CHAPTER I
INTRODUCTION

This chapter deals with the recent developments in the field of controlled drug delivery systems using polymers as carriers. Various novel drug delivery systems including micro/nanoparticles, electrically modulated drug delivery systems (EMDDS) and in-situ gel forming solutions (GFS) are covered with respect to their production, characterization and applications. Different types of polymers have been used to design such delivery systems that can effectively deliver various classes of drugs to a target site and thus increase the therapeutic benefit, while minimizing the side effects.

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I.1. Introduction

Drugs are administered through many routes by a variety of dosage forms. However, maintaining the constant \textit{in-vivo} therapeutic drug concentrations for an extended period of time has been problematic. Peaks and troughs in drug concentration are often observed when the drug is administered either intermittently via the intravenous route or upon oral administration. High drug concentrations may cause toxicity, whereas low drug concentrations may be sub-therapeutic. The best approach to eliminate the peaks and troughs during drug therapy is by continuous intravenous infusion. However, this requires constant monitoring, which can only be performed by health-care professionals. Recently \cite{1,2}, the importance of delivery was addressed and it was stated that the delivery of therapeutics could be considered as the next frontier of molecular medicine. The extraordinary advances made in the past decade in molecular biology and biotechnology have helped identifying novel targets and developing a vast array of therapeutic agents. However, the understanding of the delivery of therapeutic agents has lagged behind.

In the past decades, extensive investigation on polymeric materials for biomedical applications has promoted the development of new concepts in the treatment of human diseases. The new approaches to drug delivery are based on the realization that optimum biological response occurs when the temporal (time-dependent) and the spatial (site-specific) delivery of bioactive agents are optimized. Controlled drug delivery technology represents one of the most rapidly advancing areas of science where polymer and pharmaceutical scientists are contributing to biomedical research. These delivery systems offer many advantages over the conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and cost effective therapeutic treatment.

Targeted delivery results in a tremendous enhancement of the therapeutic efficacy and lowering of the toxic effects. Controlled and targeted drug delivery systems can have an incredible impact on nearly every branch of
medicine. Fundamental characteristics of drug delivery systems are the ability to incorporate drugs without altering their original properties, prolonged in-vivo stability, tunable release kinetics and targeting to specific organs/tissues. These fundamental characteristics can be successfully achieved by using polymer as a carrier for the bioactive molecules.

The basic components in most of the drug delivery systems are therapeutic agents and polymers. The therapeutic agents are either physically or chemically combined in the delivery systems. If the combination is physical, drugs are dispersed or dissolved in the polymer matrix (matrix system), or are constrained inside a compartment by polymer membrane (reservoir system). If the combination is chemical, drug molecules are covalently attached to the polymer chains [3].

The final design or choice of an appropriate delivery system will first require a proper consideration of three related issues; the properties of the drug; the disease and the destination in the body. To alleviate this kind of problem, a number of drug delivery systems such as oral controlled release dosage forms, transdermal, injectable and implantable drug delivery systems have been investigated and commercialized. However, this chapter addresses the technological and research developments occurred over the past few decades in the area of hydrogel-based micro/nanoparticles, EMDDS and in-situ GFS for the controlled release (CR) of drugs. Even though there are many other delivery devices, but present thesis covers only those aspects mentioned above.

1.2. Hydrogels

Hydrogels are the three-dimensional, water-swollen structures composed of mainly hydrophilic homopolymers or copolymers [4]. They are rendered insoluble due to the presence of chemical or physical crosslinks. The physical crosslinks can be entanglements, crystallites or weak associations such as van der Waals forces or hydrogen bonds. The crosslinks provide the network structure and physical integrity.
Two of the most important characteristics in evaluating the ability of a hydrogel to function in a particular CR application are the network permeability and the swelling behavior. The permeability and swelling behavior of hydrogels are strongly dependent on the chemical nature of the polymer(s) composing the gel as well as the structure and morphology of the network. As a result, there are different mechanisms that control the release of drugs from the hydrogel-based delivery devices. Such systems are classified by their drug release mechanism as diffusional-controlled release systems, swelling-controlled release systems, chemically controlled release systems and environmentally responsive systems [5].

There are many different macromolecular structures that are possible for physical and chemical hydrogels. These include: crosslinked or entangled networks of linear homopolymers, linear copolymers, and block or graft copolymers; polyion–multivalent ion, polyion–polyion or H-bonded complexes; hydrophilic networks stabilized by hydrophobic domains; and IPNs or physical blends.

Hydrogels have emerged as the promising materials for CR technology as well as site-specific delivery of bioactive molecules. Hydrogels possess several specific advantages such as: (i) have high drug holding capacity, (ii) protection of drug from the hostile environment e.g., the presence of enzymes and low pH in the stomach, (iii) control the release of drugs by chaining the gel structure in response to environmental stimuli and (iv) hydrogels are non-toxic and biocompatible. As compared to other synthetic biomaterials, hydrogels resemble the living tissues closely in their physical properties because of their relatively high water content in addition to soft and rubbery nature. Hydrogels show a minimum tendency to adsorb proteins from the body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) the hydrogels allow the possible use of dry or swollen polymeric networks as drug delivery systems for
oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration.

In the current niche of drug delivery technologies, hydrogels have made an irreplaceable space because of their unique characteristics. However, this chapter presents a brief introduction to stimuli-responsive hydrogels as well as interpenetrating polymer network hydrogels.

1.2.1. Stimuli-Responsive Hydrogels

Several terms used for hydrogels are “intelligent” or “smart” polymers [6]. The smartness of any material is the key to its ability to receive, transmit or process a stimulus, and respond by producing a useful effect [7]. Once triggered by stimuli, the hydrogel can result in changes in phases, shapes, optics, mechanics, electric fields, surface energies, recognition, reaction rates and permeation rates. Hydrogels are “smart” or “intelligent” in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behavior, resulting in the release of the entrapped drug in a controlled manner [8]. Various stimuli that have been explored for modulating drug delivery are presented in Table I.1.

Hydrogels can exhibit dramatic changes in their swelling behavior, network structure, permeability or mechanical strength in response to different stimuli, both internal and external to the body [9]. The mechanisms of action of these stimuli on structural changes in the polymer network and corresponding modulation in drug release have been well documented in the literature [7,8,10,11]. External stimuli have been produced with the help of different stimuli-generating devices, whereas internal stimuli are produced within the body to control the structural changes in the polymer network and to exhibit the desired drug release.

Ionic hydrogels are swollen polymer networks containing pendent groups, such as carboxylic or sulfonic acid, which show a sudden or gradual change in their dynamic and equilibrium swelling behavior as a result of a
<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Hydrogel</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>pH</td>
<td>Acidic or Basic</td>
<td>Change in pH - swelling - release of drug</td>
</tr>
<tr>
<td>Ionic strength</td>
<td>Ionic</td>
<td>Change in ionic strength - change in concentration of ions inside gel - change in swelling - release of drug</td>
</tr>
<tr>
<td>Enzyme-substrate</td>
<td>Hydrogel containing immobilized enzymes</td>
<td>Substrate present - enzymatic conversion - product changes swelling of hydrogel - release of drug</td>
</tr>
<tr>
<td>Chemical species</td>
<td>Hydrogel containing electron - accepting groups</td>
<td>Electron - donating compounds - formation of charge/transfer complex - change in swelling - release of drug</td>
</tr>
<tr>
<td>Electrical</td>
<td>Polyelectrolyte hydrogel</td>
<td>Applied electric field - membrane charging - electrophoresis of charged active ingredient - change in swelling - release of drug</td>
</tr>
<tr>
<td>Thermal</td>
<td>Thermoresponsive hydrogel poly(N-isopropylacrylamide)</td>
<td>Change in temperature - change in polymer - polymer and water - polymer interactions - change in swelling - release of drug</td>
</tr>
<tr>
<td>Magnetic</td>
<td>Magnetic particles dispersed in alginate microspheres</td>
<td>Applied magnetic field - change in pores in hydrogel - change in swelling - release of drug</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Ethylene-vinyl alcohol hydrogel</td>
<td>Ultrasound irradiation - temperature increase - increase in hydrogel swelling - release of drug</td>
</tr>
</tbody>
</table>

change in the external pH. Ionization occurs when the pH of the environment is above the pKₐ of the ionizable group [12-24]. As ionization increases (increased system pH), the number of fixed charge will increase, resulting in increased electrostatic repulsions between the chains. This would result (i) in an increased hydrophilicity of the network and (ii) in electrostatic repulsion, thus resulting in greater swelling ratio.

The cationic materials contain pendent groups such as amines [12-20, 25-27]. These groups ionize in media, which are at a pH below the pKₐ of the ionizable species. Thus, in a low-pH environment, ionization increases, thereby
causing increased electrostatic repulsions. The hydrogels become increasingly hydrophilic and swell to give a high swelling ratio. More importantly, the associated drug-diffusion coefficient could increase up to three orders of magnitude.

The pH-sensitivity of these hydrogels can be exploited in a wide variety of biomedical applications such as mucoadhesive CR devices, prodrugs and adjuvants, and biocompatible materials [28]. The swelling of polyelectrolyte gels is significantly affected by the ionic strength of the swelling agent [12-27]. As the ionic strength of the swelling agent increases, the concentration of ions within the hydrogel must also increase in order to satisfy the Donnan equilibrium condition. The swelling force is reduced due to increased gel-counterion interaction and a decrease in osmotic swelling forces.

Numerous researchers have studied the dynamic swelling of pH-sensitive networks. Katchalsky and Michaeli [12] established that the collapse and expansion of poly(methacrylic acid) (PMA) hydrogels occurred reversibly by simply adjusting the pH of the fluid. Ohmine and Tanaka [23] observed the sudden collapse of ionic networks in response to sudden changes in the ionic strength of the swelling medium. Studies by Khare and Peppas [24] examined the swelling kinetics of PMA or poly(acrylic acid) (PAA) with poly(hydroxyethyl methacrylate). They observed pH- and ionic strength-dependent swelling kinetics in these hydrogels.

1.2.2. Interpenetrating Polymer Networks (IPNs)

IPNs have been extensively investigated over the past three decades due to their ability to produce versatile materials with the required combination of properties. IPN is a combination of two crosslinked polymers that (ideally) are both in network form and are not bonded to each other. Usually these are the intimate mixture of two polymers, which are in network form; at least one is synthesized and/or crosslinked in the immediate presence of the other. Formation of full and semi-IPN structure is schematically represented in Figure 1.1.
CHAPTER I

Figure I.1. Schematic representation of the formation of full and semi-IPN structures.
IPNs represent the structurally complex polymer systems, since their structures can be changed not only by using a variety of chemical building blocks, but also by following various sequences of preparation to manipulate the relative rates of network formation. Due to the chemical crosslinking, IPNs can be thermosets and these do not dissolve in ordinary solvents, but only swell.

In a polymer network, hydrophilic groups or domains are present, which are hydrated in an aqueous environment, thereby creating the hydrogel structure. As the term, ‘network’ implies, crosslinks are to be present to avoid dissolution of the hydrophilic polymer chains/segments into the aqueous phase. Hydrogels can also be described in a rheological way. Aqueous solutions of hydrophilic polymers at low or moderate concentrations, where no substantial entanglement of chains occurs, but normally exhibit the Newtonian behavior. On the other hand, once crosslinks between different polymer chains are introduced, the networks obtained will show viscoelastic or sometimes, pure elastic behavior. Because of their water absorbing capacity, hydrogels are not only subject of investigation by researchers interested in aspects of swollen polymeric networks, but such systems have found a widespread applications in different areas like developing materials for contact lenses and protein separation, matrices for cell-encapsulation and devices for the CR of drugs and proteins [29-33].

Yao and Sun [34] have developed the pH-sensitive poly[(ethylene glycol-co-propylene glycol)-g-acrylamide] IPN polymer crosslinked with PAA. The pH-dependent swelling mechanism was proposed on the basis of the formation of intramolecular complexation by hydrogen-bonding between the –COOH group of acrylic acid and the –CONH₂ /ether functional groups at lower pH. Yuk et al. [35] reported the anionic pH-sensitive drug delivery systems of semi-IPN 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. Kurisawa and Yui [36] have proposed a
dual-stimuli-responsive drug release device from the IPN-structured hydrogels of gelatin and dextran, wherein lipid microspheres have been incorporated as drug micro-reservoirs.

I.3. Polymeric Micro/Nanoparticles as Drug Delivery System

In recent years, polymeric micro/nanoparticles have attracted a 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 [37-48]. Chitosan-based drug delivery systems prepared by different methods for various kinds of drugs are summarized in Table I.2.

I.3.1. Methods of Preparation of Hydrogel Micro/Nanoparticles

Different methods have been used to prepare the hydrogel particulate systems. Selection of any of the methods depends upon factors such as particle size requirement, thermal and chemical stability of the active agent, reproducibility of the release kinetics profiles, stability of the final product and residual toxicity associated with the final product. Different methods used in the preparation of hydrogel micro/nanoparticles are discussed in this section. However, the selection of any of these methods depends upon the nature of the active molecule as well as the type of the delivery device.
<table>
<thead>
<tr>
<th>Type of System</th>
<th>Method of Preparation</th>
<th>Drug</th>
</tr>
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<tbody>
<tr>
<td>Tablets</td>
<td>Matrix</td>
<td>Diclofenac sodium, Pentoxyphylline, Salicylic acid, Theophylline</td>
</tr>
<tr>
<td></td>
<td>Coating</td>
<td>Propranolol HCl</td>
</tr>
<tr>
<td>Capsules</td>
<td>Capsule shell</td>
<td>Insulin, 5-Amino salicylic acid</td>
</tr>
<tr>
<td>Microspheres/</td>
<td>Emulsion cross-linking</td>
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</tr>
<tr>
<td>Microparticles</td>
<td></td>
<td>Theophylline, 5-Fluorouracil, Diclofenac sodium, Griseofulvin,</td>
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<tr>
<td></td>
<td></td>
<td>Aspirin, Diphtheria toxoid, Pamidronate, Progesterone,</td>
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<td></td>
<td></td>
<td>Suberoylbisphosphonate, Mitoxantrone</td>
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<td></td>
<td>Coacervation/Precipitation</td>
<td>Prednisolone, Interleukin-2, Propranolol-HCl</td>
</tr>
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<td></td>
<td>Spray-drying</td>
<td>Cimetidine, Famotidine, Nizatidine, Vitamin D-2, Diclofenac sodium,</td>
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<td></td>
<td></td>
<td>Ketoprofen, Metoclopramide, Bovine serum albumin, Ampicillin,</td>
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<td></td>
<td></td>
<td>Cetyl pyridinium chloride, Oxytetracycline, Betamethasone</td>
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<tr>
<td></td>
<td>Ionic gelation</td>
<td>Felodipine</td>
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<td></td>
<td>Sieving method</td>
<td>Clozapine</td>
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<td>Emulsion-droplet</td>
<td>Gadopentetic acid</td>
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<td></td>
<td>coalescence</td>
<td>DNA, Doxorubicin</td>
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<tr>
<td></td>
<td>Coacervation/</td>
<td>DNA, Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Precipitation</td>
<td>DNA, Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Ionic gelation</td>
<td>Insulin, Ricin, Bovine serum albumin</td>
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<td>Reverse micellar method</td>
<td>Doxorubicin</td>
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<tr>
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<tr>
<td></td>
<td></td>
<td>macrophage colony-stimulating factor, Acyclovir, Riboflavin,</td>
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<tr>
<td></td>
<td></td>
<td>Testosterone, Progesterone, Beta-oestradiol</td>
</tr>
<tr>
<td>Gel</td>
<td>Crosslinking</td>
<td>Chlorpheniramine maleate, Aspirin, Theophylline, Caffeine, Lidocaine-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCl, Hydrocortisone acetate, 5-Fluorouracil</td>
</tr>
</tbody>
</table>

**Table 1.2**
Chitosan-Based Drug Delivery Systems Prepared by Different Methods for Various Kinds of Drugs
1.3.1.1. Emulsion Crosslinking

In this method, a water-in-oil (w/o) emulsion is prepared by emulsifying the polymer aqueous solution in the oil phase. Aqueous droplets are stabilized using a suitable surfactant. The stable emulsion is crosslinked by using an appropriate crosslinking agent such as glutaraldehyde to harden the droplets. Microspheres were filtered and washed repeatedly with n-hexane followed by alcohol and then dried [49]. By this method, size of the particles can be controlled by controlling the size of aqueous droplets. However, the particle size of the final product depends upon the extent of crosslinking agent used, while hardening in addition to speed of stirring during the formation of emulsion. The emulsion crosslinking method has few drawbacks, since it involves the tedious procedures as well as use of harsh crosslinking agents, which might possibly induce chemical reactions with the active agent. However, complete removal of the unreacted crosslinking agent may be difficult in this process.

1.3.1.2. Coacervation/Precipitation

This method utilizes the physicochemical properties of the polymers. For instance, chitosan is insoluble in alkaline pH medium, but precipitates/coacervates upon contact with the alkaline solution. Particles are produced by blowing chitosan solution into an alkali solution like sodium hydroxide, NaOH-methanol or ethanediamine using a compressed air nozzle to form coacervate droplets [50]. Separation and purification of particles was done by filtration/centrifugation followed by successive washing with hot and cold water. Varying compressed air pressure or spray-nozzle diameter controlled the size of the particles and then by using the cross-linking agent to harden the particles could control the drug release. In another technique [51], sodium sulfate solution was added drop-wise to an aqueous acidic solution of chitosan containing the surfactant under constant stirring and ultrasonication for 30 min. Microspheres were purified by centrifugation and re-suspended in demineralized water. Particles were crosslinked with glutaraldehyde. The
particles produced by this method have better acid stability than those observed by the other methods.

1.3.1.3. Spray-Drying

Spray-drying is a well-known technique used to produce powders, granules or agglomerates from the mixture of drug and excipient solutions as well as suspensions. The method is based on drying of atomized droplets in a stream of hot air. In this method, polymer is first dissolved in a suitable solvent, drug can then be dissolved or dispersed in the solution and afterwards, a suitable crosslinking agent is added. This solution or dispersion is then atomized in a stream of hot air. Atomization leads to the formation of small droplets from which solvent evaporates instantaneously leading to the formation of free-flowing particles [52]. Various process parameters are to be controlled to get the desired size of particles. Particle size depends upon the size of the nozzle, spray flow-rate, atomization pressure, inlet air temperature and extent of crosslinking.

1.3.1.4. Emulsion-Droplet Coalescence Method

The novel emulsion-droplet coalescence method was developed by Tokumitsu et al. [53], which utilizes the principles of both emulsion crosslinking and precipitation. However, in this method, instead of crosslinking the stable droplets, precipitation is induced by allowing the coalescence of chitosan droplets with NaOH droplets. First, a stable emulsion containing aqueous solution of chitosan along with drug is produced in liquid paraffin oil and then, another stable emulsion containing chitosan aqueous solution of NaOH is produced in the same manner. When both emulsions are mixed under high-speed stirring, droplets of each emulsion would collide at random and coalesce, thereby precipitating the chitosan droplets to give small size particles.

1.3.1.5. Ionic Gelation

The use of complexation between oppositely charged macromolecules to prepare microspheres has attracted much attention, because the process is very
simple and mild [54,55]. In addition, reversible physical crosslinking by electrostatic interaction, instead of chemical crosslinking, has been applied to avoid the possible toxicity of reagents and other undesirable effects. Recently, many researchers have explored the ionic gelation technique for potential pharmaceutical usage [56-61]. Cationic polymers such as chitosan can undergo ionic gelation when reacted with polyanion such as tripolyphosphate (TPP), whereas the anionic polymers like sodium alginate and gellan gum undergo ionic gelation with bivalent cations such as calcium or zinc. In this method, the polymer is dissolved in aqueous solution to get the charged species of the polymer. This aqueous solution of the polymer is then added dropwise under constant stirring condition to a solution containing the oppositely charged species. Due to the complexation between oppositely charged species, polymer undergoes ionic gelation and precipitates to form spherical particles.

1.3.1.6. Reverse Micellar Method

Reverse micelles are thermodynamically stable liquid mixtures of water, oil and surfactant. Macroscopically, they are homogenous and isotropic, structured on a microscopic scale into aqueous and oil microdomains separated by surfactant rich films. One of the most important aspects of reverse micelle hosted systems is their dynamic behavior. Nanoparticles prepared by the conventional emulsion polymerization methods are not only large (> 200 nm), but also have a broad size range. Preparation of ultrafine polymeric nanoparticles with narrow size distribution could be achieved by using a reverse micellar medium [62]. Aqueous core of the reverse micellar droplets can be used as a nanoreactor to prepare such particles. Since the size of the reverse micellar droplets usually lies between 1 and 10 nm [63], and these droplets are highly monodispersed, the preparation of drug-loaded nanoparticles in reverse micelles would produce extremely fine particles with a narrow size distribution. Since micellar droplets are in the Brownian motion, they undergo continuous coalescence followed by re-separation on a time-scale that varies between millisecond and microsecond [64]. The size, polydispersity
and thermodynamic stability of these droplets are maintained in the system by a rapid dynamic equilibrium.

In this method, the surfactant is dissolved in an organic solvent to prepare the reverse micelles. To this, the aqueous solution of mixture of polymer and drug is added with constant vortexing to avoid any turbidity. The aqueous phase is regulated in such a way as to keep the entire mixture in an optically transparent microemulsion phase. To this transparent solution, a crosslinking agent is added with constant stirring, and crosslinking is achieved by stirring overnight. The maximum amount of drug that can be dissolved in reverse micelles varies from drug to drug and this has to be determined by gradually increasing the amount of drug until the clear microemulsion is transformed into a translucent solution. The organic solvent is then evaporated to obtain the transparent dry mass. The material is dispersed in water and then adding a suitable salt precipitates the surfactant out. The mixture is then subjected to centrifugation. The supernatant solution is decanted, which contains the drug-loaded nanoparticles. The aqueous dispersion is immediately dialyzed through the dialysis membrane for about 1 h and the liquid is lyophilized to dry powder.

1.3.1.7. Sieving Method

Recently, Agnihotri and Aminabhavi [65] have developed a simple, yet novel method to produce chitosan microparticles. In this method, microparticles were prepared by crosslinking chitosan to obtain a non-sticky glassy hydrogel followed by passing through a sieve. A suitable quantity of chitosan was dissolved in 4% acetic acid solution to form a thick jelly mass that was crosslinked by adding glutaraldehyde. The non-sticky crosslinked mass was passed through a sieve with a suitable mesh size to get the microparticles. The microparticles were washed with 0.1 N NaOH solution to remove the un-reacted excess glutaraldehyde and dried overnight in an oven at 40°C. This method is devoid of the tedious procedures, and can be scaled up easily.
1.3.2. Drug Loading into Hydrogel Micro/Nanoparticles

Drug loading in hydrogel micro/nanoparticulate systems can be done by two methods i.e., during the preparation of particles (incorporation) and after the formation of particles (incubation). In these systems, drug is physically embedded into the matrix or adsorbed onto the surface. Various methods of loading have been developed to improve the efficiency of loading, which largely depends upon the method of preparation as well as physicochemical properties of the drug. Maximum drug loading can be achieved by incorporating the drug during the formation of particles, but it may get affected by the process parameters such as method of preparation, presence of additives, etc.

Both water-soluble and water-insoluble drugs can be loaded into hydrogel-based particulate systems. Water-soluble drugs are mixed with polymer solution to form a homogeneous mixture, and then, particles can be produced by any of the methods discussed earlier. Water-insoluble drugs can be loaded by the soaking method [66] or by using the multiple emulsion technique.

1.3.3. Drug Release and Release Kinetics

Methods to study the in-vitro release are by: (i) side-by-side diffusion cells with the artificial or biological membranes, (ii) dialysis bag diffusion, (iii) reverse dialysis sac, (iv) ultracentrifugation or (v) ultrafiltration. Despite the continuous efforts in this direction, there are still some technical difficulties to study the in-vitro drug release from the micron and submicron size particles [67,68]. 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 [69-71].
Drug release from the hydrogel-based particulate systems depends upon the extent of cross-linking, morphology, size and density of the particulate system, physicochemical properties of the drug as well as the presence of adjuvants. *In-vitro* release also depends upon pH, polarity and the presence of enzymes in the dissolution media. The release of drug from the particulate systems involves three different mechanisms: (a) release from the surface of particles, (b) diffusion through the swollen rubbery matrix and (c) release due to polymer erosion.

In majority of cases, the drug release follows more than one type of mechanism. In case of release from the surface, adsorbed drug instantaneously dissolves when it comes in contact with the release medium. Drug entrapped in the surface layer of particles also follows this mechanism. This type of drug release leads to the burst effect [52]. Increasing the crosslinking density can prevent the burst release. This effect can also be avoided by washing the microparticles with a proper solvent, but it may lead to low encapsulation efficiency.

Drug release by diffusion involves three steps. First, water penetrates into the particulate system, which causes swelling of the matrix; secondly, the conversion of glassy polymer into rubbery matrix takes place, while the third step is the diffusion of drug from the swollen rubbery matrix. Hence, the release is slow initially and later, it becomes fast. This type of release is more prominent in case of hydrogels.

The most commonly used equation for diffusion-controlled matrix system is an empirical equation used by Ritger and Peppas [72], in which early time release data can be fitted to obtain the diffusion parameters using,

\[
\frac{M_t}{M_\infty} = k t^n
\]

Here, \(M_t/M_\infty\) is the fractional drug release at time \(t\), \(k\) is a constant characteristic of the drug-polymer interaction and \(n\) is an empirical parameter characterizing
the release mechanism. Based on the diffusional exponent [73], drug transport is classified as Fickian \((n = 0.5)\), Case II transport \((n = 1)\), non-Fickian or anomalous \((0.5 < n < 1)\) and super Case II \((n > 1)\).

In swelling controlled release systems, drug is dispersed within a glassy polymer. Upon contact with the biological fluid, the polymer swells, but no drug diffusion occurs through the polymer phase. As the penetrant enters the glassy polymer, glass transition temperature of the polymer is lowered due to relaxation of the polymer chains. Drug could diffuse out of the swollen rubbery polymer. This type of system is characterized by the two moving boundaries: the front separating the swollen rubbery portion and the glassy region, which moves with a front velocity and the polymer fluid interface. The rate of drug release is controlled by the velocity and position of the front dividing the glassy and rubbery portions of the polymer.

1.4. Electrically Modulated Drug Delivery Systems

Drug delivery systems composed of electrically responsive polymeric materials that are actuated by electric stimulus are particularly interesting due to the fact that mechanical energy is triggered by an electric signal [74,75]. Electrically responsive hydrogels are usually made of polyelectrolytes and insoluble, but swellable polymer networks having cations or anions. Such a system can transform the chemical free energy directly into mechanical work to give isothermal energy conversion and can be used as actuators, electromechanical engines, artificial muscle, chemical valve and drug delivery systems. Electrically controlled drug delivery may particularly offer the unique advantages for providing 'on-demand' release of drug molecules from implants or transdermal systems.

Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field [76]. Sometimes, hydrogels show swelling on one side and deswelling on the other side, resulting in bending of the hydrogels. However, the change in the hydrogel shape (including swelling,
shrinking and bending) depends on a number of conditions. If the surface of hydrogel is in contact with the electrode, the result of applying electric field to the hydrogel may be different from systems where the hydrogel is placed in water (or acetone–water mixture) without touching the electrode. The result will be different yet if the aqueous phase contains electrolytes.

Polymers used to develop stimulus responsive systems are hydrogels with ionizable groups. However, the magnitude of their response depends on the type of functional group and the basic polymer repeat unit. Kim and Lee [77] investigated the electrically modulated properties of interpenetrating polymer network (IPN) containing poly(vinyl alcohol) (PVA) and PAA. They synthesized the IPNs by UV irradiation method and studied loading and release behavior of the two model drugs viz., cefazoline (ionic) and theophylline (non-ionic). The amount of loaded drug significantly increased with an increase in the PAA content, which contains the ionizable groups. The loading of ionic drug cefazoline, was greater than the non-ionic theophylline and the release rate of cefazoline was higher than that of theophylline. Diffusion of drug molecules from the IPN hydrogels “switched-on and –off” in a pulsatile manner and applied electric voltage played important role. As the voltage was increased from 5 to 10 volts, the drug release was also increased. An applied voltage, ionic group content of the polymer and ionic properties of the drug, influenced the rate of drug release.

Electro-sensitive hydrogels have been applied in controlled drug delivery [78-89]. Hydrogels made of poly(2-acrylamido-2-methylpropane sulfonic acid–co-n-butylmethacrylate) could release edrophonium chloride and hydrocortisone in a pulsatile manner under the influence of electric current [90]. Control of ‘on–off’ drug release was achieved by varying the intensity of electric stimulation in distilled–deionized water. For edrophonium, a positively charged drug, the release pattern was explained in terms of an ion exchange mechanism between the positively charged solute and the hydrogen ion produced by electrolysis of water.
Chemomechanical shrinking and swelling of PMA hydrogels under an electric field was used to study the pulsatile delivery of pilocarpine and raffinose. Microparticles of PAA hydrogels, which showed a rapid and sharp shrinkage after the application of electric current, recovered their original size when the electric field was turned off. The electric field-induced changes in the size of the microparticles resulted in ‘on-off’ release profiles. The electric field-induced volume changes of poly(dimethylaminopropyl acryl amide) hydrogels were used for the pulsatile release of insulin [79]. The monolithic device composed of sodium alginate and PAA was also used to release hydrocortisone in a pulsatile manner using electric stimulus [91].

In addition to hydrogel swelling and contraction, electric fields have also been used to control the erosion of hydrogels made of poly(ethyloxazoline)–PMA complex in a saline solution [89]. The two polymers form the hydrogel via intermolecular hydrogen-bonding between carboxylic and oxazoline groups. When the hydrogel matrix was attached to a cathode surface, application of electric current caused disintegration of the complex into watersoluble polymers at the hydrogel surface facing the cathode. The surface erosion of this system was controlled either in a stepwise or continuous fashion by controlling the applied electrical stimulus. However, the pulsatile insulin release was achieved by applying a step function of electric current.

I.5. In-situ Gel Forming Solutions as Drug Delivery Systems

The in-situ gel forming solutions are viscous liquids that shift to a gel phase upon exposure to physiological conditions. The term “in-situ gelling” also describes a stimulus-induced response, but is generally used more narrowly to denote formulations that gel upon contact with the mucosa. The most prominent advantage of such formulations is that they are fluid like prior to contact with the mucosa, and can thus be easily administered as a drop or by a spray device.
In-situ gelling formulations have been evaluated for several administration routes such as ophthalmic [92-110], nasal [111-114], parenteral [115-118], oral [119-124], rectal [125,126] and vaginal [127]. These kinds of formulations have shown to increase the residence time and improve the drug absorption. Various mechanisms are involved in the phase transition of these polymers. The viscosities of cellulose acetate phthalate (CAP) latex [128] and carbopol solution increase when the pH is raised from its native value to the body pH (pH = 7.4). Gellan gum [129] and alginates [130] gel in the presence of mono or divalent cations. The pluronics [131], a class of block copolymers of poly(oxyethylene) and poly(oxypropylene), and tetronics [132] as well as ethyl(hydroxyethyl) cellulose [133], exhibit thermoreversible gelation. That is, their solutions show increase in viscosity upon increasing the temperature.

Bioadhesion can be used as a means to improve the intimacy of contact, as well as a way to increase the dosage form residence time to various administration routes [134-136]. Furthermore, in order to fortify the adhesion of the administered drugs onto the mucosal surfaces, mucoadhesive polymers such as polycarbophil, carbopol, hydroxypropyl cellulose, polyvinylpyrrolidone have been added to the in situ-gelling liquids [134,137,138]. There are several ways to sustain the release of drug from the gels, which would allow us to take the full advantage of the contact time. The drug can be dispersed in the gel, giving a concentration that is higher than that corresponding to the solubility of the drug [139], formulated as particles [140,141], distributed in liposomes [142,143], interacting with an oil phase that has been included in the gel [144].

The evaluation of rheological properties for the gel-type dosage forms would be important for predicting their in-vivo behavior. The rheological properties of eye gels were reported to affect the ocular residence time of the gels [141,145,146]. The flow properties of semi-solid vaginal dosage forms might be of use to predict the spreading and coating of the formulations over the vaginal epithelia. Especially, in the thermosensitive gels containing a
mucoadhesive polymer, the rheological characteristics need to be controlled and understood, since the multi-component gels do exhibit complex flow behaviors due to the feasible interaction among the components.

However, most of the systems require the use of high concentrations of polymers. For instance, it needs 25% (w/v) pluronics and 30% (w/v) CAP, respectively, to form the stiff gel upon instillation in the eye. As the concentration of carbopol increases in the vehicle, its acidic nature would cause stimulation to the eye tissue. In order to reduce the total polymer content and improve the gelling properties, Joshi et al. [147], first used the combination of polymers in the delivery system. The main idea here is that the aqueous compositions reversibly gel in response to simultaneous variations in at least two physical parameters viz., pH, temperature, and ionic strength.

Kumar and co workers [109] following the invention of Joshi et al., have developed an ocular drug delivery system based on a combination of carbopol and methylcellulose. Carbopol is a PAA polymer, which shows a "sol-to-gel" transition in aqueous solution as the pH is raised above its pKa of about 5.5 [148]. Methylcellulose, a viscosity-enhancing polymer [149] exhibits a "sol-to-gel" transition in aqueous solution in the range of 50–55°C. Kumar and Himmelstein [150] also developed a similar delivery system by a combination of carbopol and hydroxypropyl methylcellulose (HPMC). For both the systems, it was found that a reduction in carbopol concentration without compromising the in-situ gelling properties as well as overall rheological behaviors was achieved by adding a suitable viscosity-enhancing polymer [109,150].

Srividya et al. [102] developed the in-situ gel forming ophthalmic delivery system based on carbopol and HPMC for the delivery of ofloxacin, based on the concept of pH-triggered in-situ gelation. Thus produced gel forming solution was pH-sensitive and released drug up to 8 h. Better rheological properties were obtained by blending these polymers to give improved antibacterial activity without producing the adverse effect on the eye. Gel forming solution also reduces the systemic absorption of the drug, which is
intended for local application in the eye. Jarvinen et al. [151] reported that systemic absorption of timolol could decrease in rabbit when PAA was incorporated in the formulation. Bioavailability of timolol containing PVA and PAA formulations were compared. The PAA-based formulation has shown a slow release and retained in the eye for a longer period.

### I.6. The Thesis Research Problem

In view the applications of polymeric matrices for the development of CR products; the present thesis covers several newer approaches or modifications on the existing protocols to develop CR devices by encapsulation. The release study of the active agents in a controlled manner was achieved using a variety of polymers fabricated as various delivery systems. The necessary pre-formulation studies and variations in formulation parameters have been studied for the development of novel CR formulations for the active agents. Several novel methods of encapsulation procedures to encapsulate some of the typical bioactive molecules have been developed because of the difficulties involved in encapsulation of such molecules by using the conventional methods. These aspects will be covered in subsequent chapters of this thesis. It is anticipated that results of this research will be useful in the area of pharmaceutics.
1.4. Literature Cited

CHAPTER I


CHAPTER I


