IX.1. Summary

The present thesis is aimed to synthesize/prepare novel polymeric hydrogel particulate drug delivery systems as well as floating drug delivery systems for local delivery to stomach. The drug-loaded matrices such as interpenetrating polymer network microspheres of different natural polymers have been prepared for controlled release of drugs having very short half-lives. The hydrogel matrices prepared during this research are based on the monomers/polymers, which are biocompatible and biodegradable. Controlled release (CR) of pharmacologically active agents to the specific site at the therapeutically optimal rate and dose regimen has been major goal in designing such devices. In view of this, some novel drug delivery polymeric matrices have been prepared and fully characterized for \textit{in vitro} studies.

Chapter I of the present thesis covers the historical development on the applications of hydrogels as carriers for biologically active molecules. Hydrogels based on both synthetic and natural origin are employed as carriers of drugs and proteins. But however, hydrogels of natural polymers have gained much attention recently because of their biocompatibility and biodegradability. Hydrogel micro and nanoparticles are often used as drug delivery devices. Among various classes of hydrogels, interpenetrating polymer networks (IPNs) have gained much popularity as they are they are soft and rubbery in nature and resemble the living tissues in their physical properties, biocompatibility and non-toxicity and improved mechanical properties. Therefore, these are the better choice as biomaterials to be used as drug delivery devices.
Chapter II discusses details on the materials used to prepare IPN and floating microspheres. Experimental methods adopted for the preparation of drug-loaded microspheres have been discussed. The microspheres were evaluated for drug content and encapsulation efficiencies. Microspheres were characterized using various techniques such as particle size analyses, differential scanning calorimetry (DSC), X-ray diffraction studies (X-RD), scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), mechanical properties using universal testing machine (UTM), various micromeritic properties for floating microspheres and in vitro drug release are discussed.

Chapter III is concerned about the preparation of semi-interpenetrating polymer network (IPN) microspheres of natural polymers viz., gelatin and sodium carboxymethyl cellulose (NaCMC) using glutaraldehyde (GA) as a crosslinker. Ketorolac tromethamine (KT), an anti-inflammatory and analgesic agent, was successfully encapsulated into IPN microspheres. Various formulations were prepared by varying the ratio of gelatin and NaCMC, % drug loading and amount of GA. Microspheres were characterized by Fourier transform infrared spectroscopy (FTIR) to understand the formation of IPN structure and to confirm the absence of chemical interactions between drug, polymer and crosslinking agent. Scanning electron microscopy (SEM) was used to study the surface morphology of the microspheres. Differential scanning calorimetry (DSC) and X-ray diffraction (X-RD) studies were performed to understand the crystalline nature of the drug after encapsulation into IPN microspheres. Both equilibrium and dynamic swelling experiments were performed in water. Diffusion coefficients ($D$) of water transport through the microspheres were determined using an empirical equation. Values of $D$ decrease with increasing crosslinking as well as increasing content of NaCMC in the matrix. In vitro release studies indicated a dependence of release rate on
both the extent of crosslinking and the amount of NaCMC used to produce microspheres. Cumulative release data were fitted to an empirical equation to compute diffusional exponent \((n)\).

**Chapter IV** describes results on the novel semi-interpenetrating polymer network (IPN) hydrogel microspheres of chitosan (CS) and hydroxypropyl cellulose (HPC) were prepared by emulsion-crosslinking method using glutaraldehyde (GA) as a crosslinker. Chlorothiazide (CT), a diuretic and anti-hypertensive drug with limited water solubility was successfully encapsulated into IPN microspheres. Various formulations were prepared by varying the ratio of CS and HPC, % drug loading and amount of GA. Microspheres were characterized by FTIR spectroscopy to investigate the formation of IPN structure and to confirm the absence of chemical interactions between drug, polymer and crosslinking agent. SEM was performed to study the surface morphology of the microspheres. SEM showed that microspheres have smooth surfaces. Particle size, as measured by using laser light scattering technique. DSC was performed to know the formation of IPN structure. X-RD studies were performed to understand the crystalline nature of the drug after encapsulation into IPN microspheres. Both equilibrium and dynamic swelling experiments were performed in 0.1N HCl. Diffusion coefficients \((D)\) for water transport through the microspheres were estimated using an empirical equation. *In vitro* release studies were performed in both 0.1 N HCl and pH 7.4 buffer solutions.

**Chapter V** presents results on the preparation of graft copolymer of acrylamide and dextran (AAm-g-Dex). This was then blended with chitosan (CS) and crosslinked to obtain semi-IPN microspheres using glutaraldehyde as a crosslinker. Acyclovir, an antiviral drug with limited water solubility, was successfully encapsulated into IPN microspheres by varying the ratio of AAm-g-Dex and CS, % drug loading and amount of GA. Microspheres were
characterized by FTIR to confirm the absence of chemical interactions between drug, polymer and crosslinking agent. Particle size was measured using laser light scattering technique. DSC and X-RD studies were performed to understand the crystalline nature of drug after encapsulation into IPN microspheres. Both equilibrium and dynamic swelling studies were performed in 0.1N HCl. Diffusion coefficients \( (D) \) and diffusional exponents \( (n) \) for water transport were determined using an empirical equation. *In vitro* release studies indicated the dependence of drug release rates on both the extent of crosslinking and amount of AAm-g-Dex used in preparing microspheres.

Chapter VI deals with the preparation of hollow microspheres of cellulose acetate butyrate (CAB) and poly(ethylene oxide) (PEO) by emulsion-solvent evaporation method. Repaglinide, an antidiabetic drug, was successfully encapsulated into floating microspheres. Various formulations were prepared by varying the ratio of CAB and PEO, % drug loading and concentration of poly(vinyl alcohol) (PVA) solution. The micromeritic properties of microspheres reveal the excellent flow and good packing properties. SEM was performed to study the surface morphology of the microspheres. SEM showed that microspheres have many pores on their surfaces. DSC and X-RD studies were performed to understand the crystalline nature of the drug after encapsulation into microspheres. DSC and X-RD revealed the amorphous dispersion in the polymer matrix. *In vitro* release experiments were performed in simulated gastric fluid (SGF).

Chapter VII covers the preparation of novel interpenetrating polymer network (IPN) microspheres of chitosan (CS) and methylcellulose (MC) by emulsion-crosslinking in the presence of glutaraldehyde (GA) as a crosslinker. Theophylline (THP), an antiasthmatic drug was encapsulated into IPN microspheres under varying ratios of MC and CS, % drug loading and amount of GA added. IPNs have shown better mechanical properties than pure CS.
Cross-link density of the matrices was significantly affected by the amount of GA and MC. Microspheres were characterized by FTIR spectroscopy to assess the formation of IPN structure and to confirm the absence of chemical interactions between drug, polymer and crosslinking agent. Particle size was measured by laser light scattering technique. SEM was performed to study the surface topography of the microspheres. DSC and X-RD studies were performed to understand the crystalline nature of drug after encapsulation into IPN microspheres. Equilibrium swelling was performed in distilled water. In vitro release studies were performed in both 0.1 N HCl and pH 7.4 buffer solutions. These data indicated a dependence of drug release on the extent of crosslinking and amount of MC added during the preparation of microspheres.

Chapter VIII describes the preparation of hydrogel microspheres of chitosan (CS) and pluronic F127 (PF-127) by emulsion-crosslinking method employing glutaraldehyde (GA) as a crosslinker. 5-fluorouracil (5-FU), an anticancer drug with good water solubility was encapsulated into hydrogel microspheres. Various formulations were prepared by varying the ratio of CS and PF-127, % drug loading and amount of GA. Microspheres were characterized by FTIR spectroscopy. SEM was performed to study the surface morphology of the microspheres. Particle size was measured by laser light scattering technique. DSC and X-RD studies were performed to understand the crystalline nature of the drug after encapsulation into hydrogel microspheres. Equilibrium swelling experiments were performed in distilled water. Diffusion coefficients \((D)\) of water through microspheres were estimated by an empirical equation. The release data were also fitted to an empirical equation to compute the diffusional exponent \((n)\).
IX.2. Papers Published

Several papers have been published from this thesis work. The list is given below.


IX.3. Papers Presented in Conferences


Semi-interpenetrating polymer network microspheres of gelatin and sodium carboxymethyl cellulose for controlled release of ketorolac tromethamine *

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Abstract

Semi-interpenetrating polymer network (IPN) microspheres of natural polymers, viz., gelatin and sodium carboxymethyl cellulose (NaCMC) were prepared by using glutaraldehyde (GA) as a crosslinker. Ketorolac tromethamine (KT), an anti-inflammatory and analgesic agent, was successfully encapsulated into IPN microspheres. Various formulations were prepared by varying the ratio of gelatin and NaCMC, % drug loading, and amount of GA. Microspheres were characterized by Fourier transform infrared spectroscopy (FTIR) to understand the formation of IPN structure and to confirm the absence of chemical interactions between drug, polymer, and crosslinking agent. Scanning electron microscopy (SEM) was used to study the surface morphology of the microspheres. SEM showed that particles have slightly rough surfaces. Particle size as measured by using laser light scattering technique gave an average size ranging from 247 to 535 µm. Differential scanning calorimetry (DSC) and X-ray diffraction (X-RD) studies were performed to understand the crystalline nature of the drug after encapsulation into IPN microspheres. Drug encapsulation of up to 67% was achieved as measured by the UV method. Both equilibrium and dynamic swelling experiments were performed in water. Diffusion coefficients (D) of water transport through the microspheres were determined using an empirical equation. Values of D decrease with increasing crosslinking as well as increasing content of NaCMC in the matrix. In vitro release studies indicated a dependence of release rate on both the extent of crosslinking and the amount of NaCMC used to produce microspheres, but slow release was extended up to 10 h. Cumulative release data were fitted to an empirical equation to compute diffusional exponent (n), which indicated the non-Fickian trend for drug release.

Keywords: Hydrogels; Crosslinking; Interpenetrating network; Drug delivery; Microspheres; Ketorolac tromethamine

1. Introduction

Carbohydrate polymers are extensively used in recent years in biomedical and pharmaceutical applications due to their biocompatibility and biodegradability (Tabata & Ikada, 1998). Biopolymeric hydrogels can be prepared as three-dimensional hydrophilic networks that are capable of imbibing large quantities of water or biological fluids and release drugs at the controlled rates. Such networks can be composed of homopolymers or copolymers and are insoluble in water because of the presence of chemical or physical crosslinks such as entanglements or crystal lites (Peppas, Burns, Leobandung, & Ichikawa, 2000; Sperling, 1981). Polymeric hydrogels have been studied in a variety of areas such as in chemical engineering, medicine, pharmaceuticals, food, and agriculture (Dave, Mehta, Aminabhavi, Kulkarni, & Soppimath, 1999; Dong &
Synthesis and characterization of semi-interpenetrating polymer network microspheres of acrylamide grafted dextran and chitosan for controlled release of acyclovir *

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Abstract

Semi-interpenetrating polymer network (IPN) microspheres of acrylamide grafted on dextran (AAm-g-Dex) and chitosan (CS) were prepared by emulsion-crosslinking method using glutaraldhyde (GA) as a crosslinker. The grafting efficiency was found to be 94%. Acyclovir, an antiviral drug with limited water solubility, was successfully encapsulated into IPN microspheres by varying the ratio of AAm-g-Dex and CS, % drug loading and amount of GA. Microspheres were characterized by FT-IR spectroscopy to assess the formation of IPN structure and to confirm the absence of chemical interactions between drug, polymer and crosslinking agent. Particle size was measured using laser light scattering technique. Microspheres with average particle sizes in the range of 265-388 μm were obtained. Differential scanning calorimetry (DSC) and X-ray diffraction (X-RD) studies were performed to understand the crystalline nature of drug after encapsulation into IPN microspheres. Acyclovir encapsulation of up to 79.6% was achieved as measured by UV spectroscopy. Both equilibrium and dynamic swelling studies were performed in 1 N HCl. Diffusion coefficients (D) and diffusional exponents (n) for water transport were determined using an empirical equation. In vitro release studies indicated the dependence of drug release rates on both the extent of crosslinking and amount of AAm-g-Dex used in preparing microspheres; the slow release was extended up to 12 h. The release rates were fitted to an empirical equation to compute the diffusional exponent (n), which indicated non-Fickian trend for the release of acyclovir.

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Keywords: Hydrogels; Crosslinking; Graft copolymer; Interpenetrating polymer networks; Drug delivery systems; Microspheres; Acyclovir

1. Introduction

Hydrogels are the three-dimensional network polymers that are known to swell in aqueous solutions. In the swollen state, they are soft and rubbery, resembling the living tissue exhibiting excellent biocompatibility (Hoffman, 2002). Polymeric hydrogels are of considerable interest as biomaterials in drug delivery research (Coviello et al., 2005; Liu, Lin, Lin, & Liu, 2005; Peppas, Bures, Leobandung, & Ichikawa, 2000; van Tomme, van Steenberg, De Smedt, van Nostrum, & Hennek, 2005). Among many methods of modifying the original structure of polymers, graft copolymerization is an easier method, which makes the derived polymer as attractive biomaterials in CR applications (Soppimath & Aminabhavi, 2002).

Among the many natural carbohydrate polymers, dextran (Dex) is a polysaccharide consisting of glucose...
Novel Interpenetrating Polymer Network Microspheres of Chitosan and Methylcellulose for Controlled Release of Theophylline

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Abstract

Interpenetrating polymer network (IPN) microspheres of chitosan (CS) and methylcellulose (MC) were prepared by emulsion-crosslinking in the presence of glutaraldehyde (GA) as a crosslinker. Theophylline (THP), an antiasthmatic drug was encapsulated into IPN microspheres under varying ratios of MC and CS, % drug loading and amount of GA added. IPNs have shown better mechanical properties than pure CS. Cross-link density of the matrices was significantly affected by the amount of GA and MC. Microspheres were characterized by Fourier transform infrared (FTIR) spectroscopy to assess the formation of IPN structure and to confirm the absence of chemical interactions between drug, polymer and crosslinking agent. Particle size was measured by laser light scattering technique. Microspheres with the average particle sizes ranging from 119 to 318 \( \mu \text{m} \) were produced. Differential scanning calorimetry (DSC) and X-ray diffraction (X-RD) studies were performed to understand the crystalline nature of drug after encapsulation into IPN microspheres. Theophylline encapsulation of up to 82% was achieved as measured by UV spectrometer. Equilibrium swelling was performed in distilled water. In vitro release studies were performed in both 0.1 N HCl and pH 7.4 buffer solutions. These data indicated a dependence of drug release on the extent of crosslinking and amount of MC added during the preparation of microspheres. The release was extended up to 12 h and release rates were fitted to an empirical equation to compute the diffusional parameters, which indicated a slight deviation from the Fickian trend for the release of theophylline.

Key words: carbohydrate polymers; chitosan; methylcellulose; interpenetrating networks; microspheres; theophylline

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