Chapter 8

Summary and Conclusion
SUMMARY

In recent years, the hydrogel based controlled release (CR) technology has emerged as a major multidisciplinary research frontier due to extensive research efforts. CR dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients, at a predetermined time. The major advantages of CR systems, over conventional methods include better drug utilization, controlled rate, more uniform blood concentration, improved patient compliance, reduced dosing frequency and a greater selectivity of pharmacological activity.

CR drug delivery system should necessarily consist of a barrier, which is generally a polymer. Natural polymers remain attractive primarily because they are natural products of living organisms, readily available, relatively inexpensive and capable of a multitude of chemical modifications, but they have some disadvantages such as inappropriate mechanical properties, low strength, inconsistent behavior and poor cell adhesion. To overcome these disadvantages, synthetic materials are employed, but they have much limited biocompatibility and biodegradability than those of natural polymers. In various studies, attempts have been made to overcome these shortcomings by chemical modification of polymers.

Factors that govern the mechanism of CR of an active agent across the polymeric matrix are diffusion, leaching, swelling, degradation or erosion of the polymer, and physicochemical properties of the drug molecule. Technique of production of special formulations such as controlled release, site specific and target release has been a great interest. A detailed study of chemical modification of polymers and their evaluation may help in the development of newer materials. The present study aims at chemical modification of natural as well as synthetic polymers, preparation of various drug
delivery devices using the modified polymers and their evaluation for mechanical properties, thermal properties and drug release.

First chapter is an introduction. It gives an introduction and brief history of CR drug delivery systems. Classification of CR systems has been narrated here. Microparticulate drug delivery systems (microspheres and beads), Transdermal Drug Delivery Systems (TDDS), their method of preparation and release kinetics are explained in detail. Importance and basic characteristics of various polymers and their need for chemical modification is narrated. Classification of polymers according to their sources and uses has been mentioned. Release of drugs from the drug delivery systems is determined using various mathematical models. Literature survey has been made with reference to polymers and drugs.

The second chapter is experimental. In this chapter, the materials and methods used for the preparation and evaluation of different drug delivery devices have been mentioned. Sophisticated instrumental techniques such as UV Spectrophotometry, FTIR Spectroscopy, DSC, TGA, SEM etc., were used for characterization of the formulations, confirmation of stability of drug delivery devices and intactness of drugs when incorporated into the formulations. The mechanical properties, swelling index, permeability coefficient, encapsulation techniques, film casting, entrapment efficiency, in vitro drug release, stability and skin irritancy tests are discussed.

Third chapter deals with in vitro release study of captopril from chemically modified polyvinyl alcohol (PVA) transdermal membranes. A hydrophilic synthetic polymer PVA was crosslinked using different aliphatic aldehydes for release of Captopril (an antihypertensive drug). It has a short biological half-life of 2 hrs. It has been effective where conventional antihypertensive therapies fail or have an untoward number of side effects. Formaldehyde, acetaldehyde, propionaldehyde and glutaraldehyde (GA) were
selected amongst the list of aldehydes based on their film forming ability after the reaction. Carbon chain length and percentage aldehyde conversion, affect the film characteristics. The membranes were prepared by film casting technique. The crosslinking of polymer with aldehydes leading to the formation of acetal was confirmed by FTIR spectroscopy. It also confirmed the nonreactiveness of drug with the polymer or the crosslinking agent, and its intactness in the formulation. Thermal analysis using DSC indicated that the crosslinked membranes were thermally more stable compared to the pure polymer. The tensile strength and entrapment efficiency were enhanced whereas swelling and WVT rates decreased after crosslinking. The *in vitro* drug release studies were carried out using Keshary-Chien diffusion cell and the results indicated a systematic drug release pattern with a prolonged drug action for 12 hrs. The membranes did not produce any harmful effects on skin such as erythema or edema and they were stable at all the temperature conditions of storage during study.

Chapter 4 was a study of PVA transdermal membranes, where it has been blended with natural polymers such as chitosan and sodium alginate, to prepare polymeric materials with desired properties, low basic cost, improved processability and to meet all the complex demands of the biomaterials. Varying proportions of polymers were mixed and cast into membranes by film casting technique, in which, Salbutamol sulphate (an antiasthmatic drug) was incorporated. Crosslinking reaction of PVA with chitosan and with sodium alginate using GA was confirmed by FTIR spectral data. The glass transition temperatures (T_g) of polymers were shifted towards higher temperatures after crosslinking, and showed a single endothermic thermal peak indicating homogeneous mixing of polymers, as studied by DSC. A significant weight loss was observed for the drug loaded membranes compared to the membranes without drug as observed from the TGA. Blending of polymers led to increase in tensile strength and
entrapment and decrease in elongation, swelling and permeability. After crosslinking the PVA-chitosan blend became more rigid and showed a very slow drug release pattern compared to the PVA-alginate matrix.

Chapter 5 deals with IPNs. IPN, it is a three-dimensional network of two or more polymers, one of which is crosslinked in presence of the other. Such systems create additional free space to accommodate the drug. Sodium alginate (polyelectrolyte having a rigid molecular chain and good film forming ability) and guar gum (polysaccharide) were used for IPN formation and GA was used as a common crosslinking agent, at different concentrations. Chlorpheniramine maleate (an antihistaminic drug) was used as a model drug. The membranes produced were found to have good mechanical, thermal and drug release properties. Incorporation of GG into the IPN led to the increase in swelling and vapor transmission rate as well as drug entrapment efficiency. The results of *in vitro* release indicated a more sustained effect with an increase in the concentration of crosslinking agent.

Chapter 6 refers to the development of chitosan microspheres for release of an insoluble drug-Ibuprofen, a widely used phenyl propionic acid derivative class of NSAIDs (non-steroidal antiinflammatory drugs). Its antiinflammatory, analgesic and antipyretic properties have been well established in standard animal models. The microspheres were prepared by suspension crosslinking technique and by emulsification and ionotropic gelation by NaOH method. The microspheres produced were subjected to SEM analysis and were found to be spherical shaped with a smooth surface. Higher stirring rates and increased concentrations of crosslinking agents produced microspheres of smaller size. Microspheres having the least crosslinking agent showed maximum swelling. The microspheres prepared by crosslinking technique showed controlled
release over a period of 10 hrs. The formulations were found to be stable from the stability study carried out at varying temperatures.

Chapter 7 deals with IPN beads of natural polymers sodium alginate and chitosan which were selected due to their safety, and compatibility. Formation of interpolymer complexes of chitosan with sodium alginate and development of chitosan IPN beads by crosslinking using GA has been discussed. Ofloxacin.HCl, an antibiotic was chosen as a model drug for encapsulation in the polymer matrix. IPN beads of smaller than 250 μm were produced. Chitosan beads showed lesser extent of swelling compared to those of IPN beads. Time of exposure to GA influenced both swelling and drying rate of the beads. The release profile was characterized by an important initial burst effect followed by a continuous and fast release. Both the burst effect and the continuous release phase appeared highly dependent on the concentration of the polymer used for encapsulation.

The last chapter presents a summary of the entire work carried out.
CONCLUSION

Controlled release drug delivery systems many advantages over the conventional and more invasive methods of drugs delivery like tablets, capsules, injectables and ointments. The advantages of CR preparations include decreased incidence and intensity of adverse effects and toxicity, better drug utilization, controlled rate and site of release, more uniform blood concentration, etc. CR drug delivery system necessarily consists of a barrier, which is generally a polymer. Chemical modification of biodegradable polymers (natural, synthetic or semi synthetic) is potentially important to control their degradation rates.

The polymers (chitosan, sodium alginate, guar gum and polyvinyl alcohol) used for preparation of CR devices such microspheres, beads and transdermal membranes were easily available, biodegradable, biocompatible and nontoxic. The polymers were chemically modified by using aldehydes as crosslinking agents. Various classes of drugs were incorporated into the polymeric matrices and their in vitro release was evaluated. The methods of preparation were reproducible and processing parameters were well controlled. The formulations showed prolonged drug release and were found to be stable during storage at various temperature conditions.

In conclusion, the topics presented in the thesis explore newer technologies to develop CR drug delivery systems using natural as well as synthetic polymers, alone or in combination and the formulations developed produced prolonged duration of action.