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Synthesis of macroporous hydrogels with rapid swelling and deswelling properties for delivery of macromolecules

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Thermally reversible macroporous poly(*N*-isopropylacrylamide) (polyNIPAAm) hydrogel has been synthesized in aqueous solution at a temperature above the lower critical solution temperature (*LCST*). Rapid swelling and deswelling kinetics of this macroporous hydrogel are characterized. Pore size measurement by a solute exclusion technique reveals that this macroporous hydrogel has a larger pore size distribution than the hydrogel synthesized at a temperature below the *LCST*. This kind of thermally reversible macroporous hydrogel will be very useful in delivery of macromolecules.

(Keywords: macroporous hydrogel; swelling kinetics; pore size)

Introduction

From previous work in our laboratory, thermal cycling of lower critical solution temperature (*LCST*) hydrogels near the *LCST* can significantly enhance the productivity of immobilized enzymes[1]. However, this approach is limited in releasing macromolecules due to the relatively small porosities in most hydrogels[2]. Therefore, we have developed a new type of poly(*N*-isopropylacrylamide) (polyNIPAAm) hydrogel with a macroporous structure to allow absorption of macromolecules as proteins plus rapid delivery in response to temperature change through the *LCST*.

Macroporous polyNIPAAm hydrogels can be synthesized in aqueous solution at temperatures above the *LCST*, at which the polymer phase separates as it is formed. Crosslinking between the aggregated polymer chains will create a macroporous structure in the thermally reversible hydrogel. In most cases, the diffusive transport rates within the gel membranes increase with the porosity. The pore size is also important when the diffusant is relatively large. Large pore sizes and porosities can also lead to more rapid response to temperature when the gel is cycled through the *LCST*. This will enhance 'convective' transport rate. Hydrogels which contain large pores, or 'macropores', may avoid the partial loss of drug activity due to adsorption on the surface of the delivery device; very often the drug is inactivated by conditions within the delivery device related to micro-environmental pH or concentration effects. When macroporous gels swell, they form large aqueous pores within which the peptide or protein drug may behave as if it were in bulk solution; thus, it may permeate through such pores without significant loss of activity. Thus, spongy gels with rapid swelling and deswelling response to temperature changes can increase the transport rate of macromolecules.

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Experimental

Synthesis of polyNIPAAm hydrogels. The polymerization was carried out at two temperatures: 4°C (below the *LCST*) and 50°C (above the *LCST*). A 25 ml solution of 20% (w/w) NIPAAm in deionized water with 0.5% (w/v) dihydroxy-ethylene-bis-acrylamide as crosslinker and 0.2 w/v% ammonium persulfate as initiator was degassed with N_2 for 20 min to remove dissolved oxygen. Then the solution was immediately transferred into a glass flask. The polymerization was carried out under vacuum. The polymerization temperature was controlled by using a water bath. *N',N',N',N'*-Tetramethylethylenediamine (0.001 v/v%) was added as a redox initiator for the gel preparation at 4°C.

The characterization of polyNIPAAm hydrogels. The *LCST* behaviour of macroporous polyNIPAAm gel is characterized by recording the water content change of the preswollen gel when the temperature has been cycled from 20 to 50°C.

The swelling and deswelling kinetics of the polyNIPAAm gels were studied by recording the normalized wet weight of the gel as a function of time by first wiping off the excess surface water from the discs and weighing at preset time intervals until equilibrium weight was reached. The normalized wet weight of gel was calculated from the ratio of wet weight of gel at time t, (W_t), to the equilibrium swollen weight (W_e) of the gel.

Pore size characterization. The pore size of the gels was determined by using solute exclusion technology. The dry gels were first equilibrated in deionized water at 20°C. After the first equilibration, the swollen gels were placed into fluorescein-labelled dextran (200 $\mu g\,ml^{-1}$) as a probing molecule for a second equilibration at 20°C. Equilibrium was usually reached in less than 3 days. After the second equilibration, the gels saturated with dextran were transferred into 200 ml deionized water. The release

of dextran into the deionized water was monitored by a Perkin-Elmer luminescence spectrometer at the excitation wavelength of 485 mm and emission wavelength of 515 nm. The pore size could be estimated from the volume fraction (F_i). The volume fraction, F_i, of pores larger than the probing molecule, i, was expressed by $F_i = V_a/V_o$, where V_a is the volume of pores accessible to each dextran molecule, and V_o is the total volume of deionized water in the hydrogels. A detailed explanation of this method has been given in a previous paper[3].

Results and discussion

Characterization of various polyNIPAAm hydrogels. The *LCST* behaviour of the gel prepared at 50°C was observed. The results are shown in *Figure 1*. The change of water content was rapid when the temperature was cycled from 20°C (below *LCST*) to 50°C (above *LCST*). Water content (%) is equal to

$$[(W_t - W_d)/(W_\infty - W_d)] \times 100$$

where W_t is the wet weight of the gel at time t, W_d is the dry weight of the gel and W_∞ is the wet weight of the gel at equilibrium state.

The results of swelling kinetics of various polyNIPAAm gels are given in *Figure 2*, plotted as normalized wet weight as a function of time. The normalized wet weight is used in order to compare how fast the gel can reach the fully swollen state. As seen from *Figure 2*, the gels prepared at 50°C can swell to the equilibrated state from initial dry gel in about 1 h. The results show that the gel prepared at 50°C can swell to the equilibrated state five times faster than the gel prepared at 4°C.

The gel prepared at 50°C can deswell and swell very quickly when the temperature is cycled through its *LCST*. The results of deswelling kinetics are also shown in *Figure 2*. The water content of this gel can be changed from 90 to 45% within 30 s when the gel is immersed at 50°C (above the *LCST*). Then, this gel can reswell to 90% water content within 30 s when immersed at 20°C (below

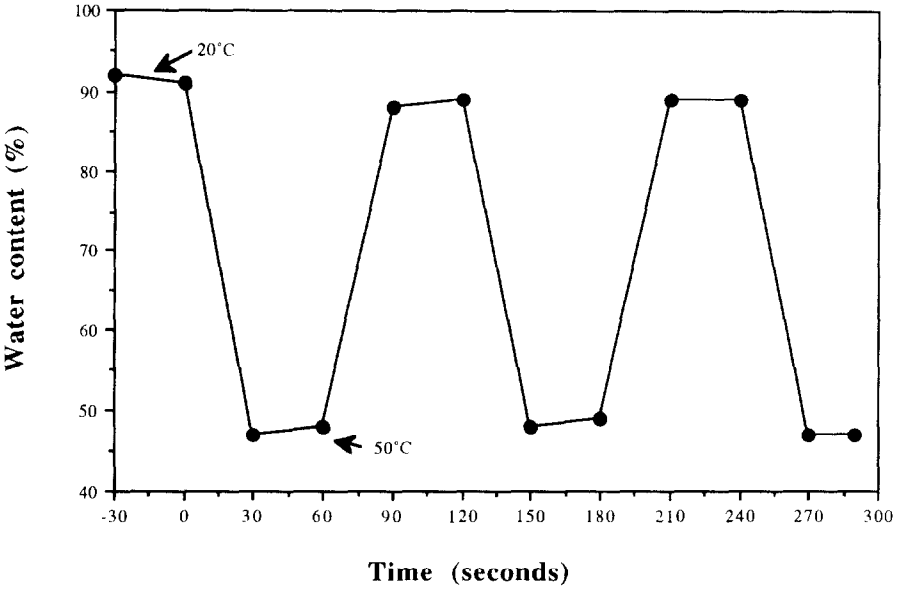

Figure 1 *LCST* behaviour of gel prepared at 50°C. Initial state, gel preswollen at 20°C; gel thickness, 4 mm; temperature cycled from 20 to 50°C

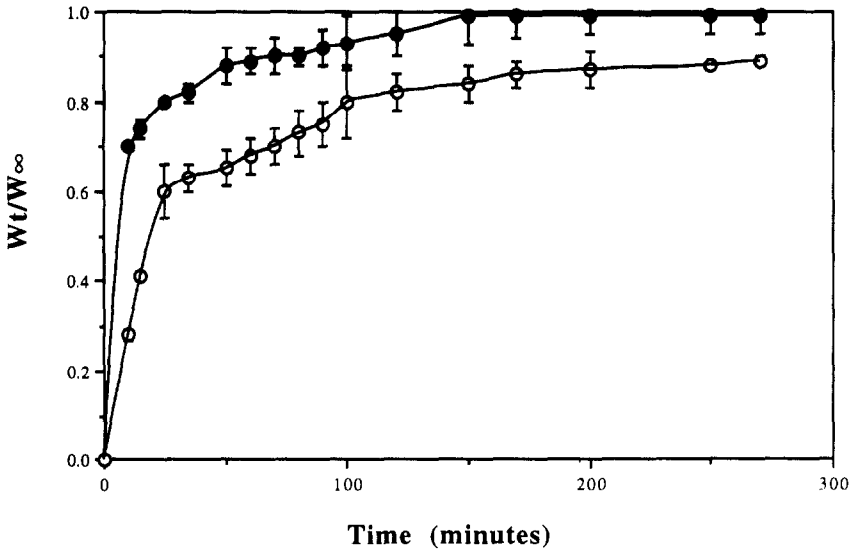

Figure 2 Swelling and deswelling kinetics of macroporous polyNIPAAm hydrogels. Initial state, dry gel; swelling temperature, 20°C. Normalized wet weight, W_t/W_∞, is the ratio of wet weight of the gel at time t to the weight of the swollen gel in equilibrium state. ●, Gel prepared at 50°C; ○, gel prepared at 4°C

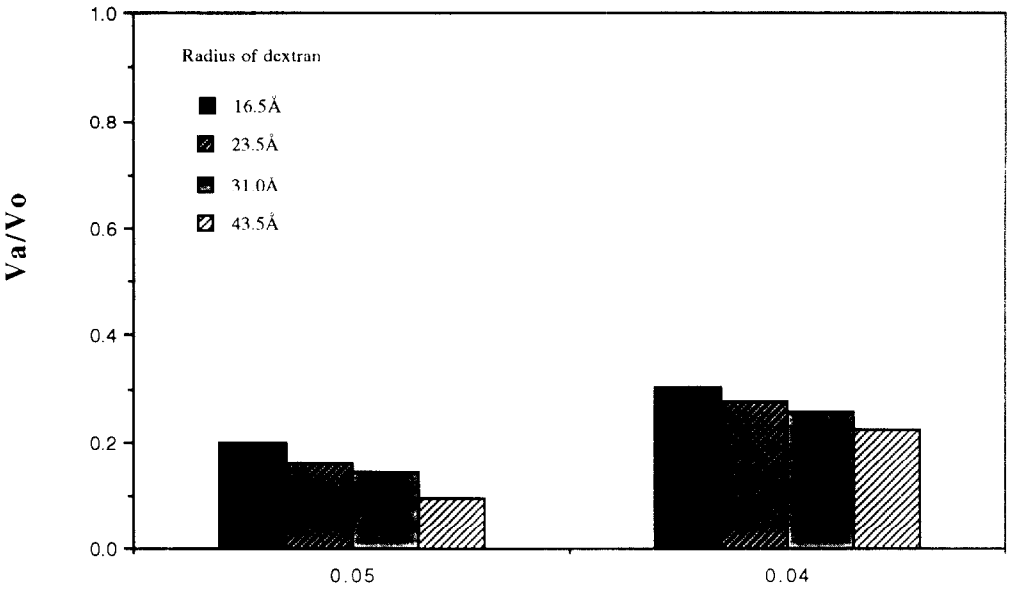

Figure 3 Comparison of pore size in polyNIPAAm hydrogels

LCST). These results show that there is a macroporous structure within the gels, causing rapid swelling and deswelling.

Characterization of pore size. The results of pore size characterization are shown in *Figure 3*. As seen in *Figure 3*, the pore size of the gel synthesized at 50°C (above the *LCST*) is much larger than that of the gel synthesized at 4°C (below the *LCST*), the temperature at which the gel is normally prepared. The gel synthesized at 50°C can accommodate 100% more dextran molecules of 43.5 Å, 80% more dextran molecules of 31.0 Å, 70% more dextran molecules of 23.5 Å, and 55% more dextran molecules of 16.5 Å, than the gel synthesized at 4°C. The results also confirm the larger pore size distribution of the gel synthesized above the *LCST*.

Conclusion

A new polyNIPAAm hydrogel with macroporous structure is presented in this paper. The *LCST* behaviour, pore size distribution and swelling/deswelling kinetics are also investigated. The gel properties at 50°C are as follows: (i) shrinking and swelling to equilibrium state within 30 s; (ii) the pore size distribution of macroporous hydrogel synthesized above the *LCST* is much larger than that of the gel synthesized below the *LCST*.

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