CHAPTER-VIII

Summary

VIII.1. SUMMARY

The present thesis is aimed at developing the polymeric matrices for the controlled release (CR) applications of both agroproducts (viz. pesticides and micronutrients) and drug delivery systems (viz., antihypertensive and anti-inflammatory drugs). This area has been quite intensely studied over the past three decades and still there is more scope to develop these products. Development of controlled release (CR) formulations containing pesticides or agroproducts have many advantages over the conventional products to reduce environmental pollution due to direct contact with skin or by inhalation. The CR formulations are safe to use due to their reduced amount of pesticides, increased persistence of the active ingredient and the overall ease in handling toxic products. In view of this, CR systems have gained widespread usage in agricultural areas since they help to reduce environmental risk factors.

Polymeric drug-loaded CR systems have several advantages over conventional dosages in optimizing patient treatment regimes. In particular, swelling controlled (hydrogels) release systems have been extensively studied for the delivery of drugs at controlled rates. These systems are capable of delivering drugs at constant rates over an extended period of time to the specific site of action. In order to pursue research in this area, we have developed polymeric matrices such as beads and microspheres as pesticide and drug delivery systems. These investigations are presented in seven major chapters.
Chapter I covers an introduction to the field. Recently, there has been a great deal of research activity in the development of hydrogels as controlled release devices. The present chapter provides a brief introduction to various methods of synthesis, properties, types of hydrogels, and cross-linking agents, which have been used for the preparation of hydrogels exhibiting suitable properties for agricultural and pharmaceutical products for CR applications.

Chapter II discusses details on the materials used, experimental methods developed and/or adopted for the preparation of beads, microspheres, and pH-sensitive hydrogels. Techniques used for the measurement of particle size, encapsulation efficiency, thermal behavior of the matrix by differential scanning calorimetry (DSC) and Fourier transform infrared spectra (FTIR), elemental analyses and also in vitro drug release kinetics have been discussed.

Chapter III is divided into two sections. First section reports on the solubility and partition coefficient data for structurally similar pesticides, fenvalerate and cypermethrin, measured by UV spectrophotometry in binary mixtures of methanol and water at different temperatures. The solubility of both pesticides is much higher in methanol than in water at all temperatures. Partition coefficients were also measured between water + heptanol immiscible mixtures at 25°C, and these data show a decrease with increasing composition of methanol in water. Such solubility and distribution coefficient data are essential in designing pesticide CR formulations.

Second section presents experimental data on the release kinetics and encapsulation efficiency of urea formaldehyde (UF) crosslinked matrices of starch (St), guar gum (GG) and starch + guar gum (St + GG) for the controlled release of solid (chlorpyrifos) and liquid (neem seed oil) pesticides. The data revealed variable release rates in relation to polymer type and especially the nature of the pesticide. It is possible to slow the release rates of both the pesticides using the cheaply available materials such as starch and guar gum.
Chapter IV reports on the synthesis and characterization of interpenetrating network beads for the controlled release of pesticides. Chapter IV has two sections. First section reports on interpenetrating network polymeric beads of poly(vinyl alcohol)-grafted-acrylamide with sodium alginate prepared by crosslinking with glutaraldehyde. Cypermethrin, a widely used pesticide, was loaded with 80% efficiency in these hydrogel beads. The beads were characterized by Fourier transform infrared spectroscopy to confirm grafting. Scanning electron microscopy was used to study morphology of the beads. Equilibrium swelling experiments indicated that swelling of the beads decreased with an increase in crosslinking. The in vitro release studies were performed under static conditions and the release data have been fitted to an empirical relation to estimate the transport parameters. The diffusion coefficients have been calculated for the transport of pesticide through the polymeric beads using the initial time approximation method. These values showed a decrease with increasing crosslinking as well as increasing pesticide loading.

The second section reports on the grafting of acrylamide onto guar gum done by Ce (IV) induced free radical polymerization to prepare the interpenetrating network beads of poly(acrylamide)-grafted-guar gum with sodium alginate crosslinking with glutaraldehyde. Solid chlorpyrifos and liquid fenvalerate, the two widely used pesticides have been loaded up to 60-70% efficiency in the beads. Polymer and the beads have been characterized by Fourier transform infrared spectroscopy to confirm grafting and to understand the possible interactions between pesticides and the polymer matrix. Scanning electron microscopy was used to know the morphology of beads. Equilibrium swelling experiments indicated that swelling of the beads decreased with an increase in cross-linking as well as increase in pesticide loading. The in vitro release studies have been performed under static conditions and the release data have been fitted to an empirical relationship to evaluate the transport parameters. Diffusion coefficients have been calculated for the transport of pesticides through polymeric beads using the initial and later-time approximation methods. These values showed a decrease with increasing crosslinking as well as increasing pesticide loading.
loading. Long-term diffusion coefficients as computed by Fick’s equations were found to be smaller in magnitude when compared to the initial time diffusion coefficients.

Chapter V reports on the development of chitosan-based microspheres for the controlled release of non-steroidal anti-inflammatory drugs. This chapter has two sections. The first section discusses about the microspheres of chitosan crosslinked with three different crosslinking agents viz., glutaraldehyde, sulfuric acid and heat treatment have been prepared for the encapsulation of diclofenac sodium. Chitosan microspheres are produced in water in oil emulsion followed by crosslinking in the water phase by one of the crosslinking agents. Encapsulation of diclofenac sodium (DS) is carried out by soaking the already swollen crosslinked microspheres in the saturated solution of DS. Microspheres are further characterized by FTIR, x-RD and SEM. The in vitro release studies are performed in 7.4 pH buffer solution. The release data are treated with the empirical equation to investigate the type of release mechanism.

Microspheres produced are spherical and have smooth surfaces with the sizes ranging between 40 and 230 μm as evidenced by SEM. The crosslinking of chitosan takes place at the free amino group in all the cases as evidenced by FTIR. This leads to the formation of imine group or ionic bond. Polymer crystallinity increases after crosslinking as determined by x-RD. The method adopted for drug loading into the microspheres is satisfactory and up to 28 to 30 % weight/weight loading is observed for the sulfuric acid-crosslinked microspheres, whereas 23 to 29 and 15 to 23 % of loadings are obtained for the glutaraldehyde (GA) and heat-crosslinked microspheres, respectively. Among all the systems studied, the 32 % GA crosslinked microspheres have shown the least release i.e., 41 % at 420 min and a maximum release of 81% at 500 min is shown by heat crosslinking for 3 h. Drug release from the matrices deviates slightly from the Fickian trend.

The second section reports on the microspheres of poly(acrylamide)-grafted-chitosan crosslinked with glutaraldehyde prepared to encapsulate indomethacin, a non-steroidal anti-inflammatory drug. The microspheres were produced by the water in oil emulsion technique and encapsulation of...
indomethacin is carried out before crosslinking of the matrix. Extent of crosslinking was analyzed by Fourier transform infrared spectroscopy and differential scanning calorimetry. Microspheres were characterized for drug encapsulation efficiency, particle size, and water transport into the polymeric matrix as well as for drug release kinetics. Scanning electron microscopy confirmed the spherical nature and surface morphology of the particles with mean particle size of 525 μm. Dynamic swelling experiments, suggested that with an increase in cross-linking, the transport mechanism from Fickian to non-Fickian. Release of indomethacin depends upon cross-linking of the network and also on the amount of drug loading. This is further supported by the calculation of drug diffusion coefficients using the initial time approximation method. Drug release in all the formulations followed non-Fickian trend and diffusion was relaxation-controlled.

Chapter VI deals with the development of pH-sensitive polymeric matrices and the controlled release of pesticide/micronutrient. In this study, acrylic-based copolymers from methyl methacrylate (MMA), methacrylic acid (MAA) were prepared both by solution and bulk polymerization. Three different polymers were prepared by varying the ratio MMA : MAA; however, in order to increase the hydrophilicity of the matrix, one polymer was prepared by using 2-hydroxy ethyl methacrylate (HEMA). In all the cases, benzoyl peroxide (BPO) was used as an initiator and the polymers were crosslinked *in situ* by ethylene glycol dimethacrylate (EGDMA). The polymers were characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, and viscometry. Some rheological measurements were also carried out on the neat polymers to understand their viscous flow behavior.

Dynamic and equilibrium swelling experiments were carried out in varying pH conditions i.e., 0.1N NaOH, 0.1N HCl, and double distilled water. The partially crosslinked hydrogels showed varying hydrophilicity due to the presence of pendant carboxylic acid groups, thus making them pH responsive. Swelling increased with increasing – COOH groups on the polymer backbone and showed different hydrophilicity with changing pH.
Cypermethrin, a widely used pesticide, and cupric sulfate, a model micronutrient, were loaded into these pH sensitive hydrogels to investigate their controlled release behaviors. The \textit{in vitro} release of the pesticide and the micronutrient was performed under static conditions at 30°C. Release data have been fitted to an empirical relation to estimate the transport parameters. These data show a systematic trend with varying hydrophilicity of the hydrogel.

Chapter VII reports on the development of modified chitosan microspheres for the controlled release of nifedipine. In this study, grafting of acrylamide onto chitosan backbone has been carried out by taking three acrylamide concentrations (polymer: monomer), viz. 1:1, 1:2 and 1:3. Synthesis of the grafted polymer was achieved by $K_2S_2O_8$ induced free radical polymerization. Microspheres of poly(acrylamide)-\textit{grafted}-chitosan crosslinked with glutaraldehyde have been prepared and used to encapsulate nifedipine (NFD), a calcium channel blocker, an antihypertensive drug.

Microspheres of poly(acrylamide)-\textit{g}-chitosan were produced by w/o emulsion technique using three different concentrations of glutaraldehyde as the cross-linking agent. The graft copolymers and microspheres were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), viscosity measurements and elemental analyses. Extent of cross-linking was analyzed by FTIR and DSC. Microspheres were characterized for particle size; water transport into these microspheres as well as % equilibrium water uptake was studied. Scanning electron microscopy confirmed spherical nature and surface morphology of the particles with a mean particle size of 450 μm.

Individual particle dynamic swelling experiments suggested that with an increase in crosslinking, transport mechanism shifts from non-Fickian to Case-II. Release of nifedipine depends upon cross-linking of the network and also on the amount of drug loading. This was further supported by the calculation of drug diffusion coefficients using the initial time and later time approximation method. Drug release in the entire formulations followed Case-II transport showing that time dependence of NFD release follows zero order release kinetics.
Chapter VIII presents the summary of research results. In conclusion, the study demonstrates successful development of hydrogels based on natural polymers and the synthetic pH-sensitive gels. These hydrogels are successfully fabricated into beads or microspheres for the controlled release of pesticides and drugs. In the course of this study hydrogels developed here will be useful to the future researchers working in this area.

VIII.2. FUTURE CHALLENGES AND PROSPECTS

Hydrogels in soil applications facilitate an increased absorption of water so the frequency of irrigation and water loss due to evaporation can be minimized. Release of pesticides, micronutrients and various agroproducts through the hydrogel matrix are beneficial to farmers in dry land areas because the water absorbing polymers will help to reduce water loss by evaporation and thus will help to improve the life span and quality of plants. In future, there is a great need to develop hydrogel based effective systems for the delivery of many types of agroproducts for the effective control of pests like flies, nematodes, fungi, white grub, and the larva of chaffer beetles that are considered to be the serious soil pests for groundnut and several other crops.

There is a great need to develop CR systems to meet the therapeutic patient regime. The CR of bioactive molecules includes vaccines, human growth hormones, insulin, anti-tumor agents, contraceptives, genes, etc. Continuous efforts are being made in this direction and many polymeric CR systems have been developed for this purpose. From polymer chemistry viewpoint, it is desirable to synthesize newer polymers and copolymers to get the tailor-made properties.
Several papers have been originated as an outcome of this research. The list is given below.


**VIII.4. PAPERS PRESENTED IN SYMPOSIA/CONFERENCES**

Many papers out of this thesis have been presented mainly in international conferences/symposia. This list is given below.


