This chapter deals with the development and evaluation of polymeric drug delivery systems for controlled delivery of non-steroidal anti-inflammatory drug, ibuprofen (IBU) to intestine. Sequential interpenetrating polymer network (IPN) hydrogel microspheres were prepared using poly(methacrylic acid) and poly(vinyl alcohol). Formulation variables such as amount of methacrylic acid, percent drug loading and extent of crosslinking have been varied to study the effect of these variables on size, entrapment efficiency and drug release characteristics. Microspheres have been characterized by using the Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), powder X-ray diffractometer (X-RD) and scanning electron microscopy (SEM). Dynamic swelling studies were performed to compute the diffusion coefficients. Release data have been fitted to an empirical relationship to study the transport phenomenon. Results are discussed in terms of the drug release characteristics of the IPNs.
Abstract

Sequential interpenetrating network (IPN) of poly(methacrylic acid) (PMMA) and poly(vinyl alcohol) (PVA) have been prepared and crosslinked with glutaraldehyde (GA) to obtain pH sensitive microspheres by water-in-oil (w/o) emulsification method. Microspheres have been used to deliver the chosen model anti-inflammatory drug viz., ibuprofen (IBU) to the intestine. Ibuprofen was encapsulated up to 70% within polymeric matrices. The IPN formed was analyzed by Fourier transform infrared spectroscopy (FT-IR). Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) analyses were done on drug-loaded microspheres to confirm the polymorphism of IBU. Results of this study indicated the molecular level dispersion of IBU in the developed IPN microspheres. Scanning electron microscopy (SEM) confirmed the spherical nature and smooth surfaces of the microspheres produced. Mean particle size of the microspheres as measured by laser light scattering ranged between 51 and 176 μm. Swelling was performed in the simulated gastric as well as the intestinal conditions. Microspheres showed a pulsatile swelling behavior when pH of the swelling media was altered. The swelling data have been fitted to an empirical equation to understand water transport trends as well as to calculate the diffusion coefficients (D). Values of D in acidic media were lower than those found in the basic media. Values of D decrease with increasing crosslinking of the matrix. In vitro release studies have been performed in 1.2 and 7.4 pH media to simulate the gastric and intestinal conditions. The results indicated a dependence on the pH of the release media, extent of crosslinking and the amount of drug loading. The release data were fitted to an empirical relation to estimate the transport parameters and thereby to understand the transport mechanism.

Results of this chapter have been communicated to “Journal of Biomedical Materials Research”, (2006).
VII.1. Introduction

The development of microspheres for the controlled release (CR) of short lived drugs has been an area of active research for the past decades. Oral administration is a more convenient route considering the pain and possible infections caused by the injections, thus leading to higher patient compliance [1, 2]. However, the development of any successful oral drug delivery system requires that it should be resistant to both attack by enzymes and to the impact of pH gradients. Therefore, resistance to acid and enzyme along with time-controlled release properties are important in oral drug devices. The chemical and physical combination methods and combination of multipolymers are of practical and academic interest in developing CR devices for the release of drugs and proteins [3-5]. Among many methods of preparing polymeric devices, considerable interest has been given to the development of interpenetrating polymer network (IPN) Hydrogels [6-10]. A IPN is a composite of two polymers, which is obtained when at least one polymer network is synthesized or cross-linked independently in the immediate presence of the other.

Among many polymers, the poly(vinyl alcohol) (PVA) hydrogels have been used in numerous biomedical and pharmaceutical applications [11-13]. PVA hydrogels are the excellent biomaterials due to their advantages including their non-toxic, non-carcinogenic and bioadhesive characteristics in addition to associated ease of processing [8,11]. PVA hydrogels exhibit a high degree of swelling in water (or biological fluids) in addition to rubbery and elastic trends. Because of these properties, PVA is capable of simulating natural tissue and can be readily accepted in the body. Poly(methacrylic acid) (PMAA) hydrogels possess the ionizable carboxylic groups, which swell or collapse in response to changes in pH. The ionizable carboxyl group of MAA furnishes pH sensitivity to the IPN composition. Such IPN hydrogels could exhibit strong interactions
with the comonomeric units [14]. Under acidic pH, carboxylic groups of MAA become protonated, resulting in hydrogen bonding among the MAA units, and thus, PMAA will collapse. When pH is less than $pK_a$ of PMAA (4.66) [15], the H$^+$ ion strength will be high, which will effectively suppress the ionization of polycarboxylic acid groups.

Efforts are underway to develop polymeric matrices encapsulating non-steroidal anti-inflammatory drugs (NSAID) to improve therapeutic efficacy and reduce the severity of upper GI side effects [16]. These formulations could increase the patient compliance through prolonged release effect and reduce the adverse effects through lowered peak plasma concentrations. Ibuprofen, i.e., 2-(4-isobutylphenyl) propionic acid shown in Figure VII.1 is a prominent NSAID used in the treatment of various musculoskeletal disorders and painful conditions [17]. The short plasma half-life of 1–3 h following oral dosing [18] makes it an ideal candidate for developing the oral CR formulations [19]. Microencapsulation has been widely employed to develop CR dosage forms to provide long lasting and more reliable release rates with reduced GI irritation. Hydrophobic IBU drug dissolves in an alkaline solution and ethanol, but it is almost insoluble in water. This limits the development of drug release formulations containing IBU. In the literature, we are not aware of using the microspheres prepared from sequential IPN of PMAA and PVA for the CR of IBU; hence, the present study is aimed at developing sequential type IPN microspheres of PMAA with PVA. The formulation and process variables affecting the preparation of microspheres and in vitro drug release characteristics have been investigated. Swelling studies of the IPN microspheres were performed to investigate their applications as successful oral dosage formulations. The formation of IPN along with the chemical stability of IBU-loaded microspheres was confirmed by FT-IR spectroscopy. Differential scanning calorimetry and x-RD studies were performed on the
drug-loaded microspheres to investigate the drug polymorphism inside the polymer matrix. Scanning electron microscopy was employed to investigate the morphology of the microspheres. Drug release data have been analyzed using the empirical equation proposed by Ritger and Peppas [20].

![Figure III.1. Chemical structure of ibuprofen.](image)

**VII.2. Results and Discussion**

**VII.2.1. Preparation and Characterization of Microspheres**

In this research, we have prepared the new sequential IPN PMAA-PVA hydrogel microspheres from the solid-in-water (S/W) suspension of IBU. Because IBU is slightly soluble in water, a S/W suspension of drug was prepared by controlled precipitation in the polymer solution. Earlier studies [21, 22] reported the complexation-based pH-sensitive hydrogel formulations as the possible delivery devices for proteins and peptides using grafted hydrogels composed of vinyl monomers. Hence, the present study focused on the *in situ* formation of IPN and encapsulation of drug by employing GA as a crosslinking agent. The GA could crosslink with only PVA, but not with PMAA. However, many studies were reported before to evaluate the safety of GA and is proven to be non-carcinogenic and safe [23, 24]. The crosslinked hydrogel is neutral with a low flexibility of the polymeric chain. Polycarboxylic acid groups within the polymeric network ionize and attract the cations into the gel region to replace H⁺ ions, since the pH of the environmental solution rises above its pKᵦ value. This effectively increases the concentration
of free ions inside the gel. Thus, the ionic swelling pressure will increase and so will swelling. Additionally, the gel tends to expand and thereby minimizes the repulsion between ionized polycarboxylic groups.

The results of mean particle size and size distributions of microspheres were recorded by laser light diffraction technique (Mastersizer-2000, Malvern, UK). On a population basis, particle size distribution was found to be unimodal with a narrow size distribution. Calculated values of volume–mean diameter, % encapsulation efficiency and % drug loading of different formulations are included in Table VII.1. These data show a systematic dependence on the amount of drug incorporated, % PMAA content and extent of crosslinking. Particles are spherical in shape with the sizes ranging from 51 to 176 μm. Particle size of the plain PVA is smaller than the microspheres containing different amounts of PMAA. With an increase in PMAA content of the microspheres, size of the microspheres increased from 102 to 176 μm for 15 or 20 % drug containing microspheres (formulations F2 to F5). This can be explained on the basis of hydrodynamic viscosity concept, i.e., as the amount of PMAA in the microspheres increases, interfacial viscosity of the polymer droplets in the emulsion also increases because PMAA has more water uptake capacity than PVA, which might hinder the breaking of dispersed phase into smaller size particles during emulsification. For all formulations, with increasing amount of drug in the microspheres, particle size also increases. For instance, in case of 30 % PMAA containing microspheres, particle size increased from 102 to 132 μm (F2 and F4), and similar trend is observed for all other formulations (see Table VII.1). This is attributed to the fact that drug molecules might have occupied the free volume spaces within the IPN matrix, thereby hindering the inward shrinkage of the polymer matrix [25]. The 25 % drug loaded and 50 % PMAA containing microspheres (F5) have the maximum size of 176 μm. Extent of crosslinking has also shown an effect on
particle size. For instance, for microspheres containing 30 or 50 % PMAA and 15 % drug, with increasing crosslinking by GA i.e., 5 and 7.5 mL GA, particle size decreased from 135 to 78 μm. For formulations F2, F3, F6, and F7. This is attributed to the fact that with an increase in the amount of GA, the shrinkage of particles might have occurred leading to the formation of smaller particles [11].

Two different concentrations of drug, i.e., 15 and 25 wt. % were loaded during crosslinking. The results of % encapsulation efficiency are also included in Table VII.1. These data show an increase with increasing drug loading. The % encapsulation efficiency also increases with increasing amount of PMAA in the microspheres. For instance, to study the effect of PMAA in the microspheres, i.e., for microspheres containing 0, 30 and 50 % PMAA and 25 % IBU i.e., for formulations F1, F4 and F5), encapsulation efficiencies are respectively, 54.4, 66.7 and 70 %. The results of extent of crosslinking on entrapment efficiency of the microspheres are presented in Table VII.1. With increasing crosslinking, the % encapsulation efficiency has decreased, i.e., for microspheres crosslinked with 5 and 7.5 mL of GA (F4, F5, F8 and F9), the entrapment efficiencies are, respectively 66.69, 70.0, 64.28 and 66.30 %. This is because with an increase in crosslinking, microspheres become more rigid and hence, the free volume space within the polymer matrix decreases to give a reduced encapsulation efficiency. However, there was not much difference in the entrapment efficiency, probably due to hyrophobic nature of the drug.
Table VII.1
Results of % Encapsulation Efficiency and Mean Size of IPN Microspheres

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Ratio of PVA:PMAA</th>
<th>Crosslinking agent (GA in mL)</th>
<th>% Ibuprofen loaded</th>
<th>% Encapsulation efficiency</th>
<th>Mean particle size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100:0</td>
<td>5.0</td>
<td>25</td>
<td>54.4</td>
<td>51</td>
</tr>
<tr>
<td>F2</td>
<td>70:30</td>
<td>5.0</td>
<td>15</td>
<td>59.0</td>
<td>102</td>
</tr>
<tr>
<td>F3</td>
<td>50:50</td>
<td>5.0</td>
<td>15</td>
<td>61.0</td>
<td>135</td>
</tr>
<tr>
<td>F4</td>
<td>70:30</td>
<td>5.0</td>
<td>25</td>
<td>66.7</td>
<td>132</td>
</tr>
<tr>
<td>F5</td>
<td>50:50</td>
<td>5.0</td>
<td>25</td>
<td>70.0</td>
<td>176</td>
</tr>
<tr>
<td>F6</td>
<td>70:30</td>
<td>7.5</td>
<td>15</td>
<td>57.9</td>
<td>78</td>
</tr>
<tr>
<td>F7</td>
<td>50:50</td>
<td>7.5</td>
<td>15</td>
<td>60.0</td>
<td>98</td>
</tr>
<tr>
<td>F8</td>
<td>70:30</td>
<td>7.5</td>
<td>25</td>
<td>64.3</td>
<td>112</td>
</tr>
<tr>
<td>F9</td>
<td>50:50</td>
<td>7.5</td>
<td>25</td>
<td>66.3</td>
<td>141</td>
</tr>
</tbody>
</table>

VII.2.2. FT-IR Study

FTIR was used to confirm the cross-linking of the IPN matrix. Figure VII.2 compares the FTIR spectra of (a) MAA, (b) PVA, and (c) placebo microspheres. In case of PVA, a broad band observed at 3425 cm⁻¹ is due to O–H stretching vibrations, whereas a band at 1263 cm⁻¹ is due to O–H bending vibration. The band at 2850 cm⁻¹ is attributed to stretching vibration of -CH₂, while the one observed at 2912 cm⁻¹ is due to C–H stretching vibration. The band at 1430 cm⁻¹ is due to C–H bending vibration, while that at 1097 cm⁻¹ indicates C–O stretching vibration. In case of MAA, we have observed the characteristic absorption bands at 2616 and 1696 cm⁻¹, which are assigned to carboxylic acid groups and carbonyl stretching vibrations, respectively. Additional characteristic absorption bands of MAA appear at 1449 and 1301 cm⁻¹ due to C–C multiple bond stretching and C–H bending vibrations, respectively. Crosslinked IPNs of PVA and PMAA were washed repeatedly with water to remove the unbound PMAA from the matrix. Hence, FTIR peaks due to carboxylic acid groups of PMAA in the polymer network confirm the
presence of PMAA. In case of placebo microspheres, a broad band at 3447 cm\(^{-1}\) with a less intensity compared to PVA matrices is due to the presence of very few un-cross-linked hydroxyl groups of PVA. The intense bands, which appeared at 2925, 2855 cm\(^{-1}\) are due to aliphatic C–H stretching vibrations. The band at 1736 cm\(^{-1}\) is due to the presence of carboxyl groups of PMAA. The band appearing at 1017 cm\(^{-1}\) is due to the presence of an acetal ring, which might have formed due to the reaction of aldehydic groups of GA with hydroxyl groups of PVA. Thus, FTIR confirms the cross-linking reaction in addition to the formation of IPN matrix. In addition, in case of placebo microspheres, the shifting of peaks from 1696 cm\(^{-1}\) to higher absorption frequencies indicates the interactions between IPN chains and further supports the formation of IPN structure.

FTIR spectral data were also used to confirm the chemical stability of IBU in the IPN microspheres. For instance, FTIR spectra of (a) pristine IBU, (b) IBU-loaded microspheres, and (c) placebo microspheres are displayed in Figure VII.3. Pristine IBU showed characteristic bands due to different functional groups. However, the band appearing at 3355 cm\(^{-1}\) is due to O-H stretching vibrations, while that at 3052 cm\(^{-1}\) is due to aromatic C-H stretching vibrations. The bands at 2924 and 2869 cm\(^{-1}\) are due to aliphatic C-H stretching vibrations. The carbonyl (C=O) stretching and carboxylate anion stretching vibrations are seen at 1702 and 1550 cm\(^{-1}\), respectively. Bands at 1472 and 1363 cm\(^{-1}\) are due to -CH\(_2\) bending and C-H bending vibrations, respectively. The bands at 1057 and 751 cm\(^{-1}\) are due to C-O stretching and aromatic C-H bending vibrations, respectively. Spectra of IBU loaded microspheres are not characteristically different from the spectra of placebo microspheres. When the drug is incorporated into the crosslinked (PVA-PMAA) IPN microspheres, along with all characteristic bands of the crosslinked PVA and PMAA, additional bands have appeared due to the
presence of IBU in the matrix. However, some bands of IBU are not prominent in the drug-loaded microspheres due to identical strechings of placebo microspheres as well as that of drug-loaded microspheres at the same wavenumber. The peaks appearing at 3454, 2925, 2858, 1730, 1443, 1383, 1018, and 810 cm$^{-1}$ for IBU are also appearing in the IBU-loaded microspheres, indicating the chemical stability of IBU in the IPN matrix, which further indicates that IBU has not undergone any chemical change while producing microspheres.

Figure VII.2. FT-IR spectra of (a) MAA, (b) PVA, and (c) placebo microspheres.
Figure VII.3. FT-IR spectra of (a) placebo microspheres, (b) pristine ibuprofen and (c) ibuprofen loaded microspheres.

VII.2.3. X-ray Diffraction Studies

X-ray diffractograms of (a) pristine IBU, (b) placebo microspheres, and (c) drug-loaded microspheres are presented in Figure VII.4. These studies are useful to investigate the drug polymorphism in the crosslinked microspheres. Ibuprofen has shown characteristic intense peaks at 2θ of 16°, 20°, and 22° due to its crystalline nature. However, these peaks have disappeared in the IBU-
loaded microspheres. XRD peak depends on the crystal size, but in the present study, for all the drug-loaded formulations, characteristic peaks of IBU have overlapped with the noise of the coated polymer itself. This indicates that drug is dispersed at the molecular level in the polymer matrix and hence, no crystals were found in the drug-loaded matrices.

**VII.2.4. Differential Scanning Calorimetric Study**

DSC thermograms of (a) plain PVA, (b) placebo microspheres, (c) pristine IBU, and (d) IBU-loaded microspheres are presented in Figure VII.5. The polymorphism of IBU and melting temperature (T_m) of the polymer were determined. For plain PVA, two endothermic peaks were observed, one with a minimum at 192°C, which corresponds to the melting process, and the other at 321°C due to thermal decomposition. Similar peaks were observed for PVA by Corradini et al [26]. Placebo microspheres have also shown two endothermic peaks, one at 234°C and the other at 350°C, corresponding to thermal decomposition. In case of placebo microspheres, a shift in endothermic peaks is observed toward higher temperatures compared to plain PVA. This could be due to the formation of more crystalline polymer matrix as a result of cross-linking and the formation of IPN structure. This shift in endothermic peak toward higher temperature supports the formation of IPN structure due to chain entanglements. For pure IBU, an endothermic peak appeared at 80°C due to the melting of the drug. The observed endothermic peak was close to the reported [27] melting temperature of 75-78°C of IBU. In case of drug- loaded microspheres, there is no characteristic peak of IBU, suggesting that drug is molecularly dispersed in the polymer matrix.
Figure VII.4. X-RD diffractograms of (a) plain ibuprofen, (b) ibuprofen loaded microspheres, and (c) placebo microspheres.
Figure VII.5. DSC thermograms of (a) plain PVA, (b) placebo microspheres, (c) plain ibuprofen, and (d) ibuprofen loaded microspheres.
VII.2.5. Scanning Electron Microscopic Studies

Surface morphology of the microspheres was examined by SEM. SEM images of (a) placebo microspheres at 100X, (b) single placebo microsphere at 300X, (c) IBU loaded microsphere at 50X, and (d) at 100X magnifications are shown in Figure VII.6. Microspheres are spherical without agglomerations. The surfaces of microspheres are smooth without any pores. Polymeric debris is seen around some particles, which are due to the typical method of particle production (i.e., simultaneous particle production and formation of IPN). In case of drug-loaded particles, it is noticed that drug particles are adhered to the surface of microspheres, which may be due to the maximum loading efficiency of the matrix. Microspheres produced with or without drug loading did not exhibit any effect on the surface properties. Hence, the loading of IBU in IPN microspheres did not cause any significant change in morphology.
Figure VII.6. SEM images of the microspheres: (a) placebo group of particles, (b) placebo single particle, (c) IBU loaded group of particles, and (d) IBU loaded single particle.
Equilibrium swelling experiments performed in gastric and intestinal pH conditions for the microspheres are presented in Table VII.2. Equilibrium swelling of the microspheres did not exert any considerable effect on swelling data of the microspheres for plain PVA, while for remaining formulations, equilibrium swelling differed widely. For all formulations, swelling is more in 7.4 pH media than in 1.2 pH media. Equilibrium swelling is least for pure PVA and it did not show much effect with the pH of the external media. As the PMAA content increases from 30 to 50 % (F2, F3 and F6, F7), swelling decreases from 91 to 74 % in 1.2 pH media, while it increased from 164 to 198 % and 134 to 174 % in 7.4 pH media, respectively for F2, F3 and F6, F7. Such a drastic difference is due to the presence of -COOH groups, which are responsible for increased hydrophilicity of the matrix.

Different amounts of crosslinking agent added to produce microspheres containing 30 and 50 % PMAA as well as 15 and 25 % drug are presented in Table VII.2. The extent of crosslinking has shown a much difference in equilibrium swelling, only in 7.4 pH buffer media, whereas in 1.2 pH media, the difference in Q is not considerable. The swelling of 91, 86, 87 and 84 % were observed for microspheres containing 5.0 mL of GA (F2 to F5) in 1.2 pH media, which decreased as the extent of crosslinking increased, i.e., for 7.5 mL GA (F6 to F9) containing microspheres, swelling was 80, 74, 75 and 72 %, respectively. In 7.4 pH media, swelling decreased abruptly with an increase in crosslinking, i.e., for 5 and 7.5 mL GA containing microspheres (F2 to F5), and (F6 to F9), swelling was 164, 198, 155, 184 and 134, 172, 128, 152 %, respectively.

Pulsatile swelling behavior with changing pH of the external media for the formulation containing 50 % PMAA crosslinked with 5 mL GA at 15 % loading (F3) is displayed in Figure VII.7. Swelling increased in 7.4 pH media...
and reached equilibrium in about 10 min. When the pH of the media was changed to 1.2, swelling decreased considerably. Such a behavior was also observed earlier for PVA-poly(acrylic acid) and pAAm-g-GG microspheres [6, 28].

The results of equilibrium swelling diameter, $D_\infty$ normalized to original diameter, $D_0$, are presented in Table VII.3. Triplicate measurements gave errors within 2 %. Dynamic swelling of the microspheres was determined by monitoring the changes in microsphere diameter, $D_t$ with time using an optical microscope. Figure. VII 8 (A and B) displays the normalized diameter, $D_t/D_0$ (where $D_0$ is initial diameter) as a function of time for microparticles containing 30 and 50 % PMAA with 15 % drug loading crosslinked using different amounts of GA (F2, F3, F6 and F7). As the amount of GA increases, the swelling capacity of microspheres decreased considerably. These data are higher in 7.4 pH media than observed in 1.2 pH media. As the amount of GA in the microspheres increases from 5.0 to 7.5 mL, equilibrium normalized diameter decreased from 1.56 to 1.38 in 7.4 pH and from 1.28 to 1.20 in 1.2 pH media (see Table VII.3).

Dimensional changes of the microspheres due to swelling (i.e., volume change, $\Delta V_t$ with time from the initial volume, $V_0$) have been measured and used to compute the diffusion coefficient, $D$, of the drug containing aqueous media using the theory proposed by Harogoppad and Aminabhavi [29].

\[
\left( \frac{\Delta V_t}{V_0} \right) = \left( \frac{4}{D_0} \right) \left( \frac{D_0}{\pi} \right)^{1/2} t^{1/2}
\]  

(VII.1)

\[
D = \left( 1.773 \times \text{Slope} \right) \left( \frac{V_0 D_0}{4 \Delta V_\infty} \right)^{1/2}
\]  

(VII.2)
Here, $\Delta V_o$ is the change in volume at equilibrium, $V_o$ is volume at equilibrium swelling. Eq. (VII.2) was used to calculate $D_v$ from the slope of the initial linear plots of $\Delta V/V_o$ vs. $t^{1/2}$. These data are also included in Table VII.3.

Diffusion coefficients showed systematic variations with the amount of GA added in the matrix. For instance, values of $D_v$ decrease with increasing amount of GA in the microsphere formulations (F2, F3 and F6, F7). This is attributed to the fact that at higher crosslinking, free volume of the matrix will be less thereby, hindering the easy transport of molecules through the matrix. It may be noted that $D_v$ values in 7.4 pH media are higher than those observed in 1.2 pH media indicating that in the basic media, more of solvent molecules will tend to transport than in acidic media.

Table VII.2

Results of Equilibrium Swelling in Different pH Media and $n$ Values of Eq. VII.3. Along with Correlation Coefficients, $r$, for Various Formulations

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Equilibrium swelling (Q)</th>
<th>$n$</th>
<th>$r^{(a)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCl (0.1 N)</td>
<td>Buffer (7.4)</td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>74</td>
<td>76</td>
<td>0.57</td>
</tr>
<tr>
<td>F2</td>
<td>91</td>
<td>164</td>
<td>0.68</td>
</tr>
<tr>
<td>F3</td>
<td>86</td>
<td>198</td>
<td>0.57</td>
</tr>
<tr>
<td>F4</td>
<td>87</td>
<td>155</td>
<td>0.59</td>
</tr>
<tr>
<td>F5</td>
<td>84</td>
<td>184</td>
<td>0.57</td>
</tr>
<tr>
<td>F6</td>
<td>80</td>
<td>134</td>
<td>0.83</td>
</tr>
<tr>
<td>F7</td>
<td>74</td>
<td>172</td>
<td>0.66</td>
</tr>
<tr>
<td>F8</td>
<td>75</td>
<td>128</td>
<td>0.71</td>
</tr>
<tr>
<td>F9</td>
<td>72</td>
<td>152</td>
<td>0.60</td>
</tr>
</tbody>
</table>

$(a)$ $r$ values were estimated at 95% confidence limit.
Table VII.3
Transport Data of Microspheres in 7.4 and 1.2 pH Media

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>pH</th>
<th>Equilibrium normalized diameter ($D_{eq}/D_o$)</th>
<th>$D_v \times 10^6$ (cm$^2$/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2</td>
<td>7.4</td>
<td>1.56</td>
<td>8.12</td>
</tr>
<tr>
<td>F3</td>
<td>1.58</td>
<td>8.96</td>
<td></td>
</tr>
<tr>
<td>F6</td>
<td>1.38</td>
<td>5.84</td>
<td></td>
</tr>
<tr>
<td>F7</td>
<td>1.46</td>
<td>6.01</td>
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<tr>
<td>F2</td>
<td>1.2</td>
<td>1.28</td>
<td>4.81</td>
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<tr>
<td>F3</td>
<td>1.26</td>
<td>4.92</td>
<td></td>
</tr>
<tr>
<td>F6</td>
<td>1.21</td>
<td>2.84</td>
<td></td>
</tr>
<tr>
<td>F7</td>
<td>1.20</td>
<td>2.90</td>
<td></td>
</tr>
</tbody>
</table>

Figure VII.7. Pulsatile behavior plot of normalized diameter vs. swelling time for formulation (F3) containing PMAA: PVA (50:50), 15% IBU loading and 5 mL of GA with respect to change in pH of the external media ($D_i$ is initial diameter).
Figure VII.8. Plot of normalized diameter vs. swelling time for formulations F2, F3, F6 and F7 at 7.4 (A) and 1.2 (B) pH media.
VII.2.7. *In-vitro Release Studies*

*In-vitro* drug release studies were performed in gastric and intestinal pH conditions (without enzymes) for 12 h. Figures VII.9 and VII.10 display % cumulative release data of PVA microspheres for different amounts of PMAA containing 25 % drug and 5 mL of GA (F1, F4 and F5), respectively at 1.2 and 7.4 pH media with respect to time. A pronounced difference is observed in the release data at 1.2 and 7.4 pH, which is attributed to the presence of -COO\(^{-}\) groups that are responsible for higher swelling in higher pH media. Increased cumulative release is observed as the amount of PMAA in the microsphere increases. This is due to the increased -COOH groups with increasing PMAA content of the matrix, thereby inducing higher water-uptake capacity. This would consequently increase the matrix swelling. In both the release media of 1.2 and 7.4 pH, plain PVA microspheres showed the least % cumulative release, while 30 % PMAA-containing PVA microspheres showed an intermediate % cumulative release and 50 % PMAA containing PVA microspheres showed the highest % cumulative release. The cumulative release data of the drug at higher pH depends upon the extent of hydrodynamic free volume, polymer chain relaxation and availability of hydrophilic functional groups (-COO as in case of ionized polymer) for water to form hydrogen bonds. The release data shown in Figures VII.9 and VII.10 obtained in pH 1.2 and 7.4 at the fixed amount of drug (25 % IBU) and a fixed amount of crosslinking agent (i.e., 5 mL of GA) are different because of the differences in the swelling of microspheres in different media. The % cumulative release is quite fast and high in pH 7.4 media, whereas the release rate is quite slow in pH 1.2 media. The data points presented in Figures VII.8-VII.12 represent the averages of triplicate measurements obtained within 3 % standard deviations.

In an effort study the effect of drug loading on release rates, we have taken the formulations (F2, F3, F4, and F5) and their release rates were
compared in Figure VII.11. The release rates vary depending upon the amount of drug present in the matrices, i.e., release was slower for those formulations having a lower amount of the drug, while the release rate increased with increasing amount of drug in the microspheres. Release of the drug from the IPN microspheres occurs mainly by: (1) release from the surface of particles, (2) diffusion through the swollen rubbery matrix, and (3) release due to polymer erosion. The drug in the microspheres will act as an inert filler and occupies the free volume spaces inside the swollen hydrogel, thus creating a tortuous path for water molecules to permeate; however, the degree of tortuosity depends upon the volume fraction of the filler [30]. In all the formulations, release rate was extended up to 12 h. Figure VII.12 displays the release profiles of microspheres crosslinked with different amounts of GA containing 30 and 50 % PMAA with 25 % IBU (F4, F5, F8, and F9) in 7.4 pH media with respect to time. These results exhibit a pronounced effect of the matrix crosslinking on drug release rates for all the formulations. The release rates vary depending upon the amount of GA used for crosslinking. Thus, release was slower for formulations containing lower amount of GA as compared to formulations with a higher amount of GA. The % cumulative release is higher in case of microspheres crosslinked with 5.0 mL GA (F4, F5), but the least % release is observed with microspheres crosslinked with 7.5 mL GA (F8, F9). This is due to the fact that at higher crosslinking, free volume of the matrix will be small, thereby hindering the easy transport of drug molecules through the matrix. This also reduces the rate of swelling as well as rate of drug release from the matrix.
Figure VII.9. Effect of different PMAA content on \textit{in vitro} release profiles at pH 1.2.

Figure VII.10. Effect of different PMAA content on \textit{in vitro} release profiles at pH 7.4.
**Figure VII.11.** Effect of different % drug loading on *in vitro* release profiles at pH 7.4.

**Figure VII.12.** Effect of crosslinking on *in vitro* release profiles at pH 7.4.
VII.2.8. Release Kinetics

To determine the mechanism of drug release, the initial portion (i.e., \( M_t / M_\infty \leq 60 \% \)) of % drug release vs. time profiles have been fitted to the empirical equation proposed by Ritger and Peppas [20]:

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

(VII.3)

where \( M_t / M_\infty \) is the fraction of drug released at time \( t \), \( K \) is a kinetic rate constant and \( n \) is diffusional exponent characterizing the mechanism of drug release. If \( n = 0.5 \), drug diffuses and releases from the polymer matrix following a Fickian diffusion. For \( n > 0.5 \), anomalous or non-Fickian type diffusion occurs. If \( n = 1 \), Case II release kinetics is prevalent. In order to predict and correlate the release behavior of drugs from the hydrophilic matrix of this study, it is necessary to fit the data into release kinetic profiles (Fickian, anomalous or case-II) to understand the mode of drug release such as whether the release occurs by diffusion or erosion or due to combination of both. Estimated values of \( n \) along with the correlation coefficient, \( r \) values are presented in Table VII.2. For all the formulations the values of \( n \) ranged between 0.57 and 0.78, indicating that drug release deviates slightly from Fickian trend following the anomalous or non-Fickian trend. For formulations containing plain PVA, \( n \) value is 0.57, indicating Fickian diffusion, but for formulations containing different amount of PMAA, \( n \) values ranged between 0.56 and 0.65, indicating the anomalous release trend. In case of formulations crosslinked with different amount of GA, the \( n \) values ranged between 0.60 and 0.78, leading to anomalous diffusion. Fickian diffusion is observed when the time scale of the macromolecular relaxation is either effectively infinite or zero as compared to the time required to establish a concentration profile in the polymer [31]. This signifies the elastic and viscous Fickian diffusion limits. Matrix systems reach an equilibrium state of relaxation extremely fast with a
Fickian diffusion of the drug being the dominant drug transport mechanism. With the release of surface drug, numerous pores and channels are possibly generated in the matrix structure, which further elevates the rate and extent of IBU release. However, due to the hydrophilic nature of the polymer, when exposed to diffusion media, free volume spaces are generated between macromolecular chains. After solvation of the polymer chains, dimensions of polymer chains will increase due to polymer relaxation.

In non-Fickian or anomalous transport, both diffusion as well as macromolecular relaxation time scales are similar and both will control the overall rate of penetrant absorption. Non-Fickian release is described by two mechanisms: the coupling of drug diffusion and polymer relaxation. The release mechanism is known to be influenced by (i) nonhomogeneous gel microstructure as well as the existence of polymeric domains within the swollen gel, (ii) rate of fluid ingress into the matrix, (iii) dissociation/erosion and total disentanglement at the dissolution front and (iv) rate of matrix swelling, relaxation as well as molecular diffusion of drug through the swollen gel. In general, the solubility of drug itself crucially governs the rate and extent of diffusional release. For diffusion to occur, the first step is wetting of the drug by water, followed by its dissolution such that the drug molecule is available in its molecular form to diffuse out of the matrix. Hence, the net release rate observed is a cumulative effect of drug’s solubility influenced by its structure, molecular weight and pKa.
VII.3. Conclusions

Poly(methacrylic acid)-poly(vinyl alcohol) sequential IPN microspheres were prepared by emulsion crosslinking. FT-IR and DSC studies confirmed the formation of IPN structure. The IPNs prepared demonstrated a better pH sensitivity to the external media as compared to plain PVA, indicating the suitability of IPNs for microsphere preparation and thus, their use as gastric fluid-resistant drug vehicles. Ibuprofen was successfully entrapped into the IPN matrix and was stable in the matrices developed without undergoing any chemical changes during the microsphere preparation. Thermal and X-RD studies confirmed the molecular level dispersion of IBU in the polymer matrices developed. Microspheres were spherical with smooth surfaces before and after drug loading. The pH sensitivity of the microspheres developed was evaluated by monitoring their dimensional changes with time using light microscopy. The microspheres exhibited a switch “on-off” pulsatile swelling behavior by varying the pH of the external media from 1.2 pH to 7.4 pH. The release of IBU from microspheres was found to depend upon the amount of PMAA, pH of the medium, extent of crosslinking of the matrix as well as the amount of drug loading. The $n$ values varied from 0.57 to 0.78, indicating the drug release following the anomalous or non-Fickian trend.
III.4. Literature Cited


CHAPTER VII