Permeation of Solutes Through Interpenetrating Polymer Network Hydrogels Composed of Poly(vinyl alcohol) and Poly(acrylic acid)

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ABSTRACT: The swelling behaviors of poly(vinyl alcohol)–poly(acrylic acid) (PVA–PAAc) interpenetrating networks (IPN) hydrogels in the presence of electrolytes were studied. The ionized carboxylic group within IPN hydrogels at pH 7 strongly interacted with electrolytes in the medium and caused anomalous swelling pattern. The permeabilities of 5 representative solutes were regulated as a function of temperature, pH, ionic strength, solute size, and ionic properties of solutes. The permeation of nonionic solutes followed the swelling behaviors dependent on external stimuli, including the above factors. However, the ionic solutes showed different trends in their permeation through IPN hydrogels. © 1998 John Wiley & Sons, Inc. J Appl Polym Sci 69: 479–486, 1998

INTRODUCTION

Stimuli responsive hydrogels are three-dimensional polymer networks that exhibit sensitive swelling transitions dependent on pH,[1–4] temperature,[5–7] and ionic strength[8] of surrounding environments or some chemicals.[9,10] They have been considered to be useful in bioseparation and medical applications. Specifically, there have been investigations on the pulsatile drug delivery systems, which could regulate the amount of solutes absorbed in the human body. Environmentally sensitive hydrogels are attractive because solute permeabilities through them can be controlled not only by changing their structure but also by alternating external conditions.

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Gudeman and Peppas reported on the pH-sensitive membranes from poly(vinyl alcohol) (PVA) and poly(acrylic acid) (PAAc) interpenetrating networks (IPN). In this case, the IPN was crosslinked by using glutaraldehyde.[11,12] They later reported on the transport of ionizable drugs and proteins by using crosslinked poly(acrylic acid) and poly(acrylic acid-*co*-2-hydroxyethylmethacrylate) hydrogels.[13]

We prepared novel pH- and temperature-responsive IPN hydrogels composed of PVA and PAAc crosslinked by ultraviolet (UV) irradiation and a freeze–thawing method and investigated their swelling behaviors.[14,15] Crosslinked PVA and PAAc networks underwent a sharp swelling change from a highly swollen state to a collapsed state as the pH of the buffer solution is reduced into the acidic range (below 4.7). In the temperature-responsive experiments, IPN hydrogels showed negative or positive swelling changes, de-

pending on the molar ratio of each polymer (PVA–PAAc) within the structure of IPNs. We looked after the potential usefulness in the drug delivery system from these IPN hydrogels.[16] Indomethacin, which was used as a model drug, release patterns as a function of pH and temperature were in good agreement with the swelling changes of IPN hydrogels.

In the present study, our research concentrated on the solute permeation through swollen PVA/PAAc IPN hydrogel membranes. Since the solute permeation is driven by the changes in the free volume of IPN hydrogels, the several environmental factors that lead to the change of swelling in the hydrogel determines the solute permeation. The ionic strength in the buffer solution seemed to be the controlling factor to determine the swelling behaviors of IPNs because IPNs contain ionizable groups. Ionization could affect the permeation of ionizable solutes in a different manner. In this study, therefore, solute permeabilities of 5 representative solutes were compared by changing ionic strength of buffer solution and the structures of IPN hydrogel. These solutes have different characteristics, such as solute size, molecular weight, and pK_a value through swollen hydrogel membrane. They are theophylline, bovine serum albumin, vitamin B_{12}, cefazolin, and riboflavin. First, 3 solutes are selected as nonionic species and the last 2 for ionic solutes.

EXPERIMENTAL

Materials

Acrylic acid monomer (AAc) was purchased from Junsei Chem. Co. and used after purification with inhibitor removal column. Poly(vinyl alcohol) (PVA; DP = 2500, degree of deacetylation) was obtained from ShinEtsu Co., and methylenebisacrylamide (MBAAm) and 2,2-dimethyl-2-phenylacetophenone (DMPAP) were obtained from Aldrich Chem. Co. Theophylline (99%, Aldrich Chem. Co.), vitamin B_{12} (Sigma Chem. Co.), riboflavin (Junsei Chem. Co.), and bovine serum albumin (Young Science Inc.) were used. Cefazolin sodium was kindly donated from Chongkeundang R&D Center in Seoul, Korea.

Synthesis of IPN

The IPN composed of PVA and PAAc was synthesized, as previously published.[15,16] PVA/PAAc IPNs were prepared by the sequential method by which PAAc as the initial network was synthesized inside of the mixed solution of PVA and AAc monomer and PVA networks, as the secondary networks, were formed by a repetitive freeze–thawing process. PVA was dissolved in the water to make the 10 wt % aqueous solution, and AAc monomers were mixed with 0.2 wt % DMPAP and 0.5 mol % MBAAm. The molar ratios of PVA to PAAc mixture were adjusted to 3 : 7, 4 : 6, 5 : 5, 6 : 4, and 7 : 3, respectively. The mixture solutions were poured onto the petri dishes and irradiated by using a 450-W UV lamp (Ace Glass Co.) for 20 min under N_2 atmosphere. The irradiated samples were placed at −50°C for 6 h and at room temperature for 2 h. These cycles were repeated 8 times. To produce a thinner hydrogel membrane, the amount of poured solution in the petri dishes was 10 g, and the dried samples with the thickness of 1 mm were obtained.

Swelling Tests

For the characterization of the response of hydrogels to external ionic strength in buffer solution, the IPN disks were immersed in either pH 4 buffer or pH 7 buffer solution at 25°C. In the respective buffer solution, the total ionic strength was adjusted to 0.01 or 0.1 by adding a precalculated amount of NaCl. For the kinetic measurements in the swelling of IPN gels, the disks were withdrawn from the buffer solutions and weighed periodically after the removal of surface water. The swelling ratio of each sample was evaluated as being equal to $(W_s - W_d)/W_d$, where W_s and W_d are fully swollen and dry weight of each sample, respectively.[17] Usually, the equilibrium of the hydrogels was obtained after 24 h of swelling.[15]

Partition of Solutes

The equilibrium partition coefficient of each solute between hydrogel membrane and surrounding solution was obtained by soaking the gel membranes in each solute solution of known concentration, pH, ionic strength, and temperature. After IPN hydrogels in each solute solution reached an equilibrium state, the hydrogel membranes were taken out from the solution and then the change of absorbance in the surrounding solution was measured by UV spectroscopy (Shimadzu, Model UV-2101PC). The partition coefficients (K_d) were defined as the ratio of solute concentration in hy-

drogel membrane to that in surrounding solution and expressed as

$$K_d = \frac{C_m}{C_s} = \frac{V_{\text{sol}}(C_i - C_t)}{V_m C_t} \quad (1)$$

Here, C_m is the concentration of the solute in the hydrogel membrane, C_s is the concentration in the solution, C_i is the initial concentration of surrounding solution, C_t is the concentration after hydrogels have reached an equilibrium state, and V_{sol} and V_m are the volume of the surrounding solution and the hydrogel membrane, respectively.[18]

Permeation Studies

The permeation studies were carried out using a two-chamber diffusion cell. The IPN hydrogels were fully swollen in various conditions maintaining different temperature, pH, and/or ionic strength (0.1, 0.01) and placed in the middle of the two-chamber cell. Each half cell has an equal volume of 25 mL and effective membrane area of 2.5 cm^2. The solution to be permeated was added in the donor cell, and the receptor cell was filled with a buffer solution. The concentration of solutes in the receptor cell was determined periodically by UV spectroscopy. The solutes permeated were theophylline with UV absorbance at λ_{max} = 274 nm, BSA (λ_{max} = 280 nm), and vitamin B_{12} (λ_{max} = 361 nm) as nonionic solutes and cefazoline (λ_{max} = 270 nm) and riboflavin (λ_{max} = 375 nm) as ionic solutes. From UV absorbance data, the permeability coefficients were calculated with the following equation:[19]

$$\ln\left(1 - \frac{2C_t}{C_0}\right) = -\frac{2A}{V\delta}Pt \quad (2)$$

Here, C_t is the solute concentration in the receptor cell at time t, C_0 is the solute concentration in the donor cell at initial state, A is the surface area, V is the volume of each cell, δ is the membrane thickness, and P is the permeability coefficient.

The diffusion coefficients (D) of each solute in the hydrogel membrane was evaluated by

$$D = \frac{P}{K_d} \quad (3)$$

where K_d is the partition coefficient of the hydrogel membrane, and P is the permeability coefficient, respectively.[20]

Table I Effects of pH and Ionic Strength in the Swelling Medium on the Equilibrium Swelling Ratio of IPN Hydrogels

Sample	pH of Swelling Medium	Ionic Strength of Swelling Medium	Swelling Ratio[a]
IPN 37	7	0.01	32.3 ± 0.92
IPN 46	4	0.1	6.8 ± 0.44
		0.01	6.0 ± 0.91
	7	0.1	16.3 ± 1.8
		0.01	28.0 ± 0.36
IPN 55	4	0.1	4.2 ± 0.47
		0.01	4.4 ± 0.3
	7	0.1	11.9 ± 1.8
		0.01	21.5 ± 1.5
IPN 64	4	0.1	5.5 ± 1.32
		0.01	4.9 ± 1.2
	7	0.1	10.1 ± 0.67
		0.01	17.4 ± 0.58
IPN 73	7	0.01	14.5 ± 1.13

[a] Mean ± standard deviation (n = 3 for each sample).

RESULTS AND DISCUSSIONS

The temperature- and pH-dependent aqueous swelling changes of PVA/PAAc IPN hydrogels are already reported in our previous articles.[14,15] All IPN hydrogels showed a temperature-dependent swelling behavior in response to temperature changes resulting from the association/dissociation of the hydrogen bonding in the IPN hydrogel as the temperature decreased and/or increased. Also, pH-dependent swelling behaviors were observed with changes in pH. The pK_a value of PAAc is known to be 4.7.[21] Therefore, at pH 7, PAAc is in the form of carboxylate ion, which causes a repulsion between them, resulting in the increase of free volume in a polymer matrix, and, thus, an increase in swelling ratio is obvious.

The relationship between the changes in molecular structure in the IPN hydrogel and electrolytes in the buffer solution is shown in Table I. The ionization of carboxylic acid in the IPN hydrogel was an important factor in the pH-dependent swelling. However, an interaction between ionic groups in the IPN chains and electrolytes in the buffer solution became more intense when the

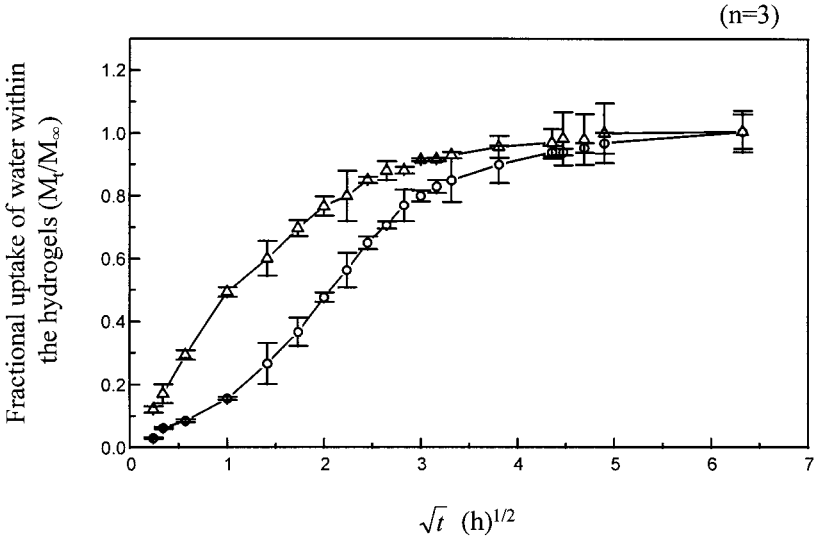

Figure 1 Swelling behavior of IPN46 in water in response to the pH change (ionic strength = 0.01): (○) at pH 7; (△) at pH 4.

pH of the buffer solution changed from 4 to 7; therefore, when a pH was below the pK_a value of the PAAc (at pH 4), in which the carboxylic acid group in the IPN hydrogel was in a hydrogenated state, the effect of the ionic strength on the swelling was less than a pH was above the pK_a value of PAAc (at pH 7), in which the carboxylic group in the IPN hydrogel was in an ionized state. For the buffer solution at pH 7, in which the ionic strength was adjusted to 0.01, the swelling ratio of each IPN sample became high, ranging from 15.2 to 33.4, while the increase of the electrolyte concentration to be 0.1 in the medium produced a drastic collapse of all the IPN hydrogels. However, the swelling of all IPN hydrogels at pH 4 was not dependent on the ionic strength, as can be seen in Table I.

Figure 1 showed the plot of a fractional uptake of water in IPN46 gel versus square root of time at pH 7 and 4. The swelling in a pH 7 buffer solution displayed an anomalous diffusion behavior compared to that in a pH 4 solution, obviously indicating a Fickian-type diffusion curve. Anomalous diffusion behavior of IPN 46 at pH 7 and ionic strength of 0.01 was due to extensive interactions between the ionized acrylic acid groups in the IPNs and electrolytes in the buffer solution, resulting in the change of network formation. At pH 4, however, hydrogenated carboxylic acid groups in the IPN hydrogels absorbed water in a normal Fickian diffusion manner.[22]

Solute permeation experiments were performed using 5 representative solutes with different molecular weights and hydrodynamic sizes. Characteristics of selected solutes are listed in Table II. In the experimental buffer solution in which pH was adjusted to 4 or 7, theophylline,[23] vitamin B_{12},[23] and BSA[23] were in a neutral state, and riboflavin[23] and cefazolin[24] showed ionized structure.

Tables III and IV show the results of solute permeation experiment measured at 25 and 45°C, respectively. In our previous experiment,[15] IPN46 exhibited a positive swelling change with temperature because of the dissociation of hydrogen bonding resulting from the increment in the temperature. The permeation of solutes through IPN hydrogels as a function of temperature was in accordance with the swelling behaviors of the IPNs; therefore, all the solutes showed higher diffusion coefficients at high temperature. This is explained by the fact that the increase of diffusion coefficients at high temperature doesn't alter the interaction between solutes and IPN structure but only causes an the expansion of IPN networks. Higher swelling in IPN at high temperature increases the free volume through which the solutes permeate more freely.

The partition coefficients (K_d) of solutes between hydrogel membranes and surrounding solutions are also shown in Tables III and IV. The value of K_d is expected to be driven by interactions between the solutes and the polymer molecular structure. Due to the hydrophilicity of PVA/PAAc IPN hydrogels, it is predicted that a more hydrophilic solutes are well distributed in the entire

Table II Characteristics of Permeating Solutes

Solute	Molecular Weight	Hydrodynamic Radius (Å)	Ionization
Theophylline	180	3.5	pK_a: 8.77
Riboflavin	376	5.8	pK_b: 1.7
Cefazoline–sodium	476	6.5	pK_a: 2.15
Vitamin B_{12}	1355	8.5	neutral
BSA	65,000	36.1	neutral

hydrogel membranes. As can be seen in Tables III and IV, K_d values of ionic solutes such as riboflavin and cefazolin are greater than those of nonionic solutes, obviously due to induced ionic interaction between ionic solutes and the carboxylic acid group. BSA showed the largest K_d value among nonionic solutes. It is believed to be caused by the protein adsorption to the polymer surfaces. However, further study is needed to verify the interaction, which affects and determines the partition coefficients of solutes within the swollen hydrogels.

The size of solute was an important factor in determining the diffusion and, thus, permeation. The hydrodynamic sizes of 3 solutes is in the range from 0.35 to 3.61 Å, as seen in Table II. For nonionic solutes that didn't have any ionic interaction with ionizable hydrogel membranes, theophylline, having the smallest molecular size of 0.35 Å, showed the most rapid diffusion through hydrogel. The diffusion of vitamin B_{12} (hydrodynamic radius = 8.5 Å) is faster than that of BSA (hydrodynamic radius = 36.1 Å). The free volume caused by hydration may allow the pathway of solutes through which the larger molecules were excluded in the permeation. However, the diffusion of ionic solutes such as riboflavin and cefazolin were independent of their hydrodynamic size. Riboflavin and cefazolin, which have smaller size than vitamin B_{12} and BSA, gave a drastic reduction of diffusion coefficients. Permeabilities of solutes through IPN46 exhibited a similar tendency with diffusion coefficients. These results are clearly indicative of the fact that in the ionizable hydrogel membranes, the solute diffusion is much affected by the solute size as well as by ionic interaction between solutes and membranes.

Figure 2 shows the selective permeation of the mixture of vitamin B_{12} and BSA using IPN46 hydrogel measured in buffer solution of pH 7 and ionic strength of 0.01. The concentration of solute in the donor cell was adjusted to be 0.22 mg/ml for each solute. As can be seen in Figure 2, the permeated amount of vitamin B_{12} was much larger than that of BSA and maintained during over 200 hours. However, after some time interval, the permeation of BSA was almost stopped.

Table V shows the results of the permeation studies of vitamin B_{12} through IPN hydrogels having different molecular compositions. It represents the increase of the permeability of vitamin B_{12} through IPN hydrogels with an increase of AAc contents in IPN measured at pH 7 and I = 0.01. As seen in Table I, the swelling ratio of

Table III The Permeation Studies of Various Solutes Through IPN46 Hydrogel at pH 7 Buffer Solution (Ionic Strength = 0.01) at 25°C

Solutes	P[a] ($\times 10^6$ cm^2/s)	K_d[b]	D[c] ($\times 10^6$ cm^2/s)
Theophylline	7.63 ± 0.127	1.55 ± 0.035	4.94 ± 0.195
Riboflavin	0.99 ± 0.007	2.97 ± 0.028	0.33 ± 0.001
Cefazolin	0.42 ± 0.007	5.67 ± 0.064	0.07 ± 0.003
Vitamin B_{12}	1.80 ± 0.099	1.20 ± 0.064	1.51 ± 0.163
BSA	1.03 ± 0.134	2.75 ± 0.043	0.41 ± 0.052

n = 3 for each sample.
[a] P denotes permeability coefficient.
[b] K_d denotes partition coefficient.
[c] D denotes diffusion coefficient.

Table IV The Permeation Studies of Various Solutes Through IPN46 Hydrogel at pH 7 Buffer Solution (Ionic Strength = 0.01) at 45°C

Solutes	P^a ($\times 10^6$ cm^2/s)	$K_d{}^b$	D^c ($\times 10^6$ cm^2/s)
Theophylline	9.90 ± 0.141	0.81 ± 0.014	12.22 ± 0.039
Riboflavin	1.52 ± 0.028	2.35 ± 0.014	0.65 ± 0.016
Cefazolin	1.38 ± 0.092	9.14 ± 0.042	0.15 ± 0.011
Vitamin B_{12}	4.06 ± 0.170	1.89 ± 0.099	2.15 ± 0.023
BSA	3.86 ± 0.134	4.74 ± 0.031	0.81 ± 0.034

$n = 3$ for each sample.
[a] P denotes permeability coefficient.
[b] K_d denotes partition coefficient.
[c] D denotes diffusion coefficient.

IPN hydrogel increased with the molar ratio of AAc in the IPN structure due to the introduction of larger amount of hydrophilic ionizable group. This effect was responsible for an almost linear decrease of diffusion coefficient of a nonionic solute, vitamin B_{12}, from $1.82 \pm 0.003 \times 10^{-6}$(cm^2/s) for IPN 73 to $0.82 \pm 0.026 \times 10^{-6}$(cm^2/s) for IPN 37. Furthermore, the values of K_d are almost the same in overall IPN hydrogels. It provided evidence that the interaction between vitamin B_{12} and ionized hydrogel membranes could be negligible, and the diffusion behavior of solutes were the controlling factor to the permeation of solutes through the present IPN membranes. In this case, since we can control the swelling ratio of IPN, we will be able to predict the permeabilities of solutes.

However, as can be seen in Table VI, for an ionized solute, cefazolin with a much lower pK_a value (2.15) than experimental condition of pH 7, the diffusion actually decreased as the swelling of hydrogel increased. This is obviously due to the dominant repulsion and partitioning between an ionized solute and a fixed charge group in the hydrogel at pH 7. This clearly shows that the permeation of solutes are dependent on various factors including ionic strength and pH of the buffer, properties of permeated solutes, and structural changes of the polymer. The permeation of nonionic solutes can be interpreted by a swelling-dependent mechanism, but for the permeation of ionic solutes, several factors mentioned above should be considered for the permeation.

Figure 3 exhibited the effect of ionic strength

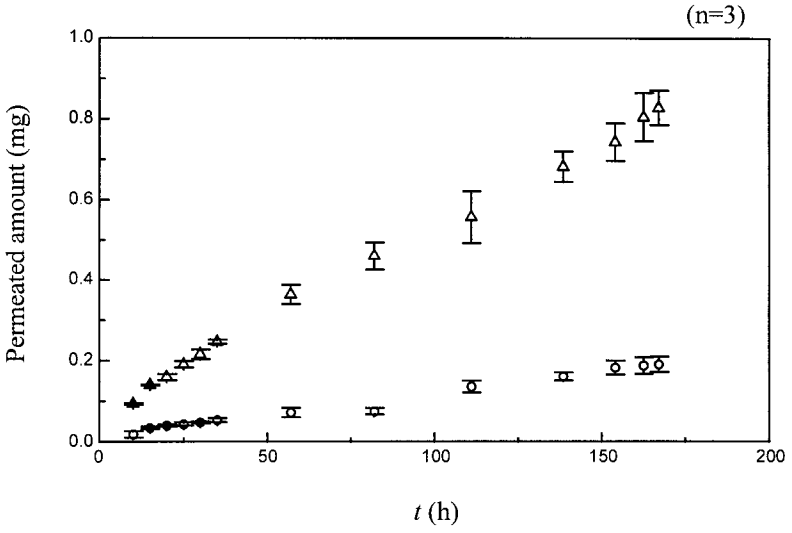

Figure 2 Total amount of permeated (△) vitamin B_{12} and (○) BSA through IPN46 hydrogel selectively at a pH 7 buffer solution (ionic strength = 0.01).

Table V The Permeation Studies of Vitamin B_{12} Through IPN Hydrogels with Different PAAc Contents within the Structure at pH 7 Buffer Solution (Ionic Strength = 0.01) at 25°C

PAAc Content (%) within IPN Gels	P[a] ($\times 10^6$ cm^2/s)	K_d[b]	D[c] ($\times 10^6$ cm^2/s)
30	0.86 ± 0.007	1.05 ± 0.042	0.82 ± 0.026
40	1.78 ± 0.049	1.33 ± 0.021	1.34 ± 0.016
60	1.80 ± 0.099	1.20 ± 0.064	1.51 ± 0.163
70	2.36 ± 0.042	1.30 ± 0.021	1.82 ± 0.003

n = 3 for each sample.
[a] P denotes permeability coefficient.
[b] K_d denotes partition coefficient.
[c] D denotes diffusion coefficient.

on the permeation of nonionic solute, vitamin B_{12} at pH 4 and 7 with ionic strengths of 0.1 and 0.01, respectively. At pH 7, the permeation rate was higher at I = 0.01 than that at I = 0.1. This is understandable because when the medium solution has more electrolytes, the ionic repulsion between the fixed charge of acrylic acid group in the IPN hydrogel and an external solution became more intense. These interactions served as a barrier to permeating solute, which resulted in the decrease in the permeation rate. However, the permeation rates of vitamin B_{12} were similar at pH 4, regardless of the ionic strength, because at pH 4, which didn't allow IPN46 to exist as a dehydrogenated state, the change in the amount of electrolytes in the buffer solution could not give any effect on the polymer swelling.

CONCLUSIONS

The swelling behavior of PVA/PAAc IPN hydrogel in the buffer solution containing electrolytes and the solute permeation through these hydrogel membranes were investigated. The IPN hydrogel showed different swelling patterns as a function of ionic strength in the buffer solution. This is due to the repulsive interaction between AAc ionic group within the hydrogels and electrolytes in the medium. At pH 7, in which the fixed charge group had a strong repulsive effect on the electrolytes in the buffer solution, the water uptake in the hydrogel followed a nonFickian swelling behavior, while the swelling behavior followed a Fickian-type at pH 4. The permeation of solutes increased in response to temperature change from 25 to 45°C. The permeation of solutes through PVA/PAAc IPN hydrogels was significantly affected by the ionic property of solutes. In the case of the permeation of nonionic solutes, the permeability changed according to the variation in swelling in IPN hydrogel. Smaller solutes and higher swelling of IPN hydrogel produced a higher diffusion coefficient. The permeated amount of solute could selectively be controlled by changing the molecular composition in IPN. However, the

Table VI The Permeation Studies of Cefazolin Through IPN Hydrogels with Different PAAc Contents within the Structure at pH 7 Buffer Solution (Ionic Strength = 0.01) at 25°C

PAAc Content (%) within IPN Gels	P[a] ($\times 10^6$ cm^2/s)	K_d[b]	D[c] ($\times 10^6$ cm^2/s)
30	0.75 ± 0.028	4.85 ± 0.233	0.16 ± 0.013
40	0.67 ± 0.028	3.68 ± 0.148	0.18 ± 0
60	0.42 ± 0.007	5.67 ± 0.099	0.07 ± 0.003
70	0.18 ± 0.007	3.91 ± 0.021	0.04 ± 0.002

n = 3 for each sample.
[a] P denotes permeability coefficient.
[b] K_d denotes partition coefficient.
[c] D denotes diffusion coefficient.

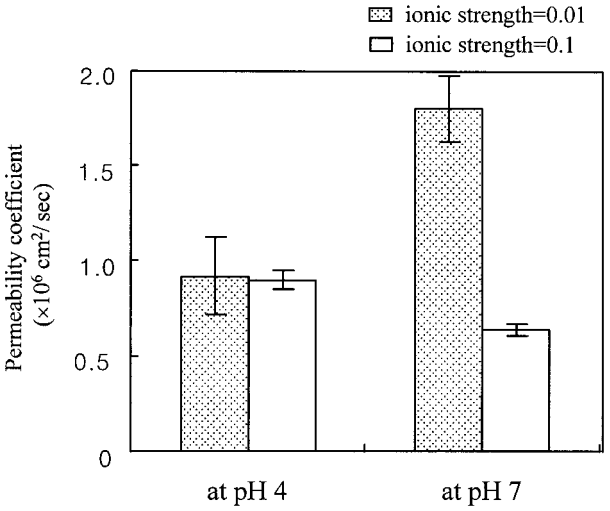

Figure 3 Effect of ionic strength of the medium on the permeability of vitamin B_{12} as a nonionic solute through IPN46 hydrogel at different pHs: (▨) ionic strength = 0.01; (□) ionic strength = 0.1.

permeation of ionic solutes showed an opposite trend. The permeability of ionic solutes at pH 7 through IPN decreased while the swelling of the IPN hydrogel increased. This is due to the attraction or repulsion between ionized AAc in the hydrogel and ionized electrolytes in the solution at different pH.

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