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

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Abstract

Poly(acrylic acid) 와 poly(vinyl alcohol) 을 이용하여 온도와 pH 에 감응성을 가지는 상호 침투 가교 고분자 히드로겔을 합성하고 약물의 투과도를 측정하였다. 이 히드로겔은 고분자 구조 내에 이온기를 포함하고 있으므로 팽윤 시에 외부의 pH 와 이온 세기의 영향을 크게 받았으며 이온기와 용액과의 상호작용이 증가할수록 팽윤도가 감소하였다. 히드로겔을 이용한 약물의 투과실험에서 비이온성 약물의 경우 약물 입자의 크기에 따른 분리가 가능하였으며 이온성 약물의 경우 고분자 히드로겔의 구조와 외부 pH, 약물의 구조에 따른 상호작용에 의하여 투과가 이루어짐을 알 수 있었다.

Introduction

Stimuli responsive hydrogels are three dimensional polymer networks that exhibit sensitive swelling transitions dependent on pH[1], temperature[2], ionic strength of surrounding environment or some chemicals. They have been investigated for use in bioseparation and medical application. 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.

Thermosensitive hydrogel based on copolymer of poly(*N*-isopropylacrylamide) has been used for the temperature controlled separation of bioactive agents. [3] It was possible to separate uranine, dextran 4.4K and dextran 15 K by using a crosslinked poly(NIPAAm-co-BMA) hydrogel membrane with high purity. High recovery of the separated compounds were obtained.

M. T. A. Ende and N. A. Peppas[4] reported on the transport of ionizable drugs and proteins and investigated the swelling behaviors of ionizable hydrophilic polymers in water and buffer solution by using crosslinked poly(acrylic acid) and poly(acrylic acid-co-2-hydroxyethylmethacrylate) hydrogels.

In the present study, solute permeabilities are investigated with changing conditions including temperature, pH and/or ionic strength. To evaluate the solute permeabilities, we used several solutes with different hydrodynamic radius and pKa values such as theophylline, Vitamin B_{12}, BSA, cefazoline and riboflavin.

Synthesis of IPN

The IPN composed of poly(vinyl alcohol) and poly(acrylic acid) was synthesized by previous method.[5,6] The molar ratios of PVA to PAAc in the IPN were adjusted to 3:7, 4:6, 5:5, 6:4, and 7:3, respectively. To produce 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.

Permeation studies

The permeation studies were carried out using a two chamber diffusion cell. The IPN hydrogels were fully swollen in various solutions maintaining different temperature, pH and/or ionic strength (0.1, 0.01) and placed in the middle of two chamber cell. Each half cell has a 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 buffer solution was filled in the receptor cell. The concentration of the solutes in the receptor cell was determined periodically by UV spectroscopy and the permeability coefficients were calculated with following equation.

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

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

The solutes permeated were theophylline with UV absorbance at λ_{max} =274 nm (MW=274, pKa= 8.75), BSA (λ_{max} =280 nm, MW=60,000), and Vitamin B_{12}(λ_{max} =361 nm , MW=1355) as nonionic solutes and cefazoline (λ_{max} =270 nm, MW=476) and riboflavin(λ_{max} =375 nm, MW=376) as ionic solutes.

Results and Discussion

The temperature and pH dependent aqueous swelling changes are reported in previous paper.[7,8] In the temperature dependent swelling measurement, all IPNs showed swelling changes in response to temperature changes in IPNs must be related to the hydrogen bonding between two polymers and ionic repulsion of carboxylate ion produced due to breakage of hydrogen bonding. pH dependent swelling behaviors were observed with changes in pH. The pKa value of PAAc is 4.28. Therefore at pH 2 and 4, PAAc is in the form of carboxylate ion, which causes a repulsion between them resulting in the increase of free volume in the polymer matrix and thus increase in swelling ratios.

Sample	pH	Ionic strength	Swelling ratio
IPN37	7	0.01	33.4
IPN46	4	0.01	5.9
		0.1	7.1
	7	0.01	27.6
		0.1	16.3
IPN55	4	0.01	4.7
		0.1	4.7
	7	0.01	21.3
		0.1	12.2
IPN64	4	0.01	5.1
		0.1	4.0
	7	0.01	17.0
		0.1	9.8
IPN73	7	0.01	15.2

Table1. The swelling ratios of IPN hydrogels at various conditions

For the characterization of the response of the hydrogels to external ionic strength, samples are allowed to swell in buffer solution of varying pH(4, 7), and ionic strength (0.1, 0.01). Below the pKa(at pH 4) of the PAAc in the IPN structure, the effect of the ionic strength on the swelling was less than that above the pKa(at pH 7). In the case of swelling at pH 7(ionic strength = 0.01), the swelling ratios of IPNs were higher than 15. Then the swelling ratio of each IPN at higher ionic strength (0.1) were drastically reduced. However, at pH 4, the swelling ratios of all IPNs decreased and were independent of the ionic strength. These are due to the interactions between the ionized acrylic acid groups in the IPNs and ionic solvents in the solution, resulting in the change of network formation.

Solute permeation was studied for five different solutes of different molecular weights and hydrodynamic sizes. In the temperature dependent permeation experiment, all samples showed high permeability coefficients at higher temperature. The permeation of solutes through IPN hydrogels was in accordance with the swelling behaviors of the IPNs. The solutes diffused through the pathway caused by the free volume within the swollen gels.

Solute	Permeability coefficient * ($P \times 10^6$)(cm^2/sec)
Riboflavin	0.99
Vitamin B12	1.03
Cefazoline	0.42
BSA	1.8
Theophylline	7.61

* at 25 ℃, pH=7, ionic strength=0.01

Table 2. The permeability coefficients of solutes

The solute size was an important factors in the permeation. In the nonionic solutes diffusion was hindered only by the hydrogel structures and the solute with smaller hydrodynamic radius permeated effectively, For the separation experiment of two solutes, the mixed solution of two solutes with same concentration was added in the donor cell and the permeated amount was measured. Vitamin B12 diffused more rapidly than BSA in the mixture solution from this size exclusion theory.

The surrounding conditions of IPN hydrogel was changed in order to investigate the interaction among solutes, permeation medium and IPN structure. For nonionic solutes the parameters which determined the rate of permeation were the solution and IPN structures.

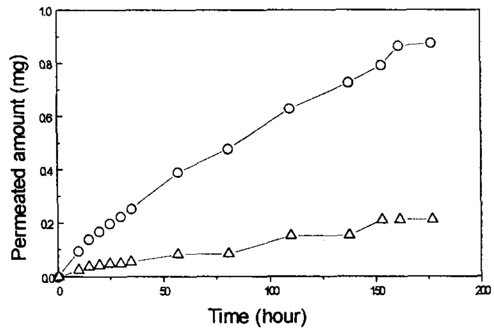

Fig.1 the molecular separation between vitamin B_{12} (○) and BSA (△)

The permeation rate was higher at pH 7 with lower ionic strength because of the ionic repulsion between the fixed charge of acrylic acid group in the IPN hydrogel and external solution. However, the permeation rates of Vitamin B_{12} were similar at pH 4 regardless of the ionic strength which results in the decrease of ionic interaction. For ionic solutes the permeation rates were reduced compared with nonionic solutes. It could be considered that the interaction between ionic groups in the IPNs and the ionic solutes was dominant in the permeation and the prediction of these behaviors was more difficult.

Conclusions

The permeability coefficients of solutes through PVA/PAAc IPN hydrogel membrane were increased in response to temperature changes from 25 ℃ to 45 ℃. For the nonionic solutes the smaller molecules permeated rapidly and the permeation in mixed medium of two different solutes. The increase in the concentration of ions in the medium was found to decrease the permeability of solutes because of the contraction due to mutual repulsion between fixed ionic groups in the gel and ions in the solution.

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