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Polymer 42 (2001) 1541–1546

polymer

www.elsevier.nl/locate/polymer

Particle size distribution analysis as a characterization method for gel particles produced in suspension reactors

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Received 27 January 2000; received in revised form 5 July 2000; accepted 13 July 2000

Abstract

For gel beads produced in suspension reactors, the properties are usually assumed to be independent of particle size over the range of sizes within a batch. However, differences in equilibrium swelling among different size fractions of particles can be distinguished by analysis of the particle size distributions (PSD) of particles in two different swollen states. The method was proven effective in revealing differences in swelling as a function of size for hydroxypropyl methylcellulose gel beads that were not otherwise apparent. Since solvent sorption controls the useful properties of gels like permeability and is a reflection of gel synthesis variables, the ability to determine variations in properties with particle size is important to predict gel performance or to modify gel synthesis conditions to improve particle uniformity. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Hydrogels; Gels; Particle size distribution

1. Introduction

Gels are crosslinked polymer networks that can absorb a significant amount of solvent while maintaining their three-dimensional structure. They are characterized in terms of their equilibrium swelling degree, permeability, kinetics of swelling and modulus. The swelling degree is most important as it affects the other properties as well as the utility of a gel in a given application. Gels are engineered with desired degrees of swelling tailored for a given application mainly through selection of the precursor polymer (polymer–solvent interaction parameter and ionization) and crosslink density. Hydrogels, which are gels that absorb water, are a particularly important class of gels, with applications in consumer products, separation media, and medical and pharmaceutical applications.

Gels can be synthesized in a variety of geometries and sizes depending upon the intended application. Gels can be created as spherical beads by suspension polymerization or suspension crosslinking techniques [1–4]. In this form, they are used in various applications such as the stationary phase in chromatography, in size selective separations, for enzyme and cell immobilization, and as drug delivery systems [5–17]. The swelling kinetics of hydrogels is often a diffusion controlled process and thus, the sorption time scales with the square of dimension [18]. Therefore, in applications such as superabsorbents, gels are used in particulate form to provide faster sorption rates than can be achieved by larger bulk gel pieces.

The swelling characteristics of gel beads, as well as particle size, are critical in the design of gels for these applications. For example, the diffusivity of solutes within hydrogels is a direct function of the swelling degree [19]. In addition, the pore size and pore size distribution, which also depend upon the swelling degree, determine the useful molecular separation range in size exclusion chromatography or gel filtration chromatography [20]. Finally, the uniformity of swelling degree between beads can be important to obtain proper mass transfer characteristics, particularly in drug delivery applications where the diffusion rate of solutes through the gels determines the rate of drug release.

The swelling properties of gel beads or particles produced from a particular batch are usually assumed to be uniform, independent of particle size. However, this assumption may not be valid for reasons related to differences in surface/volume ratios. As one example, we had previously developed a suspension crosslinking method for the preparation of spherical gel beads from linear polymers

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PII: S0032-3861(00)00545-0

like hydroxypropyl methylcellulose (HPMC) [1]. In this example, we found that the swelling properties of the gels were a function of particle size, with the smaller beads swelling relatively more than the larger beads that were produced in the same reaction vessel; the smaller beads were less crosslinked. This effect could have been the result of the diffusion of the crosslinker out of the suspended phase and into the continuous phase-a process that is a function of the surface area and the size of the droplets [1,21]. Such results suggested the need for a change to a suspending solvent in which the crosslinker was much less soluble. Other surface effects can contribute to non-uniformities for gels synthesized by conventional suspension polymerization of suspended monomer droplets. Thus the determination that such effects exist in a suspension polymerization process may suggest changes in synthesis conditions that can improve uniformity of the product.

In this paper, we present a method to determine the uniformity of swelling in a batch of gel beads. Using a particle growth analysis (PGA) method originally developed to study the change in size of aerosol particles, we are able to distinguish differences in swelling of individual hydrogel beads from within a given batch [22]. The model system used to test the utility of the PGA technique for analyzing gel particle uniformity was the synthesis of HPMC gel in bead form. These beads were made by covalently crosslinking aqueous droplets of the precursor polymer suspended in an organic solvent [1]. The analysis of bead swelling uses a comparison of the shift in the particle size distributions of the gel beads from their initial size at synthesis to their size when swollen to equilibrium in water. From the particle size distribution (PSD), changes in bead dimensions are used to obtain the swelling ratio (ratio of bead volume swollen to equilibrium in water to volume at synthesis) of individual gel beads. The analysis of the PSD in two different swollen states becomes a relatively simple means of assessing differences in swelling of beads of a given size.

1.1. PSD analysis

The method used in this work to analyze the uniformity of gel beads in a given batch is based on a procedure originally developed by Heisler and Friedlander to study the change in particle size of photochemical smog [22]. For those aerosol systems, where physical properties are strongly dependent on particle size, the PGA provided a means of comparing the size of aerosol particles as a function of time. To make these comparisons, the PGA manipulated the size distributions of particles to determine changes in aerosol particle size from one state to another as a result of particle aggregation.

For hydrogel beads, mathematics analogous to aerosol PGA are shown to allow the comparison of changes in the size of beads as they grow from one size to another upon changes in solvent. As a result of water sorption, the PSD of beads swollen in water spreads over a wider size range and shifts to a larger mean bead diameter as compared to the PSD at synthesis [1]. However, this work demonstrates that simple observation of shifts in the distribution alone may not reveal significant variability in bead swelling. Only when the size of individual particles or beads is compared in each state can swelling differences be uncovered.

The size of individual beads in different swollen states is compared when the PSD data is plotted as a cumulative oversize distribution-a plot of the number fraction of particles larger than a given size where the cumulative percentage of beads larger than a given size decreases from 100% for the smallest size to 0% for the largest size in the range measured. Changes in the particle size are uncovered by comparing the size of the particles at a given number fraction for the gel state at synthesis to the size of the beads at the same number fraction for the swollen state in water at equilibrium. It was assumed that all the beads in the same initial size fraction swell to the same degree and, therefore, the total number of beads larger than a given size is conserved. Thus, as a given bead swells, the number of larger beads remains constant. This assumption is valid when the size increment is chosen so that differences in bead swelling do not change the number of beads within a size fraction. This is true for the 50 μm size increment used here for the HPMC gel beads [21].

2. Materials and methods

2.1. Reagents and chemicals

HPMC (Methocel®E5 PREM) was a sample from Dow Chemical, Inc. (Midland, MI) and used as received. 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 at a concentration of 5 N. Concentrated hydrochloric acid (Fisher Scientific, Pittsburgh, PA) was diluted with distilled water to prepare a 1 N solution. Toluene (Aldrich) was used as received.

2.2. Gel synthesis

The HPMC gel beads were synthesized by suspension crosslinking as described in detail previously [1]. Briefly, polymer was dissolved in water to produce a 20% w/w solution to which the catalyst, sodium hydroxide (0.11 g 5 N NaOH/g polymer), and the crosslinker, DVS, were added. The ratio of DVS in grams/polymer in grams was 0.017, 0.018 and 0.023 for batches 1, 2 and 3, respectively. The aqueous polymer solution was dispersed into toluene at a phase ratio of 7% v/v (dispersed to continuous phase) stirring at fixed speeds in a 1 l round bottom, baffled, glass reaction kettle. Agitation was provided by an overhead stirrer equipped with a 3.8 cm six-bladed disk turbine. The reaction was allowed to proceed for 22 h after which the toluene was decanted and the gel spheres were transferred to a beaker filled with water. The beads were then repeatedly swollen and shrunken in water, by alternately heating to 80°C and cooling to room temperature, to remove all unreacted polymer from the gels (the water content of these gels is a strong function of temperature). Residual base released from the network was neutralized with 1 N HCl solution. Three batches of the gel beads were produced at stirring speeds of 740, 650 and 600 rpm for batches 1, 2 and 3.

2.3. Bead size measurement

The mean number average bead size, d_p, for each batch was determined by individually measuring a random sample of beads (~450–500) using a video microscope and image analysis system, as described elsewhere [23]. The diameters of the beads were measured immediately after they were removed from the reaction suspension (the "at synthesis" diameter) and again when swollen to their equilibrium value in water at room temperature (the swollen diameter). The same beads were measured in each state. For each batch, the bead sizes were separated into 50 μm size increments to obtain the PSD. A small size increment was chosen to minimize swelling differences within a size fraction. The particle sizing was tabulated as a differential analysis to show the number fraction of beads in each size increment as a function of the average bead size, d_i, in the increment.

The PSDs were fit with a lognormal distribution function. For aerosol dispersions, the lognormal function is selected empirically to fit to the wide size range and skewed shape of the size distributions. The size distributions of the gel beads are also found to be fit well by the lognormal function. The lognormal number frequency function gives the fraction of particles whose diameters lie between d_i and $d_i + \mathrm{d}d_i$ as expressed in Eq. (1):

$$\mathrm{d}f = \frac{1}{\sqrt{2\pi}\ln\sigma_g}\exp\left[-\frac{(\ln d_i - \ln d_g)}{2(\ln\sigma_g)}\right]\mathrm{d}d_i \tag{1}$$

where d_g is the geometric mean diameter and σ_g is the geometric standard deviation within a given size fraction [24]. The geometric mean was calculated from the arithmetic mean of the natural log of the average bead diameter within a given size fraction. The geometric standard deviation was calculated from the standard deviation of the logarithms of the average particle diameters within a given size fraction. The change in average particle size, $\mathrm{d}d_i$, is kept at 50 μm.

For the bead growth analysis, cumulative oversize distribution plots were created for each bead batch at each swollen state-the "at synthesis" and water-swollen states-and plotted on a semi-log scale. In this representation of the PSD, all beads are greater than or equal to the smallest size in the distribution, a size at which the cumulative number fraction corresponds to a value of 1.0. As bead size increases, the number of beads greater than or equal to a given size decreases up until the largest bead size where the number fraction of larger beads is zero. When the two different size distributions are plotted together, a horizontal line at a given number fraction intersects the two curves to reveal the sizes of the beads in the two states.

2.4. Measurement of gel swelling degree and swelling ratio

The average volume swelling degree, Q_{ave}, of the gel beads was measured in the swollen state in water at 25°C. This measurement was made by placing a sample of beads from a batch ($n > 2000$) into a 100 ml graduated cylinder with an excess of distilled water, for ~24 h to allow the volume of the beads to reach an equilibrium state. After this time, the beads were filtered, carefully blotted dry of excess water with a lint free tissue, weighed (swollen weight) and placed in a 60°C oven to dry. The blot-and-weigh method was repeated in triplicate (±10%) to get an average swollen weight. The gel beads were again weighed after drying to obtain the dry gel or polymer weight. The swollen and dry gel volumes were calculated by multiplying the measured weight by the gel density. In the swollen state, a density of 1 g/ml was assumed since the swollen gels are mostly water and almost neutrally buoyant in water. The dry gel density is 1.25 ± 0.02 g/ml [21]. The volume swelling degree was then obtained by dividing the swollen gel volume by the dry gel volume. The swelling ratio, S, represents the ratio of the volume of the gel beads in their fully swollen state in water (25°C) to their volume "at synthesis". When comparing swelling ratios of individual beads for the size analysis, the "at synthesis" and swollen gel volumes were calculated from the measured bead diameters.

3. Results and discussion

Analysis of the PSD in two different states was proposed as a means of uncovering differences in gel properties as a function of particle size. To demonstrate the analysis, three batches of HPMC gel beads produced by a suspension crosslinking method were examined. The gels were prepared under similar reaction conditions except for modest variations in crosslinker ratio and stirring speeds. These differences in synthesis conditions lead to differences in size and swelling degree of the beads. Differences in the swelling degree and thus effective crosslink density of gel beads produced by the suspension process cannot be attributed solely to crosslinker ratio. Other factors such as the stirring speed, impeller size, and ratio of suspended to continuous phases, all of which affect bead size, also cause changes in bead swelling [1]. In fact, as will be shown by the PSD analysis for the HPMC gel beads, within a bead batch, the swelling degree of the gels is also a function of bead size, which reflects the nature of the synthesis process.

3.1. Bead size

The HPMC hydrogel beads produced by the suspension crosslinking method are typically around 1–2 mm in

Table 1
HPMC gel bead swelling properties at synthesis and swollen in water (n is the number of beads measured; other variables are defined in the text)

Batch	Q_{ave}	S_{ave}	n	At synthesis			Swollen (25°C)		
				d_p	d_g	σ_g	d_p	d_g	σ_g
1	40 ± 4	4.8	492	1.05 ± 0.26	1.02	1.27	1.82 ± 0.39	1.78	1.23
2	31 ± 3	3.9	455	0.92 ± 0.26	0.88	1.30	1.52 ± 0.38	1.47	1.25
3	21 ± 2	2.8	440	1.14 ± 0.36	1.09	1.33	1.65 ± 0.48	1.55	1.29

diameter and have been prepared with swelling degrees ranging from 10 to 100 [21]. The swelling degree in water at 25°C, the average swelling ratio (S_{ave}), the sizes at synthesis and after swelling in water of three bead batches examined here are listed in Table 1. The values of the swelling degrees and swelling ratios listed in Table 1 are average values calculated from a sample of beads covering a wide size range within a batch. Measurement of the swelling degree in this manner does not allow differences in swelling of beads in different size fractions to be distinguished. To make the distinction among size fractions, the size distributions of the beads in two different swollen states were determined.

The diameters of the gel beads were measured immediately after they were synthesized and again after they were swollen to their equilibrium swelling degree in water at room temperature (≈25°C). The beads were separated into 50 μm size increments and by counting the number of beads in each size increment over the entire size range the PSDs were created. Fig. 1 displays the size distribution of bead batch 1 in the "at synthesis" state. Shown is the number fraction — the number of beads in a given size fraction divided by the total number of beads — plotted against bead diameter. For each batch in either swollen state, the particle size histogram is asymmetrical, with a skewed shape toward the larger sizes, characteristic of a lognormal distribution. The distributions for each batch were fit using the lognormal distribution function (Eq. (1)). In all cases, the function was a good approximation of the PSD.

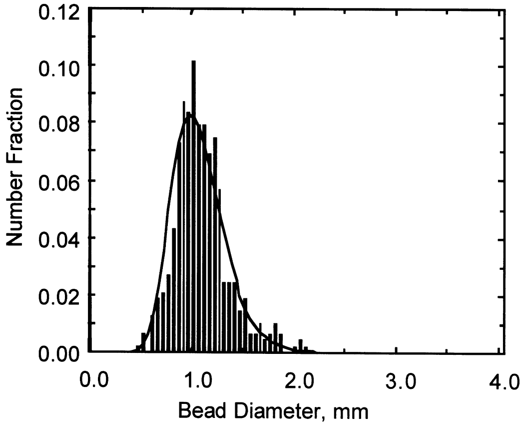

Fig. 1. Size distribution of gel beads "at synthesis" for batch 1. The columns represent the measured bead diameters and the line is the lognormal fit. The average size and geometric mean and standard deviations are listed in Table 1. For all batches, the bead size in a batch is distributed over a wide size range that is fit well by the lognormal distribution function.

The average arithmetic mean size of the different batches of gel beads "at synthesis" and when equilibrated in water at room temperature (25°C), found from the size distributions, are listed in Table 1. In the previous work, it was shown that the initial gel bead size was influenced by several factors including the ratio of the aqueous polymer phase to the organic suspending phase, the stirring speed, and the size of the impeller [1,21]. The similarity in initial size for the beads in Table 1 reflects the fact the synthesis conditions were similar. Differences in swollen sizes are due to the differences in the effective crosslink density of the beads which, as discussed, is influenced by several variables.

In Fig. 2, the size distributions in the two swollen states are shown for bead batch 1 as represented by lognormal curve fits to the data; figures for the other batches are similar. The size distributions for each of the bead batches in the swollen state shift to a larger mean diameter and have a lower peak covering a wider size range as compared to their "at synthesis" distribution. This change in the shape of the PSD for the swollen state is to be expected as the

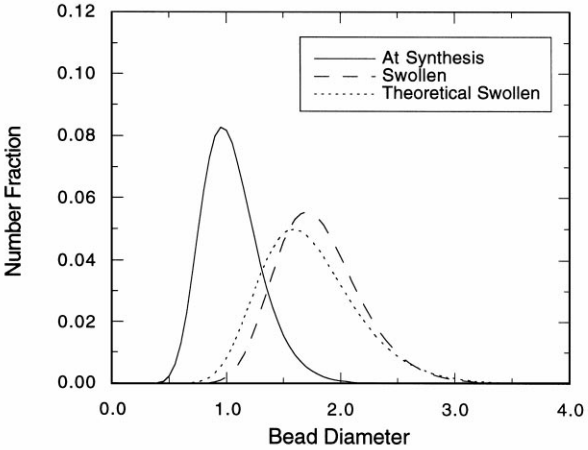

Fig. 2. Size distributions of gel beads "at synthesis" and when swollen in water at 25°C for batch 1. The distributions are represented by their lognormal curve fit. The theoretical swollen curve is based on uniform swelling of the beads. As shown, the theoretical swollen and actual swollen PSD curves are not superimposable, indicating non-uniformities in bead swelling. See text for details.

spherical gels get larger. This is true even if the all of the gel beads within a batch swell uniformly. If the beads were to swell uniformly, the distribution that would be obtained is represented by theoretical swollen PSD curve in Fig. 2. The theoretical PSD was generated by multiplying the initial volume of each individual bead (calculated from measured diameters) by the average swelling ratio for the bead batch, as listed in Table 1, to obtain a theoretical swollen volume. Using this swollen volume, the theoretical swollen diameters were derived, the beads were fractioned by size and a lognormal curve was fit to represent the distribution. Although the differences in shapes of the swollen PSD and theoretical PSD may appear subtle — possibly leading one to conclude that a uniform swelling degree exists for all beads in a batch — closer analysis of the swelling of individual beads using the PSD reveals a consistent trend of differences in bead swelling that the swelling of the gel beads within a batch is not constant over the entire size range.

3.2. PSD analysis

Comparisons of swelling among the different size fractions in the two swollen states can be made when the size distribution is plotted as a cumulative oversize distribution. This type of distribution, obtained by plotting the number fraction of beads larger than a given size against bead diameter, was created for each of the batches. Shown in Fig. 3 as an example are the results for bead batch 1. Using these plots, the size of a bead in each swollen state was found at a given number fraction. For example, for batch 1, beads at a number fraction of 0.1 had an initial diameter of 1.4 mm as found on the "at synthesis" curve and a swollen diameter of 2.3 mm as found on the swollen curve. In a similar manner, sizes over the entire size range were found from the cumulative plots. These values were then used to calculate the volume of individual beads in each swollen state. By comparison of the volume of a bead in each swollen state at a given number fraction, the volume change from the initial size to the swollen size (bead growth) was calculated.

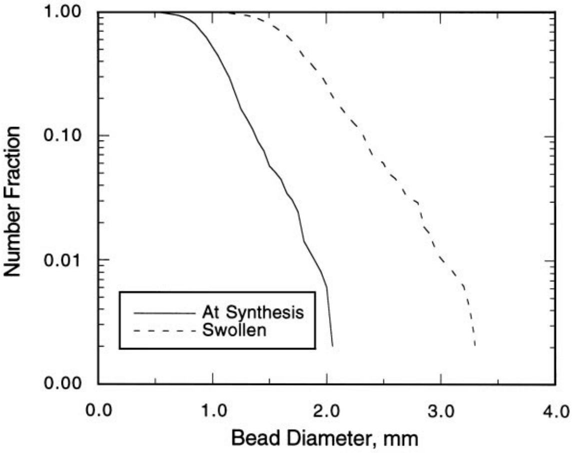

Fig. 3. Cumulative oversize distribution plots of HPMC gel beads of batch 1. At a given number fraction, these plots reveal the size of beads in each swollen state.

For each batch, the swelling ratios of individual beads (calculated by dividing the volumes of the beads in the

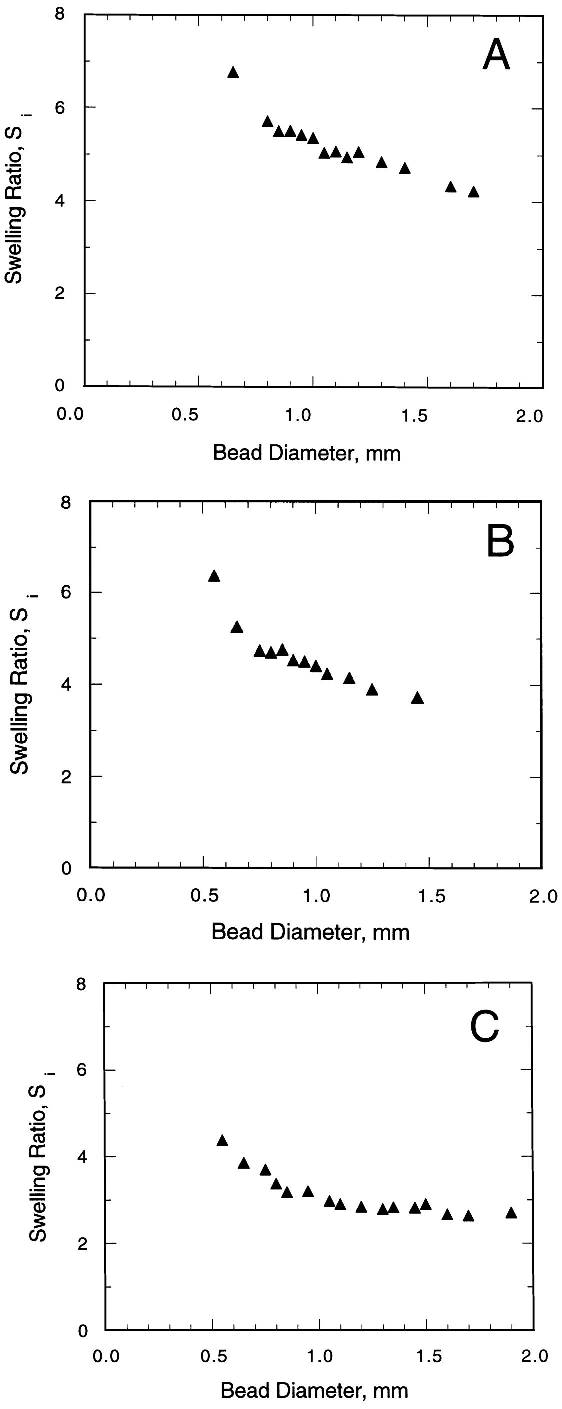

Fig. 4. Swelling ratio of gel beads as a function of size. Plotted are swelling ratios against initial "at synthesis" bead size for three bead batches produced using different amounts of crosslinker: (A) batch 1; (B) batch 2; (C) batch 3. The swelling ratio within a bead batch decreases as bead size increases.

swollen state by their initial volume) were plotted against the "at synthesis" bead size. Fig. 4 shows that for each bead batch, the swelling ratio decreased as the bead diameter increased. Thus, within a batch, the swelling degree was not uniform as the initially smaller gel beads swell much more (around 75%) than the initially larger beads. This indicates that the smaller beads were less crosslinked than the larger beads. Therefore, in the suspension crosslinking synthesis, beads were being produced with effective crosslink densities, which varied with particle size. These swelling differences could be recognized only after the full PSD analysis illustrated in Figs. 3 and 4.

The ability to uncover size-dependent swelling differences has important implications to the production and application of gel beads produced by suspension processes. Differences in swelling degree as a function of bead size may indicate that there are surface area or dimensional effects needing control during synthesis. In the HPMC gel bead synthesis example examined here, the crosslinker was found to distribute between the aqueous polymer droplets and the suspending toluene phase [1,21]. There was a complex interplay between crosslinking reaction kinetics and crosslinker diffusion between the phases during synthesis. Since diffusion is a function of dimension, the observed dependence of crosslinking efficiency on particle size is understandable. The results of Fig. 4 suggest that selection of a suspending solvent in which the crosslinker is completely insoluble could yield more uniform beads.

Recognizing or minimizing differences in swelling degree among gel particles can be an important to factor to consider when designing the use of gel beads in applications where swelling degree and permeability play critical roles. For instance, in size selective separations the uniformity of gel properties is important to obtain high resolution in separations. Also, when gel beads are used as drug release matrices where the controlled diffusional transport of solutes is critical, it is important to accurately assess the swelling properties of the gel. Size-dependent swelling differences also can reveal shortcomings in synthesis conditions that cause the non-uniformities in bead swelling and suggest strategies for change, as noted above for the HPMC gel beads. Thus, the PSD analysis described herein can be a diagnostic tool to examine the properties of a large batch of gel particles. It also demonstrates that inspection of the PSD alone is insufficient to make a diagnosis of swelling uniformity.

4. Conclusions

The PSD analysis procedure described here provides a method to examine the uniformity of swelling of gel particles within a batch. This method, previously applied to predict the change in dimensions of aerosol particles as they aggregate, can be used to assess differences in swelling degree for gel beads as a function of size. The method uses differences in the PSDs in the initial and swollen states to distinguish swelling properties of particles. Since swelling degree is a function of crosslinking, differences in swelling can be used to estimate differences in effective crosslinking among different size fractions within a batch. The PSD analysis as applied to the example of HPMC hydrogel bead production uncovered and quantified non-uniformities in bead swelling not apparent from examination of PSD curves alone; specifically, that the smaller beads swelled much more than the larger beads. This means that the smaller beads would have different performance properties than larger beads in applications like drug delivery or separations. The PSD analysis could be used as a diagnostic tool to suggest appropriate modifications in synthesis technique to minimize possible dimensional effects during synthesis.

Acknowledgements

The authors would like to thank Dr Sotiris Pratsinis and Dr Patrick Spicer for their helpful discussions.

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