SYNOPSIS

Controlled release (CR) drug delivery systems cover a wide range of prolonged action formulations, which provide continuous release of their active ingredients, at a predetermined time. Tremendous opportunities exist for utilizing advanced drug delivery systems for acute diseases or chronic illnesses. The hydrogel based CR technology has emerged as a major multidisciplinary research frontier due to extensive research efforts. It finds major applications in the delivery of a wide range of bioactive molecules such as drugs, hormones and vaccines. The most important objective for the development of these systems is to furnish an extended duration of action.

The advantages of CR preparations include: (1) decreased incidence and intensity of adverse effects and toxicity, (2) better drug utilization, (3) controlled rate and site of release, (4) more uniform blood concentrations, (4) improved patient compliance, (5) reduced dosing frequency, (6) more consistent and prolonged therapeutic effect, and (7) a greater selectivity of pharmacological activity. Technique of production of special formulations such as sustained release, site specific and target release has been a great interest. Products of this type have been formulated for oral, injectable, topical use and as inserts for placement in the body cavities.

CR drug delivery system necessarily consists of a barrier, which is generally a polymer. To be successfully used in the CR formulations, a polymer must have an appropriate physical structure, be chemically inert, readily processable and biocompatible.

The present study concentrates on chemical modification of both natural polymers (chitosan, sodium alginate, guar gum etc.) and synthetic polymer (polyvinyl alcohol) by chemical crosslinking using a number of aldehydes such as formaldehyde,
acetaldehyde, propionaldehyde and glutaraldehyde (GA). The modified polymers have been used alone or in combination with other polymers for the preparation of a number of controlled drug delivery devices, which include transdermal membranes, microspheres and beads for the release of various classes of drugs, such as antihypertensive, antihistaminic, antiasthamatic and a non-steroidal antiinflammatory agent. The formulations have been evaluated for any possible chemical interactions between drug, polymer and the crosslinking agent, using FTIR (Fourier Transform Infrared) spectroscopy, and the thermal stability using DSC (Differential Scanning Calorimetry), and TGA (Thermogravimetric Analysis) techniques. The transdermal membranes were evaluated for the mechanical properties such as tensile strength and elongation, extent of swelling, vapor transmission rate, in vitro drug release, stability and skin irritancy. The surface characteristics of microspheres and beads have been evaluated using SEM (Scanning Electron Microscopy). Further they have been evaluated for degree of swelling, rate of drying, drug entrapment efficiency, in vitro drug release and stability.

The thesis comprises eight chapters.

Chapter 1 is an introduction to the CR drug delivery systems. History of CR technology and the systems containing polymers are discussed here. The pharmacokinetic analysis and diffusion of a drug from the polymer matrix has been explained using Fick’s diffusion equations.

Fick’s first law of diffusion states that the amount of drug M, diffusing through a unit cross-sectional area S of a barrier, in unit time t, is known as flux F

\[ F = \frac{dM}{S \cdot dt} \]
The flux ($F$) is proportional to the concentration gradient $\partial c / \partial \chi$,

$$F = -D \frac{\partial c}{\partial \chi}$$

where $D$ is diffusion coefficient in cm$^2$/sec, $c$ its concentration in g/cm$^3$, $\chi$ the distance in cm of movement perpendicular to the surface of a barrier.

Fick's second law of diffusion may be expressed as

$$\frac{dc}{dt} = D \frac{\partial^2 c}{\partial \chi^2}$$

where $dc/dt$ denotes the concentration gradient from the surface of the layer in the direction of flow.

The different methods of preparation and mechanism of drug release from particulate drug delivery systems (microspheres and beads) have been explained in detail. Topical administration of therapeutic agents known as Transdermal Drug Delivery System (TDDS), offers many advantages over the conventional and more invasive methods of drugs delivery like tablets, capsules, injectables and ointments. The components of TDDS and kinetics of transdermal permeation across the skin has been explained. Different classes of biodegradable polymers (natural, semi synthetic and synthetic) with suitable examples and their uses have been mentioned.

Chapter 2 is experimental. It presents details about the experimental procedures and the instruments used during the research. The different methods adopted for the preparation of transdermal membranes and particulate drug delivery systems are explained. The characterization of these formulations has been made using analytical techniques such as UV Spectrophotometry, FTIR Spectroscopy, DSC, TGA, and SEM. They have also been evaluated for weight variation, mechanical properties, swelling and
drying rate, vapor transmission rate, drug entrapment efficiency, \textit{in vitro} drug release, skin irritancy, and stability.

Chapter 3 defines \textit{in vitro} release study of Captopril (an antihypertensive drug) from chemically modified polyvinyl alcohol (PVA) transdermal membranes. PVA, a synthetic polymer has been chemically modified by crosslinking using different aldehydes as crosslinking agents, such as formaldehyde, acetaldehyde, propionaldehyde and glutaraldehyde (1 \% w/w) in presence of an acid to form acetal. The membranes have been prepared by film casting technique. The possible interaction between polymer, drug and the crosslinking agents has been studied by FTIR spectroscopy. The thermal stability and the mass loss of the above materials have been studied using DSC and TGA respectively. Tensile strength, elongation, swelling and vapor transmission rate through the membranes have been determined. Drug entrapment efficiency and \textit{in vitro} drug release profile have also been determined for all the formulations. Any undesired effect and irritation on the skin has been tested using rabbits. Stability of the membranes at different temperature conditions has been studied.

Chapter 4 deals with preparation and evaluation of transdermal membranes of PVA with natural polymers such as chitosan and sodium alginate. This study has been carried out to prepare polymeric materials with desired properties and to meet the complex demands of the biomaterials. PVA was mixed with other two polymers in different ratios (1:1, 1:2 and 2:1) and Salbutamol sulphate, an antiasthmatic drug having a biological half-life of 4 hrs has been incorporated into the membranes. Crosslinking of PVA with chitosan and with sodium alginate separately, by using a common crosslinking agent GA, (to form Schiff's base and acetal respectively), has been confirmed by FTIR spectral studies. Thermal analysis has been carried out by DSC and TGA techniques. Effect of blending of polymers on polymer rigidity and thereupon its effect on
mechanical properties, drug content, rate of drug release and stability at elevated temperatures have been evaluated.

Chapter 5 deals with the preparation and evaluation of interpenetrating polymer networks (IPNs) for \textit{in vitro} release of Chlorpheniramine maleate (an antihistaminic drug). IPNs create additional free space to accommodate the drug. Sodium alginate and guar gum are used for the IPN formation and GA has been used as a crosslinking agent at different concentrations (0.5 \% and 1 \% w/w). Effect of incorporation of guar gum into sodium alginate transdermal membranes for membrane forming capacity and further evaluation of these membranes for swelling, vapor transmission rate, entrapment efficiency and \textit{in vitro} drug release have been discussed here.

Chapter 6 refers to the development of chitosan microspheres for the release of an insoluble drug – Ibuprofen (a non-steroidal antiinflammatory drug). Different methods of preparation such as suspension crosslinking technique and emulsification and ionotropic gelation by NaOH are adopted to know their effect on particle size, size distribution, and \textit{in vitro} drug release. The processing parameters such as rate of stirring and concentration of crosslinking agent GA have been altered and microspheres produced have been subjected to SEM analysis to study the morphology.

Chapter 7 deals with blends of two natural polymers sodium alginate and chitosan, which are chosen due to their safety, biodegradability and biocompatibility. Formation of IPN of chitosan and sodium alginate and development of chitosan-alginate IPN beads by crosslinking using GA has been discussed here. Ofloxacin hydrochloride, an antibiotic has been chosen as a model drug for encapsulation into the beads. A comparative study of swelling and drying among the beads of plain chitosan and in combination with sodium alginate has been carried out. Since the effect of time of
exposure to the croslinking agent is the most important factor in deciding the pattern of drug release, it has been studied in detail.

Chapter 8 gives the summary of the entire study that has been carried out and conclusion has been derived. The present study covers newer approaches in the preparation of drug delivery devices using both natural and synthetic polymers. The problems associated with polymers and the techniques to overcome these problems by several treatments have been explained in detail. A number of carriers for bioactive materials such as drugs and their utilization have been highlighted.