

# Synthesis and Characterization of Thermally-Responsive Hydroxypropyl Methylcellulose Gel Beads

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**ABSTRACT:** Thermally responsive gels of hydroxypropyl methylcellulose (HPMC) were produced in spherical form by a suspension crosslinking technique. The suspension crosslinking of HPMC with divinylsulfone was accomplished by dispersing aqueous polymer droplets, containing all of the reactants, in a continuous organic phase. The gel beads were characterized in terms of their swelling properties and particle size distribution. The swelling degrees at 25°C of different formulations of the gel beads ranged from 12 to 123 times their dry volume and shrank to 4 to 18 times dry volume at 75°C. The spherical beads were made in diameters ranging from 500 to 3000  $\mu\text{m}$ . Bead size generally decreased with use of a larger impeller, suspending at high stirring speeds, or at a lower phase ratio. As bead size decreased, the size distribution also narrowed. When compared with bulk HPMC gels, the gel beads demonstrated the same swelling properties and crosslinked network formation. © 1997 John Wiley & Sons, Inc. *J Appl Polym Sci* **66**: 1279–1290, 1997

**Key words:** suspension polymerization; hydrogels; gel synthesis; cellulose ethers; thermally responsive gels

## INTRODUCTION

Hydrogels are polymeric networks which can swell by the absorption of many times their weight of water. The three-dimensional structure of gels is created by crosslinks between polymer chains which can be provided by covalent bonds, physical entanglements, hydrogen bonding, van der Waals interactions, or hydrophobic interactions.<sup>1</sup> The single most important property of a gel is the swelling degree, which directly influences most of the gel's other properties.<sup>2–4</sup> Responsive or stimuli-sensitive gels respond to changes in their solution environment such as temperature, pH, solvent composition, ionic strength, electric field, light intensity and wave-

length, and specific chemical stimuli such as glucose.<sup>5–12</sup> The primary response is most generally a reversible, macroscopic change in the gel volume.

Gels are used in analytical chemistry, chemical separations, and controlled drug delivery, and as artificial organ implants or tissue replacements. Other uses include diapers, feminine hygiene products, and contact lenses. In many of these applications, it is desirable to have short contact times between gel and solution for both functional and economic reasons. Therefore, gels are often used in particulate form, since the kinetics of gel swelling is a diffusion-controlled process and scales with the square of dimension. Thus a smaller-sized bead has faster absorption and desorption rates. Similar conditions also apply for systems where rapid permeation of the gel by solutes is important.

To produce gel particulates, gels are typically synthesized in bulk form, then ground into the desired size. However, this creates a large amount

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of fines which can hinder mass transfer through a bed of gel. For example, "gel blocking" can occur where, upon contact with fluid, the outer particles of the gel bed stick together, effectively blocking transport of fluid to the inner particles.<sup>13</sup> Also, the irregularly shaped pieces created from grinding are not always suitable in some applications, such as controlled drug release and chromatography, where a uniform shape is required to obtain proper mass transfer characteristics. Producing spherical gels can eliminate these problems.

A common technique of producing spherical polymer beads is suspension polymerization. In typical suspension-polymerization processes, microscopic droplets of monomer, stabilized by small amounts of surface-active polymers, are suspended in a continuous nonsolvent medium, most commonly water, with the polymerization carried out using monomer-soluble initiators. Suspension polymerization has the advantages of good temperature control, ease of handling the final product, and control of particle size.

Synthesis of polymer gels by suspension polymerization is less common, although it has been accomplished. Mueller and associates<sup>14</sup> described a technique for producing spherical hydrogels by the suspension polymerization of hydroxy-substituted esters of acrylic or methacrylic acid, such as poly(2-hydroxyethyl methacrylate). Gels were produced from monomers suspended in aqueous salt solutions, where they were copolymerized. An alternative approach, developed by Flodin, produces gels from carbohydrate polymers using a suspension-crosslinking method.<sup>15</sup> This unconventional technique is a variation of suspension polymerization in that droplets of aqueous polymer solution were crosslinked as they were suspended in a continuous organic medium. The key ingredients in this process are the two immiscible phases, the polymer, the crosslinker, and, if desired, suspending agents. However, little published information is available regarding variables which must be controlled to generalize this process for the large-scale production of spherical hydrogels such as hydroxypropyl methylcellulose (HPMC) gels.

HPMC hydrogels are thermally responsive gels; that is, they undergo a volume change induced by a change in temperature of the surrounding solution.<sup>16</sup> The degree to which the gel swells at a given temperature and the temperature which causes the sharpest rate of change in gel volume characterizes the behavior of the ther-

mally responsive gel. The swelling degree of HPMC gels can be decreased by raising the solution temperature to values above the gel's transition temperature. The transition temperature is the specific temperature at which the gel network has the steepest rate of volume change. For cellulose ether gels, the value of the transition temperature has been found to be approximately the same as the lower critical solution temperature (LCST) of the precursor polymer.<sup>16</sup> Swelling behavior is also characterized by the crosslink density, which influences the swelling degree. The crosslink density is the concentration of elastically active chains in the polymer network (chains which are deformed by an applied stress).

Since beads produced by suspension crosslinking are not monodisperse, the size of the gel beads is characterized by statistical means. Particle shape and size distribution can be critical in designing storage, conveying, and handling systems. For example, for ion-exchange resins, particle sizing is important in determining slurry properties, packing, and bed performance.<sup>17</sup> These factors are similarly expected to be important for temperature-sensitive gel bead applications such as dewatering applications.<sup>7,18-20</sup>

Size analysis also gives important information about how the synthesis conditions affect the bead size and gel properties. Changes in the physical parameters of suspension processes affect particle size and particle size distribution, as has been shown in several size correlations developed for liquid/liquid dispersions.<sup>21-24</sup> In these equations, size was most affected by the stirring speed, impeller diameter, and phase ratio. Droplet size was predicted to be inversely proportional to stirring speed and impeller diameter, and directly proportional to the ratio of the dispersed-to-continuous phases.

Gel beads of varying swelling degrees can be produced most effectively by changing the crosslinker concentration at synthesis. Because in the suspension crosslinking each droplet acts as an individual bulk-crosslinking site, it is expected that gel beads synthesized by this method will have the same characteristic properties as bulk gels produced from the same polymer and crosslinker. However, the goal of the present work was to produce HPMC gels in spherical form by a process suitable for scale-up. Therefore, along with varying the crosslinker dosage, we also examined the influence of the physical aspects of the suspension-crosslinking method.

**Table I Reaction Vessel Proportions for Gel Bead Synthesis**

Impeller Dimension	$D_a/D_t$	$H/D_t$	$J/D_t$	$E/D_a$	$W/D_a$	$L/D_a$
5 cm	0.50	1	0.08	0.64	0.20	0.24
3.8 cm	0.37	1	0.08	1	0.26	0.16

$D_a$ , impeller diameter;  $D_t$ , vessel diameter;  $H$ , liquid level;  $J$ , baffle width;  $W$ , blade width;  $L$ , blade length;  $E$ , impeller height.

## EXPERIMENTAL

### Reagents and Chemicals

HPMC, available under the trade name Methocel®, was used as received as a sample from Dow Chemical, Inc. (Midland, MI). The HPMC used in this work was Methocel-E5, or HPMC-E5, which has a total degree of substitution of 1.9 with 28 to 30% methoxyl and 7 to 12% hydroxypropyl groups.<sup>25</sup> The number average molecular weight is 10,000 and weight average molecular weight is 20,000. Aqueous solutions of HPMC-E have an LCST of 55°C at 10 wt %.<sup>16</sup> The apparent viscosity of aqueous solutions of the polymer is proportional to its molecular weight or chain length and increases with polymer concentration in a power law relationship.<sup>25</sup> For example, HPMC-E5 has a viscosity of 5 mPa/s for a 2% aqueous solution, but a 20 wt % HPMC-E5 solution has a viscosity calculated to be  $11.8 \times 10^3$  mPa/s.

The crosslinker, divinylsulfone (DVS), 97% pure (Aldrich Chemical, Inc., Milwaukee, WI), was used as received. Sodium hydroxide solution was prepared from sodium hydroxide pellets (Aldrich) dissolved in distilled water to produce a concentration of 5*N*. Toluene (Aldrich) was also used as received. Concentrated hydrochloric acid (Fisher Scientific, Pittsburgh, PA) was diluted with distilled water to prepare a 1*N* solution.

All gel bead batches were produced in a 1-L, glass, baffled, rounded-bottom reaction kettle (Ace Glass, Inc., Vineland, NJ). The proportions of the equipment used in bead synthesis are listed in Table I. Four baffles equally spaced around the vessel walls allowed for better mixing at higher stirring speeds. A motor-driven overhead stirrer equipped with a six-bladed disk turbine was used to provide the shear required to break the aqueous polymer phase into droplets and to keep the droplets suspended as the gelation reaction occurred. Two sizes of turbines, 3.8 and 5 cm in diameter, were used (Cole-Parmer Instrument Co., Niles, IL).

### Gel Synthesis

The HPMC gel beads were synthesized by suspending aqueous polymer solution, containing all of the reactants, in an organic solvent at room temperature. The three chemical reagents central to the gel-bead synthesis are the precursor polymer, the crosslinking agent, and the suspending solvent. From a wide range of possible choices, the reactants were chosen for their ease in crosslinking and the solution properties of the polymer. The cellulose ether used here, HPMC-E5, is soluble in water, is readily crosslinked, and has the desired LCST behavior which is critical to thermal responsiveness. The crosslinker, DVS, has been shown in other work to effectively crosslink cellulose ethers.<sup>16,26</sup> The suspending solvent, toluene, is practically immiscible with water and does not cause precipitation of the polymer out of the aqueous phase, a problem encountered with other organic solvents, such as dichloroethane.

The aqueous phase was prepared by dissolving the polymer in water and adding the catalyst, sodium hydroxide, to reach pH 12. The crosslinker was added by micropipette and then mixed into the viscous polymer solution by stirring with a spatula. Polymer solutions of 20 wt % HPMC-E5, with varying amounts of crosslinker, were used to make the gel beads. The amount of crosslinker ranged from 0.01 to 0.03 g of DVS/g of dry polymer while the ratio of catalyst remained nearly constant for all the batches; 0.10 g of 5*N* NaOH solution/g of dry polymer. Within 5 min after the addition of the DVS, the aqueous polymer phase was poured into toluene while it was being stirred in the reaction kettle. As the polymer phase was mixed into the toluene, it quickly dispersed into droplets. Stirring speeds ranged from 300 to 750 rpm.

The ratio of aqueous polymer phase to the organic continuous phase ranged from 2 to 17%. Higher ratios may be possible, up to the maximum of 50% typical for suspension polymerization. After 22 h the reaction was stopped, the toluene was decanted, and the gel spheres were trans-

ferred to a beaker filled with water. In water the gels swell, releasing residual base from the network which was neutralized with 1N HCl solution. The beads were then repeatedly swollen and shrunken in water, by alternately heating to 80°C and cooling to room temperature, to remove the sol fraction from the gels.

### Measurement of Gel Swelling Degree

The gel beads' volume swelling degree in water was measured in the swollen state (25°C) and the shrunken state (75°C). The volume swelling degree is the ratio of swollen gel volume to the dry gel volume and is the inverse of the volume fraction of the polymer in the gel. The swelling ratio, the ratio of the swollen gel volume at one temperature relative to its swollen volume at a reference temperature, was used to calculate the swelling degree of the gel beads at various temperatures. The transition temperature is the inflection point on a curve of normalized swelling versus temperature.<sup>16</sup> The sharpness of the transition is the slope of the normalized curve at the transition, and is reported as a percent of the total volume change per degree at that point.

To measure the swelling dependence on temperature, a sample of beads from a batch was placed into a 100-mL graduated cylinder with an excess of distilled water. The graduated cylinders were then immersed in a thermostatically controlled temperature bath ( $\pm 0.5^\circ\text{C}$ ). The temperature was increased in 10-degree intervals over the range of swelling, 7 to 95°C, except at the region where the transition temperature was expected (50 to 65°C), where the temperature was increased in 5-degree intervals. Temperatures were maintained at each interval for up to 24 h to ensure that an equilibrium state was reached (confirmed by measuring the gel volume hourly until there was no change between successive readings).

The swelling ratio was converted to swelling degree using eq. (1):

$$Q_i = Q_{\text{ref}} S_i \quad (1)$$

where  $Q_i$  is the swelling degree at temperature  $i$ ,  $S_i$  is the swelling ratio at temperature  $i$ , and  $Q_{\text{ref}}$  is the swelling degree at a reference temperature (25°C).  $Q_{\text{ref}}$  was measured by weighing a sample of beads swollen to their equilibrium value in water at 25°C. The swollen weight was then divided by the dry gel weight, which was obtained by dry-

ing the gels to remove the absorbed water. Mass swelling degree was converted to volume swelling degree assuming a density of 1 g/mL for the gels, since they are over 90% water and nearly neutrally buoyant.

### Bead Size Measurement

The average bead size for each batch was determined by measuring a sample of beads using a video microscope system, as described elsewhere.<sup>27</sup> Images captured from the microscope are displayed on the computer screen as they appear on the video monitor. The diameters of the beads in the images were then analyzed with the aid of NIH Image, a public domain image analysis program available from the National Institutes of Health. More than 100 beads can be captured on one image, depending on the size of the beads.

The diameters of the individual beads were measured as they were removed from the reaction suspension (the "at synthesis" diameter) and after they were swollen to their equilibrium value in water at room temperature (the swollen diameter). The same beads that were measured "at synthesis" were measured again in the swollen state. The particle sizing was tabulated as a differential analysis to show the number fraction of particles in each size increment as a function of the average particle size in the increment. For each batch, the bead sizes were separated into 50- $\mu\text{m}$  size fractions to find the distribution. Typically, 500 beads were taken at random from a batch and measured to obtain the size distribution.

### Measurement of Crosslinking Density and Crosslinking Efficiency

Crosslink density and efficiency were calculated from the gel modulus as measured from uniaxial compression tests on individual gel beads. The gel modulus ( $G$ ) is a measure of gel strength, critical to the gel's durability, while crosslink density and efficiency provide insight into the nature of the crosslinking reaction itself. A diagram and complete description of the compression test equipment are given elsewhere.<sup>28,29</sup>

In these compression tests, swollen gel-bead samples were placed beneath a Teflon plate which was attached to a force transducer and micrometer. To prevent the gel from drying or shrinking during the test, distilled water at room temperature was added to the sample dish to just cover

**Table II** Size and Swelling Degree of Gel Beads for Different Reaction Times

Reaction Time (h)	Swelling Degree, $Q_{25}$ (25°C)	Bead Size (mm)	Bulk Gel Swelling Degree
3	21	1.41 ± 0.35	2.9 ± 0.1
5	12	0.69 ± 0.31	3.0 ± 0.2
10	16	0.94 ± 0.36	3.6 ± 0.5
22	15	1.22 ± 0.40	3.4 ± 0.8
48	19	0.96 ± 0.34	4.1 ± 0.5

the gel. A constant strain was applied to the sample by the adjustment of the micrometer to compress the gel. The force, as measured by the transducer, was recorded over time. When the gel relaxed to a constant stress value, the plate was lowered further and another reading was taken.

With stress–strain data collected for five or six points, the modulus was calculated from the slope of the line given by eq. (2):

$$F/A_0 = G[(R_e/R_e^*) - (R_e^*/R_e)^2] \quad (2)$$

where  $F$  is the force applied at poles of gel sphere,  $A_0$  is the initial bead cross-sectional area,  $R_e$  is the equatorial radius of the bead, and  $R_e^*$  is the initial undeformed equatorial radius.<sup>30</sup> Since our system measured the polar diameter of the gel bead as it was compressed, this value was converted to the equatorial radius using equations relating the polar and equatorial radii, as developed by Rodriguez and colleagues.<sup>31</sup>

Once the modulus was determined, the effective crosslink density ( $\rho_x$ ) in terms of moles of chains per unit of dry polymer was calculated using eq. (3):

$$\rho_x = \frac{G}{\nu^{4/3}RT} \quad (3)$$

where  $\nu$  is the volume fraction of polymer,  $R$  is the gas constant, and  $T$  is temperature. Also calculated was the crosslinking efficiency, which is defined as the ratio of effective crosslink density to the theoretical crosslinking density: the crosslink density that would be obtained if each crosslinker molecule formed an elastically effective crosslink.<sup>29</sup>

## Measurement of Crosslinker Partitioning

The partition coefficient of DVS between water and toluene was measured to determine the partitioning of the crosslinker between the two phases. In these tests, DVS was added to water in concentrations comparable with those used in gel-bead synthesis. After the DVS was dissolved in the water, toluene was added to the flask again in ratios consistent with bead synthesis. The flask was stoppered and shaken vigorously to mix the two phases thoroughly, after which the phases were allowed to separate. The volume phase ratios were 7 and 13% with a contact time of 2 or 22 h (the average time the gel beads were suspended during reaction). The concentration of DVS in the aqueous phase after partitioning was measured with a spectrophotometer ( $\lambda_{\max} = 225 \text{ nm}$ ).

In the absence of chemical reaction, the fraction of crosslinker leached from the aqueous phase to the organic phase is given by eq. (4):

$$f = (RK + 1)^{-1} \quad (4)$$

where  $R$  is the volume ratio of aqueous phase to organic phase and  $K$  is the partition coefficient (aqueous-to-organic ratio of molar crosslinker concentrations).

## RESULTS AND DISCUSSION

HPMC gels were successfully produced in bead form and, in general, the swelling properties of the gel beads were consistent with those of bulk HPMC gels solution crosslinked in glass molds. The gel-bead batches were prepared from 20 wt % HPMC-E5 solutions with a constant ratio of catalyst in all batches but with differing crosslinker dosages and phase ratios. The degree of swelling, swelling ratio, transition temperature, and transition sharpness of the different gel-bead batches were used as a means of comparing the effects of the changing synthesis conditions. The physical parameters of the suspension method, stirring speed, impeller diameter, and aqueous/organic phase ratio were varied to study their influence on the size of the bead.

Numerous batches of HPMC gel beads were made with differing swelling degrees and bead sizes. In this article the reproducibility of the synthesis method was not directly examined, although the large number of successful batches indicates that beads are easily prepared and inter-

**Table III Swelling Degree, Swelling Ratio, and Transition Temperature of HPMC Gel Beads for Different Synthesis Conditions**

Batch	DVS Dosage (g DVS/g HPMC)	Phase Ratio (v/v %)	Swelling Degree, $Q_{25}$ (25°C) (swollen)	Swelling Degree, $Q_{75}$ (75°C) (collapsed)	Swelling Ratio, $Q_{25}/Q_{75}$	Transition Temperature (°C)	Sharpness of Transition (%/°C)
1	0.026	17	12.1 ± 0.2	3.0 ± 0.1	4.0 ± 0.2	61.4 ± 1.1	2.3 ± 0.3
2	0.020	16	18.0 ± 1.0	3.4 ± 0.2	5.3 ± 0.5	60.3 ± 1.2	2.8 ± 0.2
3	0.016	2	28.7 ± 0.5	3.6 ± 0.4	7.8 ± 0.7	58.1 ± 1.3	3.2 ± 0.1
4	0.012	13	46.7 ± 4.0	4.3 ± 0.9	10.8 ± 2.8	56.2 ± 3.4	3.5 ± 0.2
5	0.012	7	61.6 ± 3.0	4.4 ± 0.7	14.0 ± 2.8	57.8 ± 1.1	3.5 ± 0.2
6	0.014	13	33.3 ± 4.0	3.0 ± 0.6	11.1 ± 2.6	56.5 ± 0.9	3.6 ± 0.4
7	0.014	7	123.2 ± 6.0	7.0 ± 1.6	17.6 ± 4.1	57.2 ± 1.4	3.8 ± 0.6
8	0.016	12	29.6 ± 0.5	3.1 ± 0.3	9.5 ± 1.0	58.5 ± 1.3	3.6 ± 0.7
9	0.016	7	50.0 ± 4.0	4.5 ± 1.6	11.1 ± 3.3	54.5 ± 1.2	3.1 ± 0.4
10	0.017	7	40.3 ± 4.0	3.5 ± 0.4	11.5 ± 1.5	54.3 ± 3.4	3.2 ± 0.6
11	0.018	7	31.9 ± 3.0	3.3 ± 0.3	9.7 ± 1.6	56.8 ± 2.0	2.9 ± 0.6
12	0.018	7	38.4 ± 4.0	4.1 ± 0.3	9.4 ± 1.2	54.9 ± 3.6	3.1 ± 0.6
13	0.018	10	27.0 ± 3.0	3.2 ± 0.5	8.8 ± 1.8	57.5 ± 1.8	3.1 ± 0.4
14	0.019	7	31.1 ± 4.0	3.0 ± 0.6	10.4 ± 2.5	57.4 ± 1.1	3.2 ± 0.7
15	0.023	7	21.4 ± 2.0	3.2 ± 0.3	6.7 ± 1.1	59.1 ± 1.1	3.2 ± 0.1

Beads prepared from 20 wt % HPMC solutions with 0.1 g of 5N NaOH solution/g of polymer.

nal consistency of the results is generally good. However, there is a variability in swelling properties of the beads within the same batch. Also, not only do reactant ratios affect gel properties but the suspension variables, which directly influence bead size, may also influence the crosslinking of the gel beads.

### Crosslinker Distribution and Kinetics

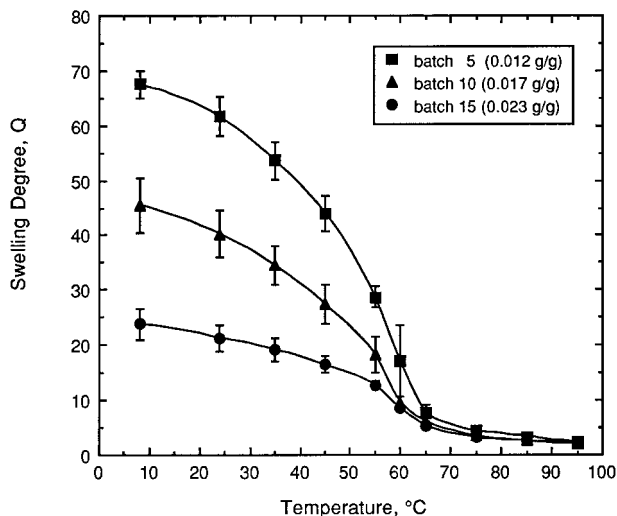
The DVS crosslinker can diffuse out of the aqueous droplets into the surrounding toluene. Therefore it is possible that the concentration of crosslinker in the droplets during synthesis is lower than the initial dosage. However, if the diffusion rate of the crosslinker is much faster than the reaction rate, a pseudosteady state may exist where crosslinker diffuses from the continuous phase into the droplets at the same rate as it is consumed in the gelation reaction. To examine the effect of crosslinker distribution, the rate of diffusion of the crosslinker into the gel was compared with the gelation reaction time.

The partition coefficient of DVS in the two-phase system of water and toluene was determined experimentally to be  $2.8 \pm 0.7$ .<sup>32</sup> Using this average value, eq. (4) predicts that 84% of the initial amount of DVS is leached out of the droplets at a

phase ratio of 7% and 74% is leached out at a 13% phase ratio. The time to reach 90% of these equilibrium concentration values of the crosslinker in the droplets was calculated using equations for the diffusion of solute in spheres.<sup>33</sup> The diffusion coefficient for the DVS in polymer solution was found to be about  $4.0 \times 10^{-6}$  cm<sup>2</sup>/s.<sup>32</sup> Using this value, droplets 1.67 mm in diameter (the largest average bead size produced in this work) would have 70% of the initial DVS dosage diffuse out of the droplet in less than 4 min. For smaller droplets, this time can be as short as 30 s.<sup>32</sup>

To determine the reaction time of the gel beads, several batches were prepared using the same reactant concentrations while varying the suspension (reaction) time from 3 to 48 h. Also for comparison, bulk HPMC gels were synthesized in glass molds at the same reactant concentrations. The swelling degree of the gels at 25°C was used as a qualitative measure of crosslinking of the networks; the results are presented in Table II.

While a reaction time of 3 h was adequate for bulk gel synthesis, the crosslinking was not complete for gel beads in this time. This conclusion was based on the fragile and tacky appearance of the gel beads and on their larger average diameter and higher swelling degree as compared with the gel beads prepared at longer times. Beyond 10 h



**Figure 1** Dependence of swelling degree on initial crosslinker concentration in reactant solution. Below the transition temperature, swelling decreases significantly with increases in crosslinker concentration (dosage given in legend as g DVS/g HPMC). These examples were suspended at a phase ratio of 7%, although at slightly different stirring speeds: batch 5, 650 rpm; batch 10, 736 rpm; batch 15, 600 rpm. Lines are drawn to guide the eye.

of reaction time properties were fairly consistent, indicating that somewhere between 3 and 10 h the reaction is virtually complete. For the gel-bead batches described later in this work the reaction time was generally fixed at 22 h.

Since the diffusion rate is much faster than the gelation time, the droplets likely maintain a pseudo-steady-state concentration with respect to the toluene phase. However, as the results show, the swelling degrees of the gel beads are significantly higher than the bulk gels, which indicates that a lower amount of crosslinking is occurring in the gel-bead synthesis. This implies that much less than the initial dosage of crosslinker actually participates in the reaction. A closer examination of the swelling degree and crosslinking in the gel beads is the subject of a subsequent paper.

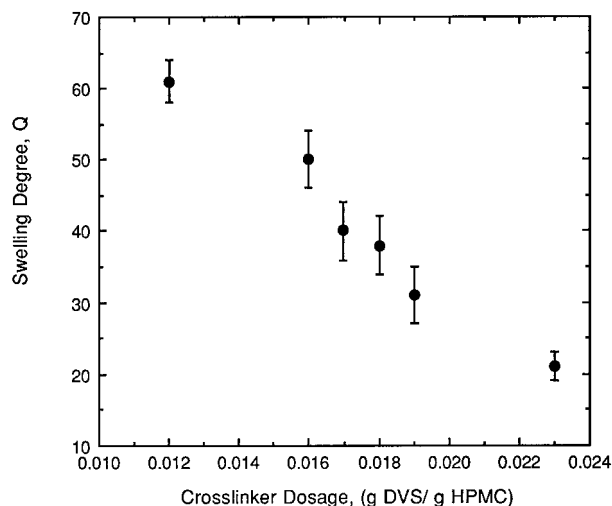
### Swelling Properties of the Gel Beads

By varying the DVS dosage and phase ratio, gel beads were created with volume swelling degrees ranging from 12 to 123 in water at 25°C, as listed in Table III. The swelling ratios of the gels (from the swollen state at 25°C to the collapsed state at 75°C) ranged from 4 to 18. Thus, collapsed gels

are able to absorb up to 18 times their volume of water as they swell from a collapsed state at 75°C to a swollen state at 25°C. The process can also be reversed, for an indefinite number of swell/shrink cycles.

The differences in swelling degree for beads synthesized with differing initial dosages of crosslinker are clearly observed when the swelling degree of different bead batches is plotted against temperature. In Figure 1 the temperature profiles for three batches prepared with 0.012, 0.017, and 0.023 g DVS/g HPMC are plotted. The difference in swelling degree is observed at low temperatures where the swelling degree is higher for gel beads synthesized with lower initial crosslinker dosages. Differences in swelling degree were not observed at higher temperatures where the gels are collapsed. The influence of crosslinker dosage is also shown in Figure 2. Here, the degree of swelling for gel-bead batches prepared at the same phase ratio (7%) decreases with increasing initial crosslinker dosage. This trend is consistent with the formation of a greater number of crosslinks at higher dosages of crosslinker. All of these results are consistent with the behavior of bulk HPMC gels.<sup>16</sup>

The variations in swelling degree between batches are mainly accounted for by differing amounts of crosslinker used in preparing the beads. However, the ratio of dispersed polymer



**Figure 2** Swelling degree in water at 25°C of gel-bead batches produced at a phase ratio of 7%. An increase in the initial amount of crosslinker results in a lower swelling degree. (Not included is batch 7, which was prepared with a lower amount of catalyst.)

**Table IV Swelling Degree for Batches Produced at Different Suspended-to-Continuous-Phase Ratios**

Batch	Crosslinker Ratio (g DVS/g HPMC)	Phase Ratio (% v/v)	Swelling Degree (25°C)
4	0.012	13	46
5	0.012	7	61
6	0.014	13	33
7	0.014	7	123
8	0.016	12	29
9	0.016	7	50

solution to continuous toluene phase was also found to have an influence on the swelling degree of the beads. This influence was examined in synthesis trials where all reaction conditions were constant except for the phase ratio. Here, gels from batches suspended at a lower phase ratio (7%) had higher swelling degrees than did gels prepared at higher phase ratios (13%) (Table IV).

The volume transition of the HPMC gel beads was continuous and occurred over a temperature range of about 50 degrees (see Fig. 1). Between 25° and 75°C, on average, 85% of the volume change occurred. The average transition temperature for these HPMC-E gel beads was  $57 \pm 2^\circ\text{C}$ , approximately that of the LCST of HPMC-E, reported to be  $55 \pm 1^\circ\text{C}$  (note that the LCST of HPMC-E reported here is of HPMC-E4M, a higher-molecular-weight version of HPMC-E than the HPMC-E5 used for the gel beads).<sup>16</sup> The sharpness of the transition averaged  $3.2 \pm 0.4\%/^\circ\text{C}$ . The values of the transition temperature and sharpness of transition indicate the most significant working range of the gel and also allow for comparison between bulk gels and gel beads.

A comparison of the transition temperatures of gel beads and bulk gels with the same swelling degrees in water at 25°C appears in Table V. As shown, the values for the transition temperature and transition sharpness for gel beads are nearly the same as those found for solution-crosslinked bulk HPMC gels. The average transition temperature of bulk gels crosslinked with DVS with volume swelling degrees ranging from 25 to 230 was  $60 \pm 2^\circ\text{C}$  with a transition sharpness of  $2.0 \pm 0.2\%/^\circ\text{C}$ .<sup>28</sup> In general, the swelling behavior of the gel beads is the same as for solution-polymerized bulk gels. Only the physical form of the gels are different. This verifies the hypothesis that the mechanism of synthesis does not affect the gel properties. Thus the suspension-crosslinking method can be used to make temperature-sensitive gels with the same properties as bulk gels.

The crosslink densities of individual gel beads were measured using the uniaxial compression test and were consistent with the published results for bulk HPMC gels.<sup>16</sup> The gel beads, made from 20 wt % polymer solution, had an average crosslinking density of  $7.9 \times 10^{-5} \text{ mol/cm}^3$  (dry

**Table V Transition Temperature and Transition Sharpness: Comparison of Gel Beads Versus Bulk Gels with Similar Swelling Degrees in Water**

Bulk HPMC-E Gels			HPMC-E Gel Beads		
Swelling Degree (25°C)	Transition Temperature (°C)	Transition Sharpness (%/°C)	Swelling Degree (25°C)	Transition Temperature (°C)	Transition Temperature (%/°C)
$62 \pm 1$	$58 \pm 2$	$3.0 \pm 0.2$	$61 \pm 3$	$50 \pm 1$	$3.5 \pm 0.2$
$29 \pm 1$	$62 \pm 2$	$3.0 \pm 0.1$	$29 \pm 1$	$59 \pm 1$	$3.6 \pm 0.7$
$24 \pm 1$	$62 \pm 2$	$3.0 \pm 0.3$	$21 \pm 2$	$59 \pm 1$	$3.2 \pm 0.1$

The bulk gels were made in glass molds from 10% aqueous HPMC-E4M solution; the gel beads from 20% HPMC-E5 solution. The results for bulk gels are taken from Harsh and Gehrke.<sup>16</sup>



**Table VI Synthesis Conditions and Size Distribution Data at Synthesis for HPMC-E Gel Beads**

Batch	Phase Ratio (% v/v)	Stirring Speed (rpm)	Impeller Diameter (cm)	Arithmetic Mean Diameter (mm)	Median (mm)	Mode (mm)	Geometric Mean Diameter (mm)	Geometric Standard Deviation (mm)
4	13	650	5.0	0.62 ± 0.14	0.60	0.59	0.61	1.22
5	7	650	5.0	0.44 ± 0.11	0.43	0.40	0.42	1.26
6	13	748	5.0	0.62 ± 0.16	0.60	0.55	0.60	1.29
7	7	637	5.0	0.79 ± 0.14	0.76	0.75	0.78	1.18
8	12	408	5.0	0.98 ± 0.32	0.93	0.85	0.93	1.35
9	7	410	5.0	1.67 ± 0.37	1.67	1.55	1.62	1.23
10	7	736	3.8	1.05 ± 0.26	1.01	0.95	1.02	1.27
11	7	650	3.8	0.92 ± 0.26	0.88	0.85	0.88	1.30
12	7	550	3.8	1.29 ± 0.47	1.17	1.10	1.22	1.38
13	10	550	5.0	0.84 ± 0.19	0.84	0.80	0.82	1.25
14	7	550	5.0	0.89 ± 0.19	0.89	0.85	0.87	1.24
15	7	600	3.8	1.14 ± 0.36	1.07	1.00	1.09	1.33

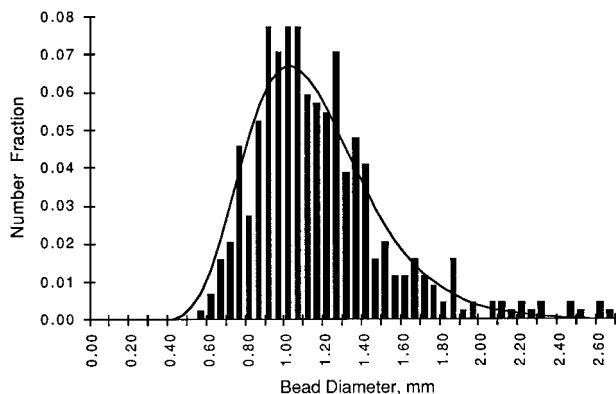
basis) and crosslinking efficiency of 20%. In comparison, solution-crosslinked bulk HPMC-E gels, made from 10 wt % polymer solution, had an average crosslinking density of  $2.5 \times 10^{-5}$  mol/cm<sup>3</sup> and crosslinking efficiencies from 5 to 12%.<sup>16</sup>

The gel beads used in the compression tests had swelling degrees ranging from 12 to 54 at room temperature; gels with higher swelling degrees were too soft to be measured with the compression equipment. It should be noted that although the values obtained were of the same order of magnitude as bulk HPMC gels, there was a large variability in measurement of the crosslink density within a batch of gel beads. It was impractical to measure more than 3 to 10 beads per batch, and these were not large enough samples to draw statistically significant conclusions regarding batch-to-batch variations. Nevertheless, the crosslinking results do indicate that the beads from the measured batches have the same elastic behavior as bulk gels, which was the primary objective of the tests.

### Physical Form of the Gel Beads

Like bulk HPMC gels, the gel beads are clear and colorless in appearance when swollen. The beads are quite resilient and bounce when dropped onto a hard surface—except for the most highly swelling gels with low crosslinking, which, as for bulk gels, are easily fractured. As the gels are warmed and shrink, they become opaque at and above the transition temperature. Dry and free of water, the gel beads are nonspherical, glassy particles, yellow-brown in color, which is the same color as aqueous solutions of HPMC-E5. When dry gel beads are immersed in water, they swell and again become spherical beads.

Table VI lists the arithmetic mean diameter, mode, median size, and geometric mean diameter measured for each batch at synthesis, along with the phase ratio, stirring speed, and impeller size used in their synthesis. Gel beads were made with average “at synthesis” diameters that ranged from 0.44 to 1.67 mm. The arithmetic mean was



**Figure 3** Representative example of bead size distribution at synthesis (batch 15). The histogram is the number fraction of beads at a given diameter as measured. The curve is the lognormal distribution function calculated using the values of the geometric mean diameter and geometric standard deviation from Table V.

less than the geometric mean for the gel beads, indicating that the beads were not monodisperse (in which case the arithmetic mean and the geometric mean would have the same value).

The size distributions for each bead batch can be approximated with a continuous curve generated from a lognormal distribution function.<sup>34</sup> The lognormal distribution function has a characteristic skewed shape with a long tail at the larger sizes of the distribution. The distribution frequency function approximates the number fraction of particles whose diameters lie within a given size fraction.

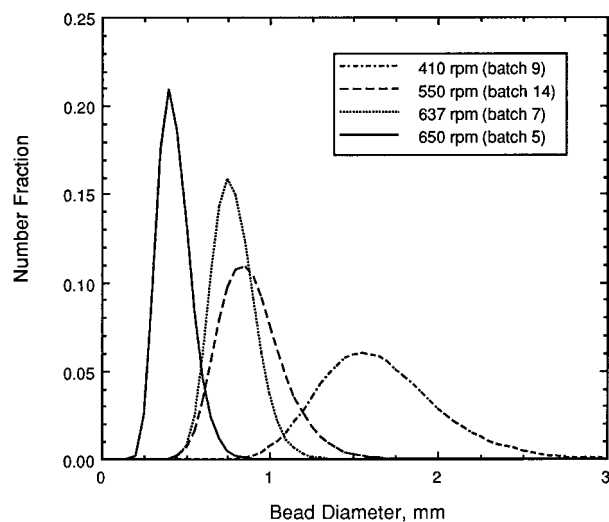
To fit the size data from each bead batch with the distribution function, it was necessary to calculate the geometric mean diameter and the geometric standard deviation. Values for the distribution function were then calculated using the average diameter within 50- $\mu\text{m}$  size fractions. When the lognormal distribution function was fit to the particle size histograms of the gel beads, as shown in a representative plot for one bead batch in Figure 3, the curve approximated the distribution. For each batch, the relationship between the mean, median, and mode was such that the mean > median > mode, which is typical of a lognormal distribution.

In general, with all other suspension variables constant, the average bead size of a batch decreased as the stirring speed was increased. This trend is best observed in Figure 4, where the size distributions of four bead batches, prepared at the same phase ratio with the same size impeller, are

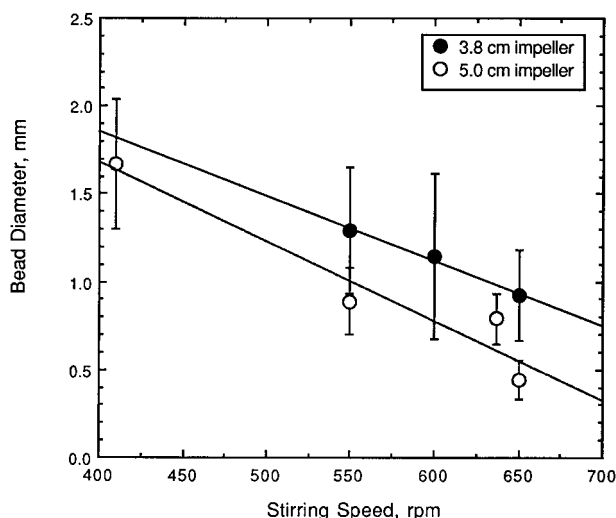
compared. As shown, the average bead size decreases as the stirring speed increases, as interpreted from the shift in the peaks of the size distributions. A similar trend is observed when the size distributions of batches 10, 11, 12, and 15 or batches 4, 6, and 8 are plotted. The decrease in average bead size with increasing stirring speed is as expected, based on drop-size correlations for liquid/liquid dispersions.<sup>21-24</sup>

As bead size decreased with increased stirring speed, the size distribution also narrowed. A narrow size distribution indicates a small width of the bead-size distribution (arithmetic standard deviation less than 0.20 mm). This was observed for gel beads produced at stirring speeds above 650 rpm. This same trend of narrow size distributions for beads prepared at higher stirring speeds was also reported for the suspension polymerization of methyl methacrylate.<sup>18</sup>

The best results for preparing gel beads were obtained when the stirring speeds were between 400 and 700 rpm. At speeds lower than 400 rpm, oblong or oval bead particles resulted (results not presented). While bead shape can be affected by other factors, such as phase ratio and viscosity, it became clear that a minimum speed, around 400 rpm for the system used here, must be reached to provide the shear stress necessary for drop breakage to occur and to stabilize the dispersion. Above 700 rpm a severe vortex formed, causing unstable



**Figure 4** Dependence of particle size distribution on stirring speed. An increase in stirring speed decreases the average bead size and narrows the distribution. These batches were produced at a phase ratio of 7% with a 5-cm impeller with all other conditions equal.



**Figure 5** Effect of impeller diameter and stirring speed on bead size. These batches were produced at a phase ratio of 7% with a 3.8- or 5-cm impeller with all other reaction conditions the same. Lines are drawn to show the trend.

mixing in the suspension which led to inconsistent trends in bead size. For example, the average diameter of beads produced in a batch at a speed of 736 rpm (batch 10) was larger than that of a batch suspended at 650 rpm (batch 11).

Bead size was also affected by the size of the impeller, as shown in Figure 5 (batches prepared at stirring speeds below 400 rpm or greater than 700 rpm were not included, for the reasons cited above). Two impellers, 5 and 3.8 cm, were used to suspend the aqueous polymer phase. The larger-diameter impeller produced a smaller average size of beads in batches made with the same phase ratio, suspended phase viscosity, and vessel dimensions. Drop-size correlations predict that the decrease in bead size is approximately proportional to the inverse of impeller size since the larger impeller creates a greater shear force.<sup>21,24</sup>

To examine the influence of the phase ratio on bead size, three sets of HPMC gel beads were synthesized with all reactant conditions constant except for the ratios of the amount of suspended phase to continuous phase, which were either 7 or 13%. Table VII lists the results obtained for comparable batches produced at the same or nearly the same stirring speeds. It was expected that bead size would decrease with decreasing phase ratios because a lower amount of dispersed phase would have less probability of droplet coalescence, which can lead to larger beads. A drop-

let size correlation for liquid/liquid dispersions predicts that droplet size is directly proportional to the volume of the dispersed phase.<sup>17</sup> However, the effect of phase ratio in our system cannot be clearly distinguished because the size distributions overlap. Nevertheless, at low stirring speeds (410 rpm) the higher phase-ratio system produced a smaller average bead size. At 550 rpm there was very little difference in bead size. At 650 rpm, the higher phase ratio had larger-sized beads.

## CONCLUSIONS

HPMC gel beads were synthesized by chemically crosslinking the linear polymer by a suspension-crosslinking method. This technique, capable of being scaled up for large-scale production, produces gels in spherical bead form. Because the polymer droplets contain all reactants prior to dispersion in the suspension method, the suspended polymer droplets in effect act as tiny solution-crosslinking reaction sites with the continuous organic phase acting as the mold.

The synthesis method does not significantly alter the performance properties of the gels. The temperature-sensitive HPMC gel beads were produced over a wide range of swelling degrees with crosslink density, transition temperature, and transition sharpness consistent with bulk HPMC gels produced in molds. Together, the temperature response along with the small spherical size of the HPMC gel beads could make them particularly useful in drug delivery or separation processes where a uniform shape is necessary for mass transfer performance and ease of handling.

The size of the gel beads was approximately 1

**Table VII** Effect of Phase Ratio on Bead Size

Batch	Stirring Speed (rpm)	Phase Ratio (% v/v)	Bead Diameter (mm)
8	410	12	0.98 ± 0.32
9	410	7	1.67 ± 0.37
13	550	10	0.84 ± 0.17
14	550	7	0.89 ± 0.19
4	650	13	0.62 ± 0.14
5	650	7	0.44 ± 0.11

Batches were produced from 20% aqueous polymer phase suspended in 700 mL of toluene with a 5-cm six-bladed turbine.

mm in diameter. Bead size was influenced by the stirring speed, impeller diameter, and phase ratio used in the reaction. Although gel-bead size can be controlled through agitation conditions, this presents the greatest challenge for process scale-up.

For the system studied here, there are also other factors affecting the beads. Evidence demonstrated that the partitioning of the crosslinker influences the gel reaction, apparently lowering the effective amount of crosslinker that participates in the reaction. There also is a wide variability in swelling properties of the gel beads produced within the same batch. In a subsequent paper, the swelling degrees of gel beads within a batch will be more closely examined. The evidence indicates that the swelling degree of the gel beads is directly related to their size at synthesis and that within a batch, the smaller beads swell more than larger beads.

Matteo Mancini contributed to the experimental work in Table II. This study was partially supported by Gel Sciences, Inc., Bedford, MA.

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