This chapter deals with the recent developments in the field of production of particulate drug delivery systems viz., micro/nanoparticles, floating microspheres and pH-responsive hydrogels. Different types of polymers have been used to effectively deliver drugs to a target site and increase the therapeutic benefit, while minimizing the side effect.

This information is presented in three review articles: (i) Journal of Controlled Release, (ii) Drug Metabolism Reviews and (iii) Drug Development and Industrial Pharmacy, (2000).

I.A. Polymeric Micro/Nanoparticles as Drug Delivery System

In recent years, polymeric micro/nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the CR of drugs, drug targeting to particular organs/tissues, as carriers of DNA in gene therapy, in the delivery of proteins and peptides through the peroral route of administration [1-11].

I.A.1. Preparation of Micro/Nanoparticles

Micro or nanoparticles have been prepared mainly by two methods: (i) dispersion of the preformed polymers and (ii) polymerization of monomers.
I.A.1.1. Solvent Evaporation Method

In this method, polymer is dissolved in an organic solvent like dichloromethane, chloroform or ethyl acetate. Drug is dissolved or dispersed into the preformed polymer solution and this mixture is emulsified into an aqueous solution to make an oil (O) in water (W) i.e., O/W emulsion by using the surfactant/emulsifying agent like gelatin, poly(vinyl alcohol), polysorbate-80, poloxamer-188, etc. After the formation of stable emulsion, organic solvent is evaporated either by increasing the temperature or under pressure or by continuous stirring. Effect of process variables on the properties of particles was discussed earlier [12]. The W/O/W method has been used to prepare the water-soluble drug-loaded particles [13]. Both these methods use a high-speed homogenization or sonication to reduce the particle size of the final product.

I.A.1.2. Spontaneous Emulsification/Solvent Diffusion Method

This is a modified version of the solvent evaporation method [14-16] wherein water-soluble solvents like acetone or methanol along with the water-insoluble organic solvent like dichloromethane or chloroform are used as an oil phase. Due to spontaneous diffusion of water-soluble solvent (acetone or methanol), an interfacial turbulence is created between the two phases leading to the formation of smaller particles. As the concentration of water-soluble solvent (acetone) increases a considerable decrease in particle size can be achieved.

I.A.1.3. Salting Out/Emulsification-Diffusion Method

Methods discussed before require the use of organic solvents, which are hazardous to the environment as well as to the physiological system [17]. The US FDA has specified the residual amount of organic solvents in injectable colloidal
systems. In order to meet these requirements, Allemann and co-workers have developed two methods: The first one is a salting out method [18,19] while the second one involves the emulsification/solvent diffusion technique [20,21].

**I.A.1.4. Polymerization Methods**

Particulate systems can also be prepared by polymerization of monomers. Couvreur et al., [22,23] reported the production of particles (~200 nm diameter) by polymerizing mechanically the dispersed methyl or ethyl cyanoacrylate in aqueous acidic medium in the presence of polysorbate-20. The cyanoacrylic monomer is added to an aqueous solution of a surface-active agent (polymerization medium) under vigorous mechanical stirring to polymerize alkylcyanoacrylate at ambient temperature. Drug is dissolved in the polymerization medium either before the addition of the monomer or at the end of the polymerization reaction. The suspension is then purified by ultracentrifugation or by resuspending the particles in an isotonic surfactant-free medium. Polymerization follows anionic mechanism since it is initiated in the presence of nucleophilic initiators like OH', CH₃O' and CH₃COO' leading to the formation of nanoparticles of low molecular mass due to rapid polymerization.

**I.A.1.5. Micro/Nanoparticles Prepared from Hydrogels**

In addition to the commonly used synthetic hydrophobic polymers, active research is now focused on the preparation of particles based on the cross-linked hydrophilic polymers like chitosan, sodium alginate, gelatin, etc. Different methods have been adopted to prepare particles from hydrophilic polymers. Calvo and coworkers [24-26] have reported a method to prepare the hydrophilic chitosan particles of size 200-1000 nm. The preparation method involves ionic gelation.
with a mixture of two aqueous phases of which one contains chitosan and a
diblock copolymer of ethylene oxide and the other contains a polyanion sodium
tripolyphosphate (TPP). In this method, the positively charged amino group of
chitosan interacts with the negatively charged TPP. Chitosan particles were also
produced by the emulsion coacervation method [27]. In this method, chitosan and
the drug to be loaded were dissolved in water and water-in-oil emulsion was
prepared in liquid paraffin using an emulsifying agent. To this stable emulsion,
another emulsion of NaOH in liquid paraffin was added. When in contact with
NaOH, chitosan particles were produced by the coacervation of the polymer.
Alginate-based particles were also developed and used for the delivery of
oligonucleotides [28]. In micro/nanoparticles, drug is entrapped, encapsulated or
attached to the polymer matrix using different methods.

I.A.2. Drug Release

Drug release from micro/nanoparticles and subsequent biodegradation are
important in developing successful formulations. The release rates of
micro/nanoparticles depend upon: (i) desorption of the surface-bound/adsorbed
drug, (ii) diffusion through the matrix, (iii) diffusion (in case of micro-
nanocapsules) through the polymer wall; in case of biodegradable polymer it is by
(iv) matrix erosion and (v) a combined erosion/diffusion process. On the other
hand, drug release from hydrogel microspheres or nanoparticles occurs by
swelling of the delivery systems, which can be monitored by maintaining the
extent of cross-linking.

Methods to study \textit{in-vitro} release are by: (i) side-by-side diffusion cells
with artificial or biological membranes, (ii) dialysis bag diffusion, (iii) reverse
dialysis sac, (iv) ultracentrifugation or (v) ultrafiltration. Despite continuous
efforts in this direction, there are still some technical difficulties to study the \textit{in-}
*vitro* drug release from micron and submicron size particles [29,30]. In order to separate the particles and to avoid the tedious and time-consuming separation techniques, dialysis has been used; here, the suspension of micro/nanoparticles is added to the dialysis bags/tubes of different molecular mass cut-off. These bags are then incubated in the dissolution medium for the release study [31-33].

Another technique involves the use of a diffusion cell consisting of donor and acceptor compartments; this technique was used to separate through the artificial/biological membranes [34]. In this method, kinetic study was not performed under perfect sink conditions because the particles were not directly diluted in the release media, but were separated from the release media through the membrane. Thus, the amount of drug in the release media did not reflect the real amount released. In order to avoid the enclosure of particulate delivery systems in the dialysis bag, Leavy and Benita [35] used a reverse dialysis technique for the O/W emulsion. In this method, particles were added directly into the dissolution medium. The same technique was adopted by Calvo et al., [36], but method is not very sensitive for studying the rapid release formulations. However, it can only be used for the release of formulations having the release time longer than one hour [37].

Release profiles of the drugs from spherical particles depend upon the nature of the delivery system. In case of a matrix device, drug is uniformly distributed/dissolved in the matrix and the release occurs by diffusion or erosion of the matrix. A biphasic release is observed for the micro/nanoparticles i.e., an initial rapid release followed by a delayed release phase; the rapid initial release is due to the release of the drug migrated to the surface of the particles. However, the later phase is due to the diffusion of the drug from the matrix.
Recently, Polakovic, et al., [38] theoretically studied the release from PLA particles loaded with varying amounts (7-32 % w/w) of lidocaine. Two models were used to study the drug release: (i) by crystal dissolution and (ii) by diffusion through the polymer matrix. When the drug loading is < 10 % (w/w) (the drug is molecularly dispersed), the release kinetics shows a better fit to the diffusion model. The existence of lidocaine crystals at higher concentration (>10 %) is observed. Since the drug should dissolve first from the crystals and then diffuse from the matrix, the overall release mechanism was described by a dissolution model.

I.A.3. Surface Properties and MPS Uptake

When the micro/nanoparticles are administered intravenously they are easily recognized by the body immune systems, which are then cleared from the circulation based on their size and opsonization (adsorption of the plasma proteins). Particles are cleared from circulation and are accumulated in liver, spleen and bone marrow, and also in the monocytes. Surface modification of biodegradable and long-circulating polymeric micro/nanoparticles can be achieved by: (i) surface coating with hydrophilic polymers/surfactants and (ii) development of biodegradable copolymers with hydrophilic segments. The widely used surface-coating materials are: polyethylene glycol (PEG) [39], polyethylene oxide (PEO) [40], poloxamer, poloxamine [41], polysorbate (Tween-80) [42] and lauryl ethers (Brij-35).

A mechanism was proposed which assumes that the surface-grafted chains of flexible and hydrophilic polymers form the dense conformational clouds thus preventing other polymers from interaction with the surface even at lower concentrations of the protecting polymeric layer. A theoretical model of protein repulsion from solid substrate was proposed [43]. The steric repulsion, van der
Waals attractions and hydrophobic interaction free energy parameters have been correlated. The model provides a basis for the prevention of opsonin deposition. High surface density and the long chain-lengths of PEG are necessary for low protein adsorption. However, surface density has a greater effect than chain-length on steric repulsion and van der Waals attraction.

I.B. Microspheres as Floating Drug Delivery Systems to Increase Gastric Retention of Drugs

Among different routes of drug administration, oral route has by far the most common one due to the ease of administration as well as the fact that gastrointestinal (GI) physiology offers more flexibility in dosage-form design than most other routes. Development of oral drug delivery systems for a specific drug involves optimization of the dosage-form and characteristics of GI physiology. Although significant advances have been made to develop drug delivery systems, most of the dosage forms are still designed on an empirical basis.

The success of oral solid drug delivery systems is not only to achieve the better in-vitro drug release, but also to reproduce similar in-vivo performance. The developed drug delivery system should have a better in-vitro and in-vivo correlation [44]. Most often, this is not the case and there are many reasons for this failure. Major problem is the physiological variability such as GI transit. Gastric retention time (GRT) also plays a dominating role in the overall transit of the dosage form [45]. Such physiological variability makes it difficult to label the drug delivery systems with a definite in-vivo performance in spite of having reproducible in-vitro data. Another problem associated with the performance of oral controlled release (CR) systems is that even though, the slow release can be achieved, the drug released after passing the absorption site is not fully utilized
because the GRT of the delivery system is less than 12 h. Hence, it is not possible to deliver the drug for more than 12 h by oral route. This has prompted researchers to retain the drug delivery systems in stomach for prolonged and predictable time. Such a prolonged gastric retention not only controls the time, but also the space in the stomach by maintaining the delivery system positioned at a steady site and thereby properly delivering the drug.

Targeting drug to stomach is attractive for several other reasons: (i) for the weakly basic drugs having poor solubility in the basic environment, the floating systems will avoid any chance for solubility to become the rate limiting step in the release by restricting the drug to the stomach, (ii) any solute released in the stomach will empty along with the fluids such that the whole surface of the small intestine is available for absorption; this is particularly useful when an absorption window exists in the proximal small intestine and (iii) the positioned gastric release is useful for all substances intended to produce a lasting local action onto gastroduodenal wall. Hence, pertinent applications could be found for therapeutic agents of the ulcerous disease [46].

In the literature, there are mainly two approaches to increase GRT. One approach is to develop mucoadhesive drug delivery systems, which “stick” to the mucin-epithelial cell surface, thus providing longer transit time due to the adhesion of the device to the gastric wall [47]. Such an adhesion may lead to problems such as irritation to the mucosa due to overdose of the drug locally [48]. Another approach is the development of floating drug delivery systems, which are also called “hydrodynamically controlled systems” having density smaller than gastric fluid; thus, they remain buoyant in the stomach fluid and thereby increase the GRT [49]. Many buoyant systems have been developed based on granules [50], powders [51], capsules [52], tablets (pills) [53], laminated films [54] and hollow microspheres [55]. However, the single unit dosage forms contribute a
major share in the literature of floating drug delivery systems. However, these systems have the disadvantage to release all-or-nothing emptying process [56]. On the other hand, multiple unit dosage forms may be better suited since they are claimed to reduce the inter-subject variability in absorption and lower the probability of dose-dumping [57]. However, research efforts on floating multiparticulate systems are still under development and little has been reported in the literature. The recent review by Singh and Kim [49] covers the general aspects of all types of floating drug delivery systems. The physiology of gastric emptying and its relevance in developing floating drug delivery systems and their \textit{in-vivo} and \textit{in-vitro} performances have also been reviewed [58].

**I.B.1. Physiology of Gastric Emptying**

When a material is taken orally, first enlargement of the digestive system is the stomach tract. It has various functions such as temporary storing the ingesta, mixing it with the secretions, reduce the size of the ingesta and empty it at a rate that will help in the efficient digestion and absorption. This emptying process is mainly under the influence of chemical composition and the physical form of the ingested material. Without discussing further details of gastric emptying, it is necessary to give a brief account of the physiology of gastric emptying.

Emptying process is controlled by three segments of the gut, which include two portions of the stomach (body and antrum) and duodenum. The movement of ingesta depends upon the muscular contraction and relaxation of the segments of the gut; the muscular activity helps in pushing the ingesta from stomach to intestine. The muscular movement of the gut consists of three phases: Phase I lasts for ~ 60 min and is associated with very little motor activity relative to Phase II and III. Phase II lasts for ~ 40-60 min, which consists of an intermittent action potential and contractions that gradually increase in intensity.
and frequency as the phase progresses. Phase III is a short period of intense with large regular contractions lasting 4-6 min. The passage of Phase III to the small intestine is called as "migrating myoelectric complex". These muscular movements are influenced by the fasted (interdigestive) and fed (digestive) state of the stomach [59].

The motility of the muscle is associated with the nature of the substance ingested. Hunt et al., [60] studied water as the purest model for liquid meal and demonstrated that the gastric emptying of water follows the expediential pattern. It had a $t_{1/2}$ of 10 min. An increase in volume of water increases the gastric emptying. Emptying of liquid meal is controlled precisely by carefully controlling the chemical and osmotic properties of the ingesta. Ingestion of the solid meal stimulates the phasic motor activity of the antrum, because the solid meal is triturated in the stomach with back and forth movements by the contraction of the antrum.

In recent years, particle or pellet formulations have been the attractive choice in the delivery of drugs through oral route [61]. Physico-chemical properties of the particulate systems such as particle size, density or surface characteristics affect their gastric emptying. Gruber et al., [62] studied these parameters in dog in the fasted state. Particles of different densities ranging from 0.5 to 2.9 g/cm$^3$ emptied in a similar manner. Lack of influence of density on stomach emptying was observed and these results agree with those obtained on the fasted human [63]. In this study, no difference was observed between the rate of gastric emptying of floating and non-floating (density = 0.96 or 1.96 g/cm$^3$) single-unit dosage forms. On the other hand, particle size (ranging from 0.7 to 6.5 mm) and surface texture of the nonerodible particles ranging from polished glass beads, rough surface of Amberlite beads and porous polystyrene did not show any influence on the rate of particle emptying. This ineffectiveness of the physical
nature of the particles to exhibit any distinctions in their emptying process is attributed to: (i) when particles are fed into empty stomach, these are coated/adhered with the gastric mucous leading to a loss of their inherent physico-chemical properties and (ii) high amplitude propulsive later Phases II and III contractions of the antral migrating myoelectric complex sweeps the mucous particles from the stomach.

Lin et al., [64] demonstrated that stomach emptying of 1.6 mm diameter nylon spheres was influenced by a 300 gm steak meal. The presence of food delayed the Phase III activity. The larger number of particles was uniformly distributed amongst the meat particles in the stomach and emptying becomes proportionately slower in the presence of food. Khosla et al., [65] reported a delayed emptying of 3, 4 and 5 mm diameter tablets when taken with breakfast in humans.

In order to study the stomach emptying of spheres and tablets by the inter-digestive Phase III motor activity in human, Park et al., [66] demonstrated the need for Phase III activity in three men and three women, who ingested a variety of size and shaped tablets during the inter-digestive state in addition to three different sized tablets, each in two shapes (sphere and capsule) were evaluated. It was found that the gastric emptying time was in the range between 5 and 120 min. This has demonstrated a wide inter-subject variation. It was concluded that there is a large inter- and intra-subjective variation in the GRT of the indigestible stomach contents. Some of the important aspects of the physiology of the gastric emptying process are [67]: (i) rate of movement of the dosage form from stomach to intestine is affected by multiple chemical factors and the physical size of the medication, (ii) chemical composition of the gastric fluid will interact with the intestinal receptors, which controls the rate of gastric emptying by neuronal or hormonal means, (iii) emptying of the dosage form is also influenced by whether
it is taken on an empty stomach, inter-digestive state (with or soon after a meal) and digestive state, (iv) small particles regardless of size, density or texture that are ingested during the inter-digestive state become coated by the mucous and these coated dosage forms are emptied uniformly from the stomach, (v) during the digestive state, larger particles are retained in the stomach until the meal is essentially emptied and (vi) emptying of the solid dosage forms range from 5 min to 5 h depending upon the size of the medication and whether the individual is in the inter-digestive or digestive state when medication is administered.

An understanding of the physiology of gastric emptying is important to develop floating drug delivery systems. However, multiple unit dosage forms have many advantages over the single unit dosage forms.

I.B.2. Development of Hollow Microspheres

Conventionally, drug-loaded microspheres have been developed by emulsification and solvent evaporation methods as discussed in Section I.A.1 of this chapter. In these methods, the solvent removal from the embryonic microspheres determines their size and morphology. It has been reported [55] that the rapid removal of solvent from the embryonic microspheres leads to polymer precipitation at the oil and water interface. This leads to the formation of a cavity in the microspheres giving hollow structures thereby imparting the floating properties. This has prompted research efforts to produce the hollow microspheres [55, 68-71].

Different methods used to prepare hollow microspheres of acrylic polymers based on the solvent diffusion and evaporation methods are given in Table I.1. The acrylic polymer is dissolved in solvent mixtures such as ethanol (EtOH):dichloromethane (DCM) (1:1 v/v) along with the drug [55, 68, 70]. The
polymer solution is emulsified into an aqueous phase containing poly(vinyl alcohol), PVAL. Ethanol diffuses out of the embryonic microspheres into the aqueous phase such that the equilibrium concentration of ethanol will be retained. Dichloromethane did not diffuse, but retained in the microdroplets. Rapid diffusion of ethanol (a good solvent for the polymer) from the droplet reduces polymer solubility since acrylic polymer is insoluble in dichloromethane. Hence, the polymer precipitates instantly at the surface of the droplets, forming a shell enclosing dichloromethane. The solidified film produced due to diffusion of EtOH prevents the rupture or shrinkage of microspheres during evaporation of dichloromethane. As the solvent is evaporated at 40°C, the vapor of DCM is generated within the droplets to produce hallow microspheres [68]. The polymer concentration in the mixed solvent systems is important to produce the hollow microspheres [55]. By increasing concentration of polymer solution, particle size increased, but the yield decreased drastically.

### Table I.1

<table>
<thead>
<tr>
<th>Organic Solvent System</th>
<th>% of PVAL in Aqueous Phase</th>
<th>Polymer Type</th>
<th>Drug</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM + EtOH</td>
<td>0.75</td>
<td>Eudragit® S</td>
<td>Tranilast</td>
<td>55</td>
</tr>
<tr>
<td>DCM + EtOH</td>
<td>0.75</td>
<td>Eudragit® S</td>
<td>Ibuprofen</td>
<td>68</td>
</tr>
<tr>
<td>DCM</td>
<td>0.04</td>
<td>Polycarbonate</td>
<td>Aspirin</td>
<td>69</td>
</tr>
<tr>
<td>DCM + EtOH</td>
<td>0.75</td>
<td>Eudragit® S</td>
<td>Terfenadine,</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketoprofen,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Theophylline,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Propranalol and Tacrine</td>
<td>71</td>
</tr>
</tbody>
</table>

Recently, Lee et al., [71] developed the floating Eudragit® microspheres using DCM, EtOH and iso-propanol (IPA) in combinations, but the yield was low in case of DCM+EtOH system due to the formation of polymer precipitates as...
EtOH diffused rapidly. Hence, the diffusion of the solvent should be slow, but it was also reported that slower solvent diffusion lead to the coalescence of the microspheres [72]. However, the use of DCM, EtOH and IPA in the ratio of 5:8:2 resulted the highest yield of 96 %, but by using IPA alone along with DCM did not improve the yield.

I.B.3. *In-Vitro and In-Vivo Studies*

Internal structure of the floating microspheres can be evaluated by scanning electron microscope. For a system to float on the gastric fluid its density should be smaller than that of the gastric fluid (~1.004 g/cm³). Hence, true density of the microspheres can be determined by using (i) photographic counting method and (ii) liquid displacement method. *In-vitro* floating tests can be performed in USP II dissolution test apparatus by spreading the floating microspheres on a simulated gastric fluid (1.2 pH) containing the surfactant. The media was stirred at 100 rpm at 37°C. After specific intervals of time the fraction of the microspheres floating as well as the settled microspheres are collected and buoyancy of the floating microspheres were calculated and hollow microspheres are found to be floating for more than 12 h [55, 68].

The *in-vivo* floating behavior was investigated by taking the x-ray photographs of the floating microspheres loaded with barium sulphate in the stomach. The GI motility under fasting condition is characterized by the housekeeper wave, which occurs approximately every 1.5-2.0 h [63]. This may sweep away the content of the stomach irrespective of size, shape and density. However, the floating systems are expected to work only when there is enough water in the stomach. Therefore, the floating systems have been administered with 100 mL of water after the light meal. At the early stages i.e., within 60 min after dosing, the microspheres were found to form clouds of particles in the upper part of the stomach. At later than 60
min after dosing, the surface of the stomach contents was greatly roughened due to the pulsatile movement compared to the initial stages. Even under such a peristaltic wave propelling the antral contents towards pylorus, the microspheres were dispersed in the upper stomach. However, after 80 min, some microspheres still remained, since the system could delay their arrival at the pylorus [55]. These results are for the barium sulphate-loaded microspheres that are relatively heavier than the drug-loaded floating microspheres. Therefore, drug-loaded microspheres may show relatively better in-vivo performance.

Iannuccelli et al., [73] studied the intra-gastrie behavior of the floating multi-unit dosage forms (both floating and non-floating) loaded with barium sulphate. The study was carried out in six healthy subjects at fasted state, fed state and fed state after a succession of meals. The results showed that in the fasted state, the floating time was less than 1h, which was related to the presence of liquid in the stomach and both the control and the floating systems were emptied; Davis et al., obtained similar results [63]. In the fed state after the meal, the floating units showed a prolongation of GRT for 5 h over the control. In the fed state after a succession of meals, most of the floating units showed the floating time of 9 h and GRT prolonged up to 6-8 h over the control. These in-vivo results showed that not only the density of the system will decide about the success of these systems, but also the time of their administration is important.

I.C. Stimulus Responsive pH-Sensitive Hydrogels in Drug Delivery

Hydrogels are the cross-linked polymeric materials that are not soluble in water, but absorb large quantities of water. These are soft and rubbery in nature and resemble living tissues in their physical properties [74]. Due to their biocompatibility and non-toxicity, they are the better choices as biomaterials.
used as drug delivery devices. Such systems containing the interactive functional
groups along the polymeric chains are referred to as "smart" or "stimuli-
responsive" polymers. In these systems, the polymer conformation in solution
depends both on polymer-solvent and polymer-polymer interactions. In a good
solvent, polymer-solvent interaction predominates so that the polymer chains are
relaxed due to the minimal inter-segmental interactions. In the presence of a poor
solvent, the polymer chains will aggregate due to a restricted chain movement.
This results in changes of physical properties of the polymer solution (see Figure
I.C.1). It is however, possible to alter the polymer-solvent interactions by
changing the external stimuli. Such smart materials are recently gaining
tremendous importance as stimuli-responsive drug delivery systems.

Among the systems discussed above, the pH-sensitive polymers are
finding importance in drug delivery research. These contain weakly acidic and/or
basic pendant groups. Water uptake takes place by the ionization of these
functional groups, which depends upon pH and ionic strength of the solution. With
the ionic hydrogels having weakly acidic (anionic) groups, water uptake increases
as the external pH increases; also, swelling increases as the pH decreases in case
of weakly basic groups (cationic).

I.C.1. Anionic Acrylic Based Polymers

The anionic pH-sensitive polymers were prepared by copolymerizing or
blending with polyacrylic acids. Peppas and coworkers [75,76] reported the
syntheses of anionic copolymer of methyl methacrylate (MMA) with
hydroxyethylmethacrylate (HEMA) by bulk polymerization and cross-linked with
tetraethylene glycol dimethacrylate (TGDMA). These polymers exhibit pH-
dependent swelling. Since, the copolymer of MAA has $pK_a$ ranging from 4.3 to
5.9, an increased water uptake was observed at this pH range due to the ionization

CHAPTER I
of the carboxylic group. In another study [77], copolymers of poly(acrylic acid) (PAA) and HEMA have shown that the release of oxprenolol was increased with an increase in pH of the dissolution media. For instance, the diffusion coefficient at pH = 2.9 was $0.3 \times 10^{-7}$ cm$^2$/sec and at pH = 7.1, diffusion coefficient was increased to $4.3 \times 10^{-7}$ cm$^2$/sec. Also the release of oxprenolol hydrochloride was relatively higher from the acrylic acid copolymer than the methylacrylic acid polymers; the reason is that MAA containing polymers are more hydrophobic due to the presence of $\alpha$-methyl group [78].

Ranjha et al., [79] reported the synthesis of copolymers of poly(methyl acrylate-co-methacrylic acid), p(MA-MAA) and poly(ethyl acrylate-co-methacrylic acid), p(EA-MAA). These polymers were loaded with both water-soluble (proxyphylline) and water-insoluble (betamethasone) drugs. It was found that the copolymers containing hydrophobic unit (MA) or (EA) with MAA changes the pH-responsive pattern. Thus, the release of betamethasone starts only at pH = 6.5 for p(EA-MAA), but p(MA-MAA) releases at a pH of 5.5. It was observed that increasing the MAA fraction in the polymer shifted the threshold pH at lower side, probably due to a decrease in the apparent $pK_a$ at higher MAA content. Negishi et al., [80] synthesized the novel gel-based on thermosensitive acryloyl-L-proline ethyl ester (A-proOEt) and thermo- and pH-sensitive methacryloyl-glycine (MA-Gly) or pH-sensitive methacrylic acid (MA-Ac). The release of ketoprofen from copoly(A-ProOEt/MA-Gly) gel reached 100 % at 1.5 h after the start of the experiment in 7.4 pH buffer and after 4 h in pH 5.5 buffer. At a pH of 3.0, the cumulative amount of drug released was only 14 % even after 6 h. These findings were supportive of the pH-stimulus release from the hydrogels. Similarly, copolymerization of polyacrylamide with acrylic acid was also pH-sensitive and the release of fluorescein isothiocyanate labeled bovine serum albumin (FITC-BSA) from the polymer was pH-dependent. At pH = 2, the release of FITC-BSA was 90.5 µg, whereas at pH = 6, the release was 1485 µg [81].
Yao and Sun [82] have developed the pH-sensitive poly[(ethylene glycol-co-propylene glycol)-g-acrylamide] IPN polymer crosslinked with poly(acrylic acid). Swelling of the gels was studied in both basic and acidic pH conditions. The pH dependent swelling mechanism was proposed on the basis of the formation of intramolecular complexation by hydrogen-bonding between the –COOH of acrylic acid (AAc) and the –CONH₂ /ether functional groups at the lower pH. The pH-dependent release of sodium sulphate was observed. Yuk et al., [83] reported the anionic pH-sensitive drug delivery systems of semi-interpenetrating network beads of PAA and sodium alginate-loaded with hydrocortisone. It was observed that at pH = 1, swelling was minimum, but at pH = 4 and above, a remarkable swelling was observed. Similar pH effects were observed on the release of hydrocortisone and increase in the PAA ratio in the polymer network made the beads more sensitive to pH.

Kono et al., [84] developed the polyelectrolyte complex capsules with the size range of 2-6 μm. These capsules were prepared by adding PAA and copolymer of PAA with styrene solution to the appositely charged cationic poly(ethylenimine), which forms a polyelectrolyte complex membrane on the surface of the droplets. The permeability of poly(ethylene glycol), PEG, through these polyelectrolyte complex capsules was minimum between pH 3 and 7 where the dissociation of polyelectrolyte complex was suppressed. When the pH was decreased below 3 and increased above 8, the dissociation of polyelectrolyte complex was rapid and resulted in a drastic increase in permeability of PEG.

New types of graft copolymers based on PMMA grafted with PEG i.e., p(MMA-g-EG) pH-responsive gels were synthesized and they exhibited swelling due to the presence of ionic moieties on the backbone of PMMA. Hydrogen-bonding between -COOH protons and ether groups on the grafted chain will
stabilize the formation of interpolymer complexes that are sensitive to swelling media as well as copolymer composition [85, 86]. Initially, polymers were swollen when placed in pH 6.6 buffer due to ionization of carboxylic groups. The temporary crosslinks were broken and the mesh size of the gel was increased nearly 100 times. When placed in a solution with pH < pK\textsubscript{a} of the gels, the complexes were rapidly formed and hydrogels collapsed rapidly. Network containing larger molecular mass PEG grafts exhibited rapid syneresis. In such materials, PEG grafts were the longest and were able to reach the carboxylic groups more rapidly to collapse the network. These hydrogels have shown an oscillatory release of proxyphylline as well as large solute like FITC-dextran [87].

The graft copolymers, p(MMA-g-EG) were also used for the delivery of proteins and peptides like insulin and calcitonin [88, 89]. The microspheres of p(MMA-g-EG) were prepared and loaded with insulin by the soaking method and were evaluated for in-vivo performance in diabetes-induced Wistar rats. The insulin microspheres have decreased the blood glucose level significantly for at least 8 h. The p(MMA-g-EG) microspheres have shown better hypoglycemic activity than the insulin microspheres of Eudragit L100, possibly because PEG grafts help to maintain the biological activity of insulin. Other advantage of these hydrogels is that they have better mucoadhesive properties to adhere to the mucosa of the intestine than the stomach.

Recently Eichenbaum et al., [90] developed “microgels” based on poly(methacrylic acid-co-nitophenylcarylate) by precipitation polymerization. These microgels were chemically modified to introduce different functional groups like carboxylic acid, glutamic acid, hydroxamic acid, sulfonic acid and ethanol by set of post-polymerization reactions. These microgels were loaded with three cationic drugs like benzyl amine, dubucaine and doxorubicin. The loading efficiency was dependent upon the proton binding capacity of the
polymer. The micromanipulation technique was used to observe the environment-dependent volume change of the microgels. These microgels have shown varying volume changes with changing pH and ionic strength and the pH range was shifted by an amount proportional to $pK_a$'s of the functional groups that were derivatized on the polymer backbone.

I.C.2. Glucose Sensitive Cationic Polymers

Siegel et al., [91-94] studied the cationic hydrogels based on cationic monomers, such as dimethylaminoethyl methacrylate (DMAEM) or diethylaminoethyl methacrylate. At the pH values higher than the $pK_a$ of the cationic groups, the copolymers were hydrophilic and exclude water from the systems, whereas at pH values lower than $pK_a$, the amine groups protonate to form $\text{-NH}_3^+$ so that the gels become hydrophilic and absorb more water. These studies explain the transport properties of cationic polymers in the presence of buffers of different pH and ionic strengths. Transport through such gels in acidic media exhibit: (i) transport of protons (co-ion) and counterions to the swelling front, (ii) ionization of acidic groups of the uncharged microgel at the swelling front, (iii) relaxation of the polymer in the vicinity of ionic interface and (iv) equilibration of rubbery polymer with ions in the external media. These events are responsible for the rate controlling steps during water transport into ionic gels and these determine the mechanism of water transport. However, the Donnan exclusion of hydrogen ions from the gel was the rate-limiting factor in water transport and this can be achieved by incorporating slightly acidic ions. Transport through the cationic polymers in the presence of acidic buffer generally deviates from the Fickian trend.

Cationic polymers are used as glucose sensitive systems for the delivery of insulin. The polymers can be loaded with insulin and also glucose oxidase (GOD), an enzyme, which produces gluconic acid when reacts with glucose it oxidizes at...
the physiological pH and causes a lowering of the pH in the delivery system’s microenvironment. This lowering of pH will facilitate the syneresis of the gel and thereby squeeze out insulin from the polymeric gel. Albin et al., [95] reported the glucose sensitive cationic polymers based on polyacrylamide and poly(diethylaminoethyl methacrylate). The transport of $^{125}$I labeled insulin has shown that microporous polymers are better glucose sensitive when compared to the nonporous gels. The depletion of oxygen limited the response of these cationic gels to glucose. This oxygen depletion is strongly influenced by the extent of GOD loading and membrane thickness.

Peppas and coworkers [96] have reported on the p(HEMA-co-DEAEM) cationic polymers and found that polymer swelling was a strong function of ionic strength and pH. They have also developed the copolymers of DEAEM and poly(ethylene glycol) monomethacrylate loaded with GOD [97,98]. Their swelling studies showed that the polymers exhibited a transition at pH ~7 below which they were in the collapsed state. In addition to these polymers, some natural polymers like chitosan [99,100], alginate, pectin, [101] etc., which exhibited pH-responsive properties. The greater advantage is that these polymers are biodegradable.
I.D. Literature Cited


Figure 1.C.1. Change in the physical properties of the polymer with the external stimuli and their possible applications.