

Deswelling Characteristics of Poly (*N*-isopropylacrylamide) Hydrogel

TAE GWAN PARK^{1,*} and ALLAN S. HOFFMAN²

¹School of Pharmacy, Temple University, 3307 North Broad Street, Philadelphia, Pennsylvania 19140, and ²Center for Bioengineering, FL-20, University of Washington, Seattle, Washington 98195

SYNOPSIS

Poly(*N*-isopropylacrylamide) gels exhibit a lower critical solution temperature (LCST) behavior in aqueous solution. At temperatures below the LCST, the gel is more hydrated than at temperatures above the LCST. At the LCST, the volume change is sharp. It is shown here that the water content of the gel above the LCST depends upon previous states of the gel (e.g., dry or wet), the heating rate, and the gel thickness. Deswelling kinetics are also affected by the gel thickness. Caffeine release experiments indicate that microscopic water pockets are formed within the matrix during the rapid gel collapse procedure. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Poly(*N*-isopropylacrylamide, NIPAAm) gel, which exhibits a lower critical solution temperature (LCST) behavior, collapses and shrinks above the LCST, at around 32–33°C, but swells and reexpands below the LCST.^{1,2} Since it shows an abrupt volume change in response to temperature, poly NIPAAm gel has been utilized for drug delivery systems.^{2–4} The gel collapse at the LCST is driven by a large entropy gain in water molecules, which go from bound state to free state, and are thereby released from the gel. The release rate of water out of the gel matrix is primarily determined by the rate of collapse of the polymer network. Viscoelastic (relaxation) properties, as well as heat and mass transfer rates of the gel, are mainly responsible for the gel deswelling kinetics.

In previous studies,^{5,6} increased water contents were observed at higher temperatures than at just above the LCST, when initially wet gels were used to determine the equilibrium water content. In addition, vitamin B-12 release kinetics, during the gel collapse period, exhibited two stage release profiles:

an initial rapid release followed by a slow release.¹ These facts indicate that the gel collapse does not occur homogeneously. It has been postulated that the gel collapse proceeds via a “skin” formation. The dehydrated and densified skin progressively moves into the swollen gel matrix during the deswelling of the gel, as is schematically shown in Figure 1. The collapsed gel is likely to contain “water pockets,” where water is retained. This nonequilibrium and kinetics-limited process has also been found during the thermal cycling operation of a packed bed immobilized enzyme reactor, as described in previous report.⁷ During the cyclic swelling and deswelling processes of immobilized enzyme–gel beads, which were induced by a thermal cycling operation, two split peaks in the substrate/product conversion cycles were regularly observed. These might be caused by the repeated appearance and disappearance of the skin in gel beads, which controls the release-out rate of the product.

In this study, three different methods were used to determine the water content of the gel as a function of temperature. They were used to incubate the gels, initially in different hydration states, at the same particular temperature below and above the LCST. Since the skin would appear only when the initially swollen gels are used, this experiment will tell us whether it is formed during the gel collapse. The gel thickness was varied to investigate its effect

* To whom correspondence should be addressed.

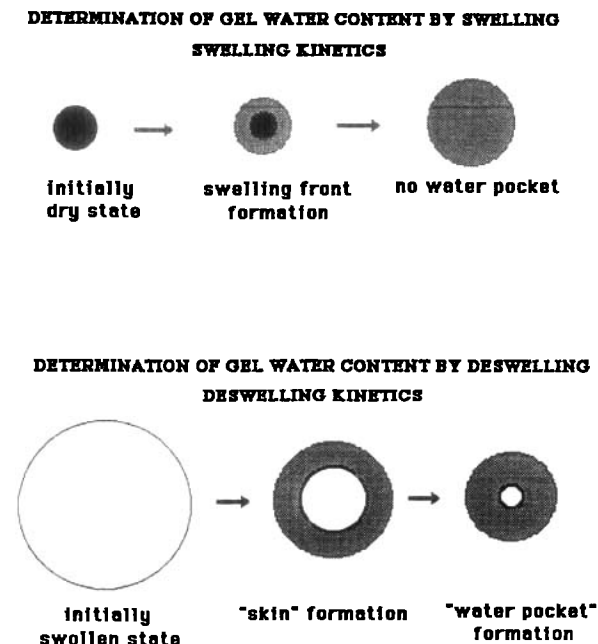


Figure 1 Schematic diagrams of “swelling front” formation by swelling and hypothetical “skin” and “water pocket” formations by deswelling.

on the water content and the deswelling kinetics of polyNIPAAm gel. If any skin and water pocket exist, the water content of the gel, measured at higher temperatures above the LCST, would have different values with respect to the gel thickness and initial hydration state. To further prove the existence of the skin, caffeine, a model drug, is loaded in the gel and its release profile during the gel deswelling is also studied as function of the gel thickness.

MATERIALS AND METHODS

Materials

N-isopropylacrylamide (NIPAAm), from Eastman Kodak, was recrystallized with hexane. *N,N'*-methylene-*bis*-acrylamide (MBAAm), ammonium persulfate (APS), *N,N,N',N'*-tetraethylmethylenediamine (TEMED), and caffeine were purchased from Sigma Co. All solvents and other chemicals were of analytical grade.

Preparation of Hydrogel Membranes

7.68 g NIPAAm and 0.32 g MBAAm were dissolved in 40 mL of deionized water and nitrogen was bubbled to remove residual oxygen. As redox initiators, 10 mg APS and 0.1 mL TEMED were added, and

the mixture was immediately injected into the space between two glass plates. The gel membrane thickness was controlled by staking teflon spacers between the two glass plates. Polymerization was carried out at room temperature for 3 h. After polymerization, the gel membrane sheets were removed, were then extensively washed with deionized water, and were punctured by a #6 cork borer. Membranes of three different thicknesses were made. These thicknesses were 0.93, 1.85, and 2.93 mm, as measured with a micrometer for the fully swollen state at 25°C.

Determinations of Water Contents

The water content of polyNIPAAm gels at various temperatures was determined by using three different methods, as follows:

1. Initially wet gel discs, equilibrated at 25°C, were abruptly transferred to new temperatures, and the gels were allowed to incubate at the new temperatures.
2. Initially wet gel discs, equilibrated at 25°C, were heated stepwise from 25°C to 50°C, and were incubated at each temperature.
3. Initially dry gel discs were equilibrated at each temperature.

Gel discs in triplicate were incubated at least for 24 h at a particular temperature for all three methods. There were no detectable weight changes in gel discs after that period. After blotting excessive surface water with a filter paper, the gel discs were weighed. Dry weights were determined after drying the gel in a vacuum oven overnight. Water content was then calculated, based on the wet weight and the dry weight. Each data point presented is an average value of three gel discs. Deswelling kinetics of the three gels, having different thicknesses, were performed by transferring the gel discs, equilibrated at 25°C, to 37°C, and by continuously monitoring the weight changes of the gels as a function of time.

Caffeine Release Experiments

In order to load caffeine into the gels, dry gel discs were equilibrated in different concentrations of caffeine solution: 3.33, 6.67, and 10 mg caffeine/mL of deionized water at 25°C for 2 days. The caffeine release experiments were carried out by transferring previously incubated drug load gel discs into 10 mL of deionized water at 37°C. At fixed time intervals, gel discs were removed and were transferred into a

fresh, 10 mL medium. The released caffeine was analyzed at 272 nm by a UV-spectrophotometer. The caffeine-loading amounts were calculated gravimetrically after drying the gel discs or were measured spectrophotometrically by the depletion of the loaded caffeine after a long incubation period in a large volume of deionized water.

RESULTS AND DISCUSSION

Equilibrium swelling degree of a hydrogel has been measured on the basis of the weight gain of imbibed aqueous medium into the gel matrix after the gel was equilibrated at a particular temperature. A crosslinked polyNIPAAm is a typical temperature-sensitive hydrogel, which exhibits an abrupt volume phase transition at its LCST, at around 32–33°C. Equilibrium swelling degree of a hydrogel has often been recognized to be independent of the history, which is what the hydrogel has previously experienced in different hydration states. A thermodynamic description for the nonionic gel swelling involves balanced free energy changes in elastic contraction of the polymer network and mixing of polymer chains with water. However, after a hydrated gel is completely dried, it can be imagined that its reswollen state could have different pore sizes, pore size distribution, and pore inter-connections (tortuosity), as compared to its previous swol-

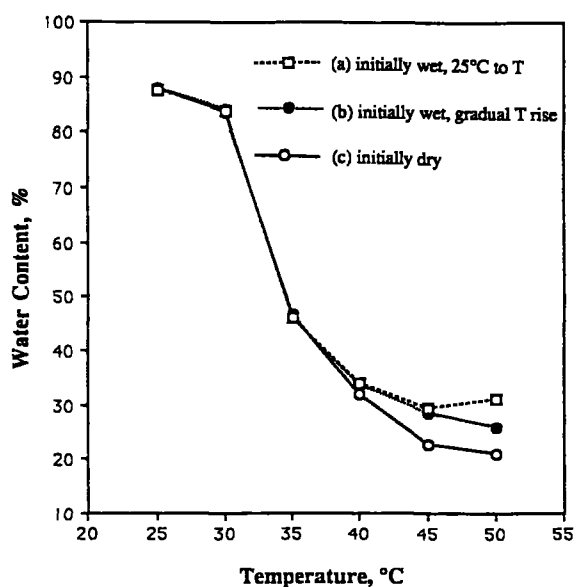


Figure 2 Temperature-dependent water contents of poly(*N*-isopropylacrylamide) gel, as determined from three different initial hydration states.

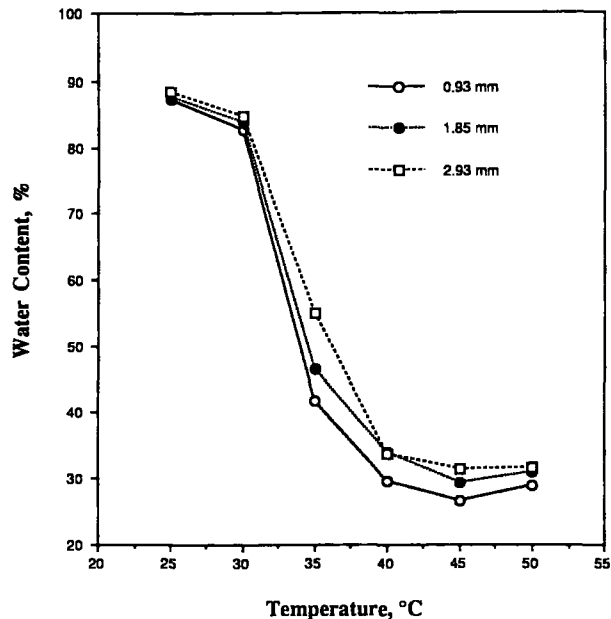


Figure 3 Water contents of polyNIPAAm gels, having different thicknesses, as a function of temperature. Initially, hydrated gels transferred from water at 25°C to water at each temperature.

len state before drying. Therefore, macroscopic and apparent physical properties of the reswollen gel, in terms of an equilibrium swelling degree, may not fully reflect the microscopic undetectable changes in the gel matrix during the swelling-deswelling process.

Figure 2 shows the temperature-dependent water contents of the polyNIPAAm gel, which were determined by the three different methods, as described in the Materials and Methods section. PolyNIPAAm gels were allowed initially to have different hydration states. It can be seen that below the LCST, at around 32–33°C, three methods result in the same water content, regardless of initial hydration states, but above that region, water contents have different values, depending on the initial hydration states. In the cases of initially wet gels, gels deswell until they reach their minimum water contents at a particular temperature. On the other hand, initially dry gels swell until they reach their maximum swelling capacities. As shown in Figure 1, the swelling of an initially dry gel is accomplished via a moving swelling front toward the core, whereas the deswelling of an initially wet gel may proceed with the development of a skin. The deswelling process may result in the formation of water pockets in which water is retained. At temperatures above the LCST, the inhomogeneous gel network, having a

microsponge structure, can be expected when deswelling methods are used to determine the water content. In contrast, the swelling method would provide a homogeneous gel structure. Thus, different water contents, observed above the LCST, can be ascribed to the different initial hydration states of the gels.

Figure 3 shows the effect of gel thickness on the water content as a function of temperature. The data were obtained from the method in which gel discs, equilibrated at 25°C, were transferred to each temperature. For thicker gels, the gel water contents are slightly higher. This is due to the kinetic limitations caused by the water pocket formation. A thicker gel should have a higher possibility of trapping water in the collapsed gel matrix, simply because of its larger dimension. The skin takes up a greater proportion of the total volume in the thinner discs, so that they end up being relatively more homogeneous. The deswelling kinetics of polyNIPAAm gels, having

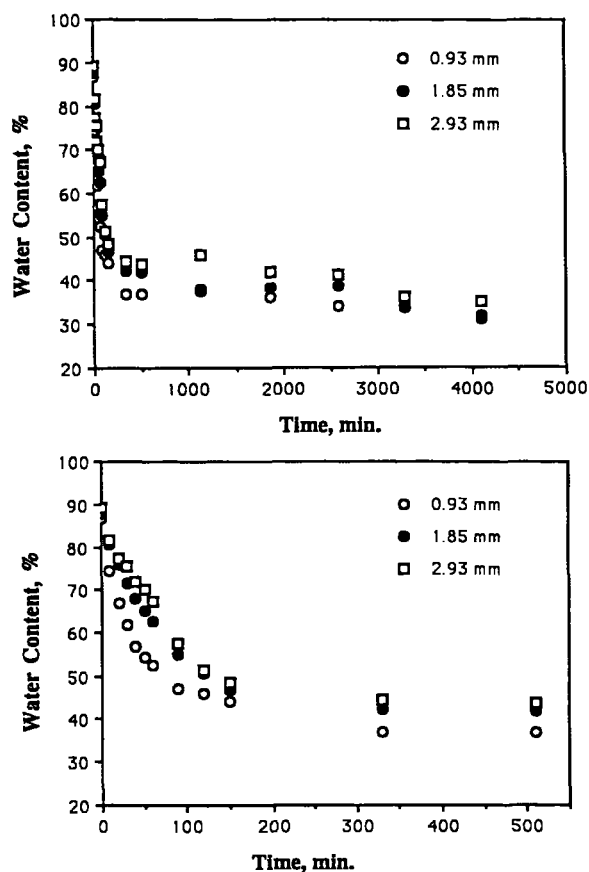


Figure 4 Deswelling kinetics of polyNIPAAm gels, having different thicknesses when the gels are transferred from 25°C to 37°C. (Top figure) long-term kinetics, (bottom figure) initial stage kinetics.

Effect of Gel Thickness on Caffeine Release during Deswelling (25° to 37°)

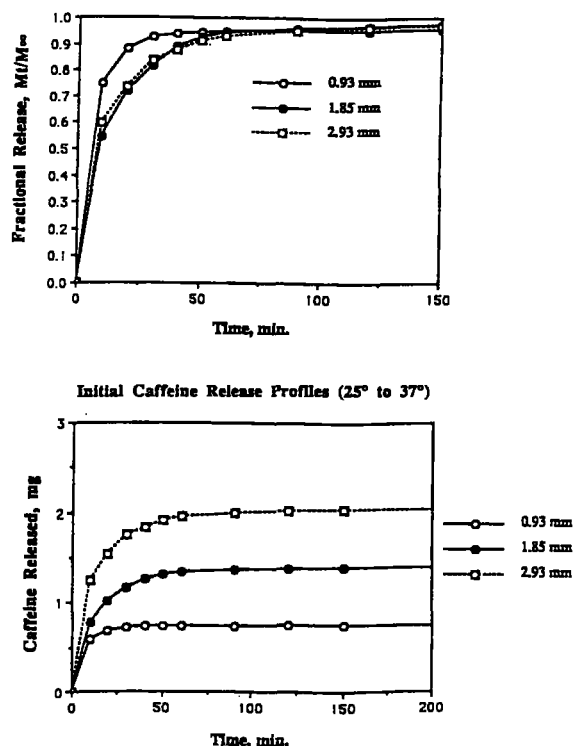


Figure 5 Effect of gel thickness on caffeine release during deswelling (the gels are transferred from 25°C to 37°C). (Top figure) fractional release vs. time, (bottom figure) initial caffeine release kinetics.

different thicknesses, were studied by transferring gel discs from 25°C to 37°C, as shown in Figure 4. It can be seen that the deswelling kinetics depend on the dimensional thickness of the gel. Thin gel discs exhibit the fastest shrinking kinetics. This is understandable when it is realized that the swelling and deswelling kinetics of the gel are related to its ability to transport water in and out of the gel, which ability is greater for thinner gels.⁸ Initial, fast decreasing rates of water contents are caused by a rapid collapse of the gel surface upon exposure to heat. The subsequent rapid movement of the skin from the surface to the core region is related to the relaxation kinetic rate of the polymer chain network in response to a thermal stimulus, because the polymer relaxation is much slower than the heat transfer rate. Since the relaxation is inherently a viscoelastic property of a particular gel type, the moving-in velocity of the skin should be similar, regardless of the gel thickness. Thus, the thick gel discs may have a higher internal hydrostatic pressure than the thin ones. More water may be trapped in thicker gel matrices at anytime during the deswelling. Apparently,

Effect of Loading Amount on Caffeine Release during Deswelling (25° to 37°)

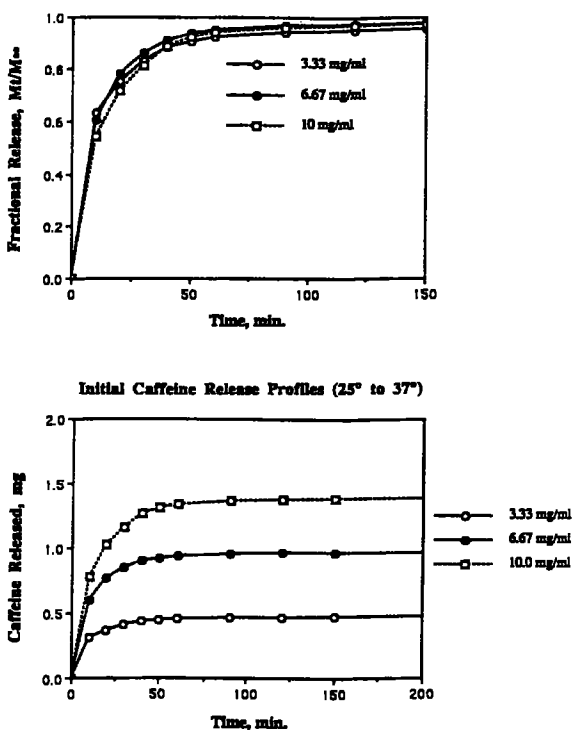


Figure 6 Effect of loading amount on caffeine release profile during deswelling (the gels are transferred from 25°C to 37°C). (Top figure) fractional release vs. time, (bottom figure) initial caffeine release kinetics.

deswelling kinetics can be divided into two steps: the first step will be the rapid water squeezing-out process through the weakly densified region, and the second step, which appears later in the deswelling stage, will be the slow release of water through the more densified, collapsed gel layer on the surface. As the gel becomes thicker, the second, slow release step will be more pronounced.

The effect of the gel thickness on caffeine release during deswelling is shown in Figure 5. It can be seen that the thin gel (0.93 mm) exhibits faster caffeine release than the other two gels, which is due to the faster deswelling kinetics. It can also be observed that the fractional release (M_t/M_∞) does not reach 1.0, which implies that the caffeine is not completely released and some portion is entrapped within the gel. This supports the idea of a water pocket formation in the collapsed gel, although partitioning of the caffeine into the collapsed polymer matrix cannot be ruled out. No significant amounts of caffeine are released after 50 min (Fig. 5), while the gel continuously deswells over a period of 150

min. This might be due to the two-step deswelling kinetics, as described above. Assuming that caffeine is dissolved only in the free water fraction, caffeine molecules, located in the porous region of the gel, may be squeezed out quickly or trapped in water pockets as the gel collapses. However, water molecules (perhaps bound water molecules, which are initially associated with hydrophobic regions of the gel) would still be released, probably through the micropores (or "crack") formed during the densification of the gel. Figure 6 shows the effect of the caffeine-loading amount on the release during deswelling of the gel (thickness: 1.85 mm). There are no significant differences in the fractional release profiles as a function of the loading amount. This indicates that, even though the caffeine concentration in the same volume of trapped water pockets increases, there is no measurable difference in the amount of caffeine released. This supports the concept of water pockets.

In summary, it has been demonstrated that water contents of polyNIPAAm gel depend on the previous hydration state, especially above the LCST. Gel thickness affects the water contents, due to the formation of varying degrees of the skin densification around the water pockets during the gel collapse. The caffeine release study supports the concept of trapped water pockets. Based on these results, it can be concluded that the deswelling of polyNIPAAm gel proceeds with a skin, which ends up with the formation of trapped water pockets in collapsed gel matrix.

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