conditions prevalent in the stomach. The rate of swelling / dissolution depended on the polymer composition. The graft copolymers would serve as enteric coatings as well as sustained release matrices for drugs. The graft copolymer films were intact at acidic pH and then underwent swelling, rupturing followed by dissolution at near neutral pH as observed by Environmental Scanning Electron Microscope. The rupture behavior of polymer films can be exploited to achieve pulsatile delivery of drugs. The graft copolymers synthesized were evaluated for sustained and pulsatile delivery of drugs by designing the dosage form as matrix and reservoir systems and the results are described in chapters 4 and 5 respectively.

3.5 References

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Chapter 4

pH Dependent Sustained Release of Drugs: *In vitro* Evaluation

4.1 Introduction

Controlled delivery of drugs reduces the frequency of dose administration, eliminates under and overdosing, reduces toxicity, enhances bioavailability and patient compliance (Martín del Valle et al., 2009). Physico-chemical properties of drugs, *viz*., solubility, ionic nature and stability in gastric fluid, play a critical role in the design of sustained release drug delivery systems.

Kim and Fassihi, 1997 reported that pH independent hydrophilic polymers do not offer much control over the release of highly soluble drugs especially at higher loading. Diltiazem hydrochloride is a highly water soluble drug used to treat hypertension and angina. To reduce the frequency of administration from three to four times a day, once a day dosage forms have been developed. Cardizem CD™ consists of diltiazem hydrochloride particles coated with ethylcellulose. Dilacor XR™, contains 3 or 4 tablets placed in a capsule. The tablets comprise hydrophilic matrices each loaded with 60 mg of diltiazem hydrochloride. Barrier layers are coated on the matrix to limit the hydration of the core and release the drug in a sustained manner. These tablets have been prepared using multiple polymers and specialized tablet making machines by Geomatrix® technology (Wilding et al., 1995). A simple matrix tablet involving single polymer is obviously desirable for the ease of manufacture.

The release of water insoluble drugs by diffusion from hydrophilic polymer matrices is hindered and incomplete. Erodible polymer like polyethylene oxide has been used for the sustained release of poorly soluble drugs such as theophylline, sulfathiazole and salicylic acid at constant rate as a result of swelling / erosion of the matrix (Kim 1998). The solubility of weakly basic drugs decreases rapidly with increasing pH and poses a challenge for the design of diffusion controlled dosage forms for sustained release over gastrointestinal tract. The cellulosic polymers are blended with an enteric polymer to suppress the release of weakly basic drugs at acidic pH and to enhance the release at neutral pH (Goracinova et al., 1996, Yüksel et al., 1996, Dimitrov and Lambov, 1999 and Dashevsky et al., 2004). Alternately, organic acids are incorporated in the matrix to provide an acidic microenvironment. This enhances the solubility of the drug and release by diffusion (Kohri et al., 1991 and

Thoma and Ziegler, 1998). However, the loadings required are often very high and limit the dose rate that can be delivered (Dashevsky et al., 2004).

The polymers which swell and / or slowly dissolve at near neutral pH and remain in collapsed state at acidic pH would be useful for sustained delivery of drugs in intestinal region. This can not be achieved by hydrophobic modification of enteric polymers. Methylation of Eudragit® S100 leads to increase in threshold pH at which the polymer dissolves. The dissolution is complete within two hours. Caffeine was released from a methylated Eudragit® S100 film of acid value 90 after a time lag of two hours and over a period of four hours. Clearly, such polymers would not be useful for delivery of drugs over extended time periods across the gastrointestinal tract (Peeters and Kinget 2001). Hence new architectures are needed.

We developed a series of copolymers comprising an aliphatic polyester backbone and methacrylic acid graft. The synthesis and characterization of polymers have been described in chapter 3. In this chapter, the development of sustained release drug delivery system based on the pH sensitive graft copolymer has been described. These polymers swelled / dissolved at near neutral pH but collapsed at acidic pH.

Matrix tablets were made by compressing spray dried microparticles. *In vitro* release study showed that diltiazem hydrochloride was released over 18 hours and more. The release of indomethacin and verapamil hydrochloride was controlled by erosion / dissolution of matrix. In all cases the release rate was constant. The effect of swelling / dissolution of polymer, drug loading, drug solubility and tablet configuration on the release was investigated to elucidate the release mechanism. The polymers will find applications in the design of once a day dosage form of highly soluble, poorly soluble as well as weakly basic drugs.

4.2 Experimental

4.2.1 Materials

Chloroform ($CHCl_3$), Methanol (CH_3OH), Cyclohexane, Potassium chloride and n-Dibutyl phthalate (DBP) were purchased from Merck, India. Span 80 was purchased from s.d.fine-chem Ltd., India. Diltiazem hydrochloride (DH) and Verapamil hydrochloride (VH) are the gift samples from Lupin Laboratories Ltd., India. Indomethacin (IM) was purchased from Fluka chemicals, Germany.

4.2.2 Synthesis of MAA grafted polyesters

The synthesis of graft copolymers involved two steps. In the first step, unsaturated polyesters were synthesized using diol, dicarboxylic acid and glycidyl methacrylate by melt polycondensation. The frequency of unsaturation in the polyester was varied by keeping the diol and glycidyl methacrylate constant and varying the chain length of dicarboxylic acid. Succinic acid, adipic acid, sebacic acid and dodecanedioic acid were used for this purpose. In the second step, methacrylic acid was grafted on to the unsaturated polyesters at various levels. The detailed synthesis procedure and physico-chemical properties of graft copolymers have been described in chapter 3.

The polymers evaluated for sustained delivery of drug are given below.

(a) Poly [(1, 4 Butane diol - Succinic acid - Glycidyl methacrylate) - g - (MAA)]; BSG-g-MAA (MAA content: 37 and 53 wt. %)

(b) Poly [(1, 4 Butane diol - Adipic acid - Glycidyl methacrylate) - g - (MAA)]; BAG-g-MAA (MAA content: 35 wt. %)

(c) Poly [(1, 4 Butane diol - Sebacic acid - Glycidyl methacrylate) - g - (MAA)]; B(S)G-g-MAA (MAA content: 35 wt. %)

(d) Poly [(1, 4 Butane diol - Dodecanedioic - Glycidyl methacrylate) - g - (MAA)]; BDG-g-MAA (MAA content: 36, 44 and 51 wt. %)

4.2.3 Preparation of microparticles by spray drying

Microparticles were produced in a laboratory mini spray drier (Model: LSD-48 Mini spray drier, Jay Instrumentations & Systems Pvt. Ltd., Mumbai, India). Typically, the graft copolymer and drug were dissolved in $CHCl_3$ and CH_3OH mixture (6:4 v/v) to obtain 10 % w/v solution. The solution was spray dried to obtain microparticles. The experimental parameters were as follows. The feed rate was 2 ml/min. The inlet temperature was set at 60 ^oC which gave outlet temperature of 42 $\pm$ 0.2 ^oC. The nozzle diameter of 0.7 mm was used throughout all the experiments to introduce droplets. The hot compressed air aspirated by pump caused fast evaporation of solvent from droplets and the formation of solid microparticles. The microparticles were cooled to room temperature and then deposited into a product

container by a cyclone. The microparticles were dried under vacuum for 7 days at room temperature.

4.2.4 Analysis of particle size and surface morphology

The mean particle diameter was determined using PSS NICOMP 380 particle sizer. Typically, 5 mg of microparticles were suspended in 5 ml of cyclohexane using Span 80 as a stabilizer. Cyclohexane was used as a medium as the both polymer and drug do not dissolve. The suspension obtained was sonicated for 15 seconds and then particle size was measured at 30 ^{o}C. The surface morphology of microparticles was observed by Environmental Scanning Electron Microscope (ESEM).

4.2.5 Determination of drug content: Assay

10 mg of microparticles were accurately weighed and added into 10 ml of phosphate buffer solution, pH 6.8. The content was sonicated for 2 minutes and kept for a day. The solution was centrifuged and 0.2 ml of supernatant was removed and diluted appropriately. The drug concentration was determined by UV spectrophotometer (Shimadzu, UV-1061PC) at 237, 320 and 298 nm for DH, IM and VH respectively.

4.2.6 Drug-polymer interaction studies

4.2.6.1 FTIR analysis

DH and VH loaded BSG-g-MAA (MAA content: 53 wt. %) microparticles were analyzed by Fourier Transform Infrared Spectrometer (FTIR, Perkin-Elmer Spectrum One instrument) in diffuse reflectance mode. Spectra were collected in the range 4000-400 cm^{-1} by cumulating 10 scans at a resolution of 4 cm^{-1}. The scan speed was set at 0.5 cm/s. Baseline correction was made for all spectra using Perkin-Elmer spectrum software. The same microparticles were treated with phosphate buffer solution, pH 6.8 and then freeze dried. The freeze dried microparticles were characterized by FTIR.

4.2.6.2 Turbidity measurement

Turbidity of drug-polymer complex solutions was measured in terms of transmittance using UV spectrophotometer at 27 ^{o}C. The measurements were carried out at 600 nm where the drug and polymer did not show any characteristic absorption. The graft copolymer solution was prepared by adding 0.500 g of BSG-g-MAA containing 53 wt. % of MAA (equivalent to 3.07×10^{-03} moles of carboxyl

groups) in 130 ml of phosphate buffer solution, pH 6.8. The solution was sonicated for 5 minutes and then filtered. Separately, 1.388 g (equivalent to the moles of carboxylic groups present in the polymer) of DH was dissolved in 130 ml of said buffer solution. The selected concentration of polymer and drug solutions would provide the UV absorbance < 1 nm while mixing the individual solution. The solutions were mixed in different ratios by adding drug solution into the polymer solution. The UV absorbance of solutions was measured and the results were converted into % transmittance. The measurement was repeated after the addition of 50 mg of potassium chloride.

4.2.7 Preparation of matrix tablets

Monolithic matrix tablets were prepared by compressing 200 mg of drug loaded microparticles and 25 mg of binder hydroxypropyl methylcellulose (5 Cps). Thoroughly mixed mass was compressed into tablet by applying the load of 200 kg / cm^2 using a hydraulic press equipped with 8 mm die and flat faced punch. Other ingredients were not incorporated to avoid their influence on the release of drugs. The matrices of higher thickness were prepared using higher amount of microparticles and binder mixture. The enteric coating was evaluated by applying a coat of graft copolymer on the matrices. The coating solution was prepared in $CHCl_3$ and CH_3OH mixture (6:4 v/v). To this solution, DBP was added as a plasticizer at the level of 5 % and then tablets were dip coated. The coated tablets were air dried at room temperature.

4.2.8 *In vitro* release study

In vitro drug release study was carried out in 900 ml of phosphate buffer solution, pH 6.8 by paddle method using Electrolab USP type II apparatus. The paddle rotation speed was 50 rpm and the temperature was maintained at 37 ± 0.5 ^oC. The enteric property of graft copolymer was studied in 0.1 N HCl for the first two hours followed by phosphate buffer solution, pH 6.8. At the predetermined time interval, a known volume of dissolution medium was withdrawn and analyzed for drug concentration by UV spectrophotometer.

4.2.9 Determination of erosion and dissolution of matrices

The amount of erosion and dissolution of matrix on drug release was studied in USP dissolution apparatus and the conditions were identical as maintained for drug

release study. At regular intervals of time, the tablets were removed and dried at 60 ^{o}C until constant weight was reached. By taking into account of the drug released, the loss in weight of polymer matrix was calculated.

4.3 Results and discussion

The release of drugs from monolithic matrices of hydrophilic polymers could be controlled by diffusion, erosion or dissolution depending upon the solubility and diffusivity of the drug and the swelling / dissolution behavior of the polymer. Design of sustained release matrix dosage forms for highly soluble, poorly soluble and weakly basic drugs pose own challenges as described earlier. Enteric polymers have been developed to protect the drugs during gastric passage and release in the intestine. pH sensitive hydrogels have been investigated extensively to sustain drug release in intestine (Shin et al., 1997 and Basan et al., 2002). However, these necessitate intricate drug loading methods not readily amenable to mass production. Further the processability of the hydrogels is limited as they are insoluble in solvents (Shin et al., 1997 and Sipahigil et al., 2006).

We developed a series of graft copolymers comprising aliphatic polyester backbone and methacrylic acid graft which swell / dissolve at near neutral pH and collapse at acidic pH. These polymers release the drug over an extended time period at near neutral pH. Sustained release of highly soluble drug diltiazem hydrochloride can be achieved by encapsulating it in swellable polymers. The polymers which undergo slow dissolution are suitable for the release of poorly soluble drug indomethacin and weakly basic verapamil hydrochloride. In the following sections we evaluate the factors influencing the release of drugs such as the swelling / dissolution behavior of polymers, drug loading, drug solubility and tablet configuration and explain the results obtained based on the mechanism governing the drug release in each case.

4.3.1 Preparation of drug loaded microparticles

Monolithic matrices can be made by the direct compression of drug, polymer and other excipients. However, this does not provide uniform mixing and the drug is present in the dispersed state. The compression of microparticles results in matrices, wherein the drug is uniformly distributed. The merits of the latter approach have been discussed by Palmieri et al., 2000.

Spray drying is the most widely used technique for making microparticles. The conditions for spray drying were optimized to maximize yield and prevent agglomeration. The mean particle diameter and recovery were in the range 3.5-5 μm and 40-50 % respectively. Since spray drying was carried out on a small scale, the recovery was low. The results show that the polymer composition, the nature of drug and its loading level did not influence the microparticle size and recovery. The drug content in feed and in microparticles was practically same indicating that the efficiency of drug encapsulation was close to 100 %. The morphology observed by ESEM revealed that the microparticles were not agglomerated (Figure 4.1).

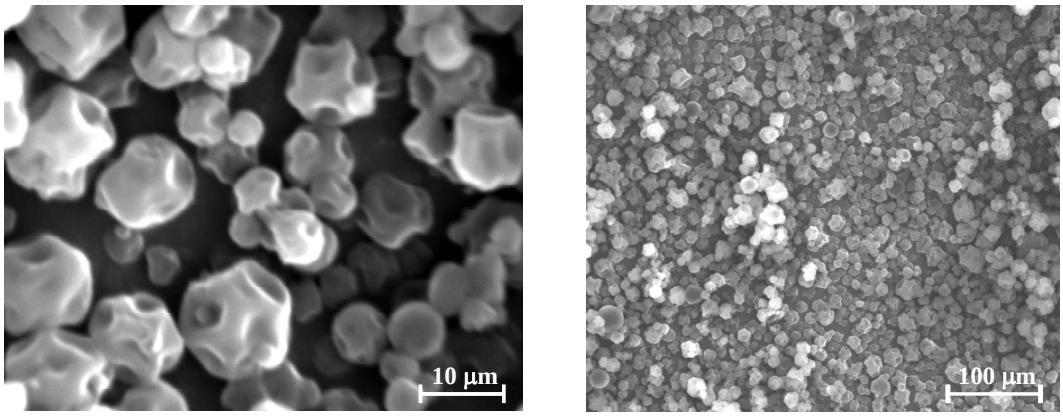

Figure 4.1. Surface morphology: DH loaded BDG-g-MAA (MAA content: 36 wt. %) microparticles

4.3.2 Drug-polymer interaction

The drug-polymer interaction plays a vital role in the performance of delivery systems. The interactions could range from complex formation, hydrogen bonding to van der waal interactions. The formation of complex on mixing the solution of cationic drug and polymer containing carboxylate or sulfonate groups is well known in the literature (Konar and Kim, 1999, Takka, 2003 and Rigo et al., 2004). Drug is released at constant rate from such system over extended time periods (Konar and Kim, 1999 and Cornejo-Bravo et al., 2005).

The imbibition of diltiazem hydrochloride by methacrylic acid based hydrogel was higher when carboxyl groups were ionized. This has been attributed to the

interaction between the drug and the polymer (Sousa et al., 2005). Bettini et al., 1995 reported that the rate of metoclopramide release decreased with increasing methacrylic acid content of poly (2 - hydroxyethyl methacrylate-co-methacrylic acid) as a result of extensive interaction between the drug and the polymer. In the present investigation, the graft copolymer contains carboxyl groups and hence interaction with cationic DH and VH is to be expected.

4.3.2.1 FTIR analysis

FTIR spectra of the graft copolymer BSG-g-MAA (MAA content 53 wt. %) microparticles containing 20 % DH and VH before and after treatment with phosphate buffer, pH 6.8 are shown in Figures 4.2 and 4.3 respectively. No interaction between the drug and the polymer is observed in the microparticles. This is evident from the fact that characteristic band positions of DH and VH are retained. In the case of buffer treated microparticles, the ionic interaction between the tertiary amine group of the drug and ionized carboxyl group of polymer resulted in the appearance of characteristic band of amine salt at 1550 and 1555 cm^{-1} for DH and VH respectively.

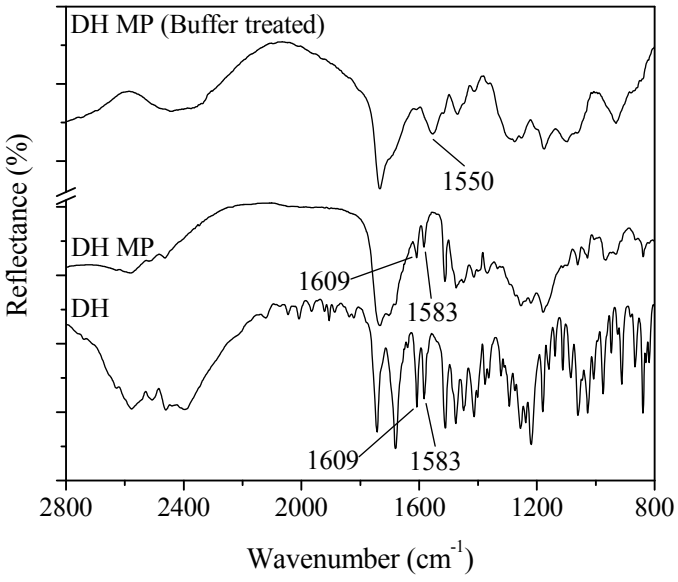

Figure 4.2. FTIR spectra (i) DH, (ii) DH loaded BSG-g-MAA (MAA content: 53 wt. %) microparticles and (iii) buffer treated microparticles

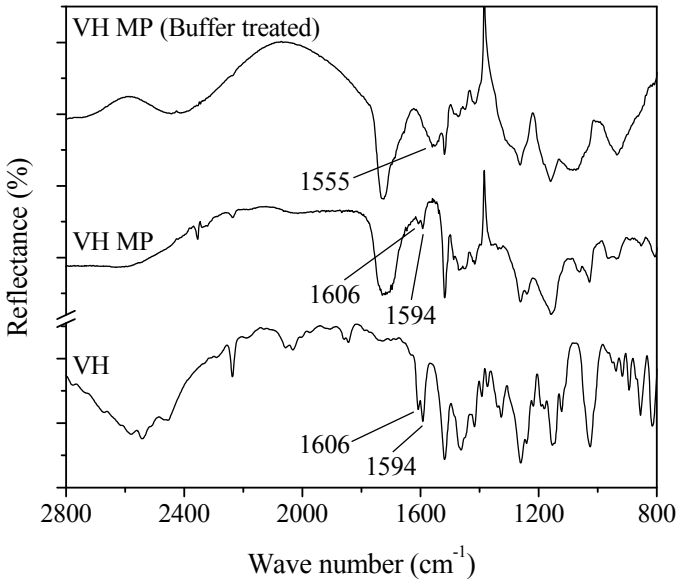

Figure 4.3. FTIR spectra (i) VH, (ii) VH loaded BSG-g-MAA (MAA content: 53 wt. %) microparticles and (iii) buffer treated microparticles

Takka, 2003 investigated the interaction between the methacrylic acid copolymers such as Eudragit® L100, Eudragit® S100 and the cationic drug propranolol hydrochloride. Band appeared at 1550 and 1556 cm^{-1} for Eudragit® L100 and Eudragit® S100 respectively because of interaction with propranolol hydrochloride and is comparable with that observed in this work. The results were further substantiated by turbidity measurements discussed in the next section.

4.3.2.2 Turbidity measurements

The formation of complex between DH and polymer and its dissociation was monitored by turbidity measurement. The graft copolymer BSG-g-MAA containing 53 wt. % MAA was selected since it was readily soluble in phosphate buffer, pH 6.8. The UV absorbance of drug-polymer complex solutions was measured and the results are shown in Figure 4.4. The measurements were performed at 5 minutes, 4 and 15 hours after mixing individual solutions. The transmittance of solution measured at 5 minutes was greater than 90 % when the molar ratio between the DH and MAA of the graft copolymer was 0.44:0.56. On increasing the molar ratio of DH, the transmittance steadily decreased since the solution became more turbid. When the molar ratio approached 0.52:0.48, the transmittance was ~ 10 %. The

solution turned almost opaque because of the extensive complex formation between the drug and the polymer.

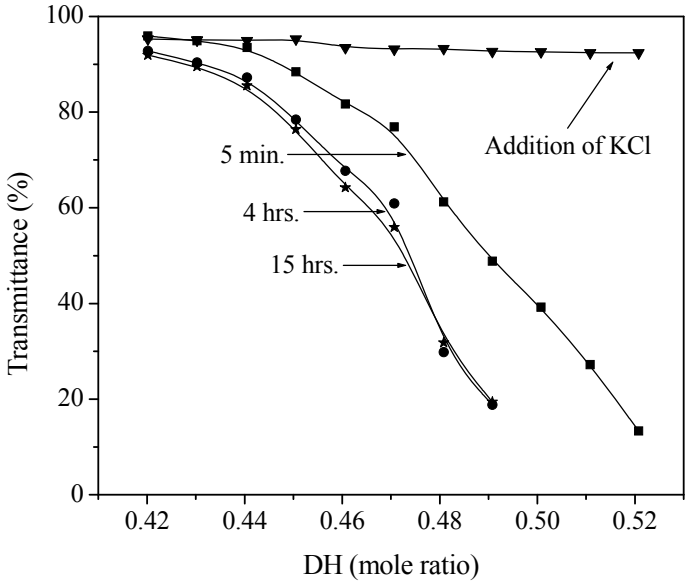

Figure 4.4. Turbidity measurement: BSG-g-MAA (MAA content: 53 wt. %) and DH complex formation in phosphate buffer solution, pH 6.8

The measurement was repeated after 4 hours which showed further decrease in transmittance. However, there was no difference in turbidity between samples analyzed at 4 and 15 hours. Thus the complex formation is complete in 4 hours. Addition of potassium chloride to these solutions led to dissociation of the complex since the drug ions associated with the polymer were replaced by potassium ions. The absence of interaction between the drug and the polymer in microparticles is desirable to ensure stability during storage. However, ionic interaction was observed in phosphate buffer, pH 6.8. Blanco-Fuente et al., 2002 investigated the interaction between carbopol® and propranolol hydrochloride by FTIR analysis as well as turbidity measurement and noted that the interaction between carboxyl and amino groups resulted in complexation immediately but equilibrium was reached in about 5 hours.

4.3.3 *In vitro* release study

In vitro release of drugs was monitored in phosphate buffer, pH 6.8. The experiments were designed to evaluate the effect of polymer swelling / dissolution behavior, drug loading, solubility and tablet configuration. The enteric behavior of the polymer was also evaluated. The release characteristics were analyzed by fitting

the early time dissolution data (up to 60 % release) into logarithmic form of Ritger - Peppas equation.

$$\text{Log } (M_t / M_\infty) = \text{Log } k + n \text{ Log } t$$

Where, M_t and M_∞ denote the fraction of drug released at time 't' and the total drug present in the matrix respectively. The constant 'k' indicates the release rate and 'n' is release exponent. In the case of cylindrical matrix such as a tablet, $0.89 < n < 1.0$ indicates zero order release and $0.45 < n < 0.89$ indicates anomalous release behavior (Ritger and Peppas, 1987).

4.3.3.1 Effect of grafting frequency of MAA on DH release

The MAA grafting frequency decreases as the dicarboxylic acid chain length increases from succinic to dodecanedioic acid. The composition and release characteristics are summarized in Table 4.1. The rate of release of DH decreased with decreasing MAA grafting frequency on the polyester backbone (Figure 4.5).

Table 4.1. Composition and release characteristics of DH tablets

Matrix code	Polymer	MAA Content (wt. %)	Drug content (%)	Mean diameter (μm)	n	k
M-1	BSG-g-MAA	37	22.02	3.96	0.5987	0.2297
M-2	BAG-g-MAA	35	21.66	5.25	0.7272	0.1039
M-3	B(S)G-g-MAA	35	21.60	4.99	0.9912	0.0389
M-4	BDG-g-MAA	36	21.89	4.76	0.9206	0.0350
M-5		44	20.66	4.32	0.9307	0.0489
M-6		51	21.44	3.84	1.0762	0.0793

The graft copolymers B(S)G-g-MAA and BDG-g-MAA released DH at constant rate (Table 4.1). The penetration of dissolution medium into the matrix led to a boundary separating a swollen and a glassy layer which moved towards the center of the tablet. The increase in diffusion coefficient of drug in the swollen layer results in the release at constant rate. Penetration of medium in glassy polymer blends of

gelatin, hydroxypropyl methylcellulose and pectin and consequent release of diltiazem hydrochloride at constant rate has been reported by Kim and Fassihi, 1997. In the present case, the swollen layer eroded after the drug released as these polymers were mechanically weak under wet conditions. Erosion of the matrix lags far behind the release of DH (Figure 4.9).

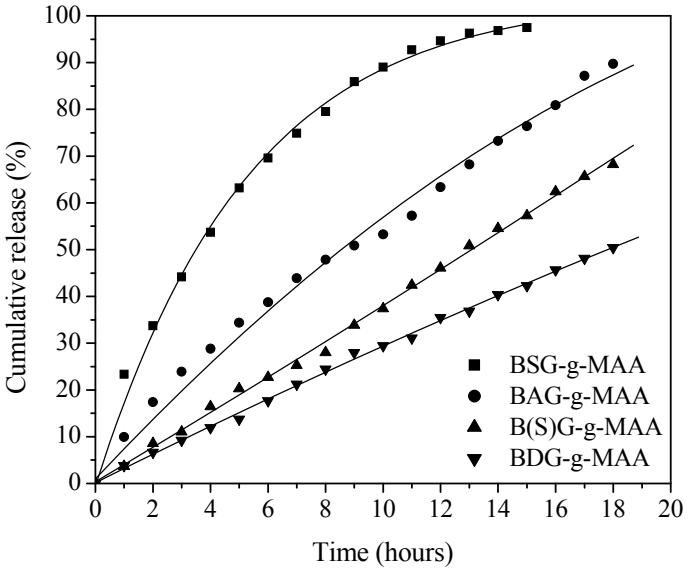

Figure 4.5. Effect of MAA grafting frequency on DH release

In contrast, in the case of polymers BSG-g-MAA and BAG-g-MAA, the swollen layer also dissolved rapidly as evident from the fact that the tablet dissolved concomitantly with the release. The release of DH in this case was controlled by complex interplay between swelling and dissolution and exhibited anomalous release kinetics.

4.3.3.2 Effect of MAA content on DH release

In the previous section it was shown that the DH was released at a constant rate from the polymer BDG-g-MAA (MAA content, 36 %) as a result of the enhanced diffusivity from the swollen layer, which subsequently eroded. The rate of release in such cases is known to be controlled by the penetration velocity of the medium which in turn is proportional to equilibrium swelling (Vyavahare et al., 1990).

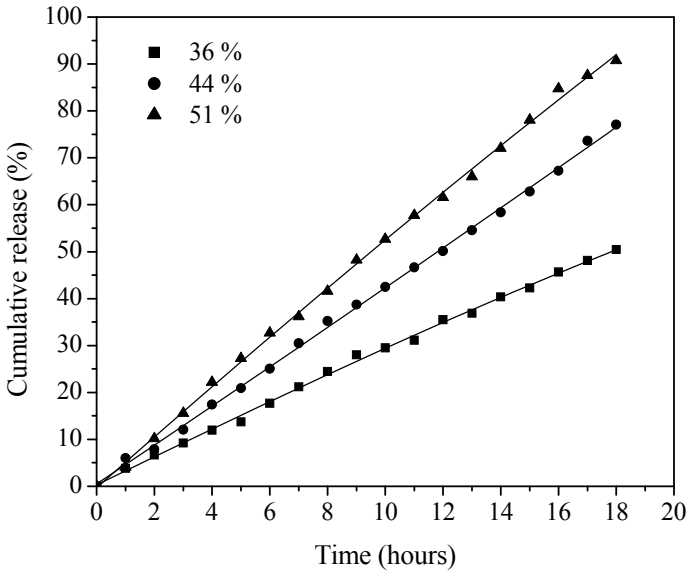

Figure 4.6. Effect of MAA content on DH release

Increasing the degree of grafting of MAA in BDG-g-MAA to 44 and 51 % results in polymers which undergo swelling and dissolution rather than erosion. Increase in the degree of hydrophilicity is reflected in enhanced initial rate of swelling but not in maximum swelling because of the dissolution of the swollen layer. This is also reflected in higher rate of release because of enhanced penetration velocity of the medium (Figure 4.6). In this case the dissolution front closely follows the boundary separating the core and swollen layer and the tablet dissolution is concomitant with the release.

The polymer BDG-g-MAA contains 51 % MAA but has lower grafting frequency compared to the polymer BSG-g-MAA which contains 37 % MAA. Both polymers swelled rapidly and then dissolved slowly. Surprisingly, the release of DH from the polymer which contained 51 % MAA was slower than from the polymer which contained 36 % MAA. This can be attributed to the complexation between the carboxyl groups and DH. On releasing the drug, the polymer dissolves. This leads to drug release at constant rate from the drug-polymer complex (Table 4.1). Similar observation has been reported for the complex of anionic polyelectrolytes and cationic drugs (Nujoma and Kim, 1996 and Cornejo-Bravo et al., 2005).

4.3.3.3 Effect of loading level of DH on release

Higher dosage of drug has to be administered for the sustained release dosage forms. For instance, once a day dosage form Dilacor XR® contains 240 mg of diltiazem hydrochloride. Higher drug loading is necessary to limit the size of the tablet. However, this should not compromise the release kinetics. The composition of matrices containing various levels of DH and their release characteristics are summarized in Table 4.2.

Table 4.2. Effect of loading on release from DH tablets

Matrix code	Drug content (%)	Mean diameter (μm)	n	k
M-7	10.42	4.02	0.9307	0.0136
M-4	21.89	4.76	0.9206	0.0350
M-8	32.36	4.84	0.9121	0.0505
M-9	40.63	4.05	0.8807	0.0594
M-10	51.95	4.10	0.7449	0.1022

Polymer: BDG-g-MAA (MAA content: 36 wt. %)

The polymer, BDG-g-MAA containing 36 % MAA was selected since it exhibited swelling over longer time period in comparison to other polymers. DH was loaded in the range 10 - 50 %. Since the release of DH occurs by enhanced diffusion from the swollen layer of the matrix, the release rate was expected to be identical irrespective of drug loading. However, the release rate of DH was enhanced (Figure 4.7). This is because DH is highly water soluble and increasing loading leads to increase in the hydrophilicity of matrix. As a result, the penetration velocity of the medium is enhanced which leads to increase in the rate of DH release.

The increase in release rate of DH with loading from the blend of gelatin, hydroxypropyl methylcellulose and pectin was reported by Kim and Fassihi, 1997. Kim and Lee, 1992 reported that the rate of release of oxprenolol hydrochloride increased with loading from poly (methyl methacrylate-co-2-hydroxyethyl methacrylate) beads. But the extent of initial burst release increased with drug

loading. In the present case an initial burst (6.7 %) was observed when DH loading was 50 %.

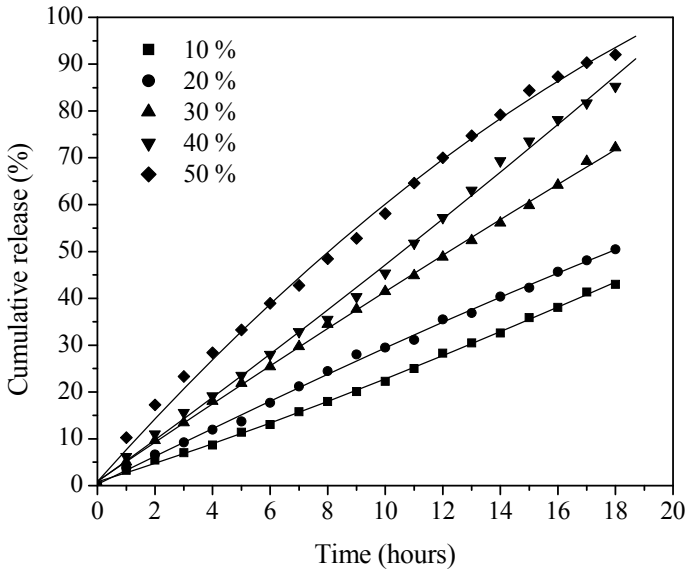

Figure 4.7. Effect of DH loading level on release

The release exponent 'n' was ~ 0.9 upto the loading level of 40 % indicating constant release rate. On increasing the loading level to 50 % although 'n' dropped to 0.74, a sustained release was observed over 18 hours after an initial burst of 6.7 %. While this is quite satisfactory, the value of 'n' can be further enhanced by modifying the configuration of the tablet as will be shown in subsequent section.

4.3.3.4 Effect of tablet configuration on release of DH

The dimension of tablet influences the release kinetics of drugs (Nujoma and Kim 1996). We designed DH matrices varying in dimensions and monitored the release behavior. Relative surface area of the matrices was calculated as follows (Table 4.3).

Relative surface area = Absolute surface area (SA) / Absolute volume (V)

$SA = 2\pi r\,(r + t)$; $V = r \times t$

Where, 'r' and 't' are the radius and thickness of the matrices respectively.

Table 4.3. Characteristics of release of DH from the matrices differing in relative surface area

Matrix code	Micro particles (mg)	HPMC (5 Cps) (mg)	Diameter / Thickness (mm)	Relative surface area (mm^2 / mm^3)	n	k
M-10	200	25.0	8.0 / 3.80	12.89	0.7449	0.1022
M-23	300	37.5	8.0 / 5.78	10.62	0.9290	0.0606
M-24	400	50.0	8.0 / 7.60	9.58	0.9684	0.0448

Increase in thickness of matrix at constant diameter led to sustained and constant release rate of drug (Figure 4.8). This can be attributed to the decrease in relative surface area of the matrix which resulted in suppression of initial burst release of the drug.

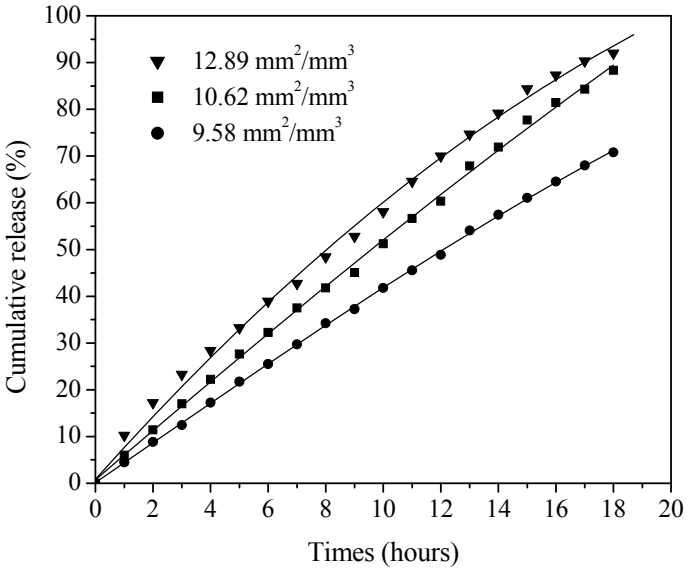

Figure 4.8. Release of DH from the matrices varying in relative surface area

4.3.3.5 Sustained release of IM and VH

In the preceding sections, we demonstrated that the release of highly soluble drug DH (660 mg/ml) from the polymer matrix BDG-g-MAA (MAA content 36 %) was sustained at intestinal pH as a result of swelling of the polymer layer and enhanced diffusivity of the dissolved drug through the swollen layer which eroded at a latter stage. This is evident from the fact that the rate of erosion lags behind the release (Figure 4.9).

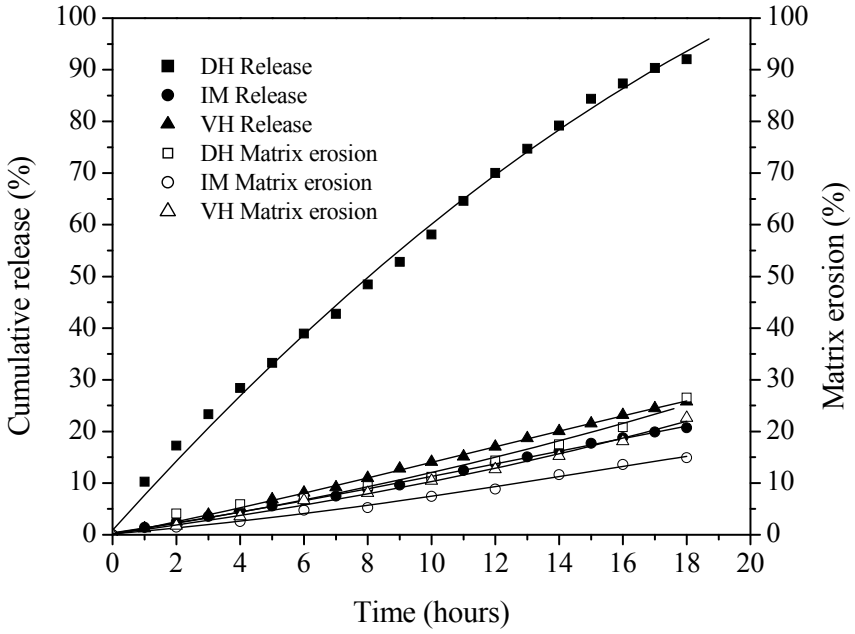

Figure 4.9. Release behavior of DH, IM and VH

The release of poorly soluble drug IM (0.23 mg/ml) is controlled by the erosion of polymer layer. Only 20 % IM was released over 18 hours and the rate of release was identical to the rate of matrix erosion (Figure 4.9). A weakly basic drug such as VH is rapidly released in acidic medium because of its high solubility (165 mg/ml at pH 5.0). However with increasing pH along the gastrointestinal tract, the solubility decreases dramatically (10 mg/ml at pH 7.0). It has been reported that the drug precipitated at higher pH and consequently the drug did not diffuse out of the system (Goracinova et al., 1996). In order to ensure diffusional release, the drug needs to be solubilized. This has been achieved in the past by incorporating organic acids.

Thoma and Ziegler, 1998 incorporated succinic acid at increasing succinic acid to Fenoldopam mesylate ratios in the range 0:1 to 18:1 and coated the same with ethylcellulose. It was noted that the loading of succinic acid and the thickness of the coating had to be so manipulated that there was enough succinic acid present within the system as to retain fenoldopam mesylate in dissolved state so that it would diffuse out of the system. However the amount of acid required is high and to that extent limits the drug loading.

In the present case, the release of VH was controlled by the erosion of swollen layer. The rate of release of VH is much slower than that of DH which is released by diffusion. The release profile compares reasonably well with that of the erosion profile. The rate of release of VH is comparable to that of IM eventhough the solubility of VH is ~ 50 times higher than that of IM. This can be attributed to the interaction between VH and polymer which suppressed the erosion of matrix and drug release.

Table 4.4. Effect of loading on release from IM tablets

Matrix code	Drug content (%)	Mean diameter (μm)	n	k
M-11	10.18	4.32	0.8470	0.0437
M-12	21.19	4.67	0.8586	0.0386
M-13	31.69	4.05	0.9217	0.0259
M-14	41.36	3.89	0.9479	0.0145
M-15	52.24	4.16	0.9551	0.0126

Polymer: BDG-g-MAA (MAA content: 36 wt. %)

Table 4.5. Effect of loading on release from VH tablets

Matrix code	Drug content (%)	Mean diameter (μm)	n	k
M-16	10.57	4.09	0.9457	0.0228
M-17	19.64	4.74	1.0438	0.0140
M-18	31.03	4.12	1.0792	0.0126
M-19	40.95	4.58	1.0764	0.0115
M-20	49.09	3.88	1.0677	0.0119

Polymer: BDG-g-MAA (MAA content: 36 wt. %)

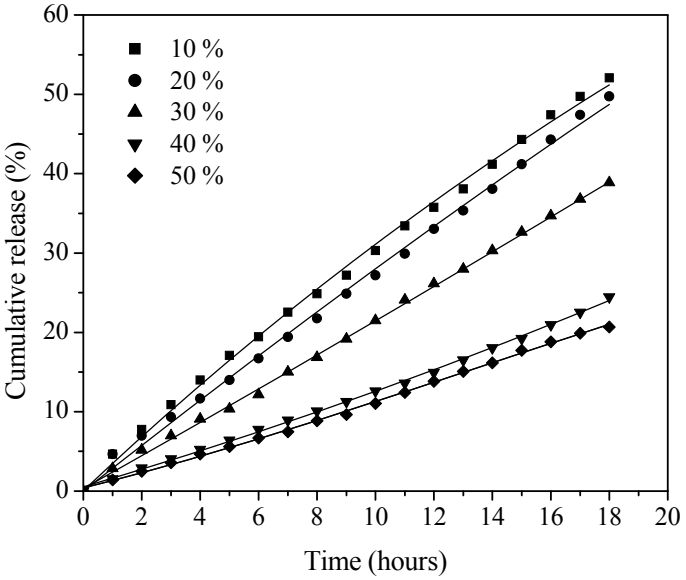

Figure 4.10. Effect of IM loading on release

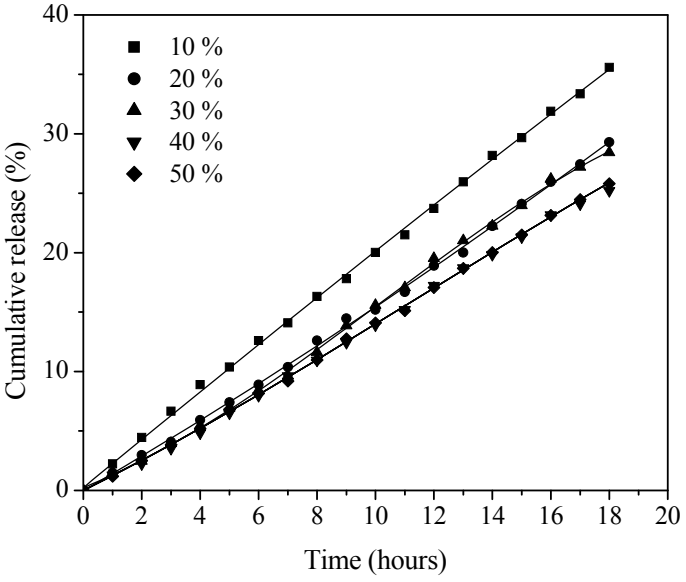

Figure 4.11. Effect of VH loading on release

Increasing the loading level of IM and VH led to suppression of the release rate (Figure 4.10 and 4.11). This can be attributed to the decrease in the penetration velocity of the medium and the erosion of the matrix and consequently release of drugs. Kim, 1998 showed that the release rate decreased with increasing loading level of poorly soluble drugs. The rate of release of IM and VH was constant as anticipated (Tables 4.4 and 4.5).

4.3.3.6 Release behavior of IM and VH from soluble polymers

The release of IM and VH from the graft copolymer BDG-g-MAA containing 36 % MAA was too slow to be completed within the gastrointestinal tract transit time. When the loading level of drug was 50 %, less than 25 % drug was released at the end of 18 hours. To enhance the rate of drug release, more hydrophilic BSG-g-MAA containing 37 wt. % MAA was used as the matrix. Since this polymer dissolves rapidly after swelling, an accelerated drug release is expected. The composition of IM and VH matrices and their release behavior are summarized in Table 4.6. The release of IM was suppressed for the first two hours as the drug is insoluble in acidic medium (Figure 4.12). Both drugs were completely released over 18 hours when the pH of the medium was switched to 6.8.

Table 4.6. IM and VH release from soluble polymer

Matrix code	Drug	Drug content (%)	Mean diameter (μm)	n	k
M-13	IM	49.21	3.69	1.18	0.0395
M-14	VH	50.66	3.52	1.01	0.0611

Polymer: BSG-g-MAA (MAA content: 37 wt. %)

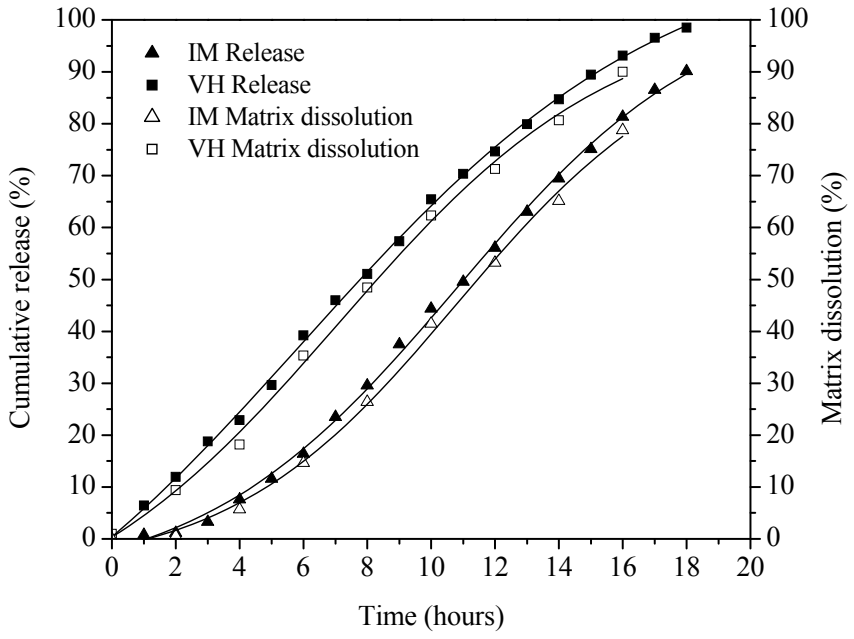

Figure 4.12. Release behavior of IM and VH from the matrices of soluble polymer

The graft copolymer suppressed the release of VH at acidic pH since the polymer remained in collapsed state. Sustained as well as complete release of drug occurred at near neutral pH as a result of dissolution of polymer matrix. Figure 14 illustrates that the drug release and matrix dissolution are concomitant.

4.3.3.7 Evaluation as enteric coating

The enteric behavior of a representative graft copolymer BDG-g-MAA containing 36 % MAA was evaluated by coating the polymer on the matrices containing DH and VH. The release from coated matrix was followed in 0.1 N HCl for the first two hours followed by phosphate buffer solution, pH 6.8. Similarly, the uncoated matrices were studied for their release behavior in identical manner.

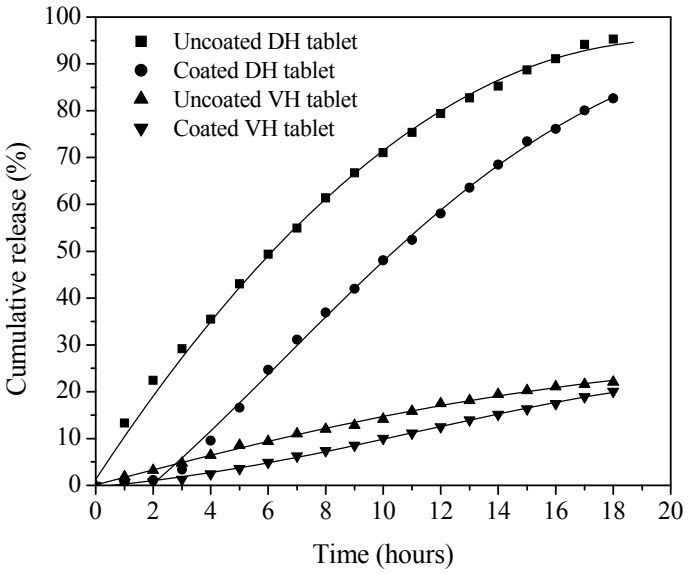

Figure 4.13. Enteric behavior: Coated and uncoated DH and VH matrices

The coated matrices did not release the drug in the acidic medium (Figure 4.13). When the pH of the medium was switched to 6.8, the polymer coating started swelling and then underwent rupture, exposing the matrix within. Thus the graft copolymer can be used for sustained delivery of drugs in intestinal region while suppressing the release in gastric region. In the case of uncoated matrices, the drug released in acidic pH medium eventhough the polymer matrix did not swell / dissolve. This is due the exposure of drug to dissolution medium unlike in the case of coated matrix. Palmieri et al., 2000 showed that the release of paracetamol occurred in acidic pH medium from the uncoated matrices of various enteric polymers and our finding is similar.

4.4 Conclusions

In this chapter, we have shown that the graft copolymers containing methacrylic acid can be used for the sustained delivery of highly soluble, poorly soluble and weakly basic drugs. Diltiazem hydrochloride was released at a constant rate as a result of increase in diffusion coefficient of drug in the swollen layer. Indomethacin and verapamil hydrochloride released at constant rate from the swellable polymers as a result of erosion of the matrix. The enhanced rate of release could be achieved from matrices which dissolve. These graft copolymers will be useful for the development of once a day matrix dosage forms comprising a wide variety of drugs.

4.5 References

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Chapter 5

pH Dependent Pulsatile Release of Drugs: *In vitro* Evaluation

5.1 Introduction

Role of polymers in drug delivery is well established. Oral route of drug administration is most preferred as it is non-invasive. Efforts were focused in the past to release the drug at constant rate. With the introduction of new drugs and improved understanding of the pharmacokinetics of existing drugs, tailoring more precise release profiles has become necessary. It is now realized that the spatial and temporal release of drugs along the gastrointestinal tract is more desirable. These requirements are often met by innovative combinations of existing polymers and designing complex geometries.

Colon is preferred absorption site for proteins and polypeptides because of low peptidase concentration and long residence time (Cheng et al., 2004). Targeting the drug to colon is desirable for the treatment of inflammatory bowel disease and Crohn's disease (Sangalli et al., 2001). This can be achieved by either time or pH dependent release mechanism. The former consists of a core of drug and superdisintegrant such as croscarmellose sodium and a brittle water insoluble coating such as ethyl cellulose. The pH dependent system comprises a core containing the drug coated with hydroxypropyl methylcellulose followed by a pH sensitive polymer such as Eudragit® L30D (Sangalli et al., 2001). Mesalazine capsule was coated with Eudragit® S100 containing the superdisintegrant, croscarmellose sodium. Extensive swelling of the superdisintegrant created cracks in the coating resulting in pulsatile release of the drug (Schellekens et al., 2008).

Bodmeier and Paeratakul, 1994 have evaluated mechanical properties of dry and wet polymeric films. Ethyl cellulose films were weak and brittle, showed low puncture strength compared to acrylate films and hence were recommended for pulsatile delivery of drugs. To achieve time controlled release in colon the cap, the body and drug container were made from ethyl cellulose. Swellable polymer hydroxypropyl cellulose was filled in the capsule and micropores were punched at the bottom. The penetration of aqueous medium through micropores caused swelling of the hydrophilic polymer and resulting pressure caused rupture of ethyl cellulose cap, releasing the drug in a pulsatile manner (Niwa et al., 1995). Clearly such systems are not easily amenable to mass production.

The time for the dosage form to reach colon can not be predicted precisely because of large variations in gastric emptying time (Davis et al., 1984). pH dependent polymers which dissolve at pH ≥ 7.0 prevalent in the ileo-colonic region have been explored for colon specific drug delivery. However, often the drug is delivered either in the upper intestine or not at all (Ashford et al., 1993 and Schellekens et al., 2007).

Temporal release is particularly useful for the treatment of diseases which follow circadian rhythm, as in cardiovascular diseases, bronchial asthma and rheumatoid arthritis (Lemmer, 1991). Pulsatile delivery is desirable for drugs which are highly susceptible to the first pass effect and drugs which react with the receptor and produce tolerance. Rupturable, erodible and osmotic systems have been exploited for the pulsatile delivery of drugs.

Cores containing diltiazem hydrochloride were press coated with hydroxypropyl cellulose (HPC) for timed release. The lag time of release was governed by the rate of polymer erosion or dissolution and hence could be manipulated by coating thickness and HPC viscosity. *In vivo* lag times were shorter than those observed under *in vitro* conditions as a result of gastrointestinal peristalsis and contractions (Fukui et al., 2000). An ideal polymer for both spatial and temporal release would combine features of pH sensitive swelling and resulting rupture. In the case of enteric polymers, the rate of polymer dissolution cannot be controlled by varying polymer composition (Peeters and Kinget, 1993) and hence new architectures are needed. We developed a series of graft copolymers comprising polyester backbone and methacrylic acid graft chains. The synthesis and characterization of polymers has been described in Chapter 3. Matrix tablets of synthesized polymers exhibited sustained release of drugs over an extended time period and the detailed investigation has been described in Chapter 4.

In this chapter, the pulsatile delivery of drugs from the graft copolymer coated reservoir tablet is described. The mechanical properties of polymers have been investigated to evaluate the suitability of polymers as a rupturable film coat. The polymers were brittle and exhibited low elongation at break in dry as well as wet conditions. Film coated tablets of highly water soluble diltiazem hydrochloride and water insoluble indomethacin as well as the macromolecular marker FITC - dextran

4000 exhibited pulsatile release after a time lag. The mechanism of release was swelling induced rupture of film coat as evidenced from Environmental Scanning Electron Microscopic analysis. The lag time of release can be varied by choosing appropriate polymer composition, plasticizer content and coating thickness.

5.2 Experimental

5.2.1 Materials

Fluorescein isothiocyanate - dextran (FITC - dextran, Average molecular weight: 4000) was purchased from Sigma-Aldrich, St Louis, USA. Chloroform ($CHCl_3$), Methanol (CH_3OH) and n-Dibutyl phthalate (DBP) were purchased from Merck, India. Indomethacin (IM) was purchased from Fluka chemicals, Germany. Diltiazem hydrochloride (DH) and other pharmaceutical ingredients were gift samples from Lupin Laboratories Ltd., India.

5.2.2 Synthesis of MAA grafted polyesters

The acidic graft copolymers comprise the hydrophobic polyester backbone and methacrylic acid graft chains. The polymer synthesis involves, the synthesis of unsaturated polyesters differing in unsaturation frequency using various diols, dicarboxylic acids and glycidyl methacrylate followed by grafting with methacrylic acid at various levels. The detailed synthesis procedure has been described in chapter 3. The graft copolymers evaluated for pulsatile delivery of drugs are given below.

(a) Poly [(1, 4 Butane diol - Succinic acid - Glycidyl methacrylate) - g - (MAA)]; BSG-g-MAA (MAA Content: 37 wt. %)

(b) Poly [(1, 4 Butane diol - Adipic acid - Glycidyl methacrylate) - g - (MAA)]; B(A)G-g-MAA (MAA Content: 35 wt. %)

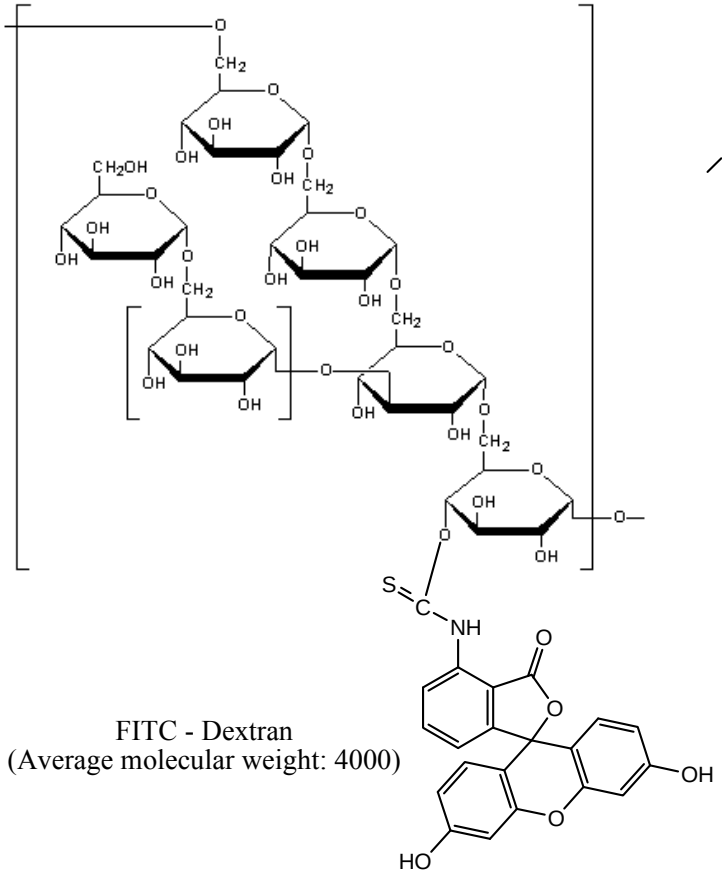
(c) Poly [(1, 4 Butane diol - Sebacic acid - Glycidyl methacrylate) - g - (MAA)]; B(S)G-g-MAA (MAA Content: 35 wt. %)

(d) Poly [(1, 4 Butane diol - Dodecanedioic acid - Glycidyl methacrylate) - g - (MAA)]; BDG-g-MAA (MAA Content: 36, 44 and 51 wt. %)

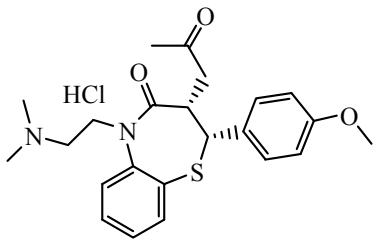
(e) Poly [(1, 4 Cyclohexane dimethanol - Dodecanedioic acid - Glycidyl methacrylate) - g - (MAA)]; CDG-g-MAA (MAA Content: 35 wt. %)

(f) Poly [(Bis 2- hydroxyethyl terephthalate - Dodecanedioic acid - Glycidyl methacrylate) - g - (MAA)]; (B)DG-g-MAA (MAA Content: 34 wt. %)

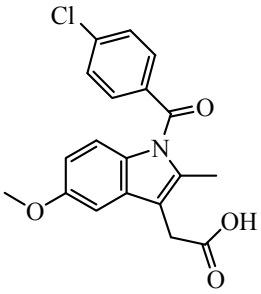
Drugs and macromolecular marker used for pulsatile delivery



FITC - Dextran
(Average molecular weight: 4000)



Diltiazem hydrochloride



Indomethacin

5.2.3 Preparation of polymer films

The films were prepared by solution casting. The polymer solution was prepared by dissolving 1.0 g of polymer in 15 ml of $CHCl_3$ and CH_3OH mixture (7:3 v/v). The lipophilic plasticizer DBP was added at various levels 5 - 25 wt. % and the solution was mixed thoroughly. The solution obtained was poured in a petri dish and the solvent was evaporated. The resulting films were dried under vacuum 7 days at room temperature. The dried films were cut to obtain rectangular strips and the dimension is depicted in the Figure 5.1.

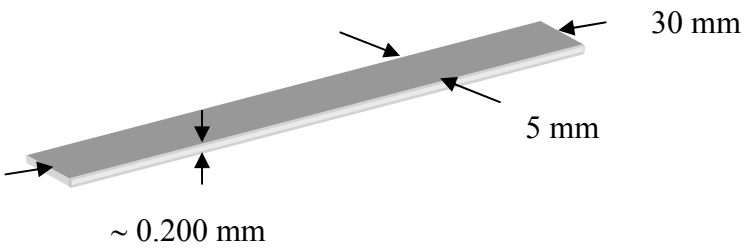


Figure 5.1. Dimension of polymer film used for tensile testing

5.2.4 Mechanical properties of polymer films

The mechanical properties of the polymer films were studied using tensile testing machine (Linkam, TST 350 Tensile Stress Testing System, UK) at room temperature (Figure 5.2). The films were clamped on the grip and the displacement speed was maintained at 100 μ / s. The films were elongated until break. From the stress-strain curve, the elongation at break and modulus of the films were calculated. Similarly, the measurement was carried out for wet films which were immersed in distilled water for the duration of 8 hours.

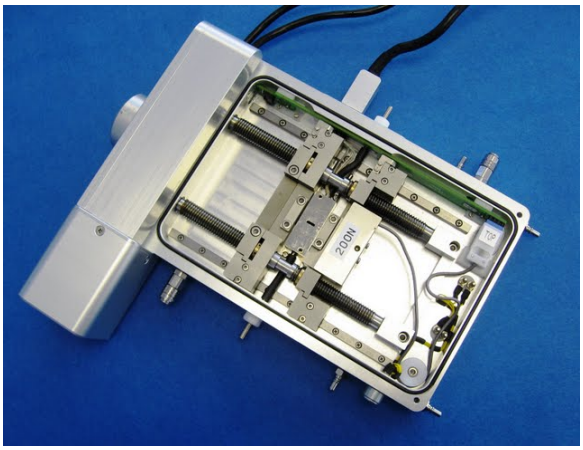


Figure 5.2. Linkam, TST 350 tensile stress testing system

The elongation at break and modulus of the polymer films were calculated as follows,

Elongation at break (%) = $(\Delta l / l) \times 100$

Where, Δl and l are the change in length and original length of polymer film respectively.

Modulus (MPa) = (σ / ε) (where, $\sigma = F / A$)

Where, σ, ε, F and A are the tensile stress, tensile strain, force and area respectively.

5.2.5 Preparation of film coated tablets

Each tablet containing 60 mg of DH was prepared by using a hydraulic press equipped with an 8 mm die and a flat faced punch. DH, Lactose monohydrate and HPMC (5 Cps) were finely ground and mixed with magnesium stearate and aerosil. The mass was compressed by applying a load of 200 kg / cm^2. The graft copolymer solution was prepared in $CHCl_3$ and CH_3OH mixture (7:3 v/v). To this solution DBP was added as a plasticizer. The solution was thoroughly mixed and then DH tablets were dip coated. The coated tablets were air dried at room temperature. Typical composition of the tablet coated with 10 % graft copolymer is summarized in Table 1. Similarly tablets were coated with 15, 20 and 25 % using various graft copolymers. The increase in coating weight was compensated by decreasing the lactose monohydrate amount so as to maintain the total weight of tablet 200 mg. Similarly, the tablet of IM and FITC - dextran 4000 was prepared and film coated.

Table 5.1. Composition of DH tablet

Ingredients	**Weight (mg / tablet)**
DH	60.00
Lactose Monohydrate	100.00
HPMC (5 Cps)	14.00
Magnesium stearate	4.00
Aerosil	2.00
Graft copolymer (coating)	20.00
Total	200.00

5.2.6 *In vitro* release study

The dissolution of film coated tablets was studied by paddle method using Electrolab USP type II apparatus. The paddle rotation speed was 50 rpm and the temperature was maintained at 37 ± 0.5 ^oC. The tablets were exposed to 0.1 N HCl for the first 2 hours followed by phosphate buffer, pH 6.8. At predetermined intervals, a known volume of dissolution medium was withdrawn and analyzed for

DH, IM and FITC - dextran 4000 concentration at 237, 320 and 495 nm on Shimadzu, UV-1061PC UV spectrophotometer.

5.2.7 Morphology of film coated tablets: ESEM analysis

The surface morphology of film coated tablets was observed using Environmental Scanning Electron Microscope (ESEM, Quanta 200 3D, FEI). The tablets were immersed in 0.1 N HCl for the first 2 hours followed by phosphate buffer, pH 6.8. The tablets were withdrawn from the medium at predetermined interval and their surface morphology was observed by ESEM.

5.3 Results and discussion

Strategies to achieve pulsatile delivery of drugs have been extensively reviewed (Anal, 2007a and b and Gazzaniga et al., 2008). Typically a core containing the drug and a super disintegrant is coated with a brittle polymer such as ethyl cellulose (Sungthongjeen et al., 2004 and Mohamad and Dashevsky, 2007). Extensive swelling of the super disintegrant caused by the penetration of the medium, ruptures the coating, resulting in the burst release of the drug encapsulated within the core. The rupture of film coating depends on the mechanical properties of the polymer, *viz*., puncture strength, energy at break, modulus and elongation at break as a function of time of exposure to the medium. These properties also offer a guide for the selection and design of the polymer for the coating (Bussemer et al., 2003).

Incorporation of features such as brittleness of ethylcellulose and pH dependent dissolution of enteric coatings would enable overcome the need for multiple coatings, complex fabrication technologies to achieve both spatial and temporal release of drugs. In the following sections we discuss the choice of the polymer backbone, the effect of grafting on the physicochemical properties of the polymer, pH dependent swelling of the polymer, morphological changes accompanying swelling which suggest the potential of the polymer as a coating for pulsatile release of the drugs. We validate the mechanism by demonstrating that the lag time is same for the highly water soluble drug DH and water insoluble drug IM as well as macromolecular marker FITC - dextran 4000. The lag time can be manipulated by varying the polymer composition, coating thickness and plasticizer content and is comparable with that achieved in the past.

5.3.1 Mechanical properties of polymer films

Most of the polymers used for film coating of tablets are cellulosic and (meth)acrylates. The mechanical properties of polymer films are depend on their glass transition temperature and additives like plasticizers. The mechanical properties of film coating change when they are exposed to aqueous medium. This is due to the absorption of water, which can act as a plasticizer and also due to the leaching of plasticizer if that is water soluble.

Based on an analysis of mechanical properties of dry and wet films of cellulosic and various (meth)acrylate polymers, Bodmeier and Paeratakul, 1994 showed that the ethylcellulose (Aquacoat and Surelease) film was weak and brittle in dry as well as under wet conditions. The films of pH independent (meth)acrylate polymers such as Eudragit® NE 30D, Eudragit® RS 30D and Eudragit® RL 30D were flexible under dry as well as wet conditions. They also have shown that the films of enteric polymer, Eudragit® L 30D exhibit weak and brittle behavior in dry condition but become flexible under wet conditions because of extensive plasticization by water.

The polymers which are soft and flexible particularly under wet conditions are not suitable for rupturable film coating (Bussemer et al., 2003). It has been shown that the Eudragit® RS 30D films were ductile and they did not break completely during the puncture test. Such flexible films could be useful to develop conventional extended release systems, but are not desirable for rupturable pulsatile delivery systems. This is because the pulsatile delivery system requires the complete rupturing of film coat in the form of large cracks or openings to achieve rapid release of drug after the lag time.

The acidic graft copolymers synthesized by us exhibited swelling and then rupturing under near neutral pH conditions which is desirable for pulsatile delivery of drugs. Therefore, we studied the mechanical properties of these polymers in dry and wet conditions to find their suitability for pulsatile delivery of drugs. The mechanical properties of BDG-g-MAA (MAA content 36 %) polymer films containing various levels of plasticizer are summarized in Tables 5.2 and 5.3. The stress - strain curves of the polymer films under dry and wet conditions are shown in Figures 5.3 and 5.4.

Table 5.2. Effect of DBP content on mechanical properties of dry polymer films

DBP content (%)	Film thickness (mm)	Elongation at break (%)	Modulus (MPa)
5	0.202	2.27	13.43
10	0.211	3.38	9.37
15	0.205	4.34	8.82
20	0.213	5.82	7.52
25	0.219	7.24	6.25

Table 5.3. Effect of DBP content on mechanical properties of wet polymer films

DBP content (%)	Film thickness (mm)	Elongation at break (%)	Modulus (MPa)
5	0.213	4.54	9.14
10	0.214	5.03	8.77
15	0.210	5.91	8.37
20	0.208	7.33	7.77
25	0.205	9.42	6.62

The percent elongation of film at break increased with increasing the plasticizer content in both dry and wet conditions due to the slippery effect of polymer molecules. The percent elongation at break of wet films was higher than corresponding dry films due to the plasticization effect of imbibed aqueous medium. However, the difference was not significant (~ 2 %) unlike in the case of random copolymer which comprises methacrylic acid and ethylacrylate (Eudragit® L 30D) wherein the percent elongation of film at break was 0.46 and > 365 % for the dry and wet films respectively (Bodmeier and Paeratakul, 1994). In the present work, the polymers did not show ductile and flexible behavior even under wet condition which makes them suitable for rupturable film coating of tablets to achieve pulsatile release of drugs.

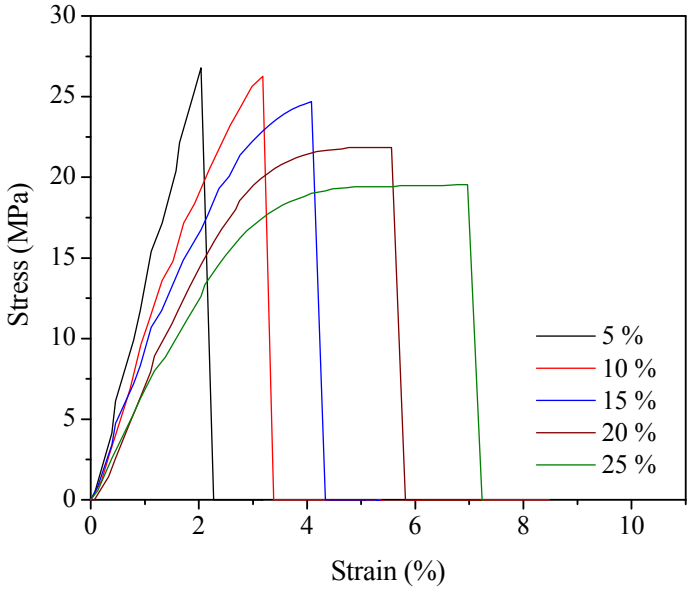


Figure 5.3. Stress - Strain curves of graft copolymer films containing various levels of DBP in dry condition

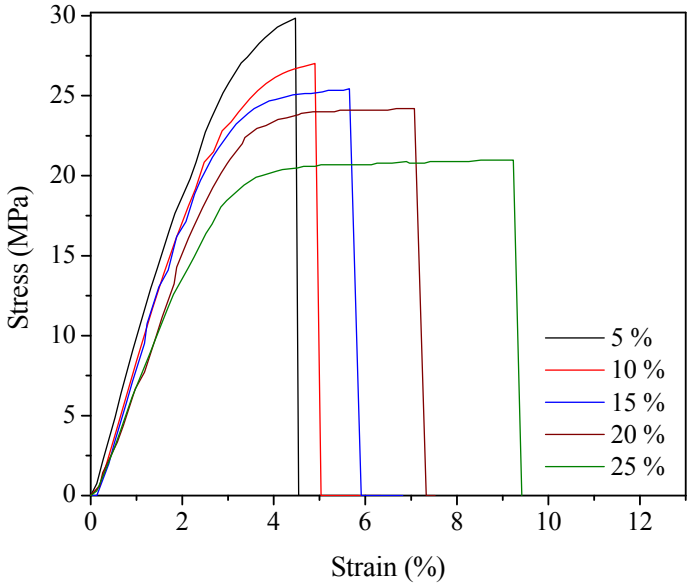


Figure 5.4. Stress - Strain curves of graft copolymer films containing various levels of DBP in wet condition

5.3.2 *In vitro* release of drugs from film coated tablets

5.3.2.1 Effect of plasticizer content

In order that the drug is rapidly released after a time lag, the coating in which the drug core is encapsulated should rupture. This has been achieved in the past by coating a core containing the drug and a super disintegrant with a brittle polymer such as ethyl cellulose. The ductile and flexible polymer film coating like Eudragit® RS led to micro fissures (Krögel and Bodmeier, 1999, Bussemer et al., 2003 and

Zhu and Zheng, 2005). As a result, although the dosage forms coated with such flexible polymer could release the drug after a time lag, the release was sustained (Krögel and Bodmeier, 1999). In the present work, the films of graft copolymers are brittle. The brittleness of the polymers is a result of hydrogen bonding interaction between the polyester backbone and methacrylic acid graft chains. It may be noted that the brittleness of ethylcellulose and Eudragit® L 30D has also been shown to result from hydrogen bonding (Krögel and Bodmeier, 1999).

Water soluble plasticizers leach out during the release in aqueous medium and are not suitable for this purpose. In contrast the water insoluble plasticizers are retained in the film coating during the release (Bussemer et al., 2003). We incorporated a lipophilic plasticizer DBP. To the solution of graft copolymer BDG containing 36 wt. % MAA, 5-25 wt. % DBP was incorporated and the coating level was maintained at 15 %. The cross sectional view of a representative film coated tablet is shown in Figure 5.5 which confirms the uniform coating of polymer on the tablet.

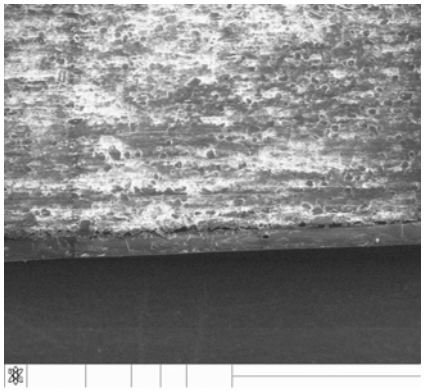
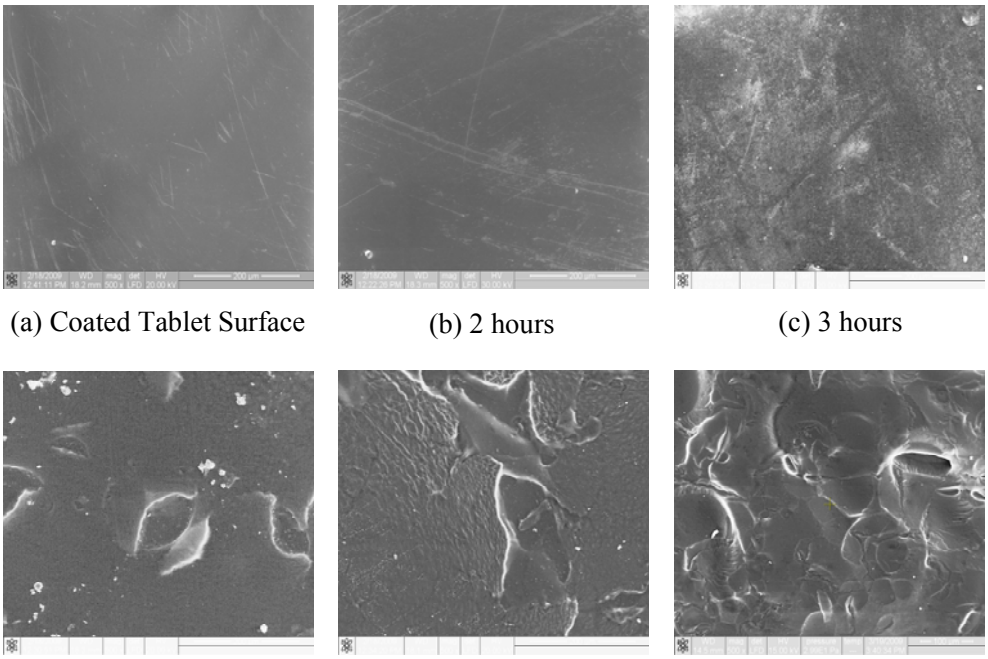


Figure 5.5. Cross sectional view: Graft copolymer coated DH tablet

The change in morphology of the coating on placing the tablets in release medium is shown in Figure 5.6. The coated tablets did not show any change on exposure to 0.1 N HCl for 2 hours. When the tablets were placed in phosphate buffer of pH 6.8, the film coating swelled and ruptured as a result of the crack formation. The lag time for the release of DH was independent of DBP content upto 15 % loading (Figure 5.7). The time taken for 10 % drug release was considered as lag time. When the DBP content increased beyond 15 % the lag time increased. Increase in plasticizer level leads to decrease in brittleness of the polymer. As a result, the film coating takes relatively longer time to undergo rupture. Also it should be noted that the drug

release was sustained after lag time as the film coating failed to undergo complete rupture and developed only small fissures (Figure 5.6f). These findings are consistent with the mechanical properties of the plasticized films which showed increase in elongation at break with plasticizer content.



(a) Coated Tablet Surface (b) 2 hours (c) 3 hours

(d) 4 hours (e) 5 hours (f) 5 hours

Figure 5.6. Surface morphology of film coated DH tablets: Plasticizer content 5% (a-e) and 25 % (f)

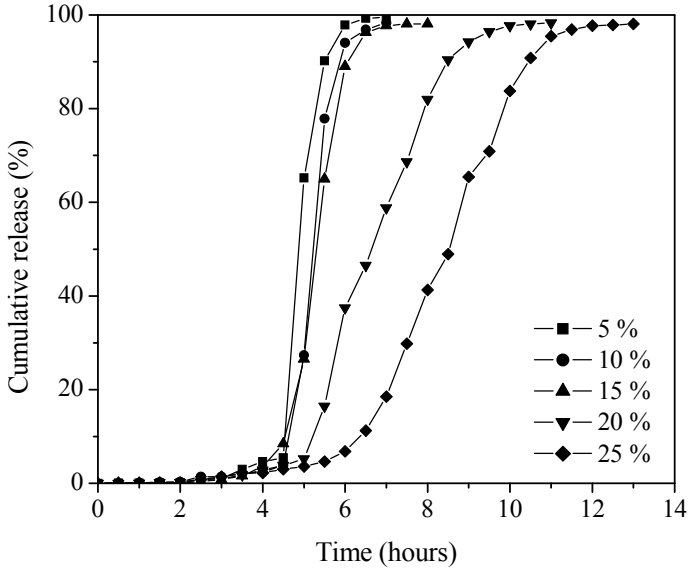


Figure 5.7. Influence of plasticizer content on lag time of release of DH from the tablet coated with graft copolymer of BDG containing 36 wt. % MAA

5.3.2.2 Effect of grafting frequency

The film coated tablets released ≤ 2 % of the drug during the first two hours in 0.1 N HCl. On changing the pH of dissolution medium to 6.8, the drug released rapidly after a lag time. Since the carboxyl groups of MAA graft chains remain unionized in acidic medium, the polymer coating was intact. The drug release was thus suppressed in the acidic medium. However, at the near neutral pH of 6.8, the carboxyl groups of polymer chains ionized. This led to swelling of the polymer which ultimately resulted in crack formation followed by rupture of the coating. As a result, the drug was released rapidly after the lag time.

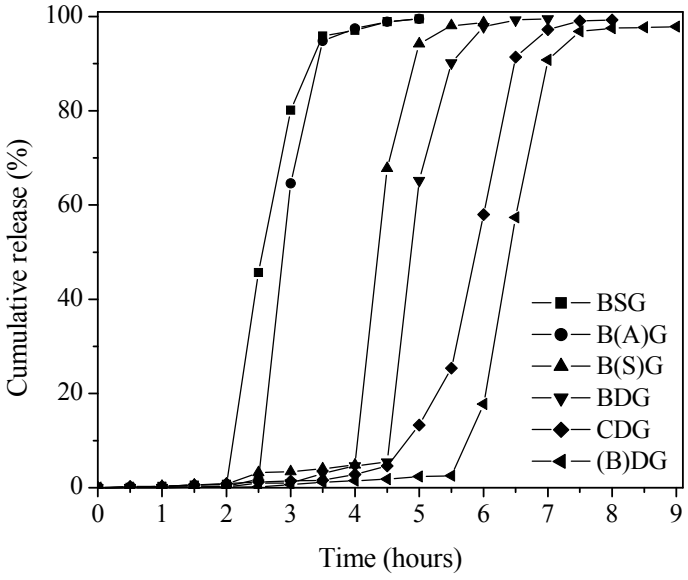


Figure 5.8. Pulsatile release of DH from the tablets coated with graft copolymers varying in MAA grafting frequency

The dissolution of DH from the tablets coated with the graft copolymers containing 34 - 37 wt. % MAA and 15 % coating level is shown in Figure 5.8. The lag time increased from 2.1 to 5.7 hours as the MAA grafting frequency decreased in the polyester backbone. This is due to the decrease in swelling rate of the graft copolymers which governs the time required for generation of cracks and then rupture. It was observed that the lag time increased significantly with the hydrophobicity of backbone on incorporation of 1, 4 cyclohexane dimethanol and bis (hydroxylethyl terephthalate).

5.3.2.3 Effect of MAA content

To study the effect of MAA content of the graft copolymers on the lag time, the tablets were coated with the BDG graft copolymer containing increasing levels of MAA. Each polymer was coated at the level of 25 wt. % on the total weight of tablet. The dissolution profiles of coated tablets shown in the Figure 5.9 indicate that the lag time decreased with increasing MAA content. This is because the presence of more MAA and their ionization provide more hydrophilicity to the polymers in near neutral pH medium. This led to faster swelling followed by rupturing of film coat and resulted in lower lag time.

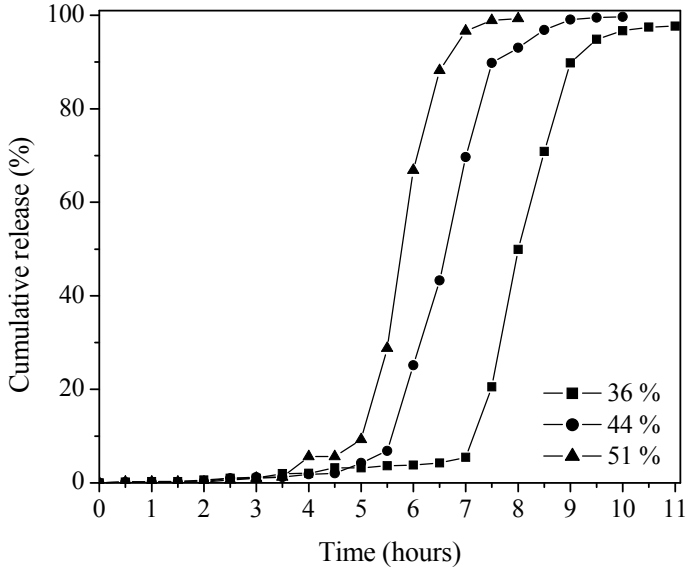


Figure 5.9. Effect of MAA content on the lag time of DH pulsatile release from the tablet coated with 25 % graft copolymer

5.3.2.4 Effect of coating thickness

The effect of coating level on the lag time of drug release was studied. The graft copolymer BDG containing 36, 44 and 51 wt. % MAA was used for coating. Each polymer coated on four different levels, *viz*., 10, 15, 20 and 25 wt. % and the dissolution profiles of coated tablets are shown in Figure 5.10 (a-c). The results show that the lag time of drug release increased with increasing the coating level for all the three graft copolymers.

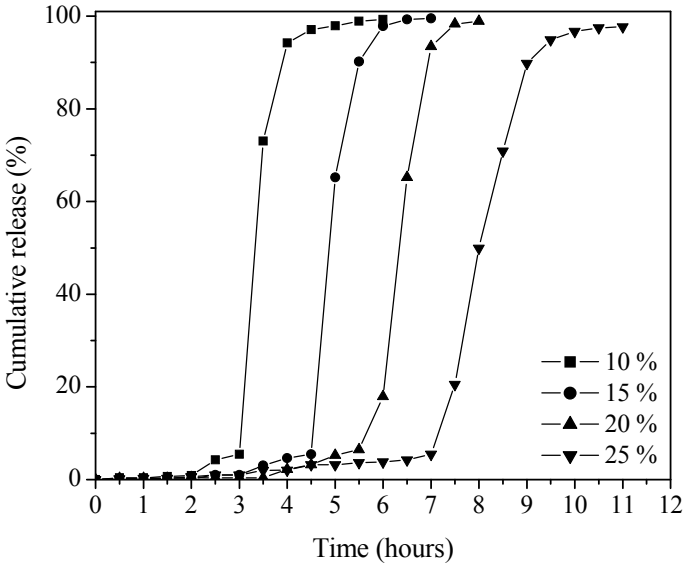


Figure 5.10a. Effect of coating thickness on the lag time of DH pulsatile release from the tablet coated with graft copolymer BDG containing 36 wt. % MAA

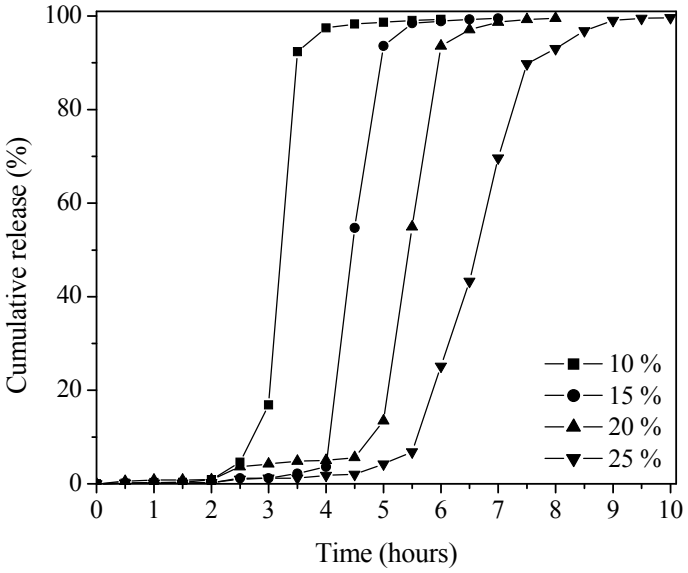


Figure 5.10b. Effect of coating thickness on the lag time of DH pulsatile release from the tablet coated with graft copolymer BDG containing 44 wt. % MAA

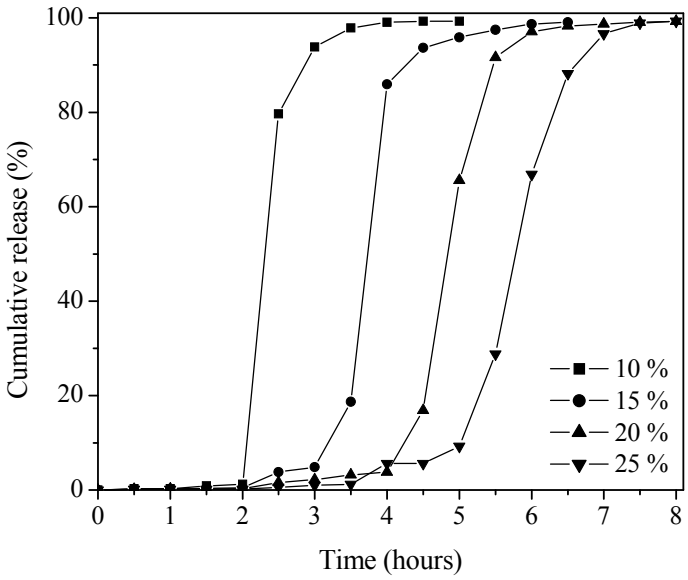


Figure 5.10c. Effect of coating thickness on the lag time of DH pulsatile release from the tablet coated with graft copolymer BDG containing 51 wt. % MAA

When the coating thickness is more, the time required for dissolution medium penetration and hence the swelling followed by rupturing of film coat is longer. Therefore, the lag time of pulsatile release increased directly with the coating thickness of graft copolymers. Similar observation has been reported in the past for the ethyl cellulose coated tablets wherein, the higher level of coating thickness led to slower hydration of coating layer and resulted in longer lag time of pulsed release (Sungthongjeen et al., 2004).

5.3.2.5 Effect of coating level on duration of pulse release

The effect of coating level on duration of pulse release is shown in Figure 5.11. The pulse duration was taken as the time interval between the 10 % (lag time) and 80 % of drug release. The graft copolymer BDG-g-MAA (MAA content: 36, 44 and 51 %) were coated at levels 10 - 25 %. It was observed that the pulse duration increased with the coating level. Since the experimented tablets do not have super disintegrant, the rate of drug release after the lag time directly related to the time interval between the initiation of crack and complete rupture of film coat. The coat of higher thickness took relatively longer time to undergo complete rupture as a result of higher mechanical strength. The pulse duration was less than 1.75 hours for the tablets containing the highest coating level 25 % (Figure 5.10a-c). This duration is

comparable with that of reported dosage form comprising the super disintegrant (Fan et al., 2004).

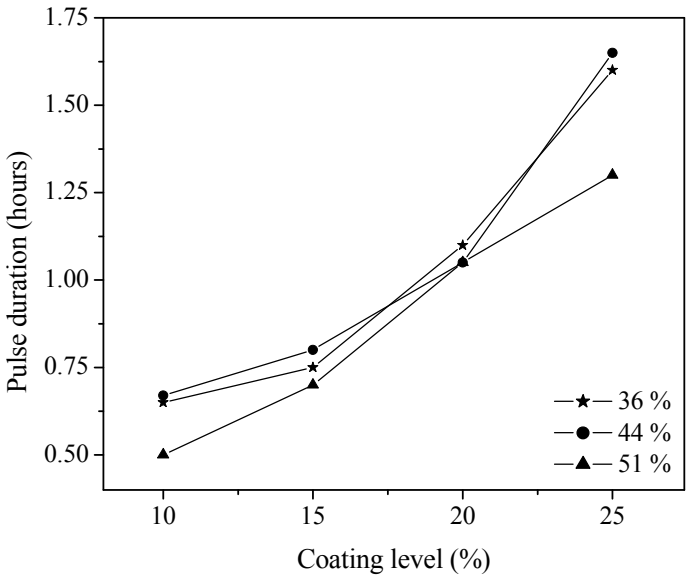


Figure 5.11. Effect of coating level of graft copolymers on the pulse duration

The above results illustrate that by selecting the appropriate graft copolymer composition and coating levels, the desired lag time could be achieved. Since the polymer coating remains intact in the acidic medium prevalent in the stomach, the peristalsis and contraction of stomach do not influence the integrity of coating as in the case of enteric coated dosage forms. So the lag time of drug release depends upon the rate at which the polymer swells and then ruptures in the near neutral pH medium prevalent in the intestinal region. In the case of tablet coated with hydroxypropyl methylcellulose, the lag time for drug release depends upon the rate of erosion. The erosion occurs even in the gastric medium as hydroxypropyl methylcellulose is a pH independent hydrophilic polymer. Since the effect of peristalsis and contraction of stomach on the erosion rate of coating can not be neglected, the lag time of drug release can not be predicted (Fukui et al., 2000). It can be concluded that the coating of dosage forms with the pH dependent graft copolymers would enable the pulsatile release of drug in intestinal region after a predetermined time lag.

Similarly, the pH dependent pulsatile release system designed herein could be used effectively for targeting the drug release to colonic region. Since, the time controlled

delayed release systems coated with the pH independent polymers suffer from variation in gastric emptying time, the drug release can not be targeted to the colonic region effectively. The colon targeting formulations coated with pH dependent polymer Eudragit® S100 showed that the drug released either prematurely or not at all. Eudragit® S100 coat has to dissolve within a short time span at pH 7.4 since the residence time of dosage form in terminal ileum is short. It was reported in the past that the Eudragit® S100 coating failed to do so, which resulted in the evacuation of dosage form from the body as an intact tablet. This might have occurred as the dosage form moves from ileum to colon, the pH drops from 7.4 to 6.0 wherein the Eudragit® S100 coating does not dissolve. However, in the case of dosage forms based on polymers developed in this work, would release the drug in the colonic region eventhough pH drops from 7.4 to 6.0 as the coated polymers can swell and then rupture at pH > 5.5. Thus by taking into account transit time of dosage form in intestine which is about 3-5 hours (Leopold, 1999) a dosage form could be designed to target the drug release in colon.

5.3.3 The mechanism of drug release

Bodmeier and Paeratakul, 1994 showed that the release of water soluble drug chloropheniramine maleate encapsulated in ethyl cellulose films occurred through the micro ruptures formed in the ethyl cellulose films as a result of osmotic pressure. The water insoluble drug ibuprofen was released by diffusion through the coated ethylcellulose film. In this study, the graft copolymers exhibited low modulus and elongation at break (Tables 5.2 and 5.3) indicating their brittle nature as in the case of ethylcellulose (Bussemer et al., 2003). Thus, while the rupture of ethylcellulose is triggered by the swelling of the hydrogel or super disintegrant layer underneath, that of the graft copolymer is triggered by its swelling. This is already validated by ESEM observation which showed the swelling induced rupture of the graft copolymer film.

To demonstrate further that the release is independent of the solubility or molecular size of the drug, we studied the release of water insoluble drug Indomethacin (IM) and macromolecular marker FITC dextran 4000 from the film coated tablet. The core tablet prepared as earlier was coated at 20 wt % level with graft copolymer BDG containing 36 wt. % MAA. IM was released rapidly after a lag time of ~ 5.5

hours (Figure 5.12). This is the same as observed in the release of DH and shows that the pulsed release of drug occurs by swelling induced rupture of film coat and not by osmotic pressure as IM is a water insoluble drug.

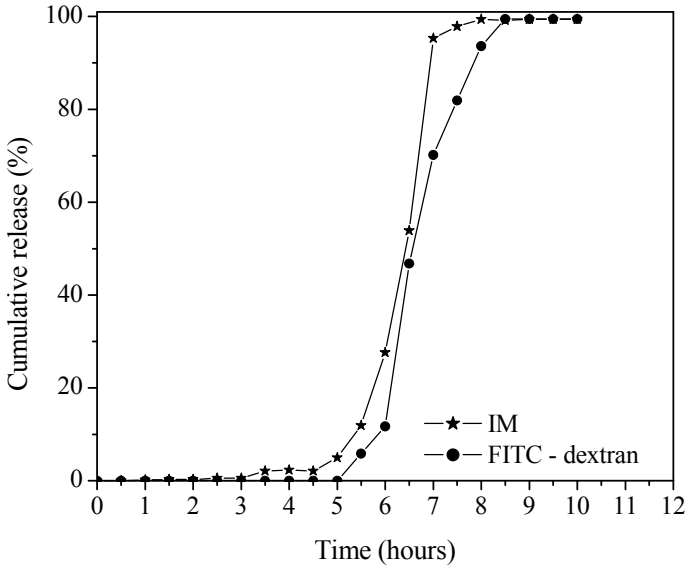


Figure 5.12. Pulsatile release of IM and FITC - dextran 4000 from the tablet coated with graft copolymer of BDG containing 36 wt. % of MAA

If the release of low molecular weight drugs occurs primarily as a result of ruptures in the film coating, the drugs of higher molecular size should also exhibit similar release behavior. To validate the assumption, the release of the macromolecular marker FITC - dextran of molecular weight 4000 was investigated. FITC - dextran was released rapidly after a lag time of ~ 5.5 hours (Figure 5.12) which is the same as observed in the case of DH and IM. Thus, the pulsed release is governed by the polymer composition, coating thickness and plasticizer content and is independent of solubility and molecular size of the drug. This confirms that the graft copolymer can be effectively used as rupturable film coating for tablets to deliver the low molecular weight drugs as well the macromolecular drugs such as proteins and peptides.

5.4 Conclusions

The evaluation of acidic graft copolymers for the pulsatile delivery of drugs in near neutral pH medium is described in this chapter. The suitability of graft copolymers as a rupturable film coating was confirmed by mechanical property measurement,

which showed their brittle nature. Interestingly, the polymers did not show ductile behavior under wet conditions which is desirable to achieve the pulsatile delivery of drugs. *In vitro* release study of the film coated tablets showed pulsatile release of drugs after a time lag. The lag time of pulsatile release increased with the hydrophobicity of polymers, coating thickness and plasticizer content. The mechanism of release was swelling followed by rupture of film coat as evidenced from Environmental Scanning Electron Microscope observation. We have shown *in vitro* study that the pulsatile delivery of proteins and peptides can be achieved in colonic region using FITC- dextran 4000 as a model compound.

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Chapter 6

Basic Graft Copolymers: Synthesis and Characterization

6.1 Introduction

Polymers which undergo reversible phase transformation are integral part of pharmaceutical dosage forms. Particularly, the pH dependent polymers are extensively investigated to target the release of drugs at particular site in the gastrointestinal tract (Lai et al., 2008). For example, the enteric polymers suppress the release of drugs at acidic pH prevalent in the stomach and release rapidly in the near neutral pH of intestine (Guo et al., 2002, Toorisaka et al., 2005, Silva et al., 2006 and Cerea et al., 2008). The reverse enteric polymers have been used as a barrier coating to protect the drug from moisture and deliver at acidic pH prevalent in the stomach (Menjoge and Kulkarni, 2007). The reverse enteric polymers contain basic groups which undergo protonation under acidic pH conditions and brought out the dissolution of polymer.

Presently available reverse enteric polymer in the market is a random copolymer of methyl methacrylate, butyl methacrylate and 2-dimethylaminoethyl methacrylate (Eudragit E). This polymer is readily soluble in gastric pH < 4.0. It swells and permeable to the aqueous medium at pH > 5.0. Since this polymer is permeable to the aqueous medium its utility in moisture protection of dosage forms is limited. Particularly in the development of oral suspensions, the drug encapsulated polymer particles have been suspended in reconstitute medium at pH ~ 5.5. If the polymer is permeable to this medium, the encapsulated drug would leach out and impart a bitter taste to the formulation (Lorenzo-Lamosam et al., 1997). The basic polymers presently available undergo rapid dissolution at acidic pH and hence their utility in gastroretentive delivery of drugs is limited.

The graft copolymer comprising poly (2-dimethylaminoethyl methacrylate) backbone and poly (caprolactone) graft chains exhibited partial solubility at near neutral pH and dissolved rapidly at acidic pH (Mespouille et al., 2005). Similarly, the graft copolymer containing poly (styrene) backbone and poly (2-dimethylaminoethyl methacrylate) graft chains dissolved freely in the water irrespective of pH (Hu et al., 2005). These reports show that the copolymers of 2-dimethylaminoethyl methacrylate swelled or dissolved at near neutral pH irrespective of their structure either random or graft. Therefore, there is a need for new reverse enteric polymers which swell or dissolve at acidic pH, while remaining

in collapsed state at near neutral pH. Such polymers would be useful for barrier coating of drugs.

A dosage form which swells under acidic pH conditions prevalent in the stomach is desirable for the gastroretentive delivery of drugs. This can be achieved by the incorporation of swellable polymers in the dosage form. However, the incorporation of swellable polymers, *viz.,* croscarmellose sodium and crospovidone led to increase in drug release rate (Chavanpatil et al., 2005 and Garg and Gupta, 2009). Therefore, we synthesized a series of basic graft copolymers which swell rapidly and then dissolve over an extended time period. The rapid swelling of polymers would ensure the equilibrium swelling of tablet within short duration. The release rate of drugs would be controlled by swelling or dissolution rate of polymers.

In this chapter, the synthesis and characterization of basic graft copolymers containing polyester backbone and 4-vinylpyridine graft chains is described. The synthesis of polymer involved two steps. In the first step, the aliphatic polyesters differing in unsaturation frequency were synthesized. In the second step, the unsaturated polyesters synthesized were grafted with 4-vinylpyridine at various levels. The graft copolymers exhibited rapid swelling and then slow dissolution at acidic pH. The polymers did not swell or dissolve at near neutral pH. The polymers which contained lower level of 4-vinylpyridine swelled more and then dissolved slowly. On the other hand, the polymers which contained higher level of 4-vinylpyridine swelled little, as they dissolved rapidly. The polymers were characterized for structure and composition, molecular weight and glass transition temperature.

6.2 Experimental

6.2.1 Materials

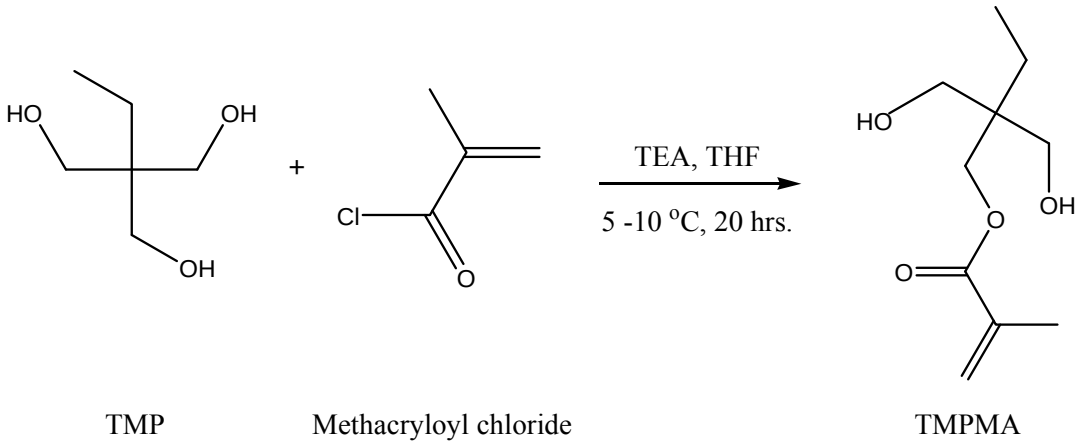
1,4 Butanediol (B), 1,4 Cyclohexane dimethanol (C), Succinic acid (S), Adipic acid [(A)], Dodecandioic acid (D), Fumaric acid (F), Itaconic acid (I), Allyl glycidyl ether (A), Trimethylolpropane (TMP), Methacrylic acid (MAA), 4-Vinylpyrridine (4VP) and Titanium (IV) butoxide were purchased from Sigma-Aldrich, St Louis, USA. Benzoyl chloride, Triethylamine (TEA), Dimethyl formamide (DMF), Chloroform ($CHCl_3$), Methanol (CH_3OH) and Tetrahydrofuran (THF) were

purchased from Merck, India. Sebacic acid [(S)] was purchased from s.d.fine-chem Ltd., India. Azobisisobutyronitrile (AIBN) was purchased from a local supplier.

6.2.2 Synthesis of methacryloyl chloride

In a 250 ml round-bottomed flask, 50.0 g (0.580 moles) of MAA, 97.96 g (0.696 moles) of benzoyl chloride were placed and refluxed for 1 hour. 0.100 g of hydroquinone was added to inhibit the free radical polymerization of MAA. Methacryloyl chloride was distilled off from the reaction mixture.

6.2.3 Synthesis of trimethylolpropane methacrylate (TMPMA)



TMP Methacryloyl chloride TMPMA

Figure 6.1. Synthesis of TMPMA

The schematic representation of synthesis of TMPMA is shown in Figure 6.1. 25.0 g (0.186 moles) of TMP and 18.85 g (0.186 moles) of TEA were dissolved in 500 ml of THF in a 1000 ml round-bottom flask. Separately, 19.47 g (0.186 moles) of methacryloyl chloride was dissolved in 100 ml of THF and added to the above reaction mixture in a drop wise manner over 4 hours under stirring. The temperature was maintained between 2 to 5 ^{o}C and the reaction was continued for 20 hours. The precipitated TEA salt was filtered off and the filtrate was concentrated on a rotary evaporator. TMPMA was separated from TMP and its di and tri methacrylate derivatives by column chromatography.

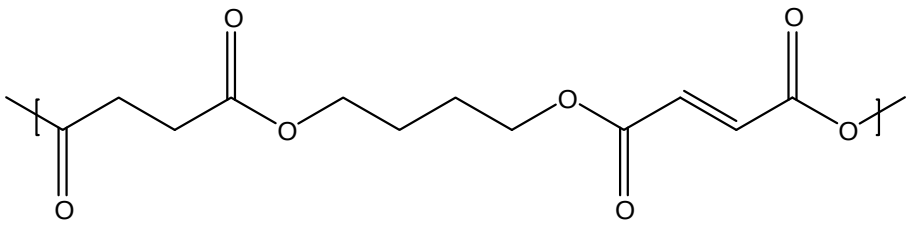
6.2.4 Synthesis of unsaturated polyesters and 4VP grafted polyesters

Unsaturated polyesters were synthesized by bulk polymerization of diol, dicarboxylic acid and an unsaturated monomer. The structure of unsaturated polyesters synthesized is shown in Figure 6.2. Synthesized unsaturated polyesters

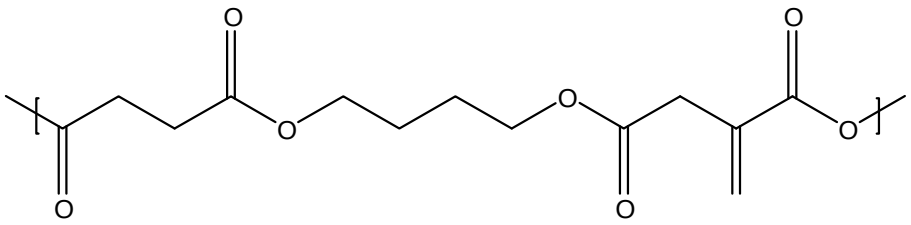
were grafted with 4VP under appropriate conditions. The graft copolymers were synthesized so as to obtain various levels 4VP content and its grafting frequency on the polyester backbone. The graft copolymers synthesized were precipitated in methanol - water mixture (1:1 v/v) in order to remove the unreacted monomer and homopolymer of 4VP. The purified polymers were dried at room temperature for 7 days under vacuum. The detailed procedure for synthesis of unsaturated polyesters and conditions to be maintained for grafting reaction has been described in chapter 3.

Structural representation

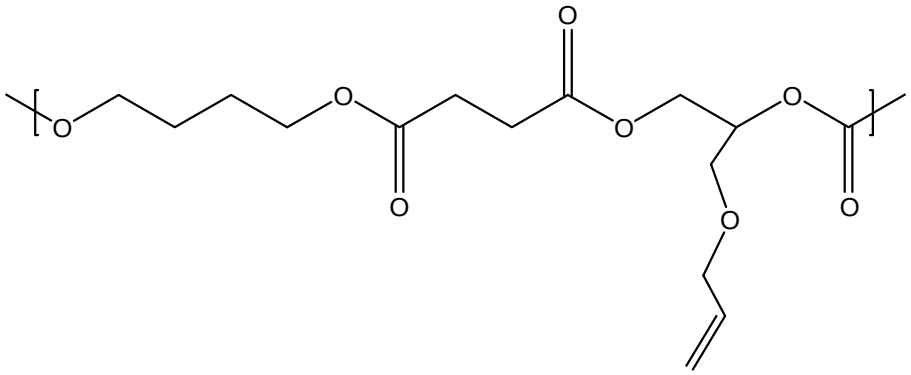
Unsaturated polyesters comprising various types of unsaturated groups



Poly (1,4 Butanediol - Succinic acid - Fumaric acid) (BSF)

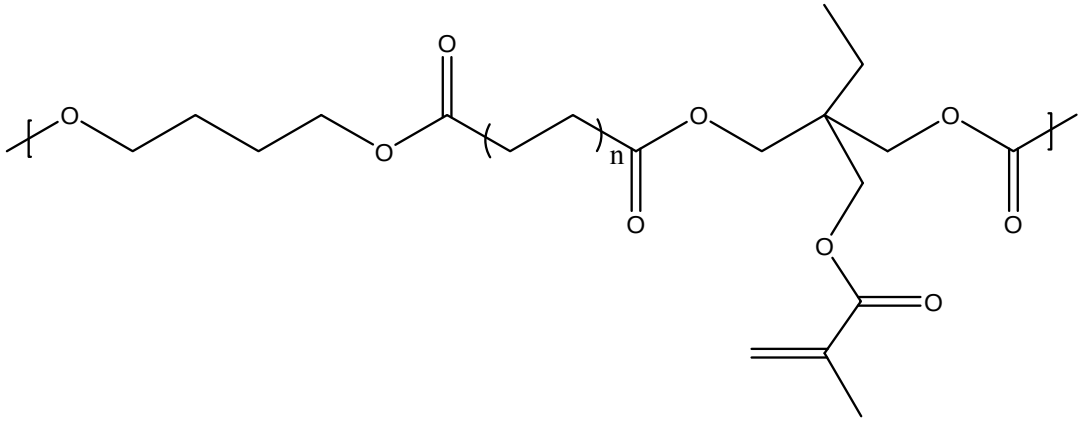


Poly (1,4 Butanediol - Succinic acid - Itaconic acid) (BSI)



Poly (1,4 Butanediol - Succinic acid - Allyl glycidyl ether) (BSA)

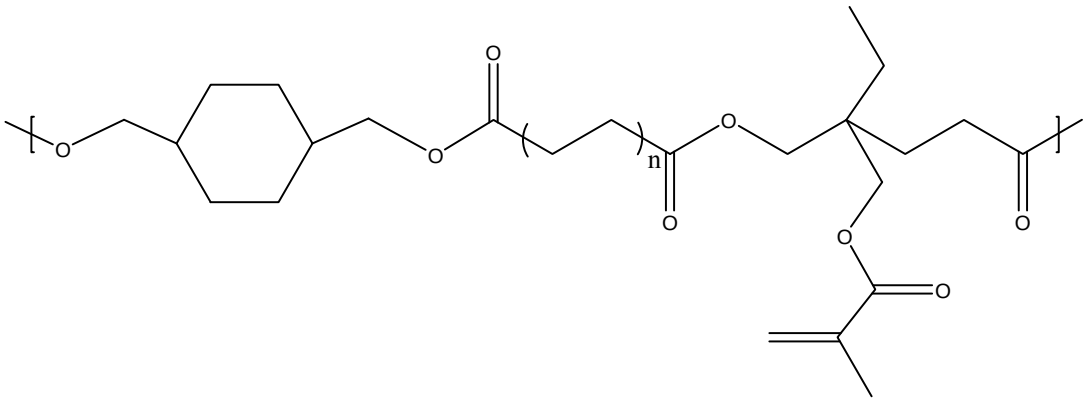
Unsaturated polyesters comprising 1, 4 butane diol, dicarboxylic acids differing in chain length and trimethylolpropane methacrylate



Poly (1, 4 Butanediol - Succinic acid - Trimethylolpropane methacrylate) (BST)

n = 1, Succinic acid (BST) and n = 5, Dodecanedioic acid (BDT)

Unsaturated polyesters comprising 1, 4 cyclohexane dimethanol, dicarboxylic acids differing in chain length and trimethylolpropane methacrylate



Poly (1, 4 Cyclohexane dimethanol - Succinic acid - Trimethylolpropane methacrylate) (CST)

n = 1, Succinic acid (CST); n = 2, Adipic acid [C(A)T];

n = 4, Sebacic acid [C(S)T] and n = 5, Dodecanedioic acid (CDT)

Figure 6.2. Structure of unsaturated polyesters

6.2.5 Characterization of unsaturated polyesters and graft copolymers

^{1}H NMR spectra were recorded on Bruker AV200 (200 MH_Z) spectrometer using $CDCl_3$ as a solvent. FTIR spectra were recorded on Perkin-Elmer Spectrum One instrument in diffuse reflectance mode at frequencies from 4000 to 400 cm^{-1}. The

composition of unsaturated polyesters and graft copolymers was determined from peak integral of ^1H NMR spectra. The molecular weight of unsaturated polyesters was determined by Gel Permeation Chromatography (Agilent Technologies, 1200 Series) using Styragel column and THF as an eluting solvent at the rate of 1ml / min. Polystyrene (Polyscience) was used as a standard. Glass transition temperature (T_g) of unsaturated polyesters and graft copolymers was determined by TA instruments DSC Q10 using nitrogen as a purging gas. Sealed aluminum pan containing ~ 5 mg of sample was scanned from - 80 to 200 ^oC at the heating rate of 10 ^oC / min.

6.2.6 Preparation of polymer films

The polymer films were prepared by solution casting. The polymer solution was prepared by dissolving 0.200 g of polymer in 2 ml of $CHCl_3$. The solution obtained was poured in a petri dish and the solvent was evaporated. The film was pealed off from the petri dish and dried under vacuum for 7 days at room temperature. Thickness and diameter of the films were 200 μm and 2 cm respectively.

6.2.7 Degree of swelling of graft copolymers

The degree of swelling of polymer films was determined in 0.1 N HCl. At regular time interval, the intact swollen film was removed and blotted with tissue paper to remove excess water on the surface and weighed. Similarly, the degree of swelling of polymer films was determined in phosphate buffer solution, pH 5.8. The degree of swelling (DS) of films was calculated as follows,

$$DS = [(W_s - W_d) / W_d] \times 100$$

Where, W_s and W_d are the swollen and dry weight of the films respectively.

6.3 Results and discussion

The graft copolymers exhibit different dissolution properties compared to their linear analogs of identical composition. For instance, the pH dependent graft copolymers undergo swelling before their dissolution. Conventionally, such pH dependent graft copolymers are synthesized by grafting acidic or basic monomer on the natural polymers. The free radical initiators, γ-ray and electron beam irradiation are used to introduce radical sites in the backbone on which grafting occurred (Hebeish et al., 1998 and Tripathy et al., 2008). Some reports reveal the surface

grafting of monomers on preformed polymer (Zhai et al., 2002). In these approaches, the grafting of monomer occurs randomly on the backbone and hence there is no control over the polymer architecture. The hydrophilic backbone is not desirable since the graft copolymer would absorb moisture.

We followed an approach wherein the grafting of functional monomer occurred only on the reactive sites of backbone. The polymer preparation involved, the synthesis of unsaturated polyesters differing in unsaturation frequency followed by grafting 4VP at various levels. This approach enabled more precise control over the polymer architecture. We showed that the content of 4VP and its grafting frequency on the backbone can be varied. These polymers swelled rapidly under acidic pH conditions prevalent in stomach and remained in collapsed state at near neutral pH. The rationale behind the design and synthesis of such pH dependent polymers is that they do not absorb moisture during the formulation and / or storage.

6.3.1 ^{1}H NMR and FTIR analysis of TMPMA

In chapter 3, we showed that glycidyl methacrylate can be used to introduce unsaturation in the aliphatic polyesters. The opening of epoxide ring in the presence of water liberated during esterification results in a diol having a primary and a secondary hydroxyl group. However, only about 50 % glycidyl methacrylate was incorporated because of the lower reactivity of secondary hydroxyl group. Therefore, we synthesized unsaturated polyesters using a diol which has both primary hydroxyl groups. The reactivity of such a diol would be better so that the polyesters containing higher levels of unsaturations can be synthesized. This was achieved by condensing methacryloyl chloride with TMP. The ^{1}H NMR spectrum of TMPMA is shown in Figure 6.3.

The ratio between the vinyl unsaturation [C$\underline{H_2}$=C (CH_3)–] and TMP unit (–$CH_2C\underline{H_3}$) was 1:1. This indicates that the TMPMA is free from unreacted TMP and its di and tri methacrylate derivatives. The peak at 4.25 ppm shows the presence of methylene protons [CH_2=C (CH_3) –C (=O) –O–C$\underline{H_2}$–] adjacent to the ester linkage. TMPMA synthesized was characterized by FTIR spectroscopy to confirm the presence of ester linkage (Figure 6.4). The strong band at 1709 cm^{-1} shows the presence of ester carbonyl in TMPMA. The vinyl unsaturation appears at 1635 cm^{-1}.

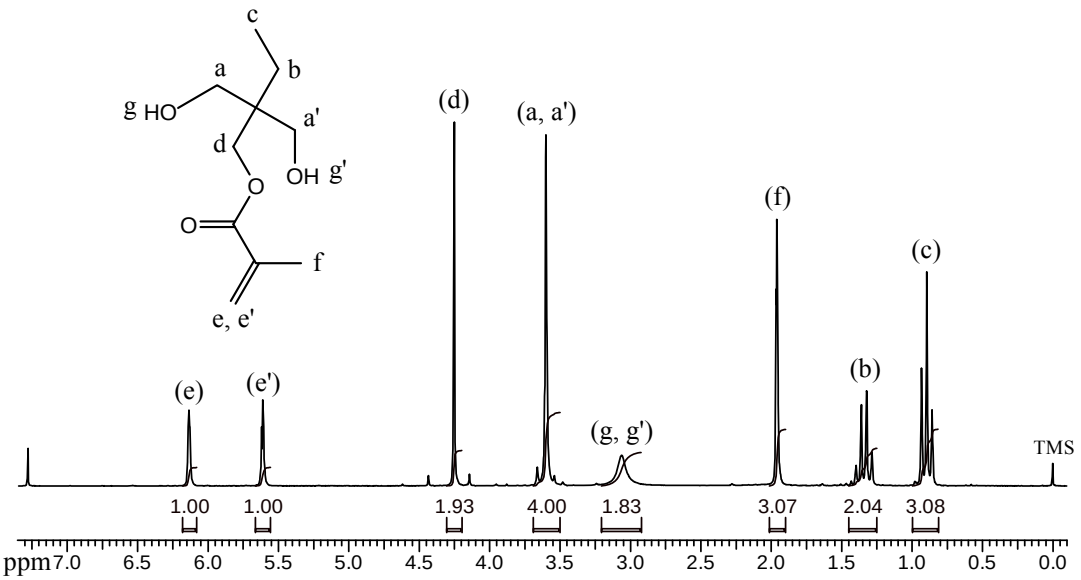


Figure 6.3. ^{1}H NMR spectrum of TMPMA

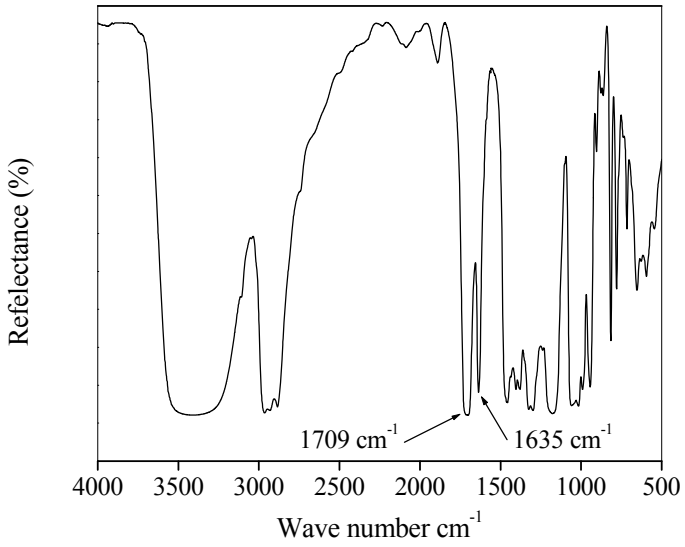


Figure 6.4. FTIR spectrum of TMPMA

6.3.2 ^{1}H NMR and FTIR analysis of unsaturated polyesters

Unsaturated polyesters were synthesized by condensing a diol, a dicarboxylic acid and TMPMA as a diol comprising vinyl group. The frequency of unsaturation in polyesters was varied by keeping the diol constant and varying the chain length of dicarboxylic acids. Succinic acid, adipic acid, sebacic acid and dodecanedioic acid

were used for this purpose. The ^{1}H NMR spectrum of representative unsaturated polyester BST is shown in Figure 6.5.

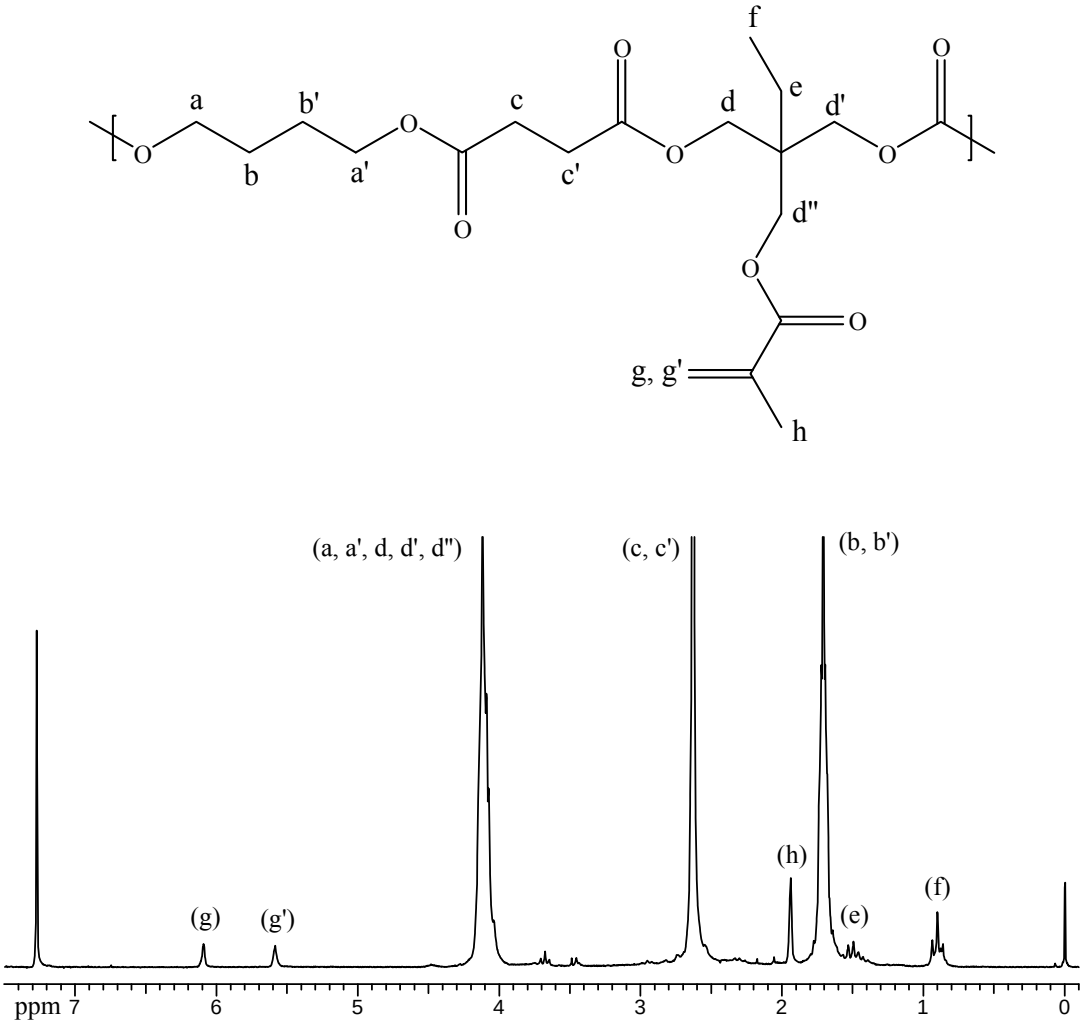


Figure 6.5. ^{1}H NMR spectrum of unsaturated polyester BST

Peak at 4.12 ppm corresponds to methylene protons of 1, 4 butanediol (–O–C<u>H</u>$_2$–CH$_2$–CH$_2$–C<u>H</u>$_2$–O–) and TMPMA {–O–C<u>H</u>$_2$–C (CH$_2$CH$_3$) [C<u>H</u>$_2$–O–C(=O)–C(CH$_3$)=CH$_2$]–C<u>H</u>$_2$–O–} which are adjacent to the ester carbonyls. Methylene protons of succinic acid [–(O=C)C<u>H</u>$_2$–C<u>H</u>$_2$(C=O)–] appear at 2.63 ppm. Peaks at 5.58 and 6.09 ppm confirm the presence of vinyl groups. FTIR spectrum of BST (Figure 6.6) shows the presence of ester carbonyl and vinyl groups at 1736 and 1635 cm^{-1} respectively.

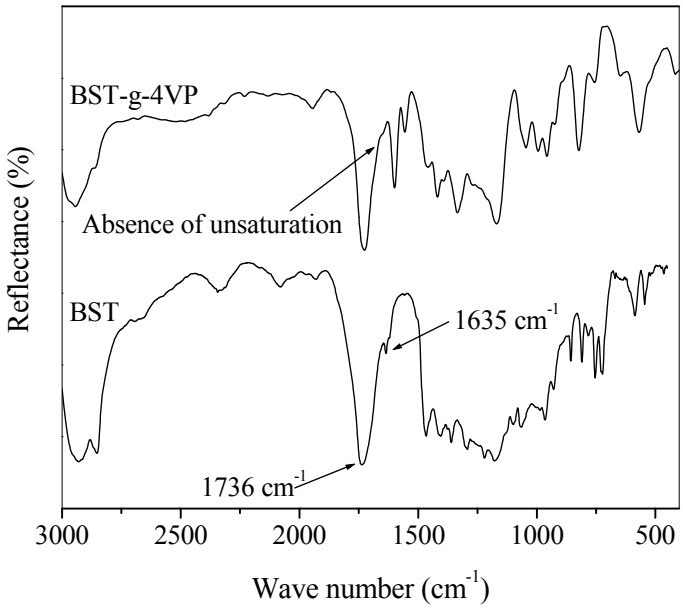


Figure 6.6. FTIR spectrum of unsaturated polyester BST and 4VP grafted BST

Table 6.1. Composition, molecular weight and polydispersity of unsaturated polyesters

Polymers	Feed Composition (Mole ratio)	Polymer Composition (Mole Ratio)	M_w (g mol^{-1})	M_n (g mol^{-1})	M_w / M_n
BSF	50:43:07	48:46:06	8486	4658	1.82
BSI	50:40:10	49:45:06	9636	6338	1.52
BSA	41:50:09	45:49:06	10446	7462	1.39
BST	43:50:07	45:51:04	7081	4914	1.44
BDT	41:50:09	44:50:06	9776	6242	1.56
CST	42:50:08	47:49:04	7926	5284	1.50
C(A)T	42:50:08	45:50:05	8880	6087	1.45
C(S)T	41:50:09	45:50:05	11361	7778	1.45
CDT	40:50:10	44:50:6	11647	7612	1.53

The composition of unsaturated polyesters was determined from the peak integral of protons corresponding to respective diol and dicarboxylic acid units in ^{1}H NMR spectra. The results show that about 60 % TMPMA reacted during polyesterification. The molecular weight of unsaturated polyesters was determined by gel permeation chromatography and the results are summarized in Table 6.1. The weight average molecular weight was in the range 7000 to 11600 and the polydispersity index was 1.44 to 1.56. These results show that TMPMA is relatively a better choice over glycidyl methacrylate because of its higher reactivity.

6.3.3 Grafting of unsaturated polyesters with 4VP

In order to ensure rapid swelling in acidic medium while retaining hydrophobicity in near neutral medium, we needed a polymer bearing basic functional group. Also the ideal polymer should have sufficiently high T_g to ensure better processability. The polymer which contains 2 - dimethylaminoethyl methacrylate exhibited low T_g as well as moisture absorption. Menjoge and Kulkarni, 2007 recently reported a random copolymer of methyl methacrylate, 2 - hydroxyethyl methacrylate and 4-vinylpyridine which exhibited high T_g and did not exhibit moisture absorption. Further, this polymer dissolves rapidly at acidic pH without swelling.

We therefore synthesized graft copolymers containing 4VP. The unsaturated polyesters reported in preceding section were grafted with 4VP using AIBN as a free radical initiator. The graft copolymers were characterized by ^{1}H NMR spectroscopy to assess the extent of conversion of unsaturations in the polyester backbone. The ^{1}H NMR Spectra of 4VP grafted polyesters BSF, BSI and BSA are shown in Figure 6.7. The content 4VP in the feed was 50 wt. % in all the cases. The polyesters comprising fumaric acid, itaconic acid and allyl glycidyl ether, the unsaturations were not reacted with 4VP completely. This evidenced from the ^{1}H NMR spectra wherein the peak corresponds to unsaturations in the region 5 - 7 ppm is not disappeared.

The extent of conversion of unsaturations on grafting of 4VP in the range 30 - 60 % is shown in Figure 6.8. The reactivity of unsaturated monomers was itaconic acid > fumaric acid > allyl glycidyl ether. The change in amount of 4VP in feed did not influence the conversion of unsaturation significantly. The graft copolymers were

analyzed for their 4VP content. Incorporation of 4VP increased with its content in the feed, but the grafting level was low (Figure 6.9).

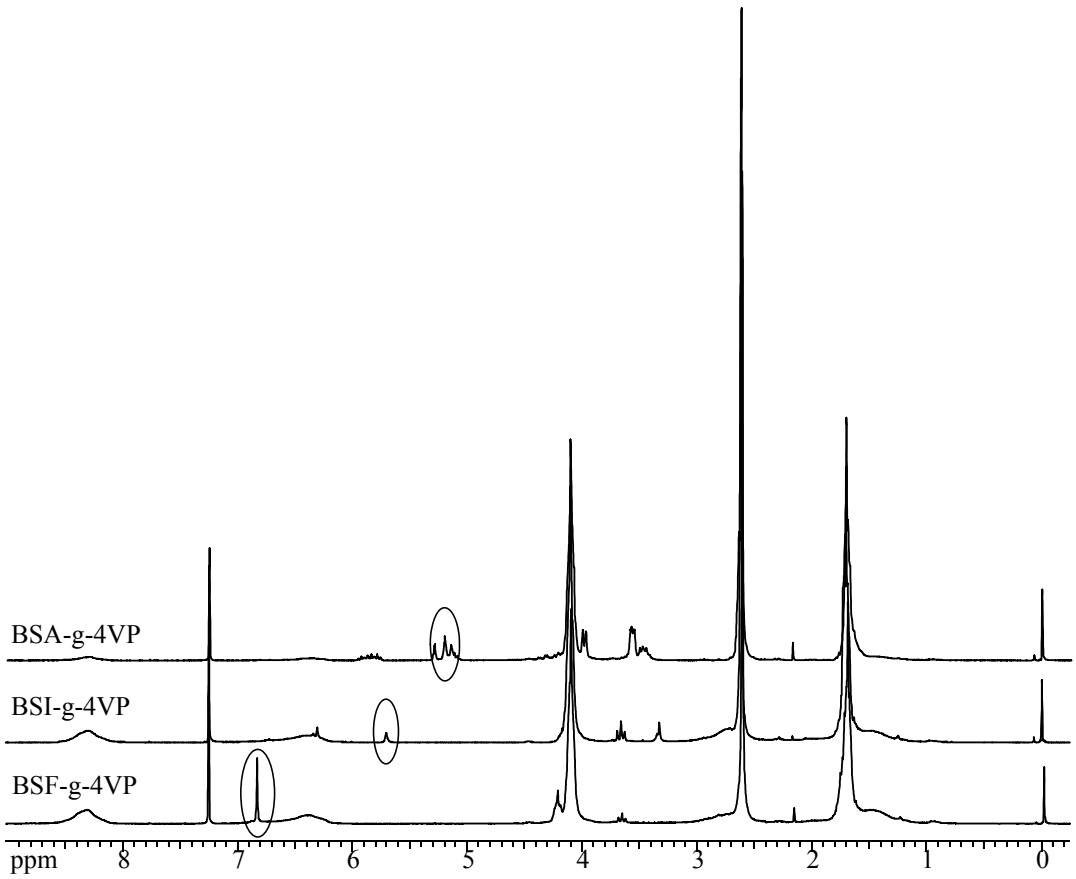


Figure 6.7. ^{1}H NMR Spectra of 4VP grafted polyesters BSF, BSI and BSA

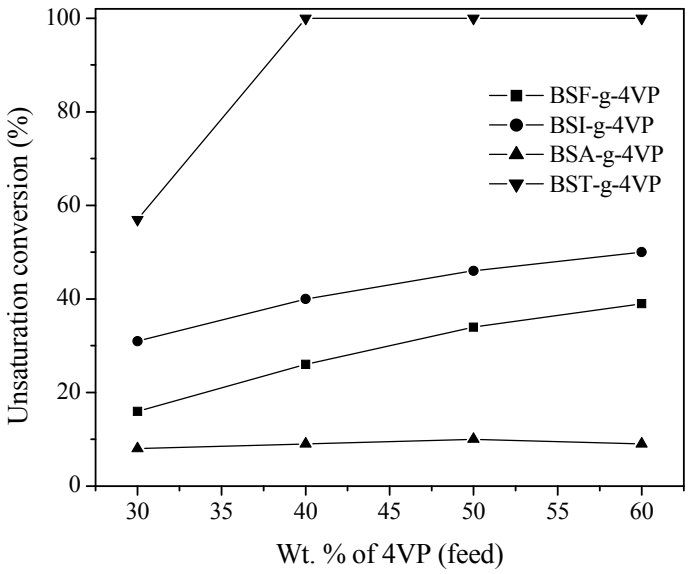


Figure 6.8. Effect of 4VP content in the feed on the conversion of unsaturation

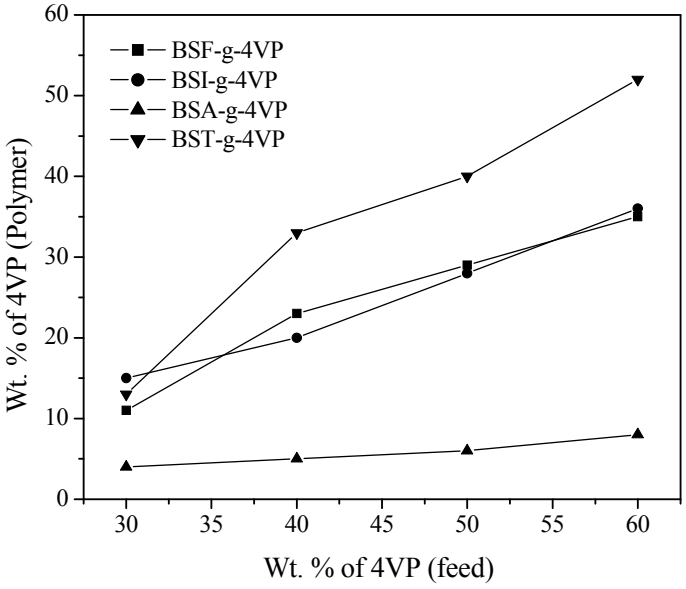


Figure 6.9. Effect of 4VP content in the feed on its level of grafting

In the case of BST, when 4VP content in the feed was 30 %, incorporation in the polymer was 17 % and only 60 % of the unsaturation in the polyester reacted. This is in contrast to the grafting of MAA wherein, 30 wt. % MAA in the feed resulted in polymers containing 27 ± 1 wt. % MAA and complete utilization of unsaturations (Chapter 3). The lower degree of 4VP incorporation can be attributed to its lower reactivity as compared to that of MAA towards the unsaturation in polyester.

However, when 4VP content in the feed was ≥ 40 wt. %, the grafting level was enhanced. ^{1}H NMR spectrum of graft copolymer BST-g-4VP containing 33 wt. % of 4VP shows that the unsaturations are completely utilized as evident from the disappearance of peaks in the region 5.58 and 6.09 ppm (Figure 6.10). Peaks at 6.32 and 8.27 ppm which corresponds to 4VP confirm its grafting on the polyester. Complete utilization of unsaturation in the polyester was further confirmed by FTIR spectroscopy as the band at 1635 cm^{-1} which corresponds to vinyl unsaturations, disappeared (Figure 6.6).

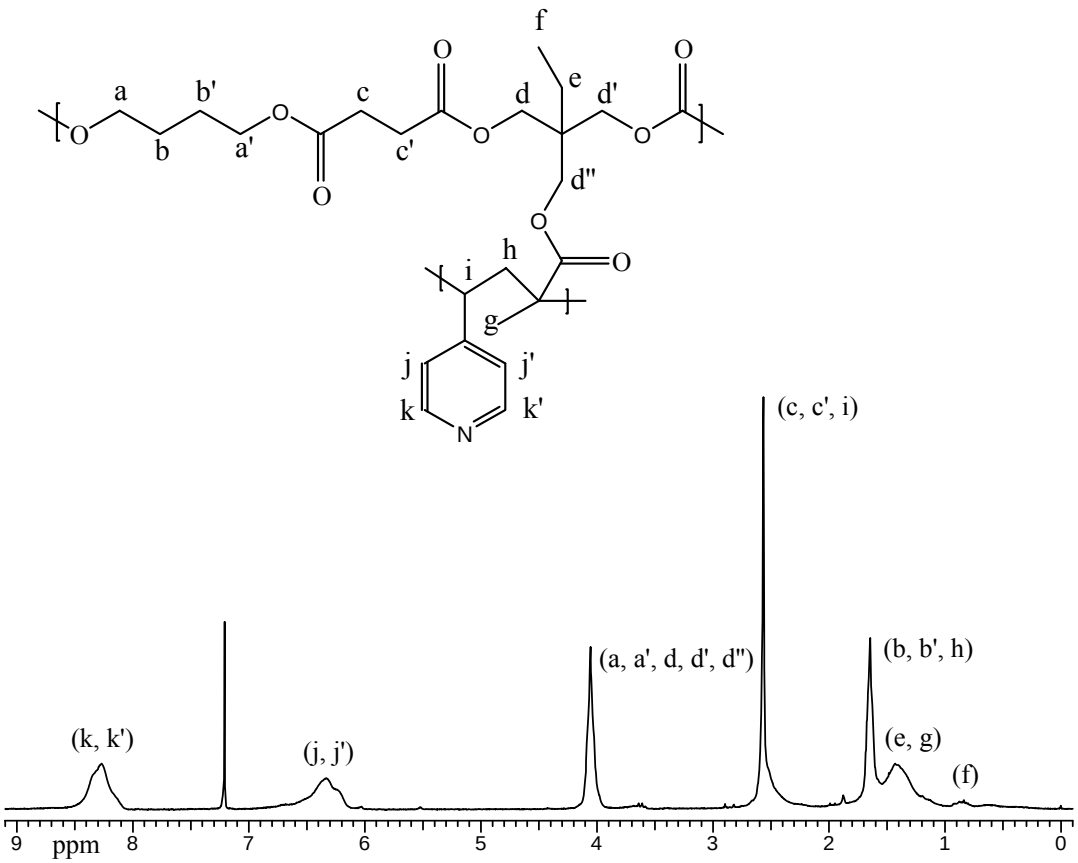


Figure 6.10. ^{1}H NMR spectrum of graft copolymer BST-g-4VP containing 33 wt. % of 4VP

Thus, grafting on unsaturated polyesters BSF, BSI and BSA resulted in graft copolymers containing unreacted unsaturations and limited level of grafting of 4VP. On the other hand, polyester comprising pendent vinyl groups as in BST effectively reacted with 4VP and yielded graft copolymers containing higher 4VP content. Hence, subsequent investigations were carried out using the unsaturated polyesters comprising trimethylolpropane methacrylate. Two serieses of unsaturated polyesters were prepared. In the first series, 1, 4 butane diol was used as a diol. In the second series, 1, 4 cyclohexane dimethanol was used as a diol.

The frequency of unsaturation along the polyester chain was varied. This was achieved by keeping the diol constant and varying the chain length of the dicarboxylic acid. Succinic acid, adipic acid, sebacic acid and dodecanedioic acid were used for this purpose. The unsaturated polyesters synthesized were grafted with 4VP at various levels. The percentage grafting of 4VP was determined by the peak

integral of protons in ^{1}H NMR spectrum of graft copolymers and the results are summarized in Table 6.2.

6.3.4 T_g of unsaturated polyesters and graft copolymers

The unsaturated polyesters and graft copolymers were characterized for their glass transition (T_g) and the results are summarized in Table 6.2. The T_g of unsaturated polyester BST was - 27.76 ^{o}C. The graft copolymer BST-g-4VP containing 33 wt. % of 4VP exhibited two T_gs at - 4.56 and 144.73 ^{o}C for BST backbone and 4VP graft chains respectively. The T_g of polyester backbones in graft copolymers was slightly higher than the corresponding unsaturated polyesters and increased with increasing level of grafting. This can be attributed to the restricted segmental motion of polyester backbone with increasing length of the graft chains since no interaction between the main chain and 4VP was detected as in the case of MAA grafted polyester. However, the T_g corresponding to 4VP graft chains did not vary with grafting level and was 144 ± 7 ^{o}C. This temperature is identical to the T_g of poly (4-vinylpyridine), *viz*., 142 ^{o}C.

In chapter 3, we showed that the grafting of methacrylic acid on polyester yielded a graft copolymer wherein, hydrogen bonding interaction between the methacrylic acid graft chains and polyester backbone resulted in suppression of segmental motion of polyester backbone to the extent that no T_g was observed for polyester backbone. Since poly (methacrylic acid) does not undergo glass transition below 180 ^{o}C, the graft copolymer did not undergo glass transition while scanning upto 180 ^{o}C.

In the present study, the existence of two T_gs shows that the polyester backbone and 4VP graft chains retain their individual characteristics. This observation is similar as in the case of poly (methyl methacrylate)-g-(propylene oxide-b-ethylene oxide) wherein, two T_gs were observed for methyl methacrylate backbone and propylene oxide-b-ethylene oxide graft chains respectively (Lucas and Porterz, 1993). This behavior was also observed in the blends of aliphatic polyester and poly (methyl methacrylate) and our finding is similar (Li and Woo, 2008).

Table 6.2. T_g of unsaturated polyesters and graft copolymers

Unsaturated Polyester	T_g	Graft copolymer	4VP content	T_g (1)	T_g (2)
BST	- 27.76	BST-g-4VP	33	- 4.56	144.73
			40	10.60	145.34
			52	15.95	142.09
BDT	- 29.65	BDT-g-4VP	30	- 29.18	141.13
			41	- 28.64	144.19
			50	- 24.32	144.41
CST	- 3.04	CST-g-4VP	25	- 0.70	137.07
			35	23.61	144.42
			51	28.65	151.87
C(A)T	- 23.04	C(A)T-g-4VP	31	1.00	142.32
			38	5.68	144.45
			51	7.22	141.08
C(S)T	- 42.66	C(S)T-g-4VP	33	- 32.06	143.25
			39	- 30.72	147.62
			50	- 27.04	143.97
CDT	- 37.79	CDT-g-4VP	30	- 34.20	143.14
			38	- 31.88	145.52
			50	- 29.23	151.86

6.3.5 Degree of swelling of graft copolymers

The degree of swelling of graft copolymer films as determined by weight gain method in 0.1 N HCl showed maximum swelling within two hours. The swollen films disintegrated then dissolved slowly over a period of time. The polymers BST-g-4VP and BDT-g-4VP had almost same 4VP content, *viz*., 33 and 30 wt. % but the grafting frequency was significantly different. Both polymers attained maximum

swelling within 0.5 hour. While the polymer BST-g-4VP disintegrated and dissolved rapidly within 2 hours, the polymer BDT-g-4VP disintegrated slowly and did not dissolve completely even at the end of 24 hours (Figure 6.11). Similarly, the graft copolymers containing 1, 4 cyclohexane dimethanol in the polyester backbone exhibited grafting frequency dependent dissolution (Figure 6.12). However, these polymers underwent dissolution over longer time period due to the greater hydrophobicity compared to those containing 1, 4 butane diol. The decrease in degree of swelling with time indicated that the decrease in swelling of the polymer was due to the removal of disintegrated particles.

The effect of 4VP content on swelling of graft copolymer is shown in Figure 6.13. The polymer having lower 4VP content dissolved slowly showing higher apparent swelling. On the other hand, the polymer having higher 4VP content started dissolving rapidly thus showing lower apparent swelling. This is because the protonation of 4VP groups in 0.1 N HCl enhanced the rate of polymer dissolution. The polymers did not swell, disintegrate or dissolve even at the end of 7 days in phosphate buffer, pH 5.8 (Figure 6.14). This is desirable as the polymers do not absorb moisture during the formulation development and / or storage. The basic graft copolymers developed herein, were evaluated to design swellable floating tablets for the gastroretentive delivery of drugs. A detailed investigation on the swelling, floating and drug release behavior has been described in chapter 7.

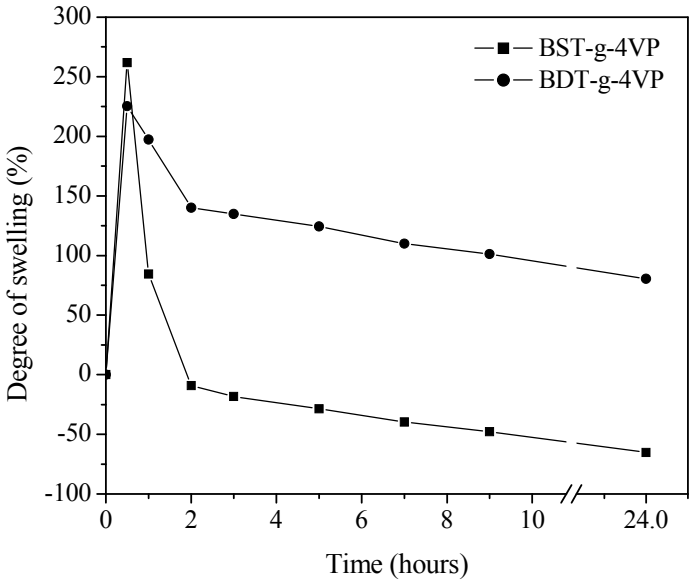


Figure 6.11. Swelling of graft copolymers containing 1, 4 butanediol in the polyester backbone in 0.1 N HCl

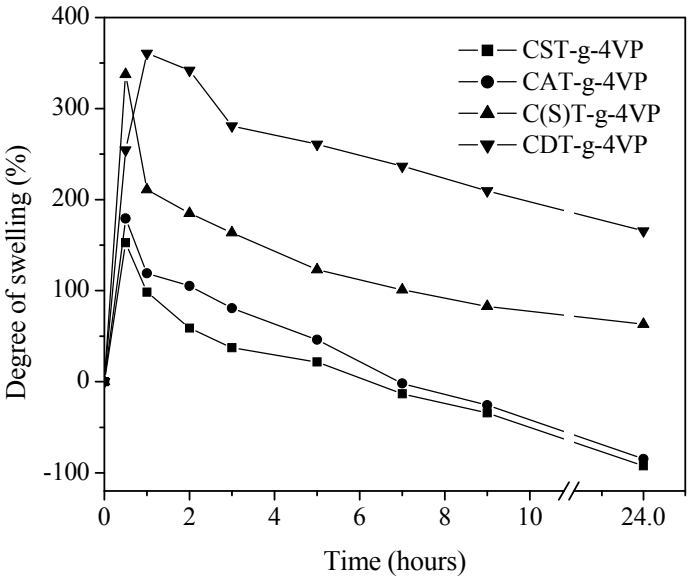


Figure 6.12. Swelling of graft copolymers containing 1, 4 cyclohexane dimethanol in the polyester backbone in 0.1 N HCl

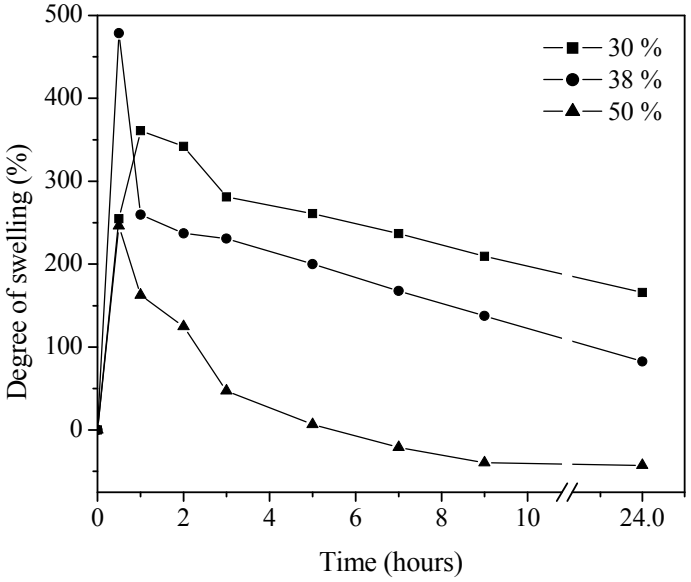


Figure 6.13. Effect of 4VP content on swelling of graft copolymers containing 1, 4 cyclohexane dimethanol in the polyester backbone in 0.1 N HCl

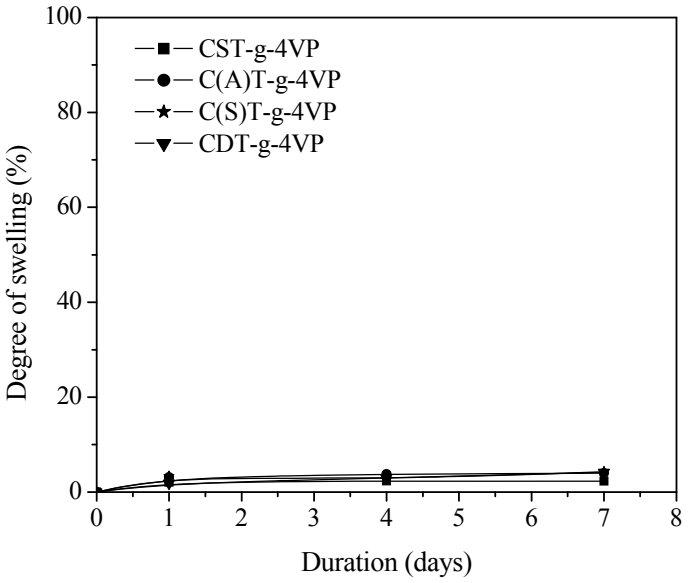


Figure 6.14. Swelling of graft copolymers containing 1, 4 cyclohexane dimethanol in the polyester backbone in phosphate buffer solution, pH 5.8

6.4 Conclusions

In this chapter, the synthesis and characterization of basic graft copolymers comprising the aliphatic polyester backbone and 4-vinylpyridine graft chains has been described. The aliphatic polyesters differing in unsaturation frequency were synthesized and grafted with 4-vinylpyridine at various levels. The structure, composition, molecular weight and glass transition temperature of the polymers were investigated. These polymers swelled rapidly at acidic pH and then dissolved over an extended time period. The swelling of polymers increased with grafting frequency of 4-vinylpyridine. When the 4-vinylpyridine content was low, the polymer swelled more and dissolved slowly. The graft copolymers did not swell or dissolve in near neutral pH medium. Thus, the graft copolymers will be useful to develop swellable floating dosage forms for gastroretentive delivery of drugs.

6.5 References

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Chapter 7

Swellable Floating Drug Delivery Systems: *In vitro* Evaluation

7.1 Introduction

Drugs which have narrow absorption window have to be delivered at the right site to enhance bioavailability (Davis, 2005). The conventional sustained release dosage forms are not site specific although they can release the drugs over an extended time period. This is because of their inability to remain at the absorption site for longer time periods. This results in incomplete delivery at absorption site and poor bioavailability of drugs (Chawla et al., 2003). For example, drugs which are absorbed in stomach and upper intestine need to be delivered in stomach (Streubel et al., 2006).

Gastroretentive dosage forms have been extensively investigated and reviewed in the literature (Talukder and Fassihi, 2004, Streubel et al., 2006 and Waterman, 2007). Such dosage forms are needed for the release of drugs for which the solubility declines with increasing pH prevalent in the intestinal region and drugs which are susceptible to degradation in intestine due to the presence of enzymes.

The most widely investigated approach to gastroretentive delivery of drugs is floatable tablets (Singh and Kim, 2000). Such tablets have been developed by using hydrophilic gellable polymer like hydroxypropyl methylcellulose, a gas generating agent and other ingredients. However, once the gastric fluid is emptied from stomach, there is no medium in which the tablet could float (Chueh et al., 1995). The adhesion of bioadhesive polymers to the gastric mucosa is poor (Cuña et al., 2001 and Säkkinen et al., 2003). Hence, the gastric retention of bioadhesive floating tablet is unpredictable.

We designed a tablet which can float on the gastric fluid as well as swell. The rationale behind this approach is that floatation can be achieved on ingestion of such tablet after little feeding. The rapid swelling of tablet on floating would prevent its passage through opened pylorus during the gastric emptying of food by ‘housekeeper wave’. Since the wave arrives in 3 to 4 hours after feeding, the tablet should attain equilibrium swelling within this duration. In order to obtain swellable tablet, it is necessary to incorporate a swellable polymer in the tablet composition. Although, the incorporation of polymers like crospovidone and croscarmellose sodium can increase the swelling of tablet, it also increases the drug release rate (Chavanpatil et al., 2005 and Garg and Gupta, 2009). Therefore, there is a need for

polymers which enhance the swelling of tablet and release the drug over an extended time period under acidic pH conditions prevalent in stomach.

We developed a series of basic graft copolymers which contain polyester backbone and 4-vinylpyridine graft chains. These polymers swelled rapidly at acidic pH and then dissolve over an extended time period. This behavior is significantly different compared to that of the random copolymer of methyl methacrylate, butyl methacrylate and 2 - dimethylaminoethyl methacrylate (Eudragit® E100) which dissolves without swelling. The polymers were characterized for structure, composition, glass transition temperature and pH dependent swelling / dissolution and the results have been discussed in chapter 6.

The evaluation of graft copolymers for the development of swellable floating drug delivery system has been described in this chapter. Blend of the basic graft copolymer and hydroxypropyl methylcellulose (HPMC K4M) incorporated with drug and other ingredients resulted in swellable floating tablet. Such tablets released the drugs which have absorption window in stomach and upper intestine over an extended time periods. Factors influencing the release of drugs, floating and swelling behavior of tablets were investigated.

7.2 Experimental

7.2.1 Materials

Hydroxypropyl methylcellulose (HPMC K4M), Magnesium stearate (MS) and Sodium bicarbonate ($NaHCO_3$) were purchased from s.d.fine-chem Ltd., India. Citric acid (CA) was purchased from Merck, India. Ciprofloxacin hydrochloride (CIPFN) and Cephalexin monohydrate (CEPLN) were gift samples from Lupin Laboratories Ltd., India. Ofloxacin (OFN) was a gift sample from Nicholas Piramal India Ltd. Riboflavin 5'-phosphate sodium (RFP) was purchased from SISCO research laboratories Pvt. Ltd., India.

7.2.2 Synthesis 4VP grafted polyesters

The basic graft copolymers comprise polyester backbone and 4-vinylpyridine graft chains. Aliphatic polyesters were synthesized using 1, 4 cyclohexane dimethanol, dicarboxylic acids differing in chain length and trimethylolpropane methacrylate. The polyesters synthesized were grafted with 4-vinylpyridine at various levels. The

detailed synthesis procedure and characterization of polymers has been described in chapter 6. The graft copolymers evaluated for the development of swellable floating tablets are given below.

(a) Poly [(1, 4 Cyclohexane dimethanol - Succinic acid - Trimethylolpropane methacrylate) - g - (4VP)]; CST-g-4VP, 4VP Content: 25 wt. %

(b) Poly [(1, 4 Cyclohexane dimethanol - Adipic acid - Trimethylolpropane methacrylate) - g - (4VP)]; C(A)T-g-4VP, 4VP Content: 31 wt. %

(c) Poly [(1, 4 Cyclohexane dimethanol - Sebacic acid - Trimethylolpropane methacrylate) - g - (4VP)]; C(S)T-g-4VP, 4VP Content: 33 wt. %

(d) Poly [(1, 4 Cyclohexane dimethanol - Dodecanedioic acid - Trimethylolpropane methacrylate) - g - (4VP)]; CDT-g-4VP, 4VP Content: 30, 38 and 50 wt. %

7.2.3 Preparation of floating tablets

The tablets of CIPFN, CEPLN, OFN and RFP were prepared by direct compression method using a hydraulic press equipped with a die and a flat faced punch. Typically, a drug and graft copolymer was finely ground and then mixed with HPMC K4M, gas generating system which includes sodium bicarbonate and citric acid. Finally, the mass obtained was lubricated with magnesium stearate and then compressed to form tablet by applying the load of 200 kg / cm^2. Diameter and thickness of the tablets were 13 and 2.8 cm respectively.

7.2.4 *In vitro* release study

In vitro release of drugs from tablets was studied in 900 ml of 0.1 N HCl by paddle method using Electrolab USP type II apparatus. The paddle rotation speed was 50 rpm and the temperature was maintained at 37 ± 0.5 ^oC. At the predetermined time interval, a known volume of dissolution medium was withdrawn and analyzed for drug concentration using spectrophotometer (Shimadzu, UV-1061PC UV) at 277, 262, 293 and 444 nm for CIPFN, CEPLN, OFN and RFP respectively.

7.2.5 Floating and swelling properties of tablets

The lag time for tablet floating and the floatation duration were visually examined during the in vitro drug release study. Lag time was measured as the duration

between dropping of a tablet into dissolution medium and its emergence to the surface. The duration of floating measured as the time period during the tablet floats continuously on the dissolution medium. The change in dimension of the tablet was analyzed by measuring the diameter and thickness.

7.3 Results and discussion

Amongst the various approaches to achieve gastroretentive drug delivery, the swellable floating tablet is a better option. The conventional floating tablets are formulated with hydrophilic gellable polymer HPMC. HPMC swells before it undergoes erosion or dissolution in aqueous medium. The swelling of HPMC tablet takes place slowly over a period of 8 hours (Maggi et al., 2000) and hence needs to be accelerated / enhanced with appropriate additives.

The incorporation of conventional swellable polymers such as croscarmellose sodium and crospovidone in HPMC leads to increase in drug release rate. Incorporation of carbopol 934 in HPMC based floating tablet results in extensive moisture intake. As a result, the density of the tablet increases which adversely affects the floating properties (Li et al., 2002 and 2003 and Prajapati et al., 2008). The random copolymer of methyl methacrylate, butyl methacrylate and 2-dimethylaminoethyl methacrylate, *viz*., Eudragit® E100 dissolves in the acidic pH media without swelling and hence is not suitable for the development of swellable floating tablets.

We synthesized a series of graft copolymers which comprise hydrophobic polyester backbone and 4VP graft chains. This involved the synthesis of aliphatic polyesters varying in unsaturation frequency followed by grafting 4VP at various levels. We showed that the content of 4VP and its grafting frequency on the backbone can be controlled by the amount 4VP in the reaction feed and the choice of the dicarboxylic acid. These graft copolymers swelled rapidly under acidic pH conditions prevalent in stomach. Further, they do not absorb moisture during formulation and / or storage. We blended these graft copolymers with HPMC K4M, incorporated the drugs to yield gastroretentive tablets. The tablets swelled rapidly after floating and released the drug for extended time period. The extent of swelling was substantially higher than the conventional floating tablets and release rate was constant under certain conditions.

7.3.1 *In vitro* release study

The graft copolymers swelled rapidly under acidic pH conditions prevalent in the stomach. The incorporation of these polymers in conventional floating tablet would enhance swelling and hence the gastric retention time. The swelling analysis showed that the graft copolymers containing 1, 4 cyclohexane dimethanol in the polyester backbone exhibited higher apparent swelling upto 350 % (chapter 6). Hence, these were selected for the preparation of swellable floating tablets.

HPMC K4M tablets exhibit shorter lag time for floating as compared to HPMC K100M tablets (Srivastava et al., 2005). In order to lower the density of tablets (< 1.0), the gas generating system comprising $NaHCO_3$ and CA was incorporated. On imbibition of dissolution medium, $NaHCO_3$ decomposed and liberated carbon dioxide. The gelling agent has to be so chosen that the gas generated is trapped within gelled tablet causing it to float within a short time (< 15 minutes) and ensures floating over the duration of release. In this context, HPMC K4M was found to be a better choice over K100M. Additional gelling agents and water soluble polymers are often incorporated in the formulation for this purpose (Talwar et al., 2000).

The incorporation of CA helps to achieve buoyancy even if the pH of the stomach is slightly increased in the fed state (Dave et al., 2004 and Garg and Gupta, 2009). 13 mm diameter floatable tablets were prepared since the tablets of this size are unlikely to empty from the stomach until the arrival of 'housekeeper wave' (Khosla and Davis, 1990). Thickness of tablets was 2.8 mm and the total weight was 500 mg. The release profile of drugs was analyzed using Ritger - Peppas equation by fitting the data up to 60 % of drug release.

$$\text{Log } (M_t / M_\infty) = \text{Log } k + n \text{ Log } t$$

Where, M_t and M_∞ denote the amount of drug released at time 't' and the total amount of drug present in the tablet respectively. The constant 'k' indicates the rate of drug release and 'n' is the release exponent which is characteristic of release. In the case of cylindrical tablet $0.89 < n < 1.0$ indicates zero order release and $0.45 < n < 0.89$ indicates anomalous release behavior (Ritger and Peppas, 1987).

7.3.1.1 Effect of grafting frequency of 4VP on CIPFN release

In vitro release of drugs was monitored in 0.1 N HCl. The floating behavior of tablets, *viz*., lag time and duration of floating was monitored during the release study. The change in the dimension of the tablet was measured at the end of 4 hours, after which the gastric emptying is normally caused by 'housekeeper wave'. The composition of tablets designed to investigate the effect of grafting frequency of 4VP in the polymer on CIPFN release is summarized in Tables 7.1 and 7.2. The rate of drug release increased with 4VP grafting frequency from CDT-g-4VP to CST-g-4VP (Figure 7.1). This can be attributed to the increase in diffusivity of the drug as a result of the dissolution of the polymer within the tablet.

Table 7.1. Composition of the tablets

Ingredients	Amount (%)
CIPFN	30
Graft copolymer	25
HPMC K4M	30
$NaHCO_3$	07
CA	07
MS	01

Table 7.2. Effect of 4VP grafting frequency in the polymer on swelling and floating behavior of tablets and release parameters

Tablet code	Graft copolymer	4VP content (wt. %)	Floating lag time (min.)	Diameter / thickness (mm)	n	k
F-1	CST-g-4VP	25	2	14 / 5	0.7656	0.1633
F-2	CAT-g-4VP	31	4	15 / 5	0.7565	0.1202
F-3	C(S)T-g-4VP	33	7	18 / 7	0.7854	0.0899
F-4	CDT-g-4VP	30	8	18 / 7	0.8803	0.0555

All tablets floated over the release period of 18 hours

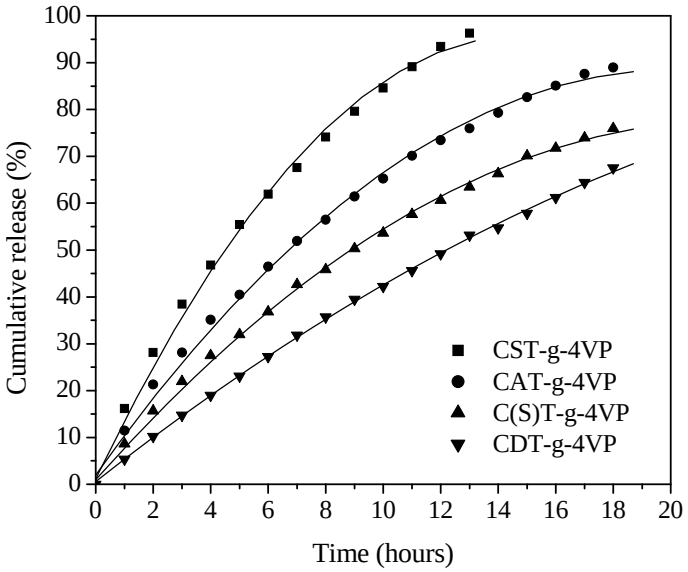

Figure 7.1. Effect of 4VP grafting frequency in the polymer on CIPFN release

Incorporation of the graft copolymers in the HPMC K4M resulted in rapid initial swelling of the tablet followed by a continuous swelling at a slower rate over an extended time period. The swelling behavior of the tablets was studied using dissolution apparatus under the same conditions maintained for drug release. Swelling index was calculated from the formula,

Swelling index = $(W_s - W_d) / W_d$

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

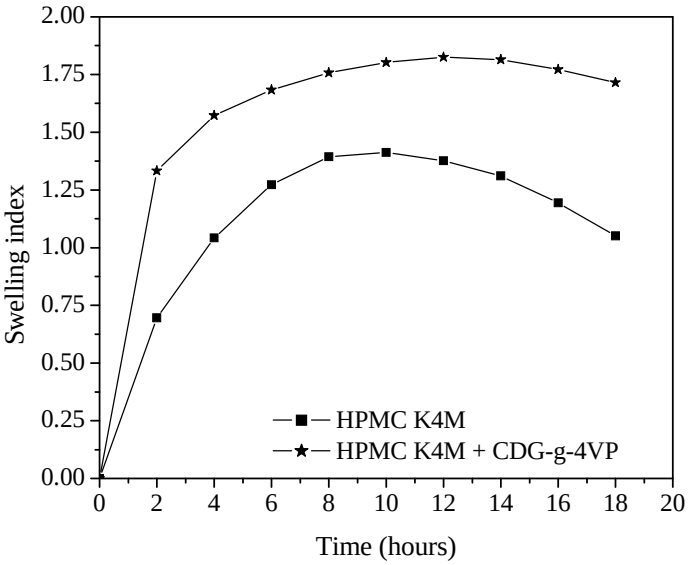

Figure 7.2. Swelling index of CIPFN tablets in 0.1 N HCl

The profiles of swelling index of representative tablet F-4 (Table 7.2) and conventional floating tablet which did not contain graft copolymer are shown in Figure 7.2. The tablet which contained graft copolymer swelled rapidly within 2 hours (swelling index 1.33) and continued to swell slowly over an extended time period thereafter. On the other hand, the tablet which did not contain graft copolymer underwent swelling relatively slowly over two hours (swelling index 0.69) and attained the maximum swelling at the end of 8 hours which declined thereafter.

In the past, it has been shown that an increase in the swelling of a hydrogel with time leads to deviations from Fickian release ($n = 0.5$) resulting in anomalous release ($0.5 < n < 1.0$) and under appropriate conditions leads to release at constant rate ($n = 1$ for film) (Lee and Lum 1992 and Shah et al., 1991). In the present case low initial swelling of the tablet containing CST-g-4VP (swelling index for film 1.5, chapter 6) followed by the dissolution of the graft copolymer within the tablet leads to anomalous release ($n = 0.76$). On the other hand, high initial swelling of the tablet containing CDT-g-4VP (swelling index for film 3.5, chapter 6) and continuous swelling over the release period results in increase in diffusivity of CIPFN with time and release at constant rate ($n = 0.88$ for cylindrical tablet). However, in view of the complexity of the system, it was not possible for us to quantify the results in the manner reported by Shah et al. 1991. The role of enhanced diffusivity in releasing the drug at constant rate is further confirmed by the fact that the release of CIPFN from HPMC K4M matrix was anomalous ($n = 0.66$). These results show that the graft copolymer not only enhanced the swelling of tablet, but also led to release of CIPFN at constant rate.

The floating and swelling parameters of the CIPFN tablets are summarized in Table 7.2. The extent of tablet swelling depended on the swelling behavior of graft copolymer incorporated. Tablets which contained low swelling graft copolymers, *viz*., CST-g-4VP and CAT-g-4VP swelled upto 15 mm in diameter and 5 mm in thickness. On the other hand, the incorporation of the graft copolymers which exhibited higher swelling, *viz*., C(S)T-g-4VP and CDT-g-4VP resulted in swollen tablets of 18 mm in diameter and 7 mm in thickness. The floating lag time of tablets which contained fast dissolving polymer was shortest as they were likely to imbibe

the dissolution medium rapidly. This led to the faster decomposition of $NaHCO_3$ and hence the floating of tablets. All tablets floated through out the release period of 18 hours.

7.3.1.2 Effect of CIPFN loading on release

The blend of graft copolymer CDT-g-4VP containing 30 wt. % 4VP and HPMC K4M was used to study the effect of CIPFN loading on release. The composition, floating and swelling properties of tablets are summarized in Table 7.3. The results show that the amount of CIPFN released at time 't' (M_t) increased with increasing loading (data not shown). However, the fractional release i.e., (M_t / M_∞) decreased with increasing loading (Figure 7.3). As the dissolution medium penetrates and swells the tablet CIPFN dissolves. The concentration of dissolved CIPFN in the swollen matrix increases with increasing loading. This results in higher release of the drug from the tablet with time (M_t). However, this increase is lower than increase in the loading. Accordingly the fraction (M_t / M_∞) decreases with drug loading. The release exponent 'n' varied between 0.85 to 1.03 indicating that CIPFN was released at constant rate (Table 7.4).

Table 7.3. Effect of CIPFN loading level on release: Composition of tablets, floating and swelling properties

Tablet code	Graft copolymer (%)	HPMC K4M (%)	CIPFN loading (%)	Floating lag time (min.)	Floating duration (hours)	Diameter / thickness (mm)
F-5	30	35	20	4	18	19 / 9
F-4	25	30	30	8	18	18 / 7
F-6	20	25	40	12	18	17 / 8
F-7	15	20	50	No floating	No floating	-

$NaHCO_3$: 7 %; CA: 7 % and MS: 1 %

The lag time for floating increased with drug loading (Table 7.3). This is because the proportion of graft copolymer and HPMC K4M decreased in relation to drug loading. As a result, the hydration of tablet and decomposition of $NaHCO_3$ was delayed, which led to delay in floating. Similarly, the extent of tablet swelling

decreased with increasing drug loading. When the drug loading approached 50 %, the tablet did not float. This may be because the trapped gas bubbles were insufficient to float the tablet.

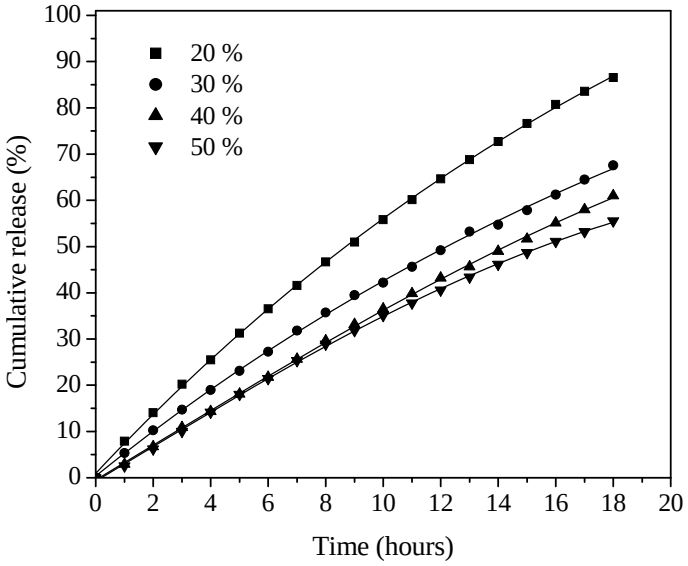

Figure 7.3. Effect of CIPFN loading on release

Table 7.4. Release parameters: Effect of CIPFN loading on release

Tablet code	Drug loading (%)	n	k
F-5	20	0.8550	0.0784
F-4	30	0.8803	0.0555
F-6	40	1.0365	0.0327
F-7	50	1.0379	0.0308

7.3.1.3 Effect of 4VP content of the graft copolymer on release: Influence of drug solubility

The increase in dissolution rate of graft copolymer with 4VP content has been shown earlier during swelling analysis. Since the graft copolymers are polybasic, their dissolution in release medium would increase the pH of tablet microenvironment. This was confirmed by dissolving 250 mg of graft copolymer CDT-g-4VP containing 30 and 50 % 4VP in 5 ml of 0.1 N HCl. On dissolution, the

pH of the medium increased from 1.2 (0.1 N HCl) to 1.81 and 3.72 for the polymer containing 30 and 50 % 4VP respectively.

The solubility of CEPLN and OFN decreases with increasing pH (Oren et al., 1990 and Chavanpatil et al., 2005), whereas RFP is poorly soluble at acidic pH (Kagan et al., 2005). The graft copolymers of the family CDT-g-4VP containing 30, 38 and 50 wt. % 4VP were used to evaluate the release behavior of these drugs. The drug loading was 30 % for CIPFN, CEPLN and OFN tablets. In the case of RFP, the drug loading was 10 % as its solubility is extremely poor. The composition, floating and swelling properties of the tablets and release parameters are summarized in Tables 7.5 and 7.6.

The rate of release of CIPFN increased with 4VP content of the graft copolymer (Figure 7.4). The dissolution rate of graft copolymer increases with 4VP content. This enhanced diffusivity and hence the release of CIPFN was accelerated. The release of CIPFN was not affected by an increase in the pH of the tablet microenvironment. In the present study, CIPFN used was in the form of hydrochloride salt and it is known to dissolve freely upto pH 4.5. Although the dissolution of the polymer increased the pH within the tablet, the pH must not have exceeded 4.5.

Table 7.5. Composition of the tablets

Ingredients	Amount (%)	
	CIPFN, CEPLN and OFN	RFP
Drug	30	10
Graft copolymer	25	35
HPMC K4M	30	40
$NaHCO_3$	07	07
CA	07	07
MS	01	01

Table 7.6. Effect of 4VP content of CDT-g-4VP polymer on release of drugs, floating and swelling properties of tablets and release parameters

Tablet code	4VP content (wt. %)	Drug	Floating lag time (min.)	Diameter / thickness (mm)	n	k
F-4	30	CIPFN	8	18 / 7	0.8803	0.0555
F-8	38		8	19 / 8	0.8461	0.0687
F-9	50		10	17 / 7	0.7982	0.0943
F-10	30	CEPLN	9	18 / 8	0.8305	0.0937
F-11	38		9	18 / 9	0.9633	0.0542
F-12	50		12	17 / 7	0.9766	0.0395
F-13	30	OFN	16	17 / 7	0.8581	0.0698
F-14	38		11	18 / 7	1.0724	0.0328
F-15	50		14	18 / 8	1.1131	0.0242
F-16	30	RFP	5	19 / 9	0.9179	0.0259
F-17	38		7	19 / 8	0.8931	0.0263
F-18	50		4	18 / 8	0.9231	0.0263

All tablets floated over the release period of 18 hours

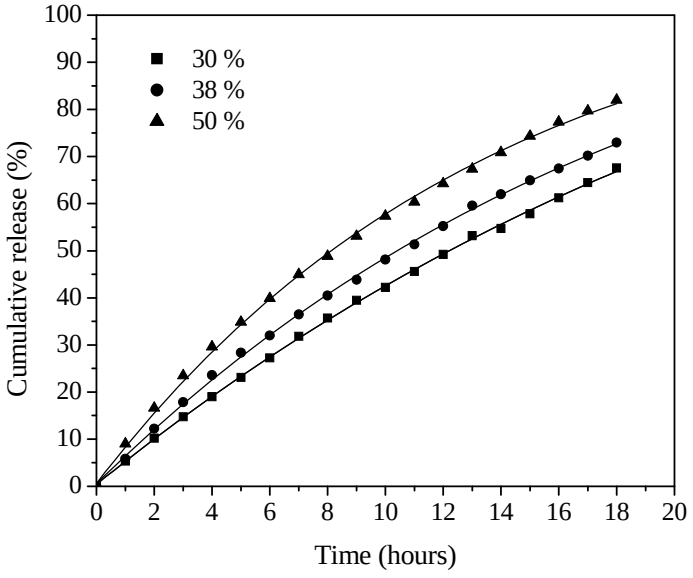

Figure 7.4. Effect of 4VP content on CIPFN release

The release rate of CIPFN was constant as explained earlier when the 4VP content of the graft copolymer was low (30 wt. %). With increasing 4VP content to 38 and 50 wt. % the release kinetics was anomalous (Table 7.6). Possibly, the polymer containing higher 4VP dissolved rapidly within the tablet and hence the diffusivity of drug increased initially and then remained constant which resulted in anomalous release.

The release rate of CEPLN and OFN decreased with increasing 4VP content of the graft copolymer (Figures 7.5 and 7.6). The dissolution of graft copolymer within the tablet increases with 4VP content resulting in lower solubility of CEPLN and OFN, which resulted in lower release rate. Chavanpatil et al., 2005 have shown that increase in loading level of sodium bicarbonate led to increase in the pH of tablet microenvironment and decrease in the solubility of ofloxacin, which resulted in the lower rate of release and our results are consistent with this finding. The release rate of RFP was not influenced by 4VP content of the graft copolymer since the solubility of drug is extremely poor and the release is dissolution controlled (Figure 7.7).

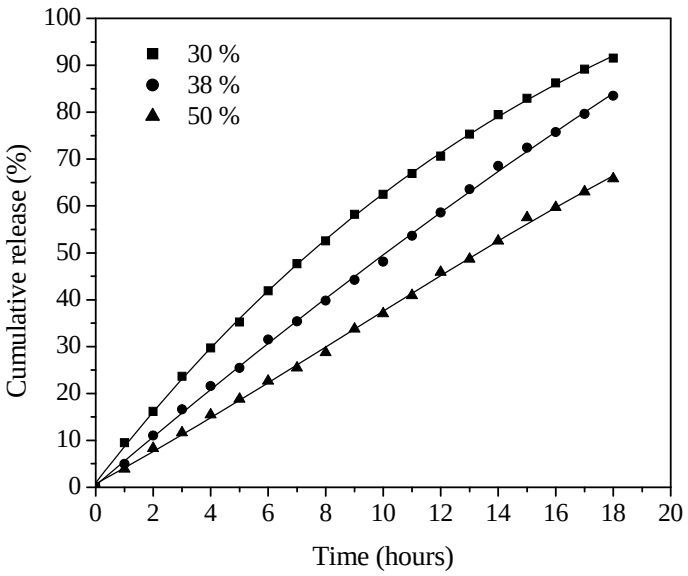

Figure 7.5. Effect of 4VP content on CEPLN release

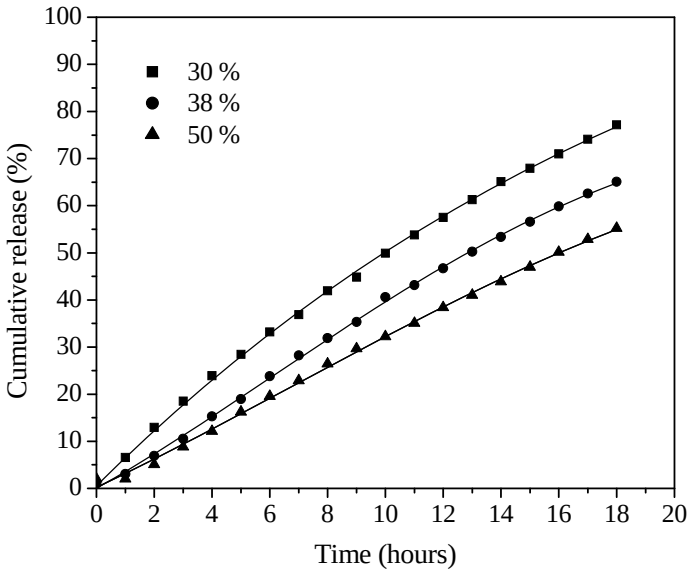

Figure 7.6. Effect of 4VP content on OFN release

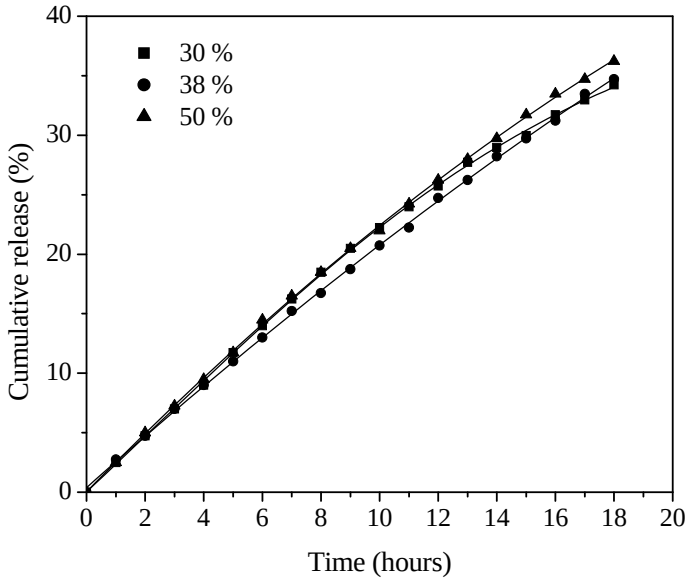

Figure 7.7. Effect of 4VP content on RFP release

These results show that the graft copolymers influenced the release kinetics depending upon their dissolution rate and the pH dependence of the solubility of drugs. The lag time of floating for all the tablets was ≤ 15 minutes and they floated throughout the release period of 18 hours. The tablets swelled substantially, the diameter and thickness were 18 ± 1 and 8 ± 1 mm respectively (Table 7.6).

7.3.1.4 The release of drugs and floating properties of tablets without CA

At acidic pH of dissolution medium, the gas generating agent $NaHCO_3$ reacts with HCl and liberates carbon dioxide gas. The gas formed gets trapped within the gelled tablet which results in reduction of tablet density and floating. However, in the fed state of stomach, the pH is normally as high as 3.5. CA is incorporated along with $NaHCO_3$, so that carbon dioxide is liberated irrespective of the pH of the stomach.

Dave et al., 2004 reported that CA reduced the lag time of floating, but enhanced the release rate of drug. Therefore, we studied the release of drugs and floating behavior of tablets in the absence of CA and compared the results with those obtained from CA incorporated tablets. Four different drugs, *viz*., CIPFN, CEPLN, OFN and RFP were incorporated in the blend of graft copolymer CDT-g-4VP containing 30 wt. % of 4VP and HPMC K4M. The composition of tablets is shown in Table 7.1. The floating and swelling properties of the tablets are summarized in Table 7.7.

Table 7.7. Release of drugs and floating properties of tablets in the absence of CA

Tablet code	Drug	Floating lag time (min.)	Floating duration (hours)	Diameter / thickness (mm)
F-19	CIPFN	48	18	18 / 9
F-20	CEPLN	Not floating	No floating	-
F-21	OFN	Not floating	No floating	-
F-22	RFP	26	18	19 / 9

Polymer: CDT-g-4VP (4VP content: 30 wt. %)

The floating lag time for tablet containing CIPFN was 48 minutes which is six times that of the tablet F-4 containing CA. Similarly, the tablet containing RFP showed floating lag time of 26 minutes which is five times that of the tablet F-16 containing CA. In the absence of CA, the decomposition of $NaHCO_3$ depended on the HCl penetrated. HCl penetrated would be also consumed by 4VP groups present in the graft copolymer. Therefore, the tablet would need relatively large amount of HCl solution for floating. As a result, the tablet floated only after a critical amount of HCl solution penetrated.

On the other hand, CEPLN and OFN tablets did not float throughout the release period of 18 hours. These drugs are free base and undergo protonation in the acidic pH medium. Therefore, the HCl penetrated consumed by not only 4VP groups of graft copolymer but also drug. As a result, the amount of HCl available for the decomposition of $NaHCO_3$ was very low, which adversely affected the floating of tablets. These results show that the tablets containing graft copolymer needed CA for buoyancy.

The release profiles of drugs from the tablets which did not contain CA are shown in Figure 7.8. The release of drugs CIPFN, CEPLN and OFN was faster than the corresponding tablets containing CA. This is due to the faster hydration of tablets under sink condition as their lag time of floating was too long. However, the release rate of RFP was same as that observed from tablet which contained CA, since the solubility of drug is extremely poor.

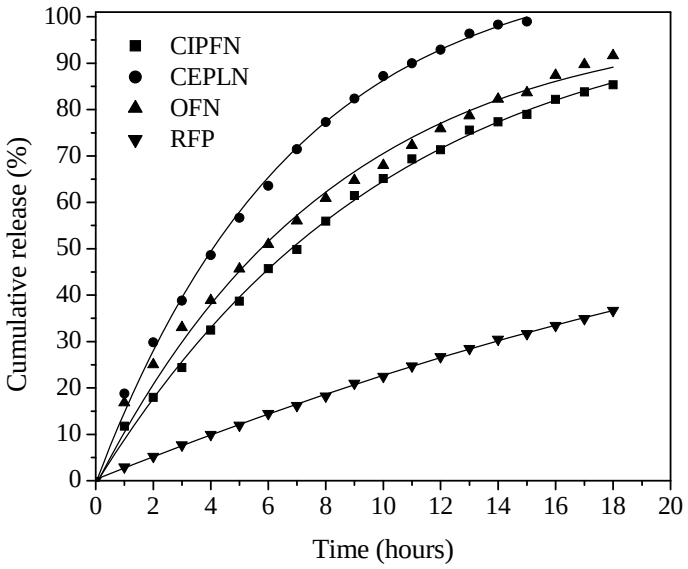

Figure 7.8. Release of drugs in the absence of CA

7.4 Conclusions

The basic graft copolymers were formulated with drugs which have absorption window limited to stomach and upper intestine. The tablets swelled rapidly after floating under acidic pH conditions prevalent in the stomach. *In vitro* release of drugs, *viz.*, ciprofloxacin hydrochloride, cephalexin monohydrate, ofloxacin and riboflavin 5'-phosphate sodium showed sustained release over an extended time

period. Floating, swelling and the release of drugs are influenced by composition of graft copolymers and the solubility of drugs. The tablets swelled substantially upto 19 mm in diameter 9 mm in thickness. The swelling occurred rapidly after floating which is desirable for gastric retention. These swellable floating tablets can be useful to deliver the drugs over an extended time period in stomach.

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Chapter 8

Conclusions and Suggestions for Future Work

8.1 Conclusions

Present investigation was undertaken to design, synthesize and evaluate pH sensitive graft copolymers for oral delivery of drugs. The development of graft copolymers involved the synthesis of aliphatic polyesters comprising pendent vinyl unsaturations followed by grafting with acidic and basic monomers. The structure and composition was tailored to achieve a wide range of polymers differing in swelling / dissolution behavior. The graft copolymers synthesized were characterized for structure, composition, molecular weight, glass transition temperature and pH dependent swelling / dissolution.

Acidic graft copolymers were formulated with drugs differing in solubility and fabricated to matrix and reservoir tablets. Similarly, the basic graft copolymers were formulated with drugs which have absorption window in stomach and upper intestine and fabricated to obtain swellable floating tablets. *In vitro* release behavior of drugs from these tablets was performed and the factors governing the release were investigated.

This chapter summarizes the conclusions arrived from the present investigation and suggestions for further work.

1. A series of acidic graft copolymers comprising aliphatic polyester backbone and methacrylic acid graft chains was synthesized. The polymers were characterized for physico-chemical, thermal and pH dependent swelling / dissolution properties *(Chapter 3).* Significant findings of this investigation are given below.

i. The aliphatic polyester comprising pendent vinyl groups showed enhanced grafting efficiency compared with those comprising unsaturations in the backbone. Glycidyl methacrylate was used to introduce unsaturation in the polyester.

ii. The grafting efficiency increased with unsaturation content of the polyester and methacrylic acid content in the reaction feed.

iii. Hydrogen bonding interactions were observed between the carbonyl groups of polyester backbone and carboxyl groups of methacrylic acid graft chains beyond a critical level of grafting as evidenced from FTIR analysis.

iv. The unsaturated polyesters were crystalline and it turned to amorphous after grafting with methacrylic acid as evidenced from X-ray diffraction analysis. This resulted in good film forming graft copolymers.

v. The unsaturated polyesters exhibited glass transition temperature - 34.93 to -10.02 ^{o}C. The methacrylic acid grafted polyesters did not show glass transition temperature while scanning upto 180 ^{o}C. This has been attributed to the hydrogen bonding interactions between the polyester backbone and methacrylic acid graft chains which suppressed the segmental motion of polyester backbone.

vi. The graft copolymers swelled and / or dissolved at near neutral pH 6.8. The polymer films underwent rupture before their dissolution as evidenced from Environmental Scanning Electron Microscope observation. The polymers were remained in collapsed state at acidic pH 1.2.

vii. The degree of swelling of the graft copolymers increased with methacrylic acid content and grafting frequency.

2. The acidic graft copolymers were co-processed with drugs to obtain microparticles by spray drying technique. These particles were directly compressed to form monolithic matrix tablets. The characteristics of microparticles and *in vitro* release of drugs from the tablets were investigated *(Chapter 4)*. Significant findings of this investigation are given below.

i. The size of microparticles was in the range 3.84 to 5.25 μm. The recovery was 41.32 to 49.66 % since the experiments were performed in small scale. The encapsulation efficiency of drug in the microparticles was close to 100 %.

ii. No interactions were observed between the polymer and cationic drugs, *viz*., diltiazem hydrochloride and verapamil hydrochloride in microparticles as evidenced from FTIR analysis.

iii. Complex formation between the polymer and cationic drugs, *viz*., diltiazem hydrochloride and verapamil hydrochloride was observed in the release

medium of phosphate buffer solution, pH 6.8 as evidenced from FTIR and turbidity measurement. This resulted in suppression of drug release under certain conditions.

iv. *In vitro* evaluation of tablets showed sustained release of drugs over 18 hours. While the swellable polymers are suitable for highly soluble drug diltiazem hydrochloride, slow dissolving polymers are suitable for poorly soluble drug indomethacin and weakly basic drug verapamil hydrochloride to achieve sustained as well as complete release.

v. The rate of release of drugs was enhanced with degree of swelling of the graft copolymers.

vi. The graft copolymer coated tablets exhibited minimal or no release of drug under acidic pH conditions prevalent in the stomach.

3. The acidic graft copolymers were coated on the drug containing core to obtain reservoir tablets. *In vitro* release study was performed to investigate the drug release behavior, the factors influencing the drug release and release mechanism *(Chapter 5)*. Significant findings of this investigation are given below.

i. Mechanical property measurement of the polymer films showed their weak and brittle behavior under dry as well as wet conditions which is desirable to achieve rupturable film coating.

ii. The reservoir tablets exhibited pulsed release of drugs after a time lag under near neutral pH conditions prevalent in the intestinal region.

iii. The lag time of release increased with decreasing degree of swelling of polymers and increased with coating thickness and plasticizer content.

iv. The lag time of release was same for highly soluble drug diltiazem hydrochloride, poorly soluble drug indomethacin and macromolecular marker FITC - dextran 4000.

v. The pulsatile release occurred as a result of swelling induced rupture of polymer coat as evidenced from Environmental Scanning Electron Microscope observation.

4. A series of basic graft copolymers comprising aliphatic polyester backbone and 4-vinylpyridine graft chains were synthesized. The polymers were characterized for structure, composition, molecular weight, glass transition temperate and pH dependent swelling / dissolution behavior *(Chapter 6)*. Significant findings of this investigation are given below.

i. The aliphatic polyester comprising pendent vinyl groups showed better reactivity towards the 4-vinylpyridine. Trimethylolpropane methacrylate was used to introduce unsaturation in the polyester.

ii. The 4-vinylpyridine content of the graft copolymer increased with increasing content in the feed.

iii. The unsaturated polyesters exhibited glass transition temperature - 42.66 to - 3.04 ^{o}C. The 4-vinylpyridine grafted polyesters exhibited two glass transition temperatures for polyester backbone and 4-vinylpyridine graft chains respectively.

iv. The basic graft copolymers swelled and / or dissolved at acidic pH 1.2 while remain in collapsed state at near neutral pH 5.8.

v. The degree of swelling of the polymers increased with 4-vinylpyridine content and grafting frequency.

5. The basic graft copolymers were formulated with drugs which have absorption window limited to stomach and upper intestine to obtain swellable floating tablets. *In vitro* release study was performed to investigate the factors influencing the drug release and the swelling and floating behavior of the tablets *(Chapter 7)*. Significant findings of this investigation are summarized below.

i. The tablets swelled rapidly after floating under acidic pH conditions prevalent in the stomach (0.1 N HCl, pH 1.2).

ii. Sustained release of drugs, *viz*., ciprofloxacin hydrochloride, cephalexin monohydrate, ofloxacin and riboflavin 5′ - phosphate sodium occurred over 18 hours.

iii. The rate of release of ciprofloxacin hydrochloride was increased with 4-vinylpyridine content and grafting frequency. This has been attributed to the increase in degree of swelling of the polymer.

iv. The rate of release of cephalexin monohydrate and ofloxacin was decreased with increasing 4-vinylpyridine content of the graft copolymer. This has been attributed to the increase in pH of tablet microenvironment as a result of polymer dissolution. The solubility of these drugs is known to decrease with increasing the pH.

v. Tablets floated throughout the release period of 18 hours and they swelled substantially higher than the conventional floating tablets.

8.2 Suggestions for future work

Present investigation was undertaken to develop a new family of pH sensitive graft copolymers for oral delivery of drugs. The validation of unique behavior of graft copolymers and their application in sustained, pulsatile and gastroretentive delivery of drugs has been demonstrated *in vitro* study. Suggestions for further work have been given below.

i. The acidic graft copolymers have been evaluated for sustained and pulsatile delivery of drugs. The results of *in vitro* study can be correlated with *in vivo* study which will be helpful for further optimization of the composition.

ii. The acidic graft copolymers which comprise low methacrylic acid content, but are soluble can be evaluated for enteric coating of acid labile drugs like proton pump inhibitors.

iii. The performance of swellable floating tablets can be evaluated in human subjects using gamma scintigraphy technique. This will help to find the gastric retention time of tablets as well as the extent of drug absorption.

iv. The acidic graft copolymers can undergo biodegradation through the chain scission of polyester backbone. This needs to be evaluated. If confirmed, the polymers could be evaluated for other applications including the cellular delivery of nucleotide complexes.

v. The basic graft copolymers are hydrophobic at near neutral pH and hence they can be evaluated for moisture protective coating of drugs.

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 route of drug delivery is most preferred as it is non-invasive and convenient for administration [1]. Polymers of natural, semi-synthetic and synthetic origin are routinely used to sustain and / or target drug delivery. The introduction of new drugs and better understanding of pharmacokinetics of existing drugs has created the need for the design of newer drug delivery systems. pH independent cellulosic polymers have been extensively investigated for sustained release of drugs [2]. Development of sustained release delivery systems which help reduce the frequency of administration, preferably to once a day dosage form has attracted the attention of researchers. The hydrophilic cellulosic polymers do not offer much control over the release of highly water soluble drugs. Currently, such drugs are formulated with multiple polymers and fabricated as multilayered tablets [3]. On the other hand, the release of water insoluble drugs from gelled cellulosic polymers is poorly regulated [4]. pH independent polymers release weakly basic drugs rapidly at acidic pH and effect minimal or no release at basic pH [5].

The pulsatile delivery of drugs after a predetermined lag time is desirable for the treatment of diseases which follow circadian rhythm, *viz.*, the cardiac arrest, bronchial asthma and rheumatoid arthritis [6]. Similarly, the pulsatile release systems are required for colon specific delivery of proteins and peptides and to treat inflammatory bowel diseases [7]. The most widely investigated polymer for colon specific drug delivery is the random copolymer of methyl methacrylate and methacrylic acid. However, the past investigations show that tablets coated with this polymer release the drug either before reaching the colon or not at all [8]. Conventional enteric polymers dissolve rapidly at near neutral pH prevalent in the intestine and hence their utility in sustained and pulsatile delivery of drugs is limited. These limitations highlight the need for the design of modified enteric and reverse enteric polymers.

Another challenge in oral drug delivery is the design of dosage form for drugs which have absorption window limited to stomach. These dosage forms need to be retained in the stomach for extended time period. Amongst the various approaches

investigated, bioadhesive, unfolding and floating delivery systems are most common. However, they suffer from non specific adhesion, risk of GIT obstruction and need sufficient gastric fluid [9]. A swellable floating tablet would be promising as it can float in the gastric fluid immediately after ingestion. Rapid swelling of the tablet after floating would ensure that the tablet is not emptied from stomach through the opened pylorus.

To develop such swellable tablets, there is a need for a polymer which swells rapidly in the gastric fluid. The swellable polymers such as croscarmellose sodium and crospovidone enhance the drug release rate. The polymer, currently used for gastric delivery of drugs is the random copolymer of methyl methacrylate, butyl methacrylate and 2 - dimethylaminoethyl methacrylate. However, this polymer dissolves rapidly at acidic pH prevalent in the stomach without swelling.

Enteric and reverse enteric polymers presently in use are linear and dissolve rapidly in the near neutral and acidic pH conditions respectively. This investigation reports the design and development of a series of modified enteric graft copolymers. These polymers swell and then dissolve at near neutral pH and remain in collapsed state at acidic pH. The polymers have been evaluated for sustained and pulsatile release of drugs as monolithic and reservoir systems respectively. *In vitro* release from matrix tablets showed that the polymers exhibit sustained release of highly water soluble, water insoluble and weakly basic drugs over an extended time period. The film coated tablets comprising low molecular weight drugs as well as macromolecular markers exhibited pulsatile release after a time lag. The lag time can be manipulated by the choice of the polymer and coating thickness.

This work also reports the development of a series of modified reverse enteric graft copolymers which swell rapidly and then dissolve at acidic pH, but resist swelling at near neutral pH. The polymers were formulated with drug and other ingredients to obtain swellable floating tablets. *In vitro* release investigations showed that the tablets exhibit rapid swelling after floating and release the drug over an extended time period. Characterization of polymers and the factors influencing the drug release kinetics were investigated.

The research work has been presented in eight chapters as outlined below.

Chapter 1: Literature survey

This chapter provides an introduction to natural, semi-synthetic and synthetic polymers and their role in the development of pharmaceutical formulations. It deals with the classification of polymers based on their origin and response to stimuli like pH, temperature, ionic strength etc. The limitations of pH independent hydrophilic polymers in the sustained delivery of drugs varying in solubility have been highlighted. The importance of pulsatile delivery of drugs and currently available chronotherapeutic drug delivery systems has been discussed. The survey reveals the need for new polymers for pH dependent pulsatile delivery for targeting the release of drugs, proteins and peptides to intestinal region. Various approaches to achieve gastroretentive delivery of drugs have been reviewed. The literature survey highlights the need for enteric and reverse enteric polymers which swell / dissolve over a period of time for the sustained, pulsatile and gastroretentive delivery of drugs.

pH dependent random copolymers currently available, dissolve rapidly and their utility is limited. The dissolution characteristics of linear and graft copolymers have been reviewed. Graft copolymers exhibit swelling before dissolution. Amongst various approaches, grafting of functional monomers on the natural polymer has been extensively studied. This method however does not ensure a precise control over the architecture of polymer to alter the swelling / dissolution of polymer reproducibly. Based on the literature survey, design and synthesis of pH sensitive graft copolymers containing well defined graft structure was undertaken. Their utility in the development of sustained, pulsatile and gastroretentive drug delivery system has been explored.

Chapter 2: Objectives and scope of work

Present research work focuses on design, synthesis and characterization of pH sensitive graft copolymers and their evaluation for oral drug delivery systems. More specifically, acidic graft copolymers have been evaluated for the sustained and pulsatile delivery of drugs at conditions prevalent in the gastrointestinal region. Basic graft copolymers have been formulated with drugs and other ingredients to

obtain swellable floating tablets for gastroretentive delivery of drugs. Major objectives and scope of the work are highlighted below.

1. To design and synthesize pH sensitive graft copolymers which swell / dissolve over an extended time period. Characterize these polymers for structure, composition and pH dependent swelling / dissolution to screen them for the development of oral drug delivery systems.

2. To identify systems which would exhibit swelling / dissolution at near neutral pH, but remain in collapsed state at acidic pH. Evaluate the effect of polymer variables on molecular interaction, glass transition and swelling / dissolution behavior of the polymers.

3. To evaluate the polymers for sustained delivery of drugs differing in solubility under conditions prevalent in the gastrointestinal region and optimize the polymer composition for sustained release of drugs over an extended time period.

4. To identify the factors such as polymer composition, drug loading, drug solubility, formulation variables and dimension of dosage form governing the release of drugs.

5. To evaluate the polymers for pulsatile delivery of drugs, and evaluate the effect of polymer composition, coating thickness and plasticizer content on the lag time.

6. Based on the above studies, identify the mechanism of pulsatile release of drugs and validate the same by supporting experiments.

7. To identify the polymer characteristics for gastroretentive delivery of drugs. Identify basic monomer which yields high T_g graft copolymers to ensure better processing and resist moisture absorption during formulation and storage.

8. To design and synthesize graft copolymers which would swell rapidly and then dissolve over an extended time period at acidic pH and remain in collapsed state at near neutral pH. Characterize these polymers for physico-chemical, thermal and pH dependent swelling / dissolution.

9. To evaluate these graft copolymers for the development of swellable floating tablets containing drugs which have absorption window limited to stomach under conditions prevalent in the stomach.

10. To investigate the role of factors governing the performance of swellable floating tablets. Evaluate the effect of polymer composition, drug loading and drug solubility on the drug release rate and swelling and floating behavior and elucidate the release mechanism.

Chapter 3: Acidic graft copolymers: Synthesis and characterization

The graft copolymers exhibit unique behavior, *viz*., swelling in aqueous medium depending on their composition. The pH sensitive graft copolymers presently available comprise hydrophilic backbone and acidic or basic monomers in the graft chains [10, 11]. The hydrophilic backbone is not ideally suited for achieving enteric characteristics and moisture protection. In this investigation, polyester backbone has been selected since it is hydrophobic and known to be biocompatible. This chapter deals with the synthesis and characterization of acidic graft copolymers. The polyesters varying in unsaturation frequency were synthesized using a diol, dibasic acid and glycidyl methacrylate by melt polycondensation. The diols were 1, 4 butane diol, 1, 4 cyclohexane dimethanol and bis (2 - hydroxyethyl terephthalate).

The dibasic acids were succinic acid, adipic acid, sebacic acid and dodecanedioic acid. The unsaturated polyesters synthesized were grafted with methacrylic acid in the range 30 - 60 % to yield graft copolymers. This approach helps vary, not only the methacrylic acid content but also grafting frequency on the backbone. The grafting efficiency of methacrylic acid increased with the unsaturation content of polyester and the amount of methacrylic acid in the feed as evident from ^{1}H NMR spectroscopy analysis and acid value estimation. The polyesters comprising pendent vinyl groups exhibited grafting efficiency up to 89 % in comparison to those comprising unsaturation in the main chain (25 to 58 %). The physico-chemical and thermal properties of polymers including the structure, composition, molecular weight, molecular interactions and glass transition temperature were investigated using ^{1}H NMR and IR spectroscopy, acid value estimation, GPC and DSC. The hydrogen bonding interaction between the polyester backbone and methacrylic acid graft chains resulted in brittle polymers as evident from IR and DSC analysis. The

change in morphology of polymer films on exposure to acidic as well as near neutral pH medium was observed by environmental scanning electron microscope. The films swelled, ruptured and then dissolved at near neutral pH, yet remained intact at acidic pH. The rate of swelling / dissolution of the polymers increased with methacrylic acid content and grafting frequency. A series of graft copolymers were obtained for delivery of drugs in intestinal region.

Chapter 4: pH dependent sustained release of drugs: *In vitro* evaluation

Sustained release formulations maintain therapeutic level of drug in the plasma over an extended time period [12]. They reduce the frequency of drug administration which enhances patient compliance. In the previous chapter, the synthesis and characterization of acidic graft copolymers was described. The evaluation of these polymers for the sustained release of drug varying in solubility has been described in this chapter. The solubility of drug influences the release kinetics significantly [13]. The drug loaded microparticles were prepared by spray drying under optimized conditions. The spray drying process yields microparticles wherein, the drug is dissolved in polymer and hence effectively encapsulated. The size of particles was in the range 3.5 to 4.5 μ. There was no agglomeration as observed by ESEM. This was attributed to high T_g of polymers. The microparticles were compressed to form a monolithic matrix tablet.

In vitro release from matrix containing highly water soluble drug diltiazem hydrochloride showed sustained release over 18 hours. The increase in diffusivity of drug as a result of swelling / dissolution of polymer with time led to release of diltiazem hydrochloride at constant rate. The mechanism proposed was validated by performing swelling analysis of polymer film, which showed swelling over 7 hours followed by slow dissolution with time. Water insoluble drug indomethacin and the weakly basic drug verapamil hydrochloride exhibited release at constant rate from swellable graft copolymer as a result of the erosion of matrix at constant rate. The enteric nature of the graft copolymer has been shown by film coating the sustained release matrix. The coating suppressed the release of drug under acidic pH conditions. Thus, the new family of graft copolymer synthesized is useful for the preparation of once a day dosage form of wide variety of drugs.

Chapter 5: pH dependent pulsatile release of drugs: *In vitro* evaluation

Pulsatile delivery of drugs from the acidic graft copolymer described in chapter 3 was investigated. Mechanical property measurements showed that the films were brittle. Hydrogen bonding in ethyl cellulose films renders them weak and brittle in dry as well as under wet conditions [14]. The brittle nature of ethyl cellulose film has been exploited to achieve pulsatile delivery of drugs [15]. The graft copolymers synthesized by us were brittle even under wet conditions. The films were therefore expected to lead to pulsatile delivery of drugs. The graft copolymers were film coated on tablets containing drug to form a reservoir system. Water soluble plasticizers are known to leach out from the film coat which would lead to premature rupture of the coat. Therefore, a lipophilic plasticizer n-dibutyl phthalate was incorporated. The results of *in vitro* release of film coated tablets showed pulsatile release of drug after a time lag, which could be tailored between 2 to 7 hours. The pulsatile release of drug was attributed to swelling induced rupture of film coat as evident from environmental scanning electron microscopy. The mechanism was further validated from the fact that the lag time was same for highly water soluble diltiazem hydrochloride and water insoluble indomethacin. The lag time increased with decreasing methacrylic content and grafting frequency in the polymer and coating thickness. The lag time increased with plasticizer content up to 15 %. Beyond this level, the film coat failed to undergo complete rupture. As a result, the release was sustained after the lag. It has also been shown using FITC-dextran as a macromolecular marker that the colon specific pulsatile delivery of proteins and peptides can be achieved. In conclusion, the pulsatile release of drugs varying in solubility and molecular weight was demonstrated. In all cases, the release was triggered by swelling induced rupture of film coat.

Chapter 6: Basic graft copolymers: Synthesis and characterization

In chapter 3, the synthesis of graft copolymers comprising polyester backbone and methacrylic acid graft chains was demonstrated. These graft copolymers were evaluated for sustained and pulsatile release of drugs under conditions prevalent in the intestine and the results are described in chapters 4 and 5. The synthesis of graft copolymers comprising polyester backbone and basic monomer 4 - vinyl pyridine graft chains has been described in this chapter. The reverse enteric polymer commercially available is a random copolymer of methyl methacrylate, butyl

methacrylate and 2 - dimethylaminoethyl methacrylate. This polymer is known to absorb moisture and exhibit low T_g. Another reverse enteric polymer comprising methyl methacrylate, 2 - hydroxyethyl methacrylate and 4 - vinyl pyridine shows high T_g and does not absorb moisture [16]. However, this polymer dissolves rapidly at acidic pH. Therefore, 4 - vinyl pyridine was selected as a basic monomer for the synthesis of graft copolymer. The polymers were synthesized by grafting 4 - vinyl pyridine on the polyesters differing in unsaturation frequency. 4 - Vinyl pyridine content of the graft copolymer increased with increase in the feed. The physico-chemical and thermal properties of polymers including the structure, composition, molecular weight and glass transition temperature were evaluated using ^{1}H NMR and IR spectroscopy, GPC and DSC. The graft copolymers exhibited two T_gs for the polyester backbone and 4 - vinyl pyridine graft chains respectively. The polymers swelled rapidly and then dissolved over an extended time period at acidic pH 1.2 (0.1 N HCl) prevalent in the stomach. The dissolution rate of graft copolymers increased with 4 - vinyl pyridine content and grafting frequency. The incorporation of reverse enteric graft copolymer in the conventional floating tablet would enhance the swelling of tablet and hence the gastric retention. The polymers did not swell or dissolve in the near neutral pH medium, which is desirable for the development of swellable floating tablets as they do not absorb moisture during the formulation and storage.

Chapter 7: Swellable floating drug delivery systems: *In vitro* evaluation

Various approaches including the bioadhesive microparticles, unfolding and / or expanding devices and floating tablets have been investigated for gastroretentive delivery of drugs. However, the performance of bioadhesive microparticles was not satisfactory because of their non-specific adhesion. The expanding devices are not safe because of the possibility of GIT obstruction. Floating tablets are effective only when the gastric fluid is present [9]. The swellable floating tablets would be desirable as they are unlikely to pass through the opened pylorus during gastric emptying. These were prepared by incorporating basic graft copolymer. The results are described in this chapter. The incorporation of drugs which have absorption window in stomach in the blend of graft copolymer and hydroxypropyl methylcellulose along with other ingredients, resulted in a tablet, which swelled rapidly after floating under acidic pH conditions prevalent in the stomach. The

tablets attained equilibrium swelling within 4 hours. The lag time for floating was ≤ 15 minutes and the tablets floated throughout the dissolution period of 18 hours. *In vitro* release of drugs, *viz.*, ciprofloxacin hydrochloride, cephalexin monohydrate, ofloxacin and riboflavin 5′ - phosphate sodium showed sustained release over an extended time period. Increase in diffusion coefficient of the drug as a result of swelling / dissolution of graft copolymers resulted in constant release rate. The parameters which influence drug release, *viz.*, dissolution rate of graft copolymer, drug loading and solubility were investigated. The rapid swelling of tablets after floating would help retain the dosage form in stomach even after the gastric emptying by 'housekeeper wave'.

Chapter 8: Conclusions and suggestions for future work

In conclusion, a new family of pH sensitive graft copolymers was synthesized and evaluated for sustained, pulsatile and gastroretentive delivery of drugs. The major conclusions drawn from the investigation are summarized below.

1. A series of acidic graft copolymers containing polyester backbone and methacrylic acid graft chains exhibited swelling and then dissolution at near neutral pH. The physico-chemical and thermal properties of the polymers revealed their suitability for the preparation of pharmaceutical dosage forms.

2. The acidic graft copolymers are versatile as they release drugs varying in solubility over an extended time period at constant rate. The dosage form developed herein, is a simple matrix tablet which does not need multiple polymers.

3. The acidic graft copolymer coated tablets exhibited pulsed release of low molecular weight drugs as well as the macromolecular marker FITC - dextran after a time lag. The lag time for pulsatile release can be tailored by selecting appropriate polymer composition, coating thickness and plasticizer content.

4. The basic graft copolymers containing polyester backbone and 4 - vinyl pyridine graft chains exhibited rapid swelling and then slow dissolution at acidic pH. The polymers remained in collapsed state at near neutral pH, which is desirable for the development of swellable floating tablets as they do not absorb moisture during the formulation and storage.

5. The incorporation of basic graft copolymer in the conventional floating tablet resulted in rapid swelling after floating under the acidic pH conditions prevalent in the stomach. The tablets floated throughout the release period of 18 hours and exhibited sustained release of drugs which have absorption window limited to stomach.

This chapter also highlights the scope for further work.

1. In the present work, the acidic graft copolymers have been evaluated for sustained and pulsatile release of drugs. The results of *in vitro* study can be correlated with *in vivo* study which will be helpful for further optimization of formulations.

2. The performance of swellable floating tablets can be evaluated in human subjects using gamma scintigraphy technique. This will help to find the gastric retention time of tablets as well as the extent of drug absorption.

3. The acidic graft copolymers can undergo biodegradation through the chain scission of polyester backbone and hence they can be evaluated for other applications including the cellular delivery of nucleotide complexes.

4. The basic graft copolymers are hydrophobic at near neutral pH and hence they can be evaluated for moisture protective coating of drugs.

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