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Semi-IPN hydrogels based on Poly(vinyl alcohol) for controlled release studies of chemotherapeutic agent and their Swelling characteristics

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Summary

Poly (vinyl alcohol)/poly(acryl amide-co-acrylamidoglycolic acid) (PVA/Poly(Am-co-AGA) based pH sensitive semi interpenetrating (semi-IPN) hydrogels were prepared by free radical polymerization in aqueous solution using N, N-methelene-bis-acryl amide (MBA) as a crosslinker. Different hydrogels with different compositions of AGA and MBA were prepared and characterized by Fourier transform infrared spectroscopy. The developed hydrogels were used for controlled release of 5-fluorouracil (5-FU). The drug entrapment efficiency up to 55% was achieved. The 5-FU loaded gels were characterized by X- ray diffraction and differential scanning calorimetric techniques, to understand the nature of drug in the polymeric matrix. The release of 5-FU through the semi-IPN was completed with in ~12h. Swelling studies performed in water have been analyzed with the help of an empirical equation to investigate the diffusion mechanism.

Introduction

Hydrogels are three-dimensional interpenetrating polymer networks (IPNs) in which individual hydrophilic/hydrophobic polymer chains are connected by physical or chemical bonds. These bonds give rise to the integrity and physical stability of the networks whereas the thermodynamic compatibility of the polymer chains with water allows these materials to swell in aqueous solutions [1, 2]. The particular suitability of hydrogels as biomaterials stems from the similarity of their physical properties to those of living tissues. This resemblance is due to their high water content, soft and rubbery consistency, and low interfacial tension. IPN materials have drawn much attention because of the special properties brought about by the interlocking of polymer chains [3]. Polyurethane, [4] acrylic acid ester, [5] and polyethylene glycol [6] are the usual materials for IPNs [7]; however, research on IPN materials made from cellulose, poly(vinyl alcohol) (PVA), [8,9] etc., also revealed interesting results.

There are many reports on hydrogels, which will be able to respond in external media, for the controlled release (CR) of bioactive molecules [10–12]. However, to develop novel polymeric hydrogels, it is important to select a desirable polymer that has at least two qualities: (i) it should swell in an aqueous media and (ii) contain the reactive functional groups for chain modification. Several efforts have been made in this direction to meet many of the above-mentioned requirements [10].
PVA, a water-soluble hydrophilic polymer, has been used in many practical applications because of its easy preparation, excellent chemical resistance, and good physical properties, and its biodegradability. The chemically crosslinked PVA hydrogels have received increasing attention in biomedical and biochemical applications, because of their permeability, biocompatibility [13–17]. PVA is a well-known biologically friendly polymer and has been developed for biomedical applications such as artificial pancreas [13–15], synthetic vitreous body [16], wound dressing, artificial skin, and cardiovascular device [17], and controlled release applications [12].

The delivery of chemotherapeutic agents using polymeric IPNs has become one of the most popular areas of research because of the possibilities of reducing toxicities and controlled release activity. 5-FU is most commonly used chemotherapeutic drug for the treatment of solid tumors of breast, stomach, colon and pancreas [18-22]. It has been widely used in drug administration due to its large number of secondary effects that accompany its conventional administration. In the present work, we introduced 5-FU in to the newly developed poly(vinyl alcohol)/poly(acryl amide-co-acrylamidoglycolic acid) (PVA/Poly(Am-co-AGA) semi-IPNs hydrogels. The resulting gels are capable of being triggered by an environmental stimulus such as pH.

Experimental

Materials

Analytical Reagent grade samples of acrylamide (Am), acrylamidoglycolic acid (AGA) 5-fluorouracil (5-FU) and poly(vinyl alcohol)(PVA) (M_W=50,000), were purchased from Aldrich chemicals co. N,N-methelene bis acrylamide (MBA), potassium persulphate (KPS) were purchased from SD fine chemicals. All the chemicals were used without further purification. Throughout the experiment double distilled water was used.

Synthesis of hydrogels

PVA/Am/AGA random copolymers with different compositions and crosslinking agent concentrations (see Table 1.) were prepared by radical polymerization. PVA solution was prepared at 80 ^{o}C. After dissolution, the solution was cooled to room temperature and required amounts of Am and AGA were added and dissolved. To this mixture crosslinking agent (MBA) and 0.25 ml of initiator (KPS) were added and stirred for 1 h. Finally, the reaction mixture was pored into a 1cm glass tubes and sealed. The tubes were transferred to electronically controlled water bath and maintained 60 °C temperature for approximately four hours until the polymerization was completed. After complete polymerization, the glass tubes were broken carefully without destroying the cylindrical hydrogels. The resulting hydrogels were sliced into

small cylinders with lengths of 3 mm and then immersed in distilled water for 3 days by changing the water for every 12 hr in order to remove the residual unreacted monomers, and the solution fraction of the polymer. The resulting ‘‘swollen’’ gels were dried in air for 2 days and then in a vacuum oven until to attain constant weight at 40 °C.

Swelling studies

Equilibrium swelling behaviour of the cylindrical gels was studied in water by mass measurements at 30 ^{o}C. Cylindrical gels were soaked in water and at different time intervals; cylindrical gels were taken out and blotted carefully (without pressing hard) to remove the surface-adhered water. The percentage of swelling ratio (%SR) and equilibrium swelling ratio (%ESR) is defined as

$$\% \text{ SR} = \left(\frac{w_s - w_d}{w_d} \right) \times 100 \quad (1)$$

$$\% \text{ ESR} = \left(\frac{w_e - w_d}{w_d} \right) \times 100 \quad (2)$$

where, W_s is the weight of the swollen gel at time t, W_e is the weight of the gel after establishment of equilibrium in the water, and W_d is the dry weight of the gel.

Loading of 5-fluorouracil in the copolymeric networks

Swelling equilibrium method was used in order to load 5-FU into semi-IPNs. The hydrogels were allowed to swell in the drug solution of known concentration for 24h at 37 °C. The solubility of 5-FU in water is very low (13mg/mL). However, the solubility of the sodium salt increases to 65mg/ml [23]. In order to load the maximum drug into the polymeric network, aqueous solution of drug was neutralized with NaOH and used in the feed mixture, instead of water. During this process, drug in the solvent was adsorbed into the networks, whereas the sodium salt of 5-FU is pharmacologically active [24].

Differential scanning calorimetry (DSC) studies

Differential scanning calorimetric (DSC) curves were recorded on Rheometric scientific differential scanning calorimeter (Model-DSC SP, UK). The instrument was calibrated using indium as the standard. Samples were heated in sealed aluminum pans between 50 and 400 °C at the heating rate of 10 °C/min under inert nitrogen purge gas at the rate of 20 mL/min.

X-ray diffraction (X-RD) studies

X-ray diffractograms of the placebo semi-IPN, plain 5-FU and 5-FU-loaded semi-IPN was recorded on a Rigaku diffractometer (Model Rigaku Miniflex) equipped with a Ni-filtered CuKά radiation (λ = 1.5418 Å). The dried gel of uniform size were

mounted on a sample holder and X-RD scans were recorded in the angle range of 5°-45° at the speed of 5°/min to estimate the crystallinity of the samples.

Estimation of drug loading and encapsulation efficiency

The loading efficiency of 5-FU in the semi-IPNs was determined spectrophotometrically. About 10 mg of the drug-loaded hydrogels were placed in 10 mL of buffer solution and stirred vigorously for 48 h to extract drug from the hydrogels. The solution was filtered and assayed by UV spectrophotometer (model Anthelie, Secomam, Dumont, France) at fixed λ_{max} value of 270 nm. The results of % drug loading and encapsulation efficiency were calculated, respectively using Eqs. (3) and (4). These data are compiled in Tables 1, respectively.

$$\%\ Drug\ loading\ =\ \left(\frac{Amount\ of\ drug\ in\ the\ gels}{Amount\ of\ gels}\right)x100 \qquad (3)$$

$$\%\ Encapsulation\ efficiency\ =\ \left(\frac{Actual\ loading}{Theoretical\ loading}\right)x100 \qquad (4)$$

In-vitro release study

Dissolution was carried out using the fully automated dissolution coupled UCV system (Logan System 888J, NJ, USA) equipped with six baskets. Dissolution rates were measured at 37 °C under 100 rpm speed. Drug release from the hydrogel network was studied in simulated intestinal (7.4 pH phosphate buffer) fluid. Aliquot samples were withdrawn at regular time intervals and analyzed by UV spectrophotometer as explained before.

Results and discussions

FTIR studies

The FTIR spectrum of semi-IPN gel crosslinked by MBA had shown a broad band at ~3430 cm^{-1} corresponds to associated –OH stretching. The characteristic peaks of the Am and AGA repeating units in the region of 3500–3400 cm^{-1} characteristic of N-H stretching vibrations which are overlapped with –OH bands of PVA. 1652 and 1600 cm^{-1} characteristic peak of stretching vibrations and amide II band of N-H bending vibrations are observed. In addition to this, another peak was observed at 1323 cm^{-1} characteristic of amide III band corresponding to C-N stretching mixed with N-H bending. The peaks corresponding to -COOH groups of AGA have overlapped with N-H stretching frequency in the region 3000 cm^{-1}. There are small humps around 1720–1710 cm^{-1} characteristic of the carbonyl group of AGA. In addition to this, other characteristic peaks related to -OH group of the carboxyl group are observed at 1455, 1149, and 1118 cm^{-1} indicating the incorporation of AGA units in the copolymer chains. Thus the IR spectra confirms the presence of two repeating units, that is, the Am and AGA in the copolymer structure. Representative IR spectra of PVA IPNs are presented in Figure 1.

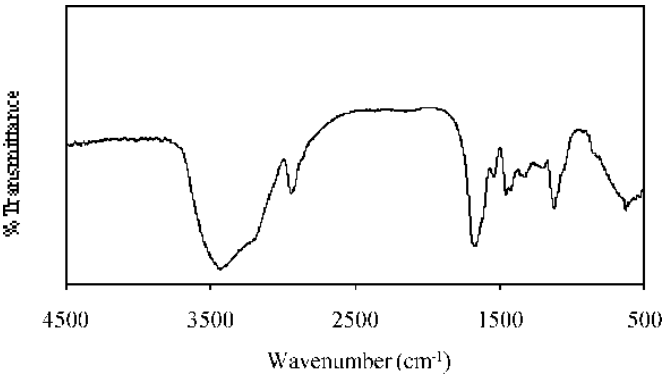

Figure 1. FTIR spectrum of semi-IPN.

Differential scanning calorimetry (DSC)

DSC thermograms of Plain semi-IPN, 5-FU-loaded semi IPN, and pure 5-FU are depicted in Figure 2. 5-FU shows a sharp peak at 285.16 ^{o}C due to polymorphism and melting, but in case of 5-FU-loaded hydrogels, no characteristic peak was observed at 285.16 °C, suggesting that 5-FU is molecularly dispersed in the semi-IPNs.

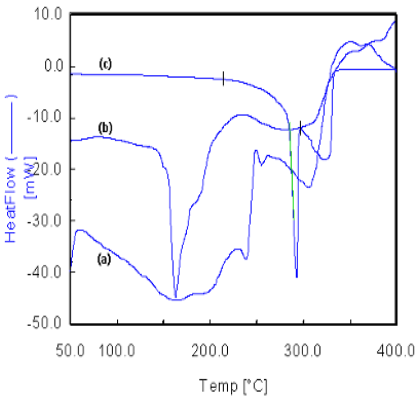

Figure 2. DSC thermograms of placebo Semi-IPN (a), 5-FU loaded Semi-IPN (b) and plain 5-FU (c).

X-ray diffraction (X-RD) studies

X-RD study helps to find the crystallanity of drug in the semi-IPNs. The most intensive peaks of 5-FU are observed at 2θ of 29^{o} and 32^{o}, suggesting its crystalline nature. But, these peaks are found in 5-FU loaded semi IPNs with very less intensity, indicating that the drug is dispersed at molecular level in the polymer matrix. These XRD curves are displayed in the Figure 3.

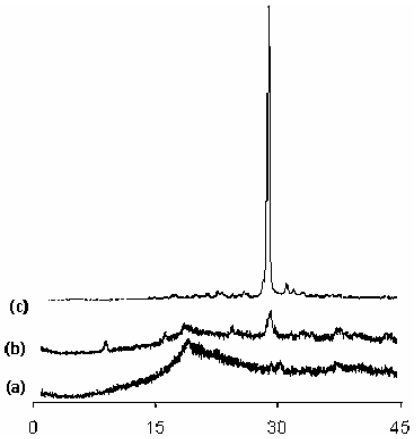

Figure 3. XRD patterns of (a) placebo Semi-IPN, (b) 5-fluorouracil-loaded Semi-IPN and (c) plain 5-fluorouracil.

Swelling studies

Table 2 gives the composition and equilibrium swelling ratio data of the semi-IPN hydrogels and the results are also depicted in Figure. 4 and 5. In the present investigation, we employed Am and AGA with different amounts to a bio-compatible polymer, namely PVA, for the preparation of the IPNs. The swelling results for the semi-IPNs in distilled water clearly showed that the addition of a small amount of AGA resulted in a gradual increase of the swelling capacity from 376 to 486. The improved swelling capacity can be explained as follows, by the addition of AGA in the preparation of semi-IPN hydrogels, the total concentration of hydrophilic units present in the network increases, which is responsible for the good swelling capacity of the gels at a fixed concentration of crosslinker. The poly(AAm-*co*-AGA) hydrogel showed faster swelling and a higher swelling capacity than semi-IPN-1. This is due to the fact that a small amount of polymer may block the pore channels of the crosslinked networks and therefore a higher swelling capacity for semi-IPN-1 could not be obtained when compared to Semi-IPN 5.

Highly water swollen polymers/hydrogels are considered as promising materials in controlled release applications. The mechanism of water diffusion in hydrogels has received considerable attention in recent years. When hydrogels are brought in contact with water, the water diffuses into the networks of the gels interior and causes the gel to swell. This results in an increase in the segmental mobility of polymeric chains and therefore increases the distance between the polymeric chains. The dynamics of water sorption process were studied by monitoring the water imbibed by the hydrogel at different time intervals. [25, 26].

$$\text{Swelling ratio} \quad = \left(\frac{w_s - w_d}{w_d} \right) = kt^n \qquad (\mathbf{5})$$

where W_s and W_d denote weight of swollen hydrogel at time t and weight of dried hydrogel at time $t = 0$ respectively; k is a swelling constant related to the structure of

the network; and n is the swelling exponent that indicates the water transport mechanism. These results along with correlation coefficients, r are presented in Table 2. If $n = 0.5$, the drug diffuses and releases from the polymer matrix following a quasi-Fickian diffusion. For $n > 0.5$ an anomalous, non-Fickian drug diffusion occurs. If $n = 1$, a non-Fickian Case II or zero-order release kinetics is operative. Values of k and n have shown a dependence on the extent of crosslinking and amount of co monomer.

Table 1. Results of % encapsulation efficiency of PVA IPNs loaded with 5-fluorouracil

Sample code	PVA(g)	AAm(g)	AGA (wt%)	MBAAm (wt%)	%Encapsulation efficiency
Semi-IPN-1	1	0.50	-	0.30	38.19
Semi-IPN-2	1	1.00	-	0.30	42.46
Semi-IPN-3	1	1.00	10	0.30	53.05
Semi-IPN-4	1	1.00	20	0.30	58.12
Semi-IPN-5	1	1.00	20	0.15	61.74
Semi-IPN-6	1	1.00	20	0.45	55.31

Table 2. Release kinetic parameters of different formulations

Sample code	%Equilibrium swelling studies	k	n	r
Semi-IPN-1	265	4.72	0.4572	0.9409
Semi-IPN-2	299	6.94	0.4104	0.9817
Semi-IPN-3	376	7.01	0.3798	0.9621
Semi-IPN-4	442	9.97	0.3438	0.9960
Semi-IPN-5	403	5.60	0.4102	0.9772
Semi-IPN-6	486	5.65	0.4187	0.9678

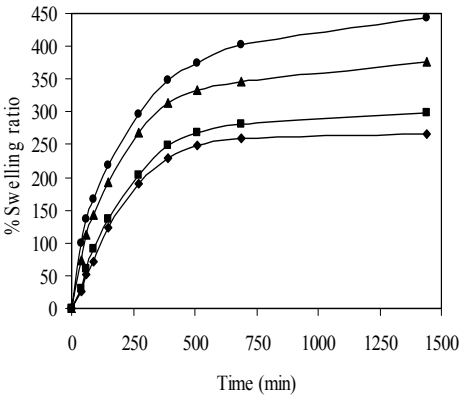

Figure 4. % Swelling of Semi-IPN hydrogels in water. Symbols for different IPNs: (♦) Semi-IPN-1, (■) Semi-IPN-2, (▲) Semi-IPN-3, (●) Semi-IPN-4.

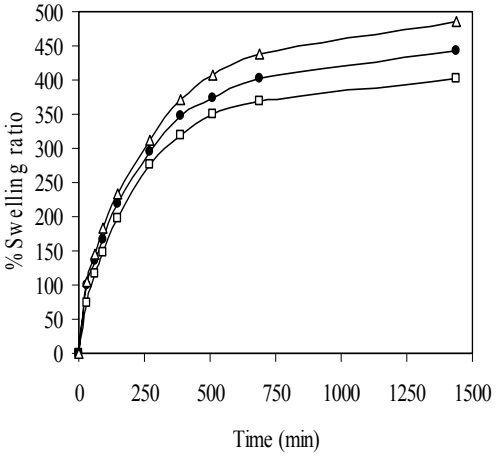

Figure 5. % Swelling of IPN hydrogels in water. Symbols for different IPNs: Symbols for (●) Semi-IPN-4, (Δ) Semi-IPN-5, (□) Semi-IPN-6.

Drug release studies

Drug release kinetics were analyzed by plotting the cumulative release data, (M_t/M_∞) *versus* time. The PVA/poly(Am-co-AGA) pH-sensitive semi-IPN hydrogels were used to study the release behavior of 5-FU in phosphate buffer (pH = 7.4). These gels released large amount of 5-FU for the small amount of AGA containing semi-IPN gels and released 100% drug in ~12 h. In the present research, MBA was employed to crosslink the IPNs and the amount of the drug released for different amounts of AGA and MBA in pH 7.4 media are displayed in Figure 6 and 7, respectively. A systematic increase in percentage cumulative release with increasing composition of AGA is observed, but the release time remains almost the same for all compositions. The reason for this effect could be that, during the process of dissolution, a general trend was observed in all the formulations. That is semi-IPNs systematically swelled more with the increasing amount of AGA, probably due to the ionization of crosslinked chains. The resulting in relaxation response of the polymer chains because of the stresses introduced during the process of dissolution. So that the resulting in an increase of dimension of the polymer coil, thus, a significant increase in molecular volume of the overall hydrated polymer matrix due to increased swelling of AGA component of the matrix. Note that, the nature of release profiles remains almost identical for all the matrices containing different amount of AGA, indicating that swelling of AGA has a linear relationship with their release profiles. The % cumulative release data versus time plots for varying amounts of MBA, i.e., 15, 30, and 25 wt% at constant drug loading are displayed in Figure 8. The % cumulative release is quite fast and large at the lower amount of MBA (i.e., 15 wt%), whereas the release is quite slower at higher amount of MBA (i.e., 45 wt%). The cumulative release is somewhat smaller when lower amount of MBA was used, probably because at higher concentration of MBA, polymeric chains become rigid due to the contraction of microvoids, thus decreasing percentage cumulative release of 5-FU through the polymeric matrices. As expected, the release becomes slower at higher amount of MBA, but becomes faster at lower amount of MBA.

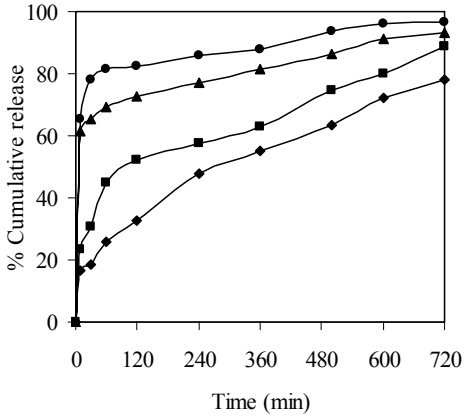

Figure 6. % Cumulative release of 5-FU through Semi-IPNs containing different ratios Am and AGA: symbols for (♦) Semi-IPN-1, (■) Semi-IPN-2, (▲) Semi-IPN-3, (●) Semi-IPN-4.

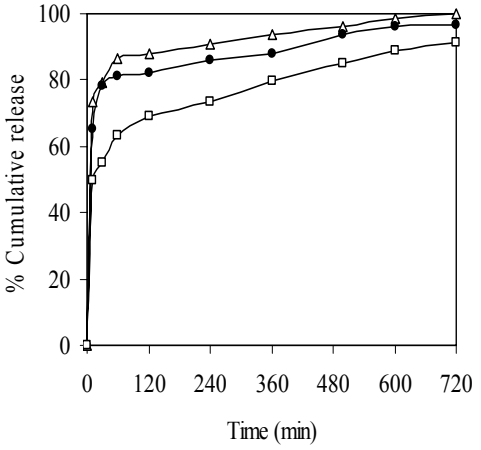

Figure 7. % Cumulative release of 5-FU through Semi-IPNs containing different amounts of crosslinking (MBA) agent: (●) Semi-IPN-4, (Δ) Semi-IPN-5, (□) Semi-IPN-6.

Conclusions

Semi-IPN hydrogels based on PVA and poly(Am-co-AGA) by radical polymerization in aqueous solution were prepared. They were characterized by FTIR spectroscopy, percentage of swelling ratio and equilibrium swelling ratio were measured in aqueous solutions at 30^{o}C, by using these results diffusional characteristics were calculated. All hydrogels swelled slowly and reached equilibrium within 24 h. 5-Fluorouracil was employed as a model drug to study its release characteristics in buffer media up to longer times of 12 h. Release profiles varied depending upon the nature of the matrix. The results of release kinetics from the hydrogels exhibited a Fickian diffusion transport. Copolymer composition as well as the extent of cross-linking agent of the matrix exerted significant effects on drug encapsulation efficiency and drug release profiles. Results of this study are useful in extending the short life of 5-fluorouracil to an extended period of time lasting up to ~12 h.

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