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Hydrogel interpenetrating polymer networks of poly(vinyl alcohol)/ acrylic acid using GA and TMPTA or BIS as cross linkers

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ABSTRACT

Hydrogels of Poly(vinyl alcohol) (PVA) and interpenetrating polymer networks of PVA and Acrylic acid (AA) were synthesized using Glutraldehyde and Trimethylol propane triacrylate (TMPTA) or N-N' Methylene-bisacrylamide (BIS) as crosslinking agent for PVA and AA respectively. The hydrogels and interpenetrating polymer networks (IPNs) were characterized by measuring their % swelling, equilibrium volume swelling ratio, number average molecular weight between cross-links, mesh size and compressive strength in buffer solutions of pH 7.4 and pH 3 at 37 ± 1°C. The effect of initial PVA/AA weight ratio, crosslinking ratio and the type of crosslinker for AA (TMPTA or BIS) on the dynamic and equilibrium swelling behavior of the IPNs were investigated. The swelling capabilities of PVA/AA IPNs were found to be higher than PVA hydrogels and the percentage swelling increased with an increase in the AA content in the IPNs.

KEYWORDS

Acrylic acid;
Glutraldehyde;
N-N' Methylene-bisacrylamide;
Poly(vinyl alcohol);
Swelling;
Trimethylol propane triacrylate.

INTRODUCTION

An Interpenetrating polymer network (IPN) is a polymer comprising of two or more networks which are at least partially interlaced on a polymer scale but not covalently bonded to each other. The network cannot be separated unless chemical bonds are broken[1].

The two or more networks can be envisioned to be entangled in such a way that they are concatenated and cannot be pulled apart, but not bonded to each other by any chemical bond.

Due to their high water up take capacity, rubbery nature and biocompatibility to natural tissues, IPNs are used in biomedical and pharmaceutical applications. Most important of which are the drug-release systems, contact lenses, implants, wound dressing etc.

Some polymeric networks show a change in their swelling properties in response to the external environment like temperature, ionic strength, pH of the swelling medium etc. This characteristic can be effectively used for the design of site-specific drug delivery systems so that it is incapable of releasing the active agent until it is placed in an appropriate biological environment[2]. In case of anionic polymeric networks, ioniza-

tion takes place as the pH of the external medium rises above the pKa of the ionizable moiety[3]. In some polymeric networks, hydrophilic groups or domains are present, which are hydrated in an aqueous environment, thereby creating the IPN structure. The hydrophilicity is due to the presence of water solubilizing groups such as –OH, -COOH,-$CONH_2$,-SO_3H and –CONHR etc.[4]. These exhibit a thermodynamic compatibility with water, which allows them to swell in aqueous media. The ability to swell depends upon the type of polymer and the degree of cross-linking[5].

Chemically cross-linked Poly(vinyl alcohol) hydrogels have received increasing attention in biomedical applications because of their permeability, biocompatibility and biodegradability. Addition of an ionic group with PVA can enhance the swelling properties of the membrane particularly at pH greater than the pKa value of that ionic group. Such systems have the potential to be used as materials for controlled delivering systems.

In the present study, PVA/AA IPNs of different PVA/ AA weight ratios have been synthesized using two different cross-linkers, Glutraldehyde (GA) for PVA and N,N' MethyleneBisacrylamide (BIS) or Trimethylopropanetriacrylate (TMPTA) for AA. IPNs were swelled in two buffer solution of pH 7.4 and pH 3.0. Parametric studies were conducted to evaluate the effect of %GA, cross-linker BIS or TMPTA and the weight ratio of PVA/AA in the IPN on percentage swelling (%S), equilibrium volume swelling ratio (Q), mesh size (ξ), number average molecular weight between crosslinks ($\overline{M}_c$) and compressive strength (Cs).

EXPERIMENTAL

Materials

Poly(vinyl alcohol) with $\overline{M}_w$ = 125 000, was obtained from S.D.Fine Chemicals limited. A 10% w/v aqueous solution of PVA was prepared by dissolving PVA in deionized water at 90^{0}C for 6 hours in hot air oven. The homogeneous solution was then allowed to cool to room temperature. Acrylic acid was obtained from Central Drug House limited and used as such. Acetic acid (glacial), sulfuric acid and methanol were procured from Qualigens Fine Chemicals. Ammonium per sulfate, N,N' Bisacrylamide (BIS), N,N,N',N' tetraethylenediamine (TEMED), Glutaraldehyde (25%w/v) were procured from MERCK. Citric acid, n-heptane, Potassium dihydrogen ortho phosphate, sodium hydroxide and trimethylopropanetriacrylate (TMPTA) were obtained from Central Drug House limited, Hydrochloric acid was obtained from S.D fine chemicals limited.

Synthesis of IPNs

For the synthesis of cross linked PVA, a 25% (w/v) aqueous solution of glutraldehyde was combined with 10% solution of sulfuric acid (the catalyst), a 50% solution of methanol (the quencher), and a 10% solution of acetic acid (the pH-controller) in the ratio 2:1:2:3 respectively. The cross-linking ratio X, defined as the ratio of moles of cross-linking agent per mole of repeat unit was varied by using different amounts of 25% aqueous solution of glutraldehyde. For example, for a cross-linking ratio of X = 0.01, 0.2 ml sulfuric acid, 0.4 ml methanol, 0.6 ml acetic acid, and 0.4 ml of 25% glutraldehyde were added to an aqueous solution containing 5g of PVA and 50 g water. Different amounts of 25% (w/v) glutraldehyde used in this work are 0.4% (v/v), 0.6% (v/v), 0.8% (v/v) and 1.0% (v/v).

IPNs were prepared from 10% aqueous solution by adding acrylic acid along with 1.25 ml of (1% by vol.) TMPTA or BIS as cross-linker, 0.625 ml of (1% by vol.) TEMED (N,N,N',N' tetramethylene ethylenediamine) as accelerator and 1.25ml (5% by vol.) of ammonium persulfate as initiator. The two components were mixed to yield PVA: AA weight ratios of 1:1, 1: 0.75 and 1: 0.5.

The mixture was then immediately transferred in the test tubes, heated at 40^{0}C for 20 hrs, and then cooled to room temperature. The IPNs were cut in small pieces and then put in deionized water for washing to remove any unreacted polymer. The IPNs were first dried in atmosphere for 24 hrs and then in the vacuum oven at 40 ^{0}C until constant weight was attained. These dried samples were stored in desiccators until further use. These IPNs were further characterized by various parameters like %S, Q, $\overline{M}_c$, ξ and Cs.

Characterization of IPNs

In order to evaluate the feasibility of using a spe-

cific hydrogel as a drug delivery device, it is necessary to know the structural properties of the polymer network. The most important parameters that define the structural properties include polymer volume fraction in swollen state, $\upsilon_{2,s}$, effective molecular weight of the polymer chain between two neighboring crosslinks, $\overline{M}_c$ and pore size or mesh size, ξ.

Percentage swelling, %S

The most important property of IPNs is the ability to imbibe water. The resulting osmotic swelling is opposed by elastic contractility of stretched hydrogen network. The net force is the swelling pressure. In response to the external conditions, the IPNs swell by absorbing the solvent until equilibrium is reached. At equilibrium, the swelling pressure is zero. If the osmotic pressure of the solution in contact with IPN is increased due to the presence of solute, the swelling pressure increases and swelling decreases.

To study the effect of pH on swelling behavior of the IPNs, weighed IPN samples were placed in buffer solution of pH 3 and pH 7.4 at a temperature of 37±1°C. The swollen IPNs were removed from the swelling medium at regular intervals of time, blotted using a filter paper, weighed and again placed in the same medium. The studies were carried out till equilibrium in swelling was reached. The percentage swelling, %S was obtained using the following relation:

$$\%S = \left(\frac{W_s - W_d}{W_d}\right) \times 100 \quad (1)$$

where, W_s is the weight of the swelled sample at time t, W_d is the weight of the dry sample.

Equilibrium volume swelling ratio, Q

In order to predict the drug release behavior from the polymeric network, analysis of equilibrium swelling ratio is essential. Buoyancy method was used to obtain the volume of the hydrogel in the swollen state (V_s) and dry state (V_d) using equation 2 and 3

$$V_d = \frac{W_{a,d} - W_{h,d}}{\rho_h} \quad (2)$$

$$V_s = \frac{W_{a,s} - W_{h,s}}{\rho_h} \quad (3)$$

where, $W_{a,d}$ and $W_{a,s}$ are the sample weights in air before and after swelling respectively and $W_{h,d}$ and $W_{h,s}$ are the sample weights in n-heptane (a non-solvent with density, ρ_h = 0.684 at 37±1°C) before and after equilibrium swelling respectively. The latter weights were obtained by placing the sample in a stainless steel mesh basket suspended in n-heptane. The equilibrium volume swelling ratio, Q was determined as the ratio of polymer volume in swollen state to the polymer volume in dry state (equation 4)[6].

$$Q = \frac{V_s}{V_d} \quad (4)$$

Number average molecular weight between cross-links, $\overline{M}_c$

Having determined the polymer volume before and after swelling, the polymer volume fraction in swollen state, $\nu_{2,s}$ was estimated using equation 5[6]

$$\nu_{2,s} = \frac{1}{Q} \quad (5)$$

Equation 6 was used to determine the number average molecular weight between crosslinks, $\overline{M}_c$ [6].

$$\left(\frac{1}{\overline{M}_c}\right) = \left(\frac{2}{\overline{M}_n}\right) - \left(\frac{\left\{\left(\frac{\nu}{V_1}\right)\left[\ln(1-\nu_{2,s}) + \nu_{2,s} + \chi\nu_{2,s}^{\,2}\right]\right\}}{\left[\nu_{2,s}^{1/3} - 0.5\nu^{2,s}\right]}\right) \quad (6)$$

where, $\overline{M}_n$ is the number average molecular weight of PVA before crosslinking and was taken as 1,25,000. υ is the specific volume of PVA=0.788 $cm^3.g^{-1}$[7], V_1 is the molar volume of the solvent (water)= 18 $cm^3.mol^{-1}$. $\nu_{2,s}$, the polymer volume fraction in swollen state was calculated using equation 4 and 5. The value of χ, Flory huggins polymer water interaction parameter equal to 0.494 was used in equation 6[8].

Mesh size, ξ

The IPNs mesh size ξ, defines the linear distance between consecutive cross-links. It indicates diffusional space available for solute transport and was calculated using equation 7[6].

$$\xi = \nu_{2,s}^{-1/3}\left[C_n\left(\frac{2\bar{M}_c}{M_r}\right)\right]^{1/2} l \quad (7)$$

where, C_n is the Flory characteristic ratio for PVA=

8.3, *l* is the carbon carbon bond length = 1.54 Å. M_r is the average molecular weight of the repeat unit of PVA and AA, $g.ml^{-1}$ based on the content of PVA and AA in the membrane.

Compressive strength, Cs

Compressive strength of the swollen gel was obtained using XT PLUS- Texture Analyzer. IPNs swollen in buffer solutions with pH 7.4 and pH 3 were cut into cylindrical shaped samples of length 8 mm. The diameter of the IPN sample D, was measured. The samples were then mounted on the stable Microsystems. For measuring the compressive strength, the pre-test, test and post-test speeds were 2, 0.5, 2 $mm.s^{-1}$ respectively. The gel sample was compressed using 8mm cylindrical probe and the maximum peak force was recorded. From these observations the compressive strength of the gel samples was estimated using equation 8.

$$Compressive\ Strength, Cs,\ g.cm^{-2} = \left(\frac{Peak\ Load}{Cross\,sectional\ area}\right) \qquad (8)$$

where, Crosssectional area, $A = \left(\frac{\pi D^2}{4}\right)$, D is the diameter of the sample in cm.

RESULTS AND DISCUSSIONS

PVA Hydrogel

Swelling response of PVA hydrogel cross linked with different amounts of GA and swelled in buffer of pH 7.4 and pH 3 is given in TABLE 1. The results show that both, the pH of the swelling medium and the cross linking ratio affect the swelling behavior of the PVA hydrogels. The hydrogels when placed in an acidic environment (pH =3) shows higher percentage swelling as compared to when swelled in a buffer of pH 7.4. This is because PVA is a weak acid and has a pKa value of 10.67. At pH 3, the PVA membrane swelled to a larger degree due to the development of a larger osmotic force. With an increase in the % swelling, the equilibrium volume swelling ratio also increased. The Q values at pH 3 were almost two times of those observed at pH 7.4. As a result, with increase in % swelling, we expect the mesh size of the network also to increase considerably. The values of mesh size ξ, molecular weight between crosslinks $\overline{M}_c$, and compressive strength of the hydrogel Cs, observed at pH 7.4 and pH 3 buffers are reported in TABLE 1. As expected the mesh size ξ and hence the molecular weight between crosslinks, $\overline{M}_c$ was higher at pH 3 than at pH 7.4. However, with increasing mesh size the compressive strength of the membranes decreased.

TABLE 1 : Effect of amount of crosslinker (GA) on %S, Q, ξ, $\overline{M}_c$ and Cs for PVA (10%w/v) hydrogels.

GA[a)] (%v/v)	pH=7.4					pH=3				
	%S	Q	ξ, Å	$\overline{M}_c$ g/mol	Cs, g/cm^2	%S	Q	ξ, Å	$\overline{M}_c$ g/mol	Cs, g/cm^2
0.8	398	3.73	54	1344	514	508	8.57	212	11999	184
1.2	257	3.31	43	933	944	466	6.41	136	6022	392
1.4	244	3.25	42	888	1048	420	6.27	132	5681	531

[a)] **25% (w/v) glutraldehyde**

The amount of crosslinker also had a significant effect on the swelling behavior of the PVA membranes. The more the cross linker molecules present in the hydrogel, denser the network, lower the degree of swelling of the hydrogel. The equilibrium volume swelling ratio, mesh size and the molecular weight between cross links were also found to decrease with an increasing cross linking ratio.

PVA/AA IPNs

The PVA/AA IPNs synthesized in this work were studied in terms of their swelling behavior as a function of pH, type of cross linker (TMPTA and BIS), amount of GA and the AA content. IPNs were synthesized with PVA and AA in the weight ratios of 1:5, 1:0.75 and 1:1. Further, to study the effect of crosslinking ratio on the swelling behavior of the IPNs, for each weight ratio of PVA to AA, the amount of glutraldehyde was varied. Data tabulated in TABLE 2 and 3 represent the effect of amount of GA and PVA/AA weight ratio on %S, Q, ξ, $\overline{M}_c$ and Cs for PVA/AA IPNs cross-linked with 25 % (w/v) GA and ((1%) BIS 2.5 %(w/v)) and 25 % (w/v) GA and ((1%) TMPTA 2.5 %(w/v)) respectively.

It is known that high content of charged anionic groups in a hydrogel increases the electrostatic repulsion between the chains as a result of increasing the degree of ionization due to change in the external pH[9,10]. When an anionic group is incorporated into

the PVA structure through AA, there is an increase in the hydrophilic character of the IPNs, thus contributing to a higher swelling as compared to pure PVA. When AA which has a pKa value of 4.3 is added to PVA to form an IPN, the %swelling (%S) for all IPN formulations presented in this work was higher in buffer solution of pH 7.4 in comparison to pH 3. The observed effect of pH on swelling behaviour were in general agreement with the conclusions of Khare and Peppas[11] and Hariharan and Peppas[12]. For IPNs cross linked with GA and BIS the % swelling (%S) varied between 136 and 629 at pH3 and 303 and 1380 at pH 7.4 while the IPNs cross linked with GA and TMPTA, the % swelling varied between 111 and 221 at pH 3 and 398 and 744 at pH 7.4. It can safely be concluded that the proper adjustment of the amount of crosslinking agent for PVA and the type of crosslinking agent for AA used in the synthesis process, is an effective means of controlling the cross linked structure of the IPN.

Effect of crosslinking ratio

Swelling response of IPNs synthesized with a constant weight ratio of PVA to AA (1:1, 1:0.75, 1:0.5), cross linked with (1%) BIS (2.5 %(w/v)) but varying amounts of Glutraldehyde is presented in TABLE 2.

TABLE 2 : Effect of amount of GA and PVA/AA weight ratio on %S, Q, ξ, $\overline{M}_c$ and Cs for PVA/AA IPNs cross-linked with 25 % (w/v) GA and ((1%) BIS 2.5 %(w/v))

Ratio of PVA/AA (w/w)	GA[b] (%v/v)	pH=7.4					pH=3				
		%S	Q	ξ, Å	$\overline{M}_c$ g/mol	Cs, g/cm^2	%S	Q	ξ, Å	$\overline{M}_c$ g/mol	Cs, g/cm^2
1:1	0.4	1380	15.43	398	34135	169.38	629	7.32	156	8609	372.69
1:1	0.6	1237	13.02	335	27162	275.08	248	5.03	84	3231	528.54
1:1	0.8	445	7.16	151	7907	394.75	154	3.64	47	1269	1377.01
1:0.75	0.4	697	7.41	160	8600	195.31	504	4.82	79	2808	508.2
1:0.75	0.6	569	7.20	147	8017	336.43	244	3.66	56	1880	692.8
1:0.75	0.8	425	6.57	132	6398	484.41	236	3.57	47	1202	2130.2
1:0.75	1.0	405	5.71	101	4448	1002.81	200	3.10	35	776	3097.0
1:0.5	0.4	489	7.28	149	8244	394.88	316	3.33	41	957	805.6
1:0.5	0.6	408	6.41	122	6002	542.89	237	2.92	31	635	1195.1
1:0.5	0.8	366	5.59	101	4316	972.78	200	2.55	23	407	2381.7
1:0.5	1.0	303	4.87	80	2958	1741.71	136	2.32	20	320	6945.1

[b] 25% (w/v) glutraldehyde

TABLE 3 : Effect of amount of GA and PVA/AA weight ratio on %S, Q, ξ, $\overline{M}_c$ and Cs for PVA/AA IPNs cross-linked with 25 % (w/v) GA and ((1%) TMPTA 2.5 %(w/v))

Ratio of PVA/AA (w/w)	GA[c] (%v/v)	pH=7.4					pH=3				
		%S	Q	ξ, Å	$\overline{M}_c$ g/mol	Cs, g/cm^2	%S	Q	ξ, Å	$\overline{M}_c$ g/mol	Cs, g/cm^2
1:1	0.6	607	8.71	195	12427	193.0	221	3.87	53	1527	309.2
1:1	0.8	521	7.63	166	9515	240.9	205	3.51	45	1123	462.9
1:1	1.0	511	7.47	161	9048	546.3	191	3.31	40	936	628.8
1:0.75	0.4	744	8.53	190	11890	193.0	298	5.35	91	3731	412.6
1:0.75	0.6	491	7.47	149	8230	203.3	191	3.62	47	1244	518.6
1:0.75	0.8	468	7.28	136	6960	252.5	181	3.42	43	1035	1089.4
1:0.75	1.0	409	6.72	121	4991	574.2	175	3.31	40	945	1574.01
1:0.5	0.4	478	6.96	145	7393	200.3	205	3.57	46	1177	896.8
1:0.5	0.6	450	6.60	134	6462	271.6	175	3.56	41	954	1147.96
1:0.5	0.8	428	6.43	128	6051	381.6	164	3.13	35	789	1631.1
1:0.5	1.0	398	5.93	112	4914	786.0	111	2.46	25	372	2080.9

[c] 25% (w/v) glutraldehyde

The data shows that with an increase in the amount of Glutraldehyde the resulting IPN's possess more compact and cross linked networks which show a decreasing degree of swelling as compared to same IPNs with lower cross-linking ratios. An increase in the amount of Glutraldehyde from 0.4% (v/v) to 1.0% (v/v) led to a fall in the value of Q, for all weight ratios of PVA to AA. Lower values of Q implies a less open network structure and hence smaller mesh size (ξ) and lower molecular weight between crosslinks ($\overline{M}_c$). However, with an increasing mesh size or molecular weight between crosslinks the mechanical strength of the membranes decreases. Similar behavior was observed for IPNs synthesized with GA and (1%) TMPTA (2.5 %(w/v)) as presented in TABLE 3.

Effect of amount of AA

IPN samples synthesized with same amount of GA and BIS but varying weight ratios of PVA/AA when subjected to swelling experiments revealed that with an increase in AA content from 33.3% to 42.6% to 50% (i.e 1/0.5, 1/0.75, 1/1) % swelling (%S) of the membranes also increases (TABLE 2). Higher percentage of AA in the IPNs resulted in a more hydrophilic polymeric network leading to a rapid absorption of water and thus higher % swelling.

An increase in the ionization of anionic AA at a pH > pKa causes electrostatic repulsion between the ionized groups, leading to chain expansion, which resulted in an increase in the mesh size of the membranes. Higher AA content in the membrane led to a more open network structure, higher molecular weight between crosslinks but lower mechanical strength.

For an IPN with 33.3% AA and 0.4% v/v (25% (w/v) GA) cross linked with BIS, swelled in pH 7.4 buffer, the mesh size was 149 Å while the same IPN with 50% AA when swelled in pH 7.4 buffer had a mesh size of 398 Å.

For IPNs synthesized with 33.3% AA and 0.6% v/v (25% (w/v) GA) cross linked with TMPTA, swelled in pH 7.4 buffer, the % swelling was 450 % which increased to 607% for the same IPN with 50% AA (TABLE 3). An increase in the % swelling was accompanied by an increase in the mesh size, an indication that the networks should exhibit greater solute permeability in the highly swollen state.

CONCLUSION

PVA being highly water-soluble, but when cross-linked with glutraldehyde in presence of sulfuric acid, methanol and acetic acid, acetyl bridges were formed between hydroxyl groups of PVA chains. As a result, its solubility in water decreased due to the physical and chemical networks formed and it retained water in these networks, when allowed to swell in aqueous media. The swelling behavior of PVA hydrogels was found to be a function of the crosslinking ratio and the pH of the swelling medium. Such hydrogels have been widely employed as pH-sensitive systems for targeted drug delivery[13].

When anionic AA was incorporated into PVA to form IPNs using GA/TMPTA or GA/BIS as cross-linkers and swelled in buffer solutions of pH 3 and pH 7.4, a considerable increase was observed in % swelling, mesh size and the molecular weight between crosslinks of the membranes. The %swelling of PVA (10%w/v) hydrogel is 398% at pH 7.4 while PVA/AA IPNs synthesized with GA/TMPTA as cross-linkers swell up to 744% at 7.4 pH and upto 1380% at pH 7.4 for IPNs synthesized with GA/BIS as cross linkers.

The mesh size of the membranes synthesized in this work with GA and BIS varied between 20 and 398 Å while those synthesized with GA and TMPTA the mesh size varied between 25 and 195 Å. Implying that solute permeation by size exclusion over a wide range of sizes would be possible.

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