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RAPID DESWELLING OF POLY(*N*-ISOPROPYL ACRYLAMIDE-*CO*-ACRYLIC ACID) HYDROGELS IN RESPONSE TO TEMPERATURE CHANGES

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Abstract- Thermo-sensitive poly(*N*-isopropyl acrylamide) (PNIPA) hydrogel has been synthesized and characterized to assess rapid deswelling kinetics for medical device development. Eighteen different (18) formulations were investigated using monomers *N*-isopropyl acrylamide and acrylic acid (i.e. *N*-isopropyl acrylamide-*co*-acrylic acid) with *N,N'*-dimethylenebisacrylamide (BIS) as a cross-linking agent. The volume-temperature behavior of the PNIPA was characterized by mass determination and surface morphology observed by scanning electron microscopy (SEM). The deswelling rate of the hydrogels at different temperatures and time were measured. For example, the hydrogel synthesized with *N*-isopropyl acrylamide-*co*-acrylic acid lost 70% of it's mass within 10 minutes over a temperature range of 25 to 42°C.
Keywords- *N*-isopropylacrylamide, hydrogel, thermosensitive, deswelling

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Introduction

Hydrogels are three-dimensional polymeric network materials that have the ability to absorb and hold large amounts of water without undergoing dissolution [1]. Many polymeric hydrogels undergo abrupt physical changes in response to temperature, shrinking abruptly losing the water absorbed [2]. The special deswelling property of PNIPA hydrogel has been applied to many fields, such as controlled drug release, pharmaceuticals [3,4], biomedical science, [1,5] and biotechnology [6]. However, the response rate of conventional PNIPA hydrogel is very slow, and greatly limits its applications in some specific fields such as microactuators, lab-on-chip diagnostics and fluid dispensing, in which a response time of several minutes or less is desired. This is the motivation of our investigation.

Copolymeric hydrogels made from *N*-isopropyl acrylamide (NIPA) and monomers containing acidic/basic groups undergo thermal transition [7]. The temperature at which the phase transition occurs is termed lower critical solution temperature (LCST). At this temperature, hydrogels undergo transformation from swollen to collapsed state. As the temperature increases above the LCST, it shrinks abruptly and loses majority of the solution absorbed, displaying phase separation. The driving force for this phase transformation is suspected to be the hydrophobic interaction within hydrogels [8]. Hydrogen bonding between the hydrophilic domain of hydrogel and water lowers the free energy of mixing at temperatures below LCST. It results in the formation of highly organized water molecules around the polar groups within the hydrogels, resulting in a decrease in the entropy of the system. When the temperature is raised close to LCST, the association of hydrophobic part of the hydrogels drives the bound water away resulting in increase of entropy and phase separation [9]. At temperatures below LCST, the rate and the extent of swelling of hydrogels is governed by chemical composition, polymerization conditions and microstructure of hydrogels [9-11].

The hydrogel of interest to us is the polymeric systems made from NIPA and acrylic acid (AA) that undergo volume phase transition around human body core temperature [2,3]. Hydrogel made from NIPA are an ideal choice for biomedical applications because of

its biocompatibility and soft mechanical properties [10,11].
The main objective of this article is to optimize the chemical composition of copolymeric hydrogel so that it has the desired deswelling specifications. Understanding the relationship between cross link density, permeability and swelling kinetics of hydrogels can lead to rational design of smart polymers for biological applications. In order to comprehend swelling/shrinking behavior of the hydrogels, we studied the microstructure using scanning electron microscope to look at the static microstructure of these systems.

Experimental

Chemicals

All the chemicals were of the highest reagent grade and were used as received from Sigma-Aldrich/Alfa-Aesar. All the sample solutions were prepared by using deionized water obtained from Millipore purification system (Bedford, MA, USA).

Synthesis

Hydrogels was synthesized by free-radical solution copolymerization of NIPA and AA in presence of *N,N*'-dimethylenebisacrylamide (BIS) as the chemical cross-linking agents. The polymerization reaction was initiated by ammonium persulfate (APS) and accelerated by tetramethylenediamine (TEMED). The reaction was carried out at 22 °C for 24 h. After the reaction, the gel was thoroughly washed with deionized water to remove unreacted compounds and dried for 48-72 hours at room temperature. The eighteen different formulations of hydrogel synthesized are summarized in Table 1.

Table 1- Feed Composition for the Synthesis of Poly(NIPA-co-AA) Hydrogels

Sample code	$[NIPA]_o/[BIS]_o$	$[AA]_o/[BIS]_o$	Notes
1.2	27	43	No gel formation
3.1	9	13	gelation
3.2	7	11	gelation
3.3	14	21	No gel formation
3.4	14	21	No gel formation
4.1	7	32	No gel formation
4.2	20	11	gelation
5.1	1	2	gelation
6.1	136	214	gelation
7.1	4	6	No gel formation
7.2	14	23	No gel formation
11.1	14	21	gelation
11.2	14	21	gelation
11.3	14	21	gelation
11.4	14	21	gelation
12.4	14	11	No gel formation
12.7	14	21	gelation
12.8	10	11	gelation

Measurements

Swelling/Shrinking- The pre-weighed, dried hydrogel was immersed in a beaker containing deionized water. At periodic intervals the sample was taken out from the beaker, the surface moisture was removed by blotting and weighed in a calibrated analytical balance. The swelling ratio was determined by normalizing the water uptake with respect to the mass of the dried gel.

$$\text{Swelling Ratio} = (M_s - M_d) \times 100 / M_d \qquad (1)$$

Where M_s, M_d indicate the mass of swollen and dry gels respectively.
The shrinking of the gels at different temperatures was monitored by using high impedance multimeter (Keithley Instruments, Cleveland, OH). The multimeter was earlier calibrated at the temperature range to be studied.

Scanning Electron Microscopy (SEM)- The surface morphology of the hydrogels was determined by JEOL scanning electron microscope (model: 6060LV, Peabody, MA) after sputter coating (Denton Vacum Desk IV, Moorestown, NJ) of the samples with gold-palladium film.

Results and Discussion

Swelling Studies

The rate and extent of swelling of poly *(*NIPA-*co*-AA) hydrogels at any given temperature depends on cross link density. The gels with low (11-4, Table 1) and high cross link density (12-7, Table 1) exhibited swelling in all directions. The swelling of the hydrogels examined was isotropic as evident from dimensional change. The dimensional change and the water uptake in the low cross link gels were greater compared to high cross link gels. The percent water uptake, calculated using equation 1, clearly indicate that low cross link gel has a higher affinity for water. For high cross link hydrogel, mass before swelling (M_d) and mass after swelling (M_s) were 0.5853g and 0.7722g respectively at room temperature (22° C) and after 30 minutes of immersion. The percent mass increase for high cross link gel was 31.93%. Under identical conditions, for a low cross link gels, the mass before swelling (M_d) and mass after swelling (M_s) were 0.6643g and 0.9181g respectively. The percent mass increase for low cross link gel was 38.21%. This result is in accordance with literature reports that indicate that increase of cross link density reduce the mass uptake of water [15-17]. In general, when hydrophilic polymers are in contact with aqueous solution, the network begins to enlarge in size due to the thermodynamic interaction between hydrophilic moieties of the polymer and water. However, the retractive forces exerted by the cross-links of the network counterbalance the swelling forces. Equilibrium swelling is reached when the two forces are equal.
The water uptake of the hydrogels is related to porosity and density. Hydrogels with high porosity is expected to have low density values. Both low and high cross link hydrogels remained at the bottom of the water container after swelling indicating that their density is greater than one.

Deswelling Studies

The deswelling kinetics of poly*(*NIPA-*co*-AA) monitored gravimetrically (Fig. 1) shows linear loss of mass with time and temperature indicating that the cross link system is a homogenous hydrogel network. On the other hand, heterogenous network will exhibit deswelling rate profile that varies with respect to time or temperature [12]. Poly*(*NIPA-*co*-AA) releases constant amount of water with time and temperature. The hydrogels lost 70% of the mass within 10 minutes at room temperature as compared to more than a month it takes for a PNIPA hydrogel [13]. Similarly when the temperature is increased to 40°C poly*(*NIPA-*co*-AA) loses 70% of water absorbed.

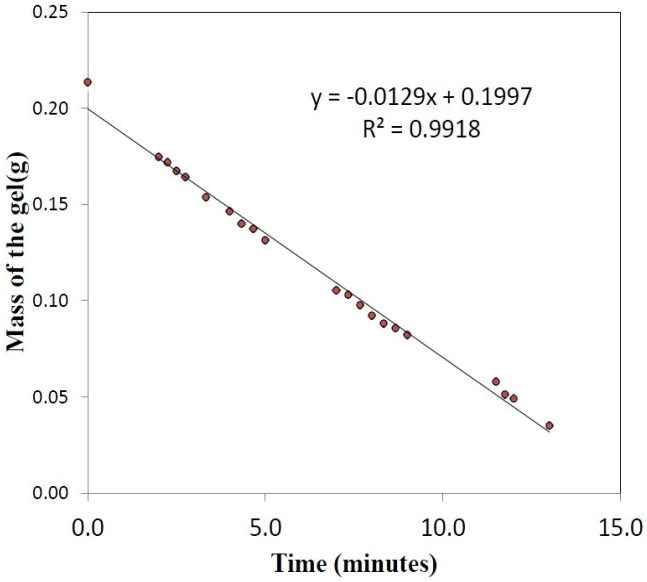

Fig. 1(a)-Deswelling behavior of PNIPA hydrogel as a function of time and temperature; Hydrogel exhibits 70% loss in mass in 10 minutes

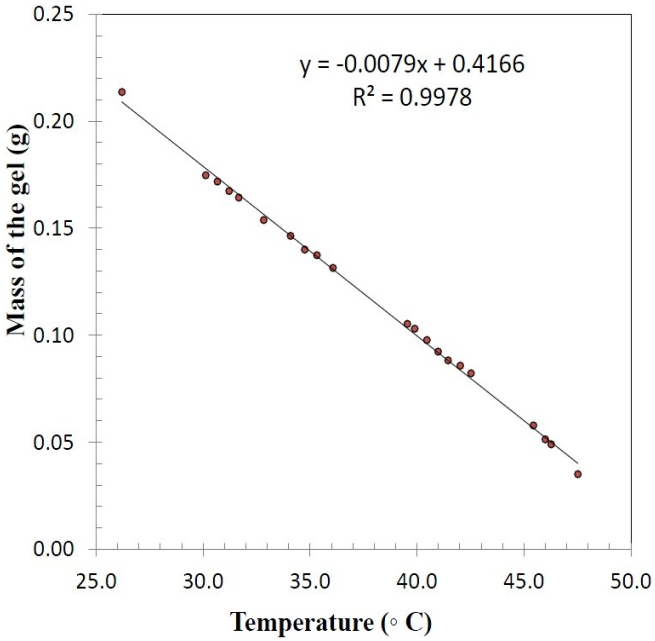

Fig.1(b)- Deswelling behavior of PNIPA hydrogel as a function of time and temperature; Hydrogel exhibits temperature range of 26 to 48° C.

Microscopy

Scanning electron microscope images were taken at different cross-link concentrations to relate the microstructure with diffusion pattern (Fig. 2). Scanning electron microscopy (SEM) pictures showed the surface morphology of low, medium and high cross-link gels. It can be seen that gel network produced more cracks and holes in the gel when cross-link density increases. This is directly due to the stress and pressure that create inside the gel. Such porous structures enable water molecules to diffuse through the polymer network easily.

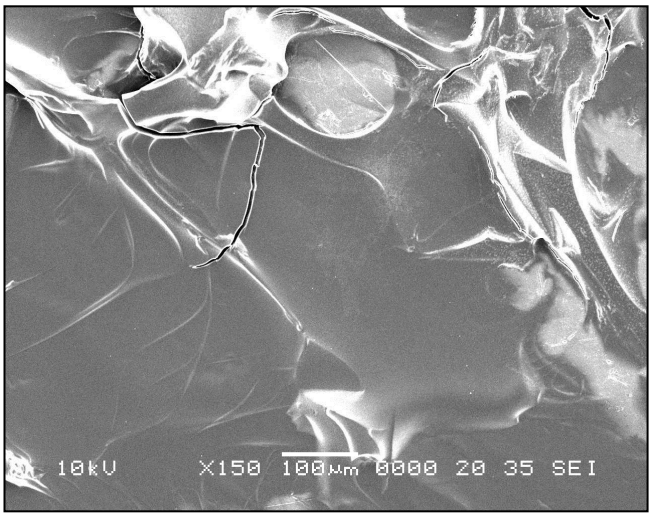

Fig. 2(a)- SEM images of Low cross linked hydrogels

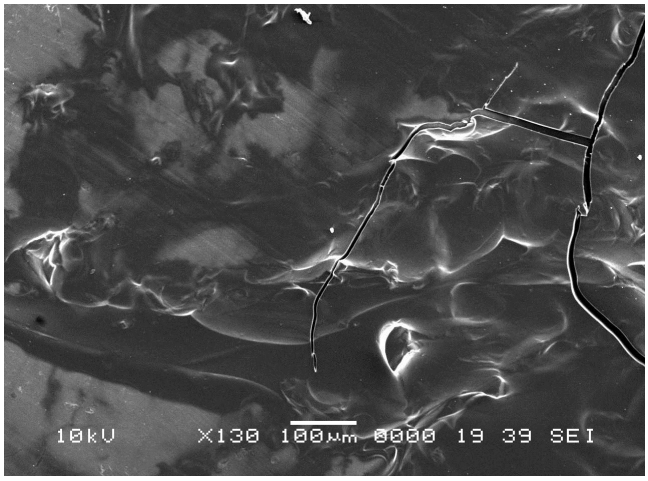

Fig. 2(b)- SEM images of Medium cross linked hydrogels

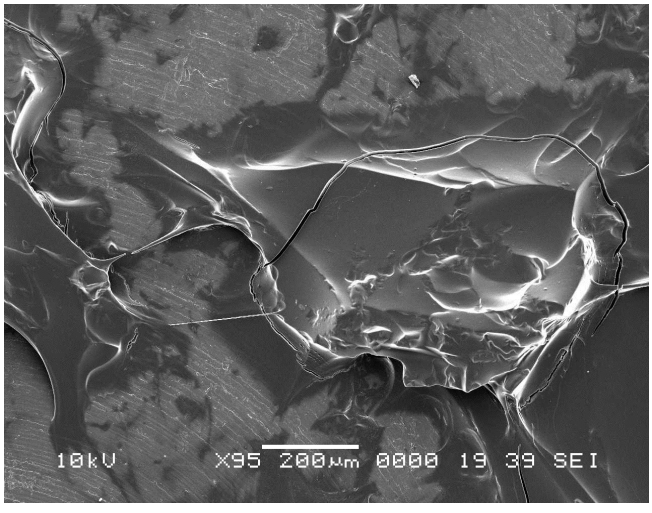

Fig. 2(c)- SEM images of High cross linked hydrogels

Conclusions

- We were able to synthesis a hydrogel that has high equilibrium and fast deswelling kinetics. The kinetics of deswelling of these hydrogels are fast and can be controlled by varying the

cross link density. Deswelling response times of less than 10 minutes are achievable.

- The concentration of crosslink, initiator and accelerator play an important role in influencing the dynamics of the gel. Swelling data show that gel with high amount of accelerator, initiator and cross-link has less swelling properties
- SEM surface morphology indicates that high cross-link gels create more stress inside the gel. As the cross link density increases the gels become rigid and easily susceptible to surface cracks and fractures.

Acknowledgements

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