Synthesis and Characterization of pH- and/or Temperature-Sensitive Hydrogels

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SYNOPSIS

A series of pH-sensitive hydrogels that exhibit volume phase transition phenomena have been synthesized in aqueous solution and characterized with respect to their dynamic swelling behaviors. Positively charged hydrogels were prepared by copolymerizing varying ratios of *N*-isopropylacrylamide and *NN'*-dimethylaminopropylmethacrylamide. The hydrogels based on a temperature-sensitive hydrogel demonstrate a large change of equilibrium swelling in response to small variations of pH and/or temperature. These hydrogels exhibit different lower critical solution temperature (LCST) ranges depending on the environmental pH values. Below their LCST, they exhibit small and broad pH sensitivities normally observed in most hydrophilic polyelectrolyte gels, but above their LCST, they exhibit sharp pH-dependent phase transition behaviors. The pH-dependent phase transition is strongly affected by temperature, while the temperature-dependent transition is, in turn, largely influenced by the pH. As the temperature is raised, the transitional degree of gel swelling change becomes sharper and larger, and the phase transition pH value shifts to a lower pH. It was also found that swelling is faster than deswelling for these cationic hydrogels, which suggests the existence of a water diffusion barrier during the deswelling. The swelling kinetics of initially dry and glassy gels were strongly dependent on both the pH value and temperature.

INTRODUCTION

Hydrogels, which swell in aqueous environment, have been widely utilized in drug delivery systems.[1,2] Charged polymeric networks have been recognized as useful matrices for delivering drugs because their volume changes in response to an external pH variation.[3-5] Negatively or positively charged hydrogels usually exhibit different degrees of equilibrium swelling at different pH values depending on the ionic composition and polymeric molecular structure. The main driving force responsible for such a volume change is the ionic repulsion between charged groups incorporated in the gel matrix by an external pH modulation.

There has been a growing interest in a group of hydrogels exhibiting a sharp volume phase transition when an external stimulus such as pH is varied slightly. Such hydrogels have been applied to fabricate a glucose-sensitive insulin release device,[6,7] an osmotic insulin pump,[8] and site-specific drug delivery in the gastrointestinal tract.[9] A hydrophobic hydrogel containing cationic groups, which exhibited an abrupt and discontinuous phase transition at a particular pH was reported.[10] It was found that the gel hydrophobicity plays an important role in exhibiting such a phenomenon. However, the gel that shows a pH-dependent phase transition behavior has been often confused with the gel that demonstrates a simple pH-dependent polyelectrolyte behavior. Many polyelectrolyte gels so far studied, which normally possess pendant ionic groups in their hydrophilic polymeric networks, exhibit a broad transition of equilibrium swelling degree as a function of pH.

In order to utilize a pH-sensitive phase transition hydrogel as an applicable biomedical device, the gel should have a sharp volume change near the phys-

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iological pH (7.4) and at body temperature (37°C), especially when the pH-sensitive gel matrix is implanted in the body for the stimulus-responsive drug delivery. The hydrogel synthesized by Siegel and Firestone,[10] however, was not reported to exhibit an abrupt pH-dependent phase transition at 37°C. All experiments were carried out at 25°C. It can be imagined that most pH-sensitive hydrogels could have a temperature sensitivity to some extent. A delicate balance of the molecular structure in the gel may determine its phase transition behavior. For example, gel characteristics such as the balance between hydrophilicity and hydrophobicity, chain stiffness, and specific functional groups might affect the phase transition pH, degree of volume change, and temperature dependence.

A primary purpose of the present study is to develop a pH-sensitive phase transition hydrogel, in which biocatalysts will be immobilized. Since most hydrophobic monomers utilizable in the previous pH-sensitive hydrogels are not soluble in the aqueous phase,[10] a great loss of the biocatalyst activity can be expected during the immobilization procedure. Therefore, it is needed to synthesize a hydrogel that exhibits a large volume phase transition at the desirable pH value and temperature, based on water-soluble monomers. Minimizing the loss of biocatalytic activity during the immobilization procedure has been a major concern in the immobilization technology. In this respect a series of cationic, pH-sensitive copolymeric hydrogels, based on a temperature-sensitive hydrogel exhibiting a lower critical solution temperature (LCST) behavior, were synthesized in the aqueous solution and characterized in terms of pH-dependent swelling properties. These gels were prepared by copolymerization of *N*-isopropylacrylamide and *N,N'*-dimethylaminopropylmethacrylamide in various molar ratios in the presence of a small amount of crosslinker. The degree of equilibrium swelling was determined at various pH values and at different temperatures. The swelling kinetics of initially wet and dry gels were also investigated at different pH values and temperatures.

MATERIALS AND METHODS

Materials

N-isopropylacrylamide (NIPAAm) from Eastman Kodak was recrystallized with hexane, *N,N'*-dimethylaminopropylmethacrylamide (DMAPMAAm) obtained from Virginia Chemical Co. was vacuum distilled (6 mmHg/127°C). *N,N'*-methylene-bis-acrylamide (MBAAm), ammonium persulfate (APS), and *N,N,N',N'*-tetramethylethylenediamine (TEMED) were purchased from Aldrich Co. Other chemical reagents were all analytic grade.

Preparation of Hydrogels

A series of hydrogel membranes were prepared by copolymerizing NIPAAm with DMAPMAAm in various molar ratios at a fixed crosslinker (MBAAm) concentration. The total weight of monomers plus crosslinker was fixed—4 g in all cases. The amounts of each chemical needed in different formulations are listed in Table I. Monomers and crosslinker were dissolved in 20 mL of distilled, deionized (DDI) water. Nitrogen was bubbled to remove any residual oxygen. Redox initiators composed of 25 mg of APS and 0.25 mL of TEMED were added and then immediately injected into the space between two silanized glass plates. Polymerization was performed at room temperature for 2 h. The gel membrane was taken out and washed extensively with deionized water. After the gel sheet was completely swollen in DDI water, gel discs (10 mm diameter, 1 mm thickness at room temperature) were made by puncturing with a No. 6 cork borer.

Table I Gel Composition Used in Preparing pH/Temperature-Sensitive Hydrogels

Gel Code[a]	NIPAAm[b] (g)	DMAPAAm[c] (g)	MBAAm[d] (g)
ND-0	3.840	0	0.16
ND-1	3.782	0.058	0.16
ND-3	3.688	0.172	0.16
ND-5	3.557	0.283	0.16
ND-10	3.287	0.553	0.16
ND-15	3.031	0.809	0.16
ND-20	2.786	1.054	0.16

[a] X in gel code (ND-X) represents the mole ratio of DMAPMAAm to total amount of monomers (NIPAAm + DMAPMAAm) except for MBAAm. Total weight of monomers including MBAAm is kept constant, 4 g.
[b] NIPAAm: *N*-isopropylacrylamide.
[c] DMAPMAAm: *N,N'*-dimethylaminopropylmethacrylamide.
[d] MBAAm: *N,N'*-methylene-bis-acrylamide.

Determination of Water Content

Gel discs in triplicate were incubated in buffer solutions ranging from pH 4 to 12 at a particular temperature. 0.05 *M* citrate/0.05 *M* NaCl buffer was used for pH 4, 5, and 6, and 0.05 *M* phosphate/0.05 *M* NaCl buffer for the rest of the pH values. The incubation time was approximately 24 h. It was confirmed that 24-h equilibration was long enough to reach the equilibrium swelling of the gel. Wet weight was determined by weighing wet gel discs after blotting surface water with a filter paper. Dry weight was determined after drying gel discs in vacuum overnight. Based on these two values, the water content was calculated. Swelling ratios were defined as the wet weight divided by the dry weight.

Swelling and Deswelling Kinetics

The degree of swelling was determined by weighing gel discs as described above at regular time intervals. Two kinds of swelling kinetic experiments were carried out. First, swelling–deswelling kinetics of initially wet gels were determined by transferring gel discs from one combination of pH and temperature to another. Second, swelling kinetics of initially dry gel discs were measured as functions of both pH and temperature.

RESULTS AND DISCUSSION

Equilibrium Swelling Degree

Equilibrium swelling of the ionic gel is determined by three major forces: mixing of the polymer network with a swelling medium, the elastic-retractive force exerted on the network, and the ionic osmotic pressure generated from mobile counterions to charged ions in the network (Donnan equilibrium).[11,12] A delicate combination of these three contributions dictates the equilibrium swelling state of the ionic gel at a particular environmental condition. Even though the swelling behavior of many hydrophilic pH-sensitive hydrogels including hydrolyzed or positively charged polyacrylamide,[12,13] polymethacrylic acid,[14] and polyacrylic acid[15] are well predicted

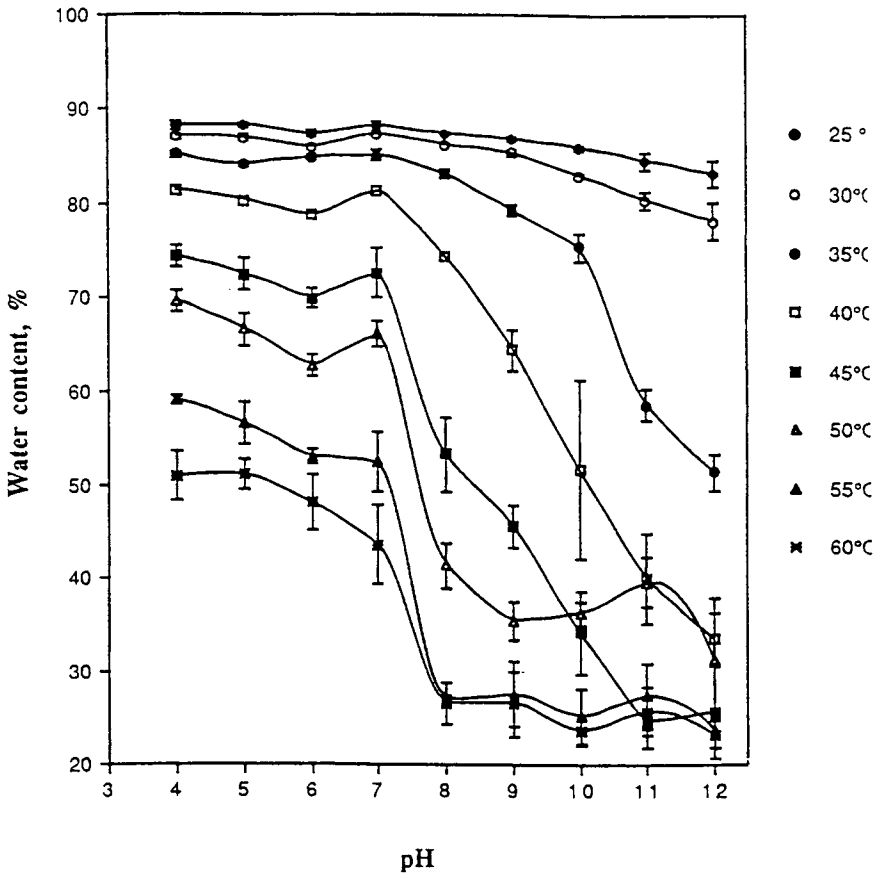

Figure 1 Water contents of the ND-5 gel at different pH values as a function of temperature.

theoretically, the phase transition behavior of hydrophobic pH-sensitive hydrogels has been difficult to predict.[10] Tanaka claimed that polymer chain stiffness in the network plays an important role in determining the continuity and discontinuity of the phase transition.[12]

Gel hydrophobicity has been usually defined as an accessibility of water to the polymer chains, that is, the degree of hydration. When the hydrophobic polymer chain network is placed in water, it is often imagined that more structurally ordered water molecules surround the hydrophobic region of the polymer chain.[16] In most of the phase transition gels, external stimuli like pH, temperature, salt, electric field, and organic solvent elicit an abrupt transition of water from the icelike structure in the vicinity of the hydrophobic polymer chains to an unstructured one in the bulk medium, resulting in the sudden gel collapse. The destruction of water structure is the main entropic driving force for the phase transition.[17] An appropriate balance of hydrophilicity and hydrophobicity in the molecular structure of the polymer chain is believed to be a key component in demonstrating the phase transition. As a result, different degrees of structurally organized water molecules near the polymer network may determine the overall characteristics of the phase transition behavior in the gel.

A typical nonionic temperature-sensitive hydrogel, crosslinked poly(*N*-isopropylacrylamide, NIPAAm), has a lower critical solution temperature (LCST) at 32–33°C.[18,19] Below that temperature, the gel is in the swollen, hydrated, and hydrophilic state, and above the LCST the gel becomes collapsed, dehydrated, and hydrophobic. Furthermore, its phase transition behavior can be controlled by incorporating more hydrophilic or hydrophobic monomers in the gel composition.[20–22] For instance, a copolymeric hydrogel composed of NIPAAm and acrylamide (AAm) exhibits a broader phase transition and a shift of the LCST to a higher temperature. Similarly, when a small amount of ionic monomer containing carboxylic or amine groups is incorporated into a polyNIPAAm gel, it can be ex-

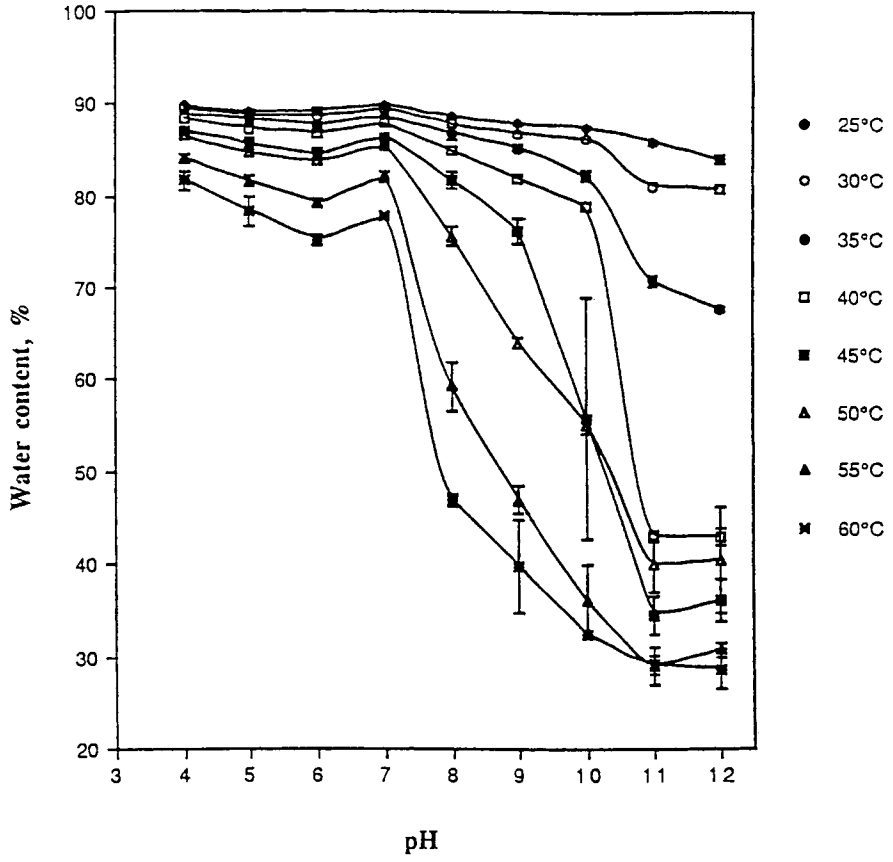

Figure 2 Water contents of the ND-10 gel at different pH values as a function of temperature.

pected that in addition to the generation of the pH sensitivity, the gel would still exhibit a higher LCST and a broader phase transition.

The swelling equilibria of a series of poly(NIPAAm-co-DMAPMAAm) hydrogels at different pH values and temperatures are shown in Figures 1–4. These copolymer hydrogels have varying molar ratios of NIPAAm and DMAPMAAm from 95/5 to 80/20. It can be seen that water contents of the gels are strongly dependent on both pH and temperature. Since positively charged, tertiary amine groups are incorporated into the polymer network, the gel swells at low pH region due to the ionic repulsion of the protonated amine groups, and collapses at high pH values because of unprotonated amine groups. However, the degrees of the water content change induced by medium pH are significantly affected by temperature. As the temperature increases, the degree of volume phase transition becomes sharper and its transition pH shifts to a lower pH in all the hydrogels. It can also be found that at low temperatures, the gel exhibits the typical behavior of the hydrophilic polyelectrolyte gel, and the gel demonstrates a progressively sharper phase transition phenomenon with increasing temperature. This suggests that the gel hydrophobicity increases with the temperature. As shown in Figure 5 (the plot of water content versus temperature as a function of medium pH), the shift of the LCST and its broader transition can be clearly seen as the pH increases. In this sense the hydrophobicity of a particular gel can be dynamically manipulated by varying the temperature and the pH. It is of great advantage to control the gel hydrophobicity and concomitant phase transition behavior as desired without changing the gel composition. All the gel synthesized in this study has an LCST that is influenced by the gel composition as well as the medium pH. To our knowledge, there have been no systematic studies of dynamic swelling behaviors in a series of hydrogels that exhibit a pH sensitivity as well as temperature sensitivity.

There may be several factors governing the complicated swelling behavior of this particular hydrogel system. At a fixed gel composition, the variation of the bulk pH at a particular temperature changes the degree of ionization, which results in the change of the gel hydrophobicity. On the other hand, the variation of the temperature at a specific pH changes the gel hydrophobicity, which in turn changes the

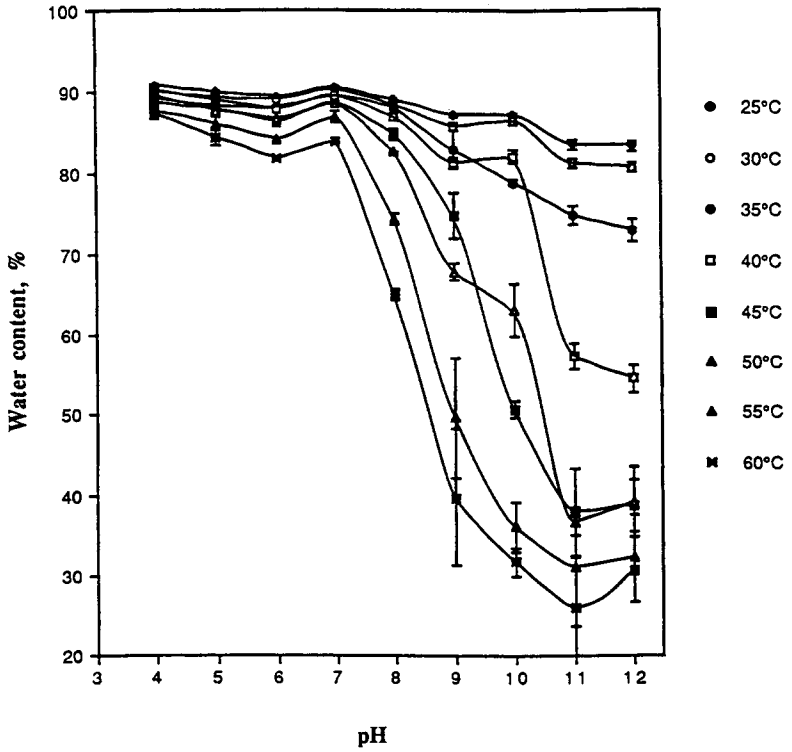

Figure 3 Water contents of the ND-15 gel at different pH values as a function of temperature.

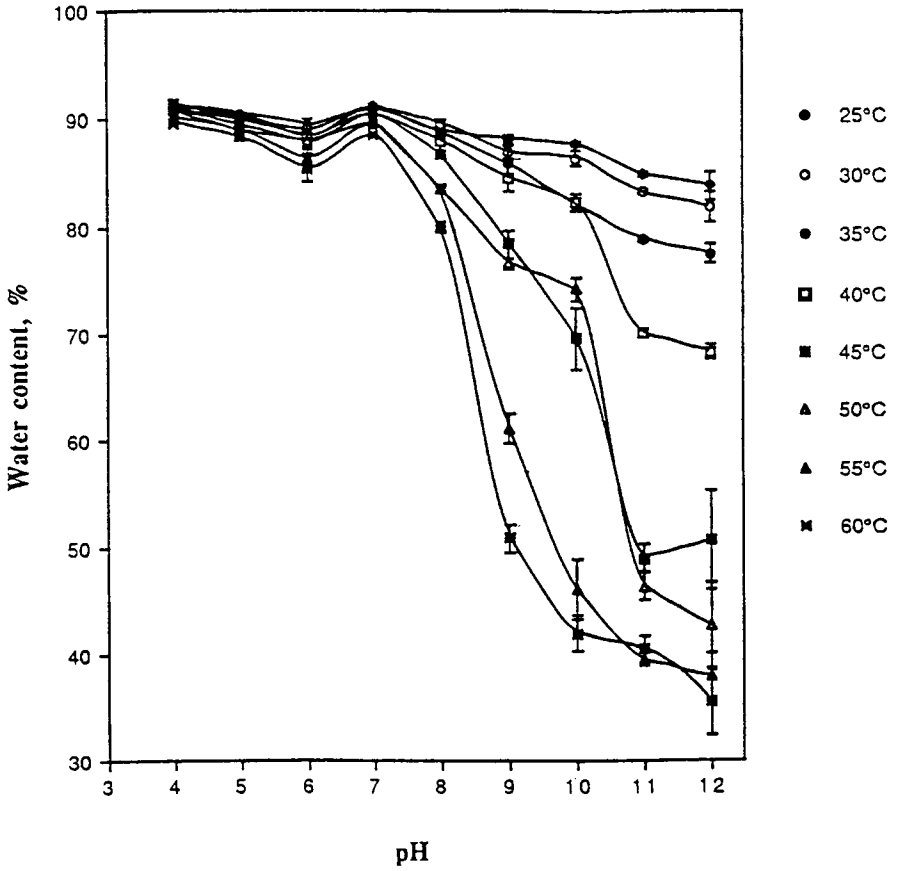

Figure 4 Water contents of the ND-20 gel at different pH values as a function of temperature.

degree of ionization. Therefore, the gel hydrophobicity and the degree of ionization are closely related as evidenced by the previous report.[10] Since the degree of ionization decreases with the increase of the gel hydrophobicity, which lowers the dielectric constant in the vicinity of ionizable charges, the transition pH shifts to a lower pH region with temperature because more hydrogen ions are needed to achieve a transition. The microenvironment around charged groups pendant on the organic polymeric backbone is different from the bulk solution. For instance, the dielectric constant in the vicinity of the ionic species is known to be quite low compared to that of water in the bulk solution.[23] Correspondingly, the ionic interaction between the same charges are largely affected. The concomitant enhanced steepness of the phase transition upon ionization might be due to the distinctive molecular feature of polymer network chains that are associated with structurally organized water molecules. Polymer chain "stiffness," a parameter defined by Tanaka,[17] may play an important role in exhibiting such a sharp phase transition. Presumably, a hydration depth surrounding the polymer chain may determine the sharpness.

As more cationic groups are incorporated into the gel, as seen from Figures 1–4, a phase transition pH at a particular temperature tends to shift to a higher pH, and the degree of its transition becomes sharper and larger with temperature, while a temperature-dependent variation of the water content gets smaller in the low pH region between 4 and 7. The increased amount of charged groups in the gel decreases the gel hydrophobicity while raising its LCST. Consequently, the ionization of the charged groups with a high concentration of ionic groups is easily accomplished with a higher pH than that with low concentration of ionic groups, and end up with a higher phase transition pH.

A slight increase of water content is observed, when the medium pH is changed from 6 to 7. Citrate buffer was used below pH 6 and phosphate buffer

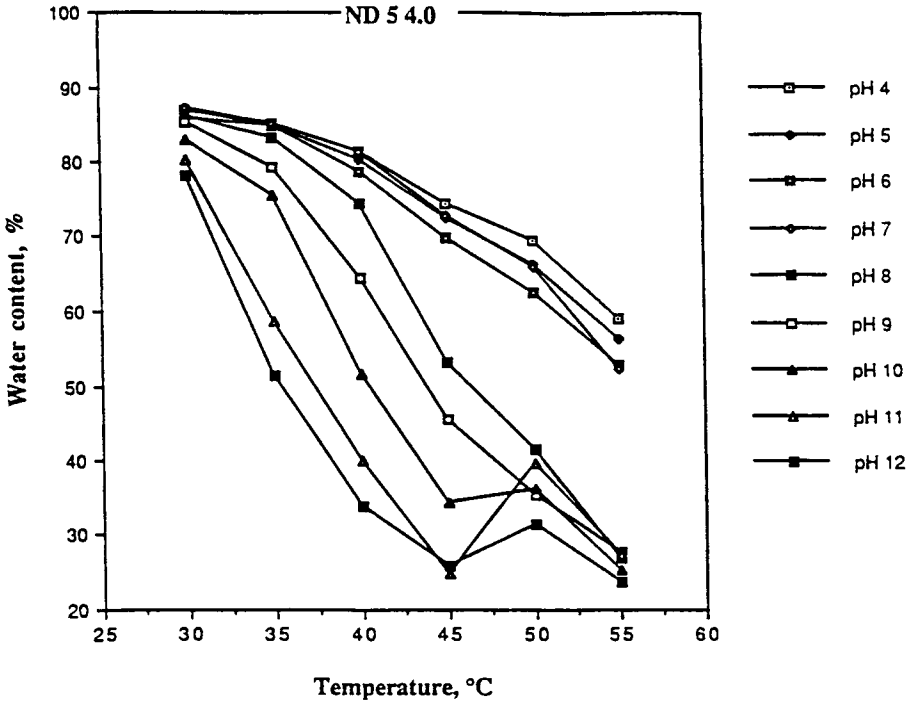

Figure 5 Water contents of the ND-5 gel at different temperatures as a function of pH.

was used above pH 7. This is due to the effect of the buffer ions used. The valency of the buffer ion influences the swelling degree of the charged gel by the different shielding efficiency of ionic groups in the gel, as observed earlier by Siegel and Firestone.[10]

Swelling–Deswelling Kinetics (Initially Wet Gel)

Rapid swelling and deswelling kinetics of pH/temperature hydrogel upon exposure to external stimuli of pH and temperature are desirable because the fast volume change of the gel exhibits a quick response to the input signal. For example, stimuli-sensitive hydrogels used as artificial muscles (robotic arm), drug delivery matrices, osmotic pump, and matrix for biocatalyst immobilization require such fast swelling and deswelling kinetics. For nonionic and hydrophobic gels, polymer visco-elastic (relaxation) behavior significantly contributes to the overall swelling kinetics.[24] In pH-sensitive hydrogels, however, the Donnan equilibrium is an additional factor to be considered, which results in the slower kinetics. The rate of counterion diffusion into the charged gel matrix depends on temperature, the medium pH, kinds of buffer used, ionic strength, and concentration of charged groups in the gel.

Table II Initial and Final Conditions of Swelling and Deswelling Kinetics of Initially Wet Gels,[a]

Process	Initial Condition	Final Condition	Variable
Swelling	45°C, pH 10	45°C, pH6	pH
Swelling	45°C, pH 10	25°C, pH 10	Temperature
Swelling	45°C, pH 10	25°C, pH 6	pH, temperature
Deswelling	25°C, pH 6	25°C, pH 10	pH
Deswelling	25°C, pH 6	45°C, pH 6	Temperature
Deswelling	25°C, pH 6	45°C, pH 10	pH, temperature

[a] Gels were transferred from inital and final conditions.

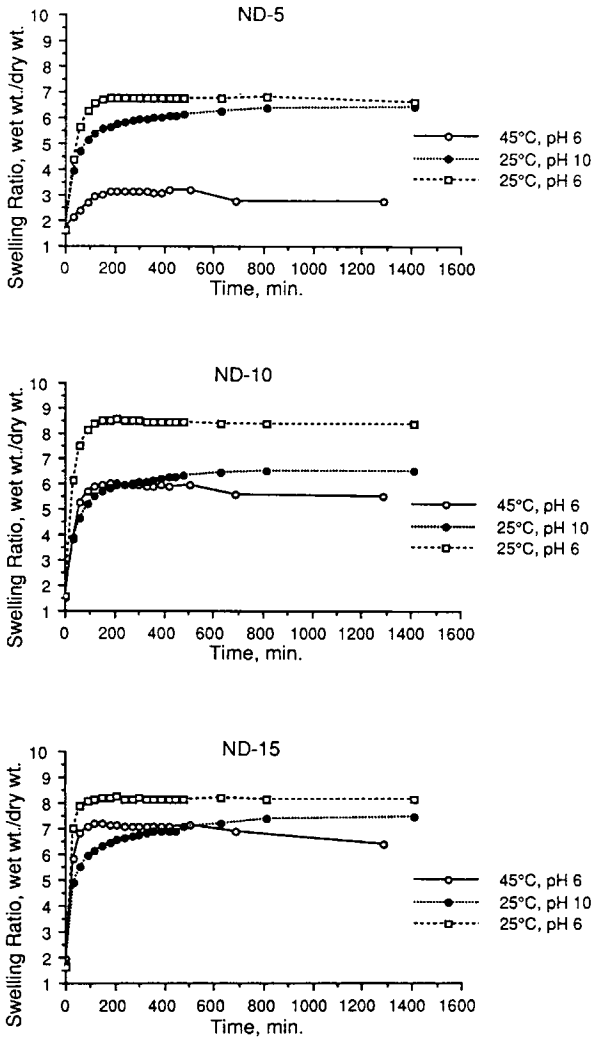

Figure 6 Swelling kinetics of initially collapsed hydrogels. Swelling was induced by transferring the gel discs in different medium conditions of pH, temperature, and both.

Swelling and deswelling of hydrogels were induced by changing pH and/or temperature. Table II lists the initial and final conditions for the swelling and deswelling processes of the gel. Figure 6 shows the swelling kinetics of three collapsed gels that were initially equilibrated at 45°C and pH 10 for 24 h. It can be seen that the simultaneous variation of both pH and temperature (open square) exhibits the fastest swelling in all cases, where the equilibrium swelling can be reached within 200 min. On the other hand, the relative rates of pH- and temperature-dependent swelling change with the concentration of ionic groups in the gel. As more cationic groups are incorporated in the gel matrix, pH-induced swelling becomes faster than the temperature-induced swelling. This may be because the higher ionic osmotic pressure generated from the more charged groups speeds up the counterion diffusion from the bulk into the gel matrix. The shift of the gel's LCST to higher temperature with the incorporated ionic groups is an additional reason to lower the temperature-induced swelling rate.

In deswelling experiments, as shown in Figure 7, all the gel samples were initially equilibrated at 25°C and pH 6 for 24 h, in which the gels were swollen. All the deswelling kinetics are slower than the swelling kinetics shown in Figure 6. In particular, when both temperature and pH are varied (open

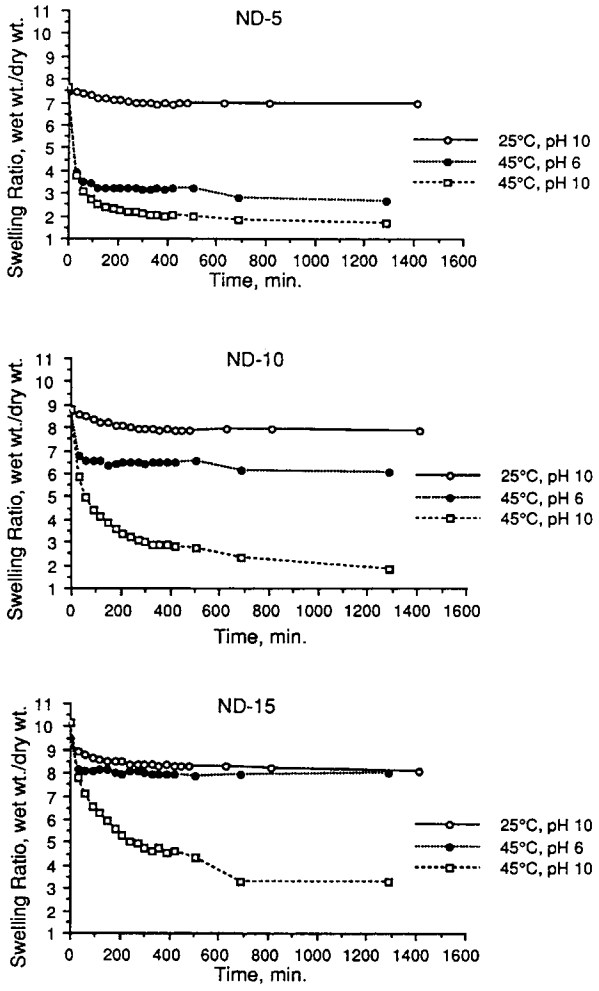

Figure 7 Deswelling kinetics of initially swollen hydrogels. Deswelling was induced by transferring the gel discs in different medium conditions of pH, temperature, and both.

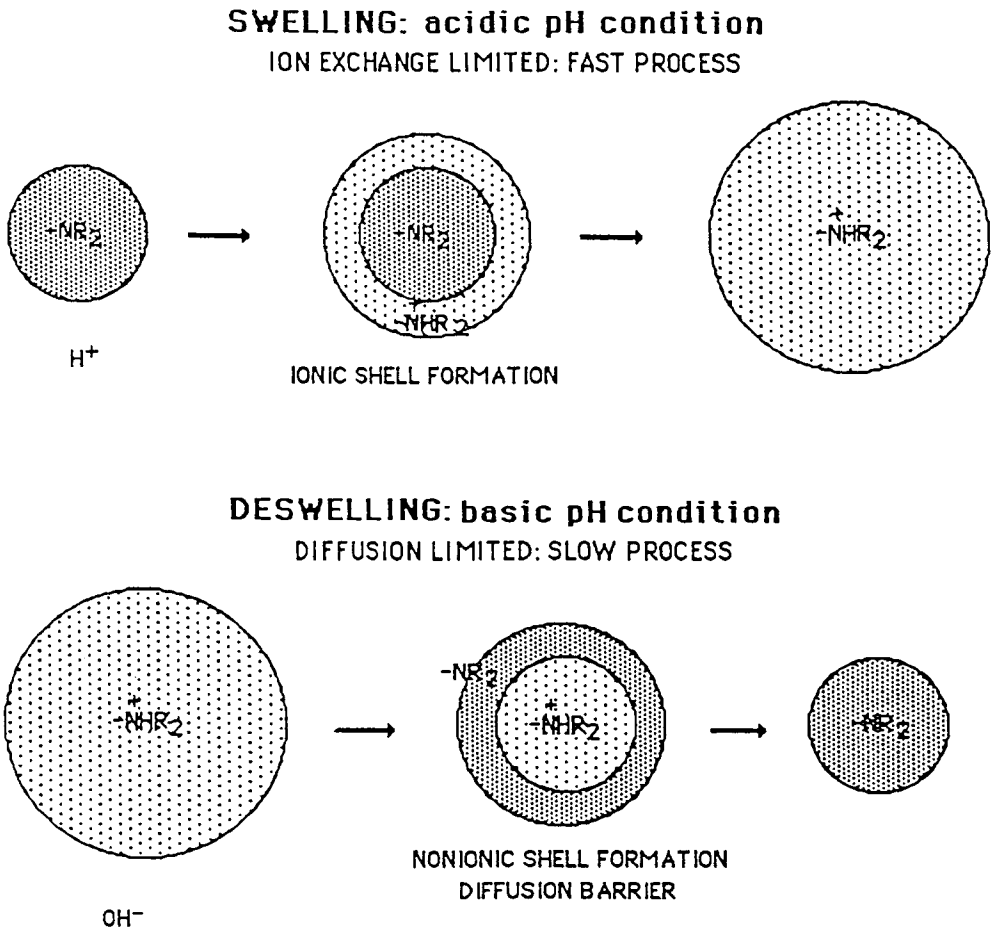

Figure 8 A schematic diagram of the swelling and deswelling of pH/temperature-sensitive hydrogels.

square), the deswelling rate decreases as more ionic groups are incorporated in the gel. Compared to the swelling kinetics in Figure 6, it can be clearly seen that the swelling is much faster than the deswelling. This is interesting because deswelling is usually faster than swelling. This is due to different mechanisms for the swelling and the deswelling, as schematically illustrated in Figure 8. During the deswelling process, an uncharged shell layer will be formed on the surface and move to the core region of the gel. The dehydrated and nonionic gel layer retards the further release of water as a diffusion barrier. This may be the most probable reason for slower kinetics. Thus, deswelling kinetics are diffusion limited. On the other hand, in the swelling process, a relatively more hydrated, charged shell will first form around the surface. Through it the counterions are easily imbibed into the collapsed core region. Therefore, the overall swelling kinetics may be governed by the ion exchange rate. In anionic hydrogel matrices, it can be expected that deswelling is faster than swelling because of the diffusion barrier during the swelling.

Swelling Kinetics (Initially Dry Gel)

The swelling kinetics of a series of initially dry pH/temperature-sensitive hydrogels were measured at different pH values and at 37°C. The dry state of all the gel discs is glassy. As shown in Figures 9–11, there are remarkable differences in swelling kinetics depending on the pH. At pH 6 (Fig. 9), as more cationic groups are incorporated in the gel, the equilibrium swelling can be reached more quickly. This

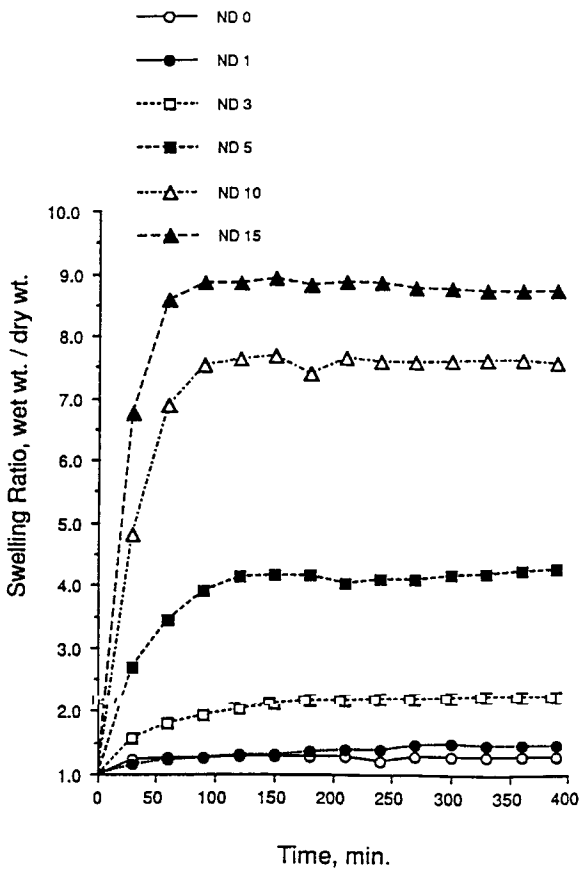

Figure 9 Swelling kinetics of a series of initially dry pH/temperature-sensitive hydrogels at 37°C and pH 6.

is related to the LCST as well as the amount of ionic charged groups in the individual gel matrix. As the charge density rises, the driving force for swelling also increases. Swelling kinetics can be generally described in two terms, the diffusion rate of imbibing solvent into the gel and the relaxation rate of the polymer network. Many hydrophobic hydrogels exhibit a relaxation-controlled swelling, while hydrophilic gels demonstrate a diffusion-controlled swelling. At a given pH, it can be observed that the gels containing higher amounts of charged groups tend to exhibit the typical Fickian diffusion-controlled swelling, while the gels containing a lower amount of ionic groups, and therefore having an LCST above 37°C, tend to exhibit the relaxation-controlled swelling. Figure 12 shows the swelling kinetics of the ND-5 gel at pH 8 as a function of temperature. This result suggests that the temperature is also an important parameter to determine the swelling rate of the pH/temperature-sensitive hydrogel. Therefore, one may manipulate the gel composition in order to obtain the desired gel swelling kinetic rate at a specific pH and temperature. In particular, zero-order release of a drug from the hydrogel matrix system can be achieved by matching the gel composition with pH and temperature. A slight increase in the swelling ratio observed at the end stage seen in Figure 11 might be due to the hydrolysis of amide bond in *N*-isopropylacrylamide monomer in the high pH region, leading to the formation of ionic acid groups.

In order to theoretically predict the pH/temperature-dependent swelling behaviors for these hydrogels, one should consider the Flory polymer–solvent interaction parameter (χ), which varies as functions of pH and temperature, and should take into account the ionization constant (pK), which depends on the gel hydrophobicity. More importantly, a theoretical modeling about the collapse of a series of hydrogels composed of *N*-isopropylacry-

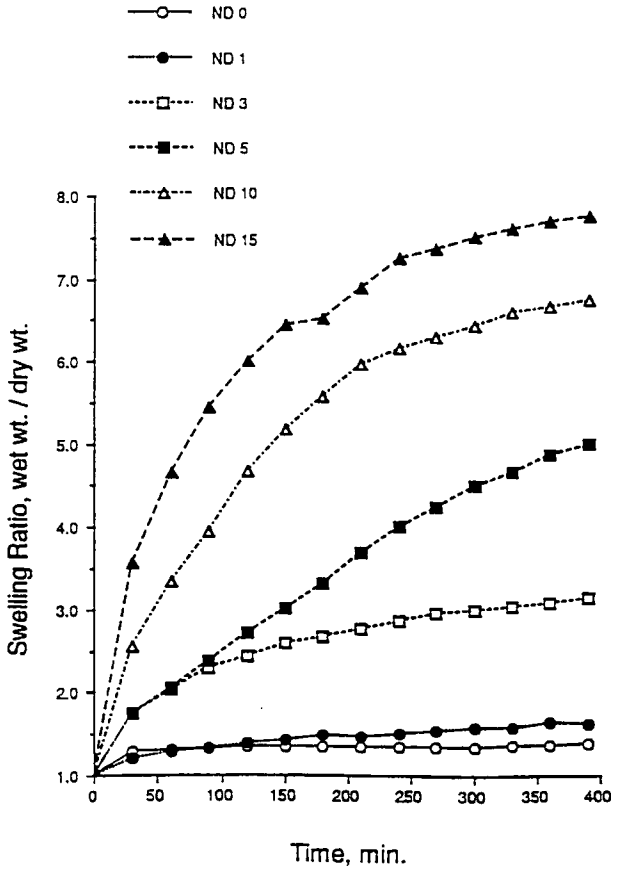

Figure 10 Swelling kinetics of a series of initially dry pH/temperature-sensitive hydrogels at 37°C and pH 8.

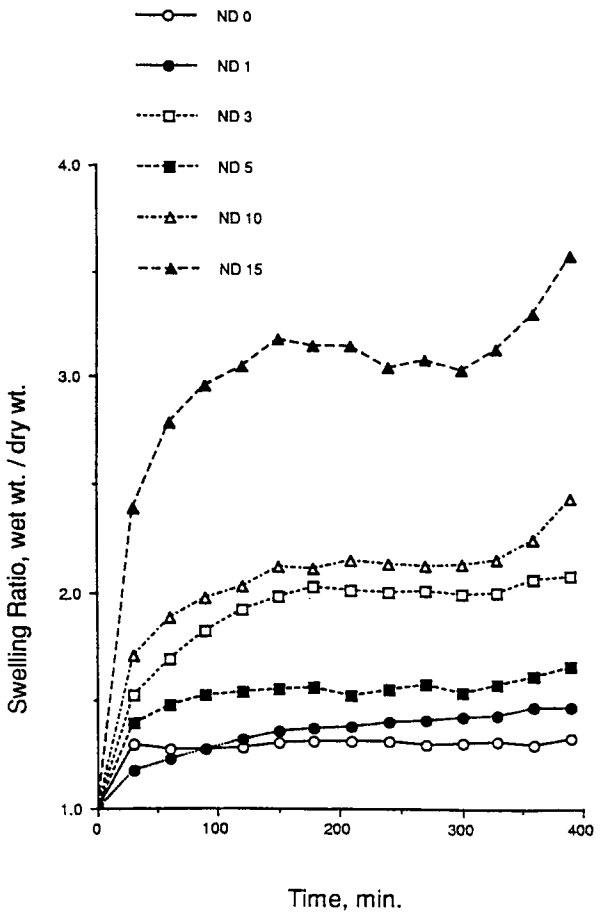

Figure 11 Swelling kinetics of a series of initially dry pH/temperature-sensitive hydrogels at 37°C and pH 10.

lamide and another hydrophilic monomer should be developed. That simulation should predict the LCST and its sharpness as a function of the gel composition.

In our pH-sensitive hydrogels based on polyNIPAAm, we could dissolve monomers with crosslinker in deionized water solution instead of using any organic solvents to prepare the pH-sensitive gel. Thus, we could avoid an extensive loss of the biocatalytic activities during the immobilization. As described earlier, the gel hydrophobicity is a key parameter in obtaining an abrupt pH-dependent phase transition of the gel that, in turn, cannot be obtained unless water-insoluble, hydrophobic monomers are used. In this sense polyNIPAAm is a good starting material to synthesize a pH-sensitive hydrogel because, unlike other hydrophobic monomers, it is soluble in water as well as in most organic solvents. The hydrophilicity/hydrophobicity of the gel formed with a small amount of crosslinker in aqueous solution changes drastically as the temperature is raised. The unique behavior of polyNIPAAm can be successfully utilized to solve a major obstacle in the way of achieving our goal, the immobilization of biocatalysts in a pH-dependent volume phase transition gel. If one desires to synthesize a truly pH-sensitive gel that exhibits a phase transition at the desired pH and temperature, one may use more hydrophobic, water-insoluble LCST monomers instead of NIPAAm with the same cationic monomer used in this study.

In our previous studies immobilized enzymes and cells in temperature-sensitive hydrogels exhibited significant increase in biocatalytic activities when thermal cycling operation was applied around the LCST of the gel matrices, compared to the activities for isothermal operations.[21,22] This is due to the facilitated mass transfer rates of substrate in and product out of the gel matrix during the repeated expansion and shrinkage of the gel matrices. Certain enzymes that catalyze to convert neutral substrate to acidic or basic product may be immobilized in the pH-sensitive hydrogels. The gel matrices containing the enzymes would collapse or expand as the local pH of the gel matrices is changed as a result of the enzymatic reaction. This will lead to "shut off" or "turn on" of the immobilized enzyme activity in response to the medium pH due to the volume phase transition of the gel induced by the biochemical reaction. Variation in the gel pore size in response to pH will be responsible for such "on/off" activities of the immobilized enzyme. Urease, glucose oxidase, and penicillin G acylase would exhibit such behaviors. In our laboratory the penicillin G acylase has been immobilized in the poly(NIPAAm-co-DMAPAAm, ND-5) hydrogel. The kinetic behaviors of the immobilized penicillin G acylase are being investigated.

In summary, a new series of pH-sensitive hydrogels that exhibit temperature sensitivity were synthesized in aqueous solution and characterized in terms of swelling degree and swelling kinetics. Depending on the pH of the swelling medium, temperature, and the gel composition, equilibrium swelling degrees and swelling kinetics were remarkably different. In addition, this class of hydrogels not only exhibit the behavior of a hydrophilic polyelectrolyte gel but also demonstrates dynamic phase transition behaviors. These kinds of pH-sensitive hydrogels will be very useful as matrices to immobilize biocatalysts such as enzymes and cells because

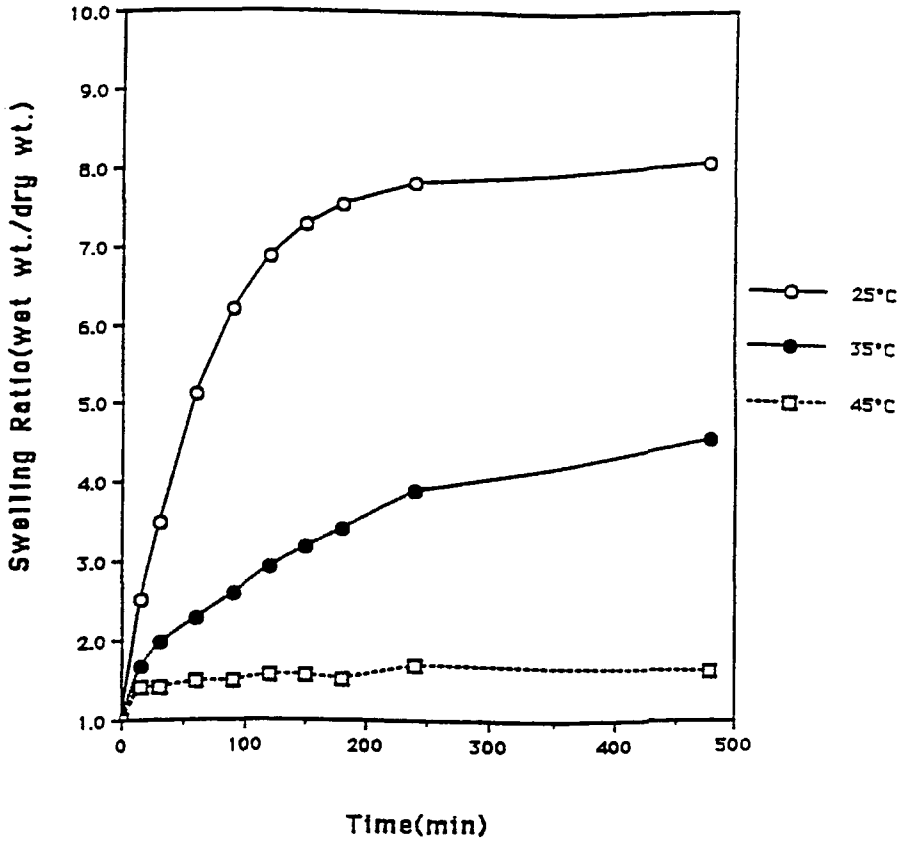

Figure 12 Swelling kinetics of initially dry ND-5 gel at pH 8 as a function of temperature.

no organic solvents are involved during the polymerization.

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