# Pulsatile Interpenetrating Polymer Networks Hydrogels Composed of Poly(vinyl alcohol) and Poly(acrylic acid) ; Synthesis, Characterization, and its Application to Drug Delivery Systems.

Heung Soo Shin, So Yeon Kim, and Young Moo Lee

Department of Industrial Chemistry, College of Engineering, Hanyang University

**Abstract**

Pulsatile swelling behaviors and their application to drug delivery system were studied by using interpenetrating polymer networks(IPN) hydrogels constructed with poly(vinyl alcohol) and poly(acrylic acid). The PVA/PAAc IPNs hydrogels were synthesized by UV irradiation followed by repetitive freezing and thawing method. These hydrogels showed pH and temperature sensitive swelling behaviors. From the release experiment, the release amount of model drug incorporated into these hydrogels showed pulsatile patterns. Permeability coefficients obtained by various solutes differed in response to changes of permeation conditions.

**Introduction**

Recently, there have been many investigations on pulsatile and self regulated drug delivery systems, which release proper amount of drug at suitable timing and period in response to various stimuli; e.g. electric field[1], pH, temperature, ionic strength[2], or other chemicals. These systems offer major advantages such as reduction in side effect and effective bioavailability over conventional delivery forms. Among these, pH and/or temperature responsive systems have been potential candidates because these factors could be the most available environment in human body.

Temperature sensitive drug delivery systems have been extensively studied. Katono *et al.*[3] obtained on-off release profiles as a function of temperature from IPNs composed of poly(acrylamide-co-butylmethacrylate) and poly(acrylic acid). PNIPAAm hydrogels demonstrated negative temperature sensitivity with lower critical solution temperature (LCST) in aqueous solution. By utilizing PNIPAAm hydrogels, Bae *et al.*[4]achieved temperature controlled on-off drug delivery system of indomethacin.

In the case of pH dependent drug delivery system, many researchers focused on swelling properties of hydrogels. The acidic or basic components in the hydrogels which led to reversible swelling/deswelling because they changed from neutral state to ionized state and vice versa in response to the change of pH. Peppas *et al.* [5]reported pH sensitive drug release system composed of copolymer of hydroxy ethyl methacrylate (HEMA) and methacrylic acid

(MAAc) or maleic anhydride. Poly(NIPAAm-co-VTPDMS-co-AAc) hydrogel synthesized by Hoffman *et al.* [6] permitted release of drugs at pH 7.4, and showed release-off at pH 1.4, and was proved to be suitable carrier for indomethacin through the gastrointestinal(GI) tract.

Our previous studies[7,8] reported on the pH and temperature sensitive hydrogels and membranes.

In present study, we would like to report on the preparation and swelling properties of novel temperature/pH dependent PVA/PAAc IPNs hydrogels by UV-freezing-thawing method and their applications to drug delivery systems. The pH/temperature sensitive release of drug from IPN hydrogels is reported on the basis of the idea that swelling controlled mechanism attributes to the drug release kinetics, and solute permeabilities are investigated with changing conditions including ionic strength, pH, and different molecular weigtht.

## Experimental

### Materials

Acrylic acid monomer(AAc) obtained from Junsei Chemical Co. was purified by inhibitor remove column (Aldrich Chem. Co.) Poly(vinyl alcohol) (PVA ; DP=2500, degree of deacetylation = 99 %) was purchased from Shinetsu Co. Methylenbisacrylamide (MBAAm) as a crosslinking agent and 2,2- dimethoxy-2-phenylacetophenone (DMPAP) as a photoinitiator were purchased from Aldrich Chem.Co. Indomethacin (Anhydrous Mol. Wt.357.8), used as a model drug, was obtained from Sigma Chem. Co.

### Synthesis of IPN hydrogels

Poly(acrylic acid)(PAAc) was synthesized inside of PVA solution by using UV irradiation, and then PVA networks were formed by repetitive freezing- thawing process. PVA was dissolved at 80 ℃, and AAc monomer was mixed with a photoinitiator and a crosslinking agent. This solution mixtures were poured into the petri dishes and irradiated using a 450 W UV lamp (Ace glass Co.) under $N_2$ atmosphere and were placed at -50 ℃ for 6 hours and at room temperature for 2 hours for 8 times.

The synthesized gels punched into 23 mm diameter disks were washed by deionized water to remove the unreacted AAc monomers and were dried *in vacuuo*.

### Characterization and swelling measurement

Fourier transform-infra red (FTIR) spectroscopy (Nicolet Model Magna IR550) was used to confirm the structure of the IPNs. For the swelling kinetics measurement, the IPN disks were soaked in various conditions, and were weighed periodically until the hydrated weight reached a constant value. Equilibrium water content (EWC) was measured from the equations in pH changes between 4 and 7 ,and temperature changes between 25 ℃ and 45 ℃,respectively. The melting endotherm of dry disks and the state of waters in the IPN hydrogels were investigated by differential scanning calorimeter(DSC; Du Pont Instruments 910 DSC) from the IPN disks which were fully equilibrated. The amount of free

water and bound water was calculated from the melting enthalpies.

**Drug loading and releasing**

Indomehtacin, as a model drug, was loaded into IPN disks by solvent sorption method.. Indomethacin release experiment was conducted in various conditions changing pH and / or temperature of the release medium. The IPN disks loaded with indomethacin were placed in the desired release medium under stirring to remove the boundary layer. 3 ml aliquots sampled periodically from the medium were analyzed by using UV spectrophotometer (UV-2101PC ; uv-vis scanning specteophotometer SHIMATZU) at 320 nm, and then returned back into the medium solution.

**Solute permeability measurement**

The permeabilities of several kinds of solutes which had different molecular weights and/or pKa values were measured using two chamber diffusion cell. The IPN hydrogels were fully swollen in various solutions maintaining different pH and/or ionic strength and placed in the middle of diffusion cell. Donor and receiver chamber having equal volume were stirred. The concentration of solute was measured with UV spectrophotometer.

**Results and Discussion**

The sequential method by UV irradiation followed by freezing-thawing we used at present study would be a breakthrough and a novel method to prepare stimuli-sensitive polymer hydrogel. This technique used to prepare IPNs was successful in providing the desired crosslinked hydrogel. The IPN hydrogel were subsequently used in swelling studies for evaluation of their response to changes in external pH and temperature.

IPNs composed of PVA and PAAc are expected to be the temperature-sensitive hydrogel, since these hydrogels are considered to have hydrogen bonding due to PAAc as the proton donor and PVA as proton acceptor. FTIR spectroscopy is one of the powerful techniques used to investigate multi-component system, because it provides information on the polymer-polymer interaction as well as on each components.

In the temperature dependent swelling measurement, all IPNs showed swelling changes in response to temperature changes from 25 ℃ to 45 ℃. The swelling 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. Step-wise swelling/deswelling patterns were obtained by alternating the temperature between 24 ℃ and 45 ℃.

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 carboxylic acid which forms hydrogen bonds with hydroxyl groups in PVA and water, and swells as temperature increase. However, at pH 7 and 9, PAAc forms 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.

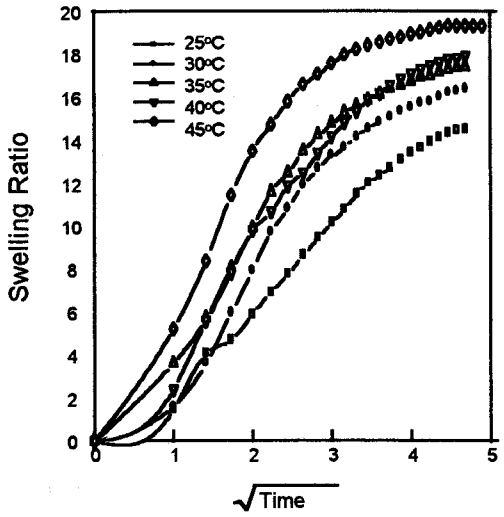


Fig.1 swelling kinetics of IPN46 with Changing temperature

The EWC was calculated both at pH 4 and 7 buffer solutions and the result that EWC determined at pH 7 was larger than 90 % was equal to above swelling results. Since IPN46 possesses more hydrophilic and ionizable group within its structure, the swelling degree may be the highest among the other IPNs, resulting in the highest total water content.

Since the structure of water in the swollen polymer matrix may play significant role in the release of model drug in response to the swelling mechanism, the melting endotherm of swollen gels were investigated in order to calculate the free water and bound water content in the IPN hydrogels.

From the d.s.c. thermogram of fully swollen IPN hydrogels we confirmed that the endothermic peak of swollen gel appeared between 0 and 10 ℃ and the fraction of free water is approximately estimated by the ratio of endothermic peak integrated between these range to the melting endothermic peak of heat of fusion for pure water.

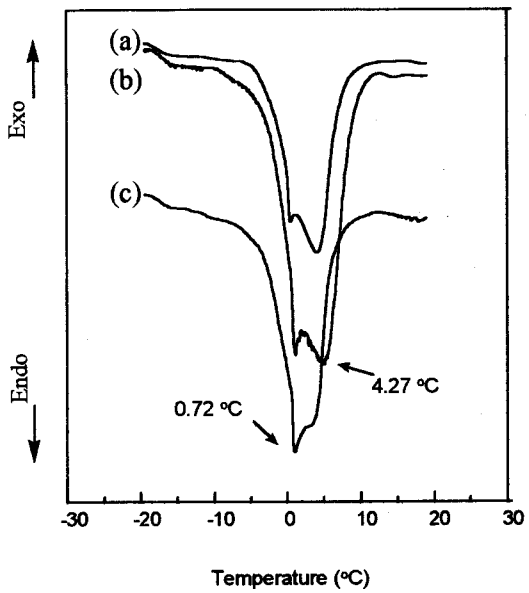


Fig.2 DSC thermograms of IPN hydrogels which were fully swollen in pH 7 buffer solution : (a) IPN46; (b) IPN55; (c)IPN64

In the temperature sensitive indomethacin release experiments from drug loaded hydrogels by putting them into 25 and 45 ℃ pH 7 buffer solutions, respectively, all samples exhibited high release rate at higher temperature. These results are in correspondence with the results about the temperature dependent swelling behaviors of IPN hydrogels..

pH-sensitive release behaviors of indomethacin were observed at 25 ℃ with change in pH. In this system, the major factor for controlling the release amount is the swelling of the hydrogel affected by the surrounding pH. Indomethacin is expected to diffuse through the free volume increase in the polymer gel. Since the pKa value

of PAAc is 4.28, at pH 4, PAAc is in the form of carboxylic acid which produces hydrogen bonding with hydroxyl group of PVA, resulting in the decrease of drug release. However, at pH 7, carboxylate ions formed in PAAc induced the drastic increase of swelling which exhibits high release rate. At pH 4, the release amount from IPN46 and IPN55 was almost identical and IPN64 gives lower value due to significant low swelling compared to the others. It is considered that the release rate from IPN hydrogels is independent on composition of samples at pH 4.

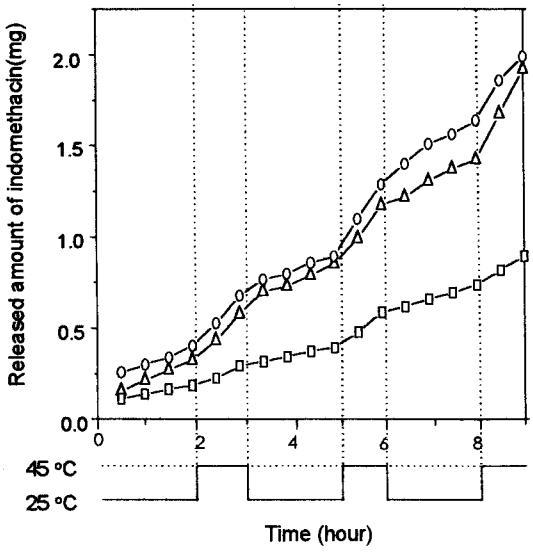


Fig.3 Release change of indomethacin from IPN hydrogels in response to stepwise temperature change between 25 and 45 ℃: (○) IPN46 ; (△) IPN55 ; (□) IPN64

Solute permeation behavior and the effects of solute molecular weight, pH, degree of ionization of solutes, and ionic strength on the permeation were investigated. In the case of ionic solutes, the permeabilities of them were significantly influenced by the ionization degree of hydrogel membrane and ionic strength within the permeation media.

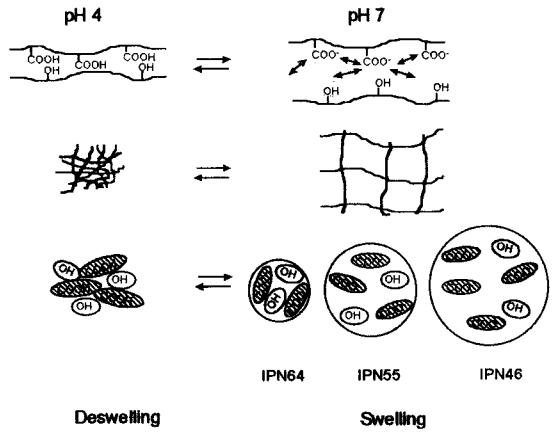


Fig.4 Schematic diagrams of swelling /deswelling behaviors of IPN hydrogels dependent on pH change

## REFERENCES

1. I. C. Kwon, Y. H. Bae and S. W. Kim, *J. Controlled Release*, 30, 155 (1994)
2. R. A. Siegal and B. A. Firestone, *Macromolecules*, **21**, 3254, (1988)
3. H. Katono, A. Maruyama, K. Sanui, N. Ogata, T. Okano and Y. Sakurai, *J. Controlled Release*, **16**, 215 (1991)
4. T. Okano, Y. H. Bae and S. W. Kim, *Pharm. Res.*, **8**, 624 (1991)
5. L. Brannon Peppas and N. A. Peppas, *J. Controlled Release*, **8**, 267 (1989)
6. S. Hoffman and L. C. Dong, *J. Controlled Release*, **15**, 141(1991)
7. J. I. Byun , Y. M. Lee and C. S. Cho, *J. Appl. Polym. Sci.*, **61**, 697 (1996)
8. Y. M. Lee and J. K. Shim, *J. Appl. Polym. Sci.*, **61**, 1245 (1996)