

Sedimentation polymerization

Eli Ruckenstein* and Liang Hong

Department of Chemical Engineering, State University of New York at Buffalo, Buffalo, NY 14260, USA

(Received 12 December 1994; revised 24 February 1995)

An aqueous monomer solution, also containing a crosslinker (methylenebisacrylamide) and an initiator (ammonium persulfate), was introduced dropwise with a syringe into a vertical glass column containing hot paraffin oil. The partial gelation of the droplets, which took place during their sedimentation (about 7–9 s), allowed them to maintain their spherical shape and not coalesce during their polymerization (for 2 h at about 50°C) at the bottom of the column. A narrow size distribution of beads was achieved for droplets between 1 and 2.5 mm in size. Six hydrophilic monomers (acrylamide, acrylic acid, 2-acrylamino-2-methyl-1-propanesulfonic acid, 2-hydroxyethyl-methacrylate, 2-vinyl-1-pyrrolidone and sodium styrenic sulfate) were used to illustrate the new methodology.

(Keywords: sedimentation polymerization; microspheres; droplets; hydrophilic monomers)

Introduction

Polymer microspheres in the size range 50 nm to 2 mm have been widely used for biomedical applications¹, as label or sensing-device carriers. They have also been employed for affinity chromatography, immobilization of enzymes, solid-phase synthesis of proteins, and drug delivery. Being related to aqueous surroundings, most of these applications involved hydrophilic polymeric microspheres from natural or synthetic sources. The general synthesis strategy was to polymerize small droplets of aqueous monomer solution into a hydrocarbon medium. Three major techniques have been employed to generate polymer microspheres²: the water in oil (W/O) micro-emulsion polymerization to prepare nanospheres; the W/O emulsion polymerization to prepare submicrometre to micrometre-sized spheres; and the W/O suspension polymerization to obtain up to submillimetre-sized spheres. Among these techniques, the W/O suspension polymerization was most often used, because the sizes of the hydrophilic beads it provides (10–500 µm) find more numerous applications than the smaller ones^{3–5}. However, in all cases, the particle sizes obtained via suspension polymerization were polydisperse. The sizes of the polymeric beads could be controlled by using suitable stabilizing agents (low HLB (hydrophilic–lipophilic balance) surfactants) or suspending aids (fine inorganic powders)⁶.

A novel pathway to synthesize microspheres, which we call sedimentation polymerization, is presented in this paper for the synthesis of relatively large water-swallowable polymeric microspheres with narrow size distribution. The mean diameter of the spheres is in the range of 1–2.5 mm. Sedimentation polymerization is a process in which droplets of aqueous monomer solution containing an initiator and a crosslinking agent are allowed to sediment through a heated hydrocarbon medium (paraffin oil is used in the present case) located in a

vertical cylindrical reactor. Although the time of sedimentation (7–9 s) was much shorter than the time needed to complete polymerization, the droplet overcame the solution stage and entered the gelation stage during sedimentation. Consequently, the droplets, which completed their polymerization in 2 h at the bottom of the cylindrical column, maintained their spherical shape and did not coalesce.

Compared to the W/O suspension polymerization, the sedimentation polymerization method provides the following advantages: (1) no stabilizing agent is necessary; (2) the size of the microspheres can be controlled by adjusting the size of the droplets with suitable syringe pumps; (3) the heat of polymerization evolved at the bottom of the cylindrical reactor can be used for the heating of the sedimentation medium and for maintaining a suitable temperature at the bottom.

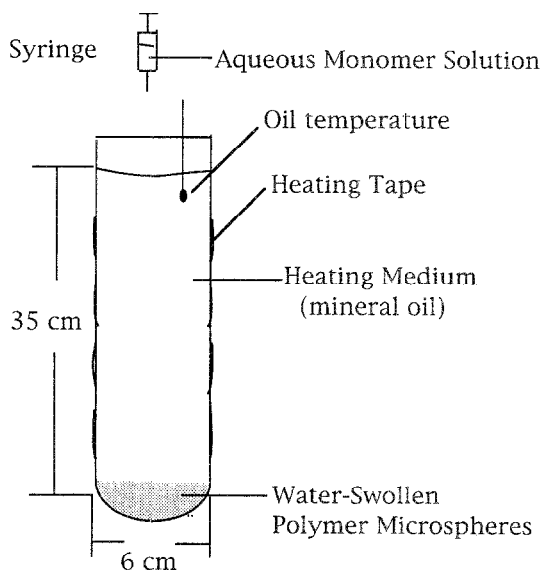


Figure 1 The cylindrical reactor used for sedimentation polymerization

* To whom correspondence should be addressed

Table 1 Minimum concentration of initiator needed to form spherical particles during the sedimentation polymerization^a

Monomer/crosslinker	Minimum concentration of (NH ₄) ₂ S ₂ O ₈ (mmol/ml water)	Molar ratio of monomer + crosslinker to the initiator
AA/MBAM	2.2×10^{-3}	2.8×10^3
AM/MBAM	1.7×10^{-3}	3.2×10^3
AMPS/MBAM	4.5×10^{-3}	1.2×10^3
VPLD/MBAM	1×10^{-3}	5.5×10^3
AM + HEMA/MBAM	5.5×10^{-1}	1.4×10
AMPS + NaSS/MBAM		(AM/HEMA = 1.5) unpolymerized during sedimentation (AMPS/NaSS = 1.6)

^a In all cases, 100 mmol of monomer(s) and 10 mmol of crosslinker were dissolved in 20 ml aqueous solution of (NH₄)₂S₂O₈.

Table 2 Minimum concentrations of monomer and crosslinker needed to form spherical particles during the sedimentation polymerization^a

Monomer/crosslinker	Minimum concentrations of monomer and crosslinker (mmol/ml water)
AA/MBAM	2.5/0.25
AM/MBAM	1.7/0.17
AMPS/MBAM	1.0/0.10
VPLD/MBAM	1.7/0.17

^a In all cases, the monomer and the crosslinker were dissolved in an aqueous solution having a concentration of initiator [(NH₄)₂S₂O₈] of 5.5×10^{-3} mmol/ml water.

Table 3 Effect of crosslinking on the formation of spherical particles during the sedimentation polymerization^a

Monomer/crosslinker	Minimum crosslinking (molar ratio of monomer to crosslinker)
AA/MBAM	100/1.3
AM/MBAM	100/5.2
AMPS/MBAM	100/3.4
VPLD/MBAM	100/5.2

^a In all cases, 100 mmol of monomer and the proper amount of crosslinker were dissolved in a 20 ml aqueous solution of (NH₄)₂S₂O₈ (2.2×10^{-2} mmol/ml water).

Experimental

Water-soluble monomers. Acrylamide (AM; 99+%), 2-acrylamino-2-methyl-1-propanesulfonic acid (AMPS; 99%), acrylic acid (AA; 99%), 2-hydroxyethyl-methacrylate (HEMA; 99+%), 2-vinyl-1-pyrrolidone (VPLD; 99+%), sodium styrenic sulfate (NaSS; 99%) and *N,N'*-methylenebisacrylamide (MBAM; 99+) were purchased from Aldrich. AA, HEMA and VPLD were passed through an inhibitor removal column before use.

Sedimentation polymerization. A representative preparation of P(AM-MBAM) was carried out as follows: AM (7.1 g, 100 mmol) and the crosslinker MBAM (1.54 g, 10 mmol) were dissolved in an aqueous solution of (NH₄)₂S₂O₈ (1.6×10^{-2} g in 20 ml water). This solution was introduced dropwise with a syringe into heated (90°C) mineral oil (white, light from Aldrich) located in a cylindrical polymerization reactor (Figure 1). During the sedimentation process, which lasted 7–9 s, partial gelation of the drops took place. When the gelation was sufficiently advanced, the droplets deposited at the bottom of the cylinder (where they were kept for 2 h at a temperature of about 50°C in order to complete the polymerization) maintained their spherical shape and did not coalesce. The P(AM-MBAM) beads collected were finally extracted with acetone in a Soxhlet apparatus overnight. White P(AM-MBAM) spherical beads were obtained. Six hydrophilic monomers (AM, AA, AMPS, HEMA, VPLD and NaSS) were used in the experiments.

Instrumental analysis. Photographs were taken with a Sony MPI-DAGE video camera and the size distribution was measured with a Quantimet 570. The scanning electron micrographs were obtained with a Hitachi

S-800 instrument and show the matrix morphology of the polymer beads.

Results and discussion

The main characteristic of the sedimentation polymerization is the partial gelation which, generating a network, prevents the deformation of the spherical droplets and their coalescence at the bottom of the reactor. The sedimentation time of a 2.5 mm diameter droplet of an aqueous monomer solution in a cylindrical column 35 cm high containing hot mineral oil is 7–9 s. Several factors affect gelation.

(1) *The concentration of initiator.* Table 1 lists the minimum concentration of initiator [(NH₄)₂S₂O₈] needed for the formation of undeformed spherical particles at given concentrations of monomer and crosslinker. One may note that for the monomers with higher polymerization rate, such as AA, AM and VPLD, the concentrations of the initiator are comparable to those used in the other polymerization methods. For the other ones they are much higher, and for some almost no gelation occurred for any concentration of initiator. For instance, for HEMA and NaSS and the conditions noted in Table 1, not enough crosslinking occurred for any concentration of initiator within the sedimentation time, because the polymerization rate is slow. However, when AM was mixed with HEMA at a molar ratio (AM/HEMA) of at least 1.5, spherical particles could be generated for a large ratio of initiator to monomers and crosslinker.

(2) *The concentration of monomer and crosslinker.* When the concentrations of the monomer and crosslinker were too low, the network formed during partial gelation could not maintain the spherical shape of the beads. In addition, the droplets coalesced at the bottom of the tube. The minimum concentrations needed to form spherical non-coalesced beads are listed in Table 2 for a fixed amount of initiator.

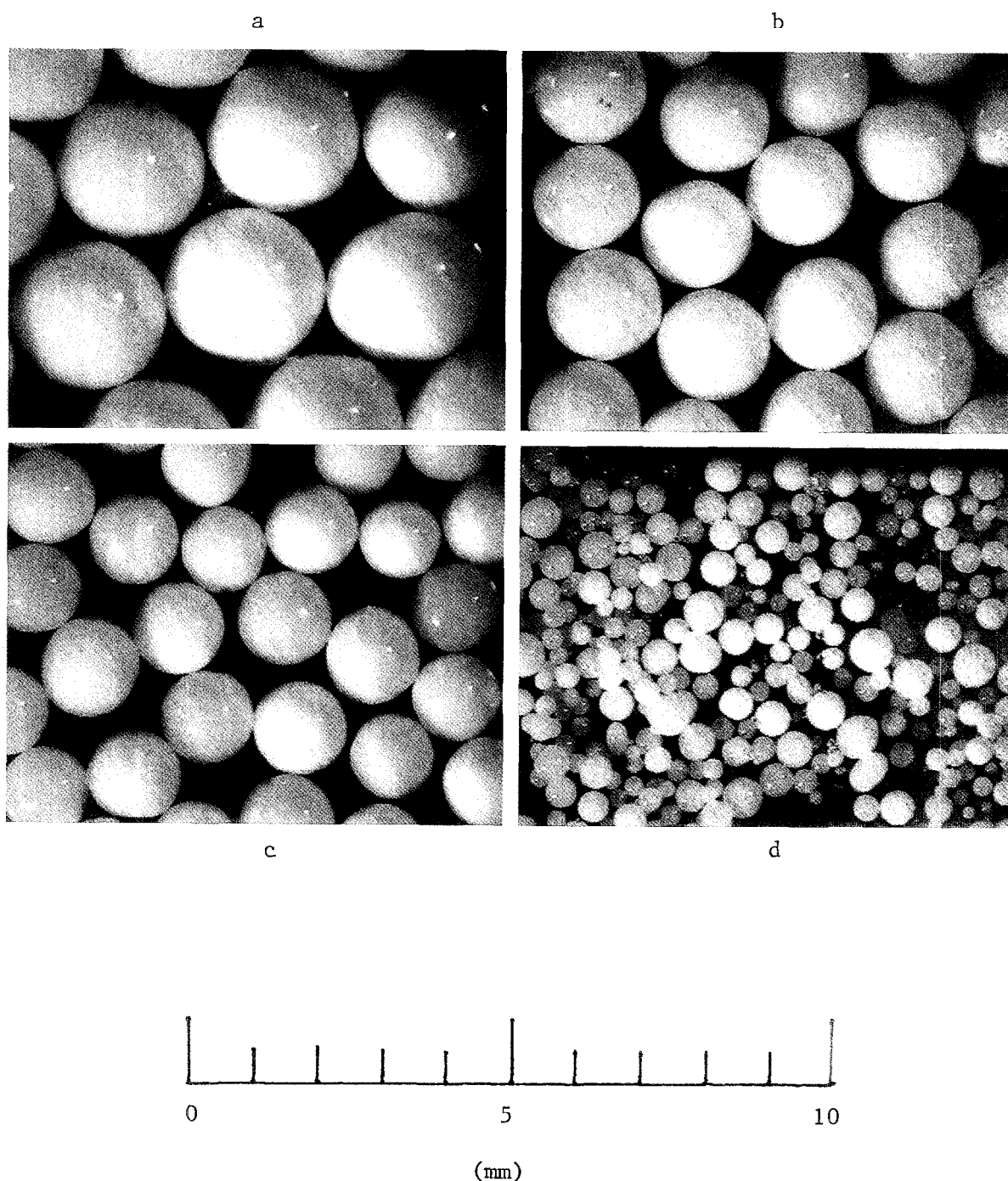


Figure 2 The poly(AM-MBAM) particles prepared using: (a) 0.495 mm needle diameter; (b) 0.241 mm needle diameter; (c) 0.140 mm needle diameter; (d) 0.140 mm needle diameter with rapid injection

(3) *The extent of crosslinking.* Table 3 provides the minimum amount of crosslinker needed at a fixed monomer concentration to generate spherical non-coalesced beads.

In sedimentation polymerization, the size of the polymer microspheres is controlled by the size of the aqueous monomer solution droplets, which can be controlled by the needle employed in their generation and by the injection speed. Three needle sizes (i.d. = 0.140, 0.241 and 0.495 mm) were used to synthesize different sizes of spherical beads. As examples, Figures 2a-d present four sizes of P(AM-MBAM) spheres prepared by hand extrusion from a syringe.

One can note that a very narrow size distribution has been achieved in three cases (Figures 2a-c). The average diameter and the relative standard deviation, respectively, are 2.457 mm and 5.59% for Figure 2a, 1.816 mm and 5.01% for Figure 2b and 1.34 mm and 5.51% for Figure 2c. It is clear that if, instead of generating them by hand extrusion, the droplets had been generated with suitable syringe pumps, the relative standard deviations would have been much smaller. In Figure 2d the particles are polydisperse in size, because the small sizes could be generated only by rapid injection. The average in this case is 0.462 mm but the relative standard deviation (34%) is quite large.

In addition, the morphologies of P(AM-MBAM)

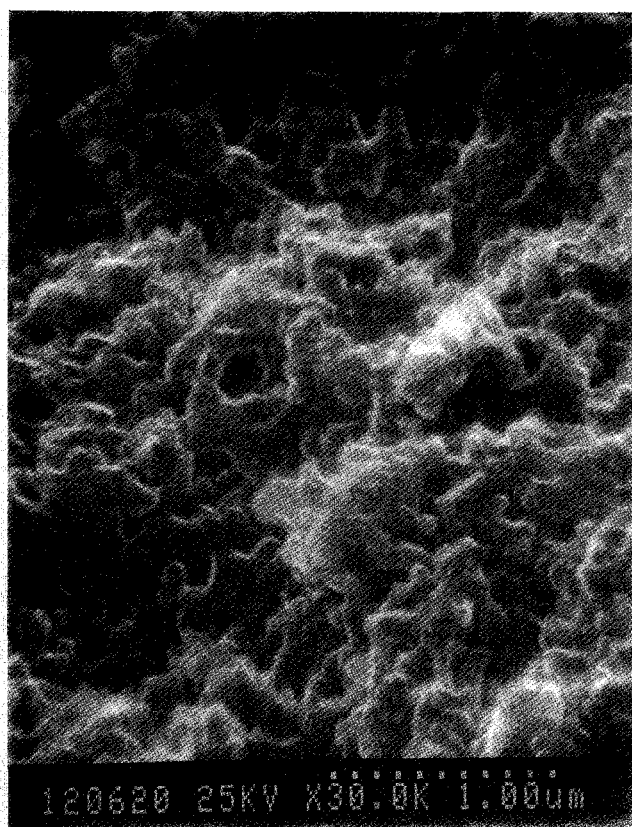


Figure 3 Scanning electron micrograph of a cross-section of a P(AM-MBAM) prepared by dissolving 100 mmol of AM and 10 mmol of MBAM in 40 ml aqueous solution of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ ($2.2 \times 10^{-2} \text{ mmol ml}^{-1}$)

beads for polymerizations of different concentrations of monomer were investigated by scanning electron microscopy, by cutting the particles into two hemispheres and examining the cross-section. One of the representative morphologies is shown in *Figure 3*. The presence of the submicrometre-sized cavities indicates that water functions as a porogen during gelation.

References

- 1 Arshady, R. *Biomaterials* 1993, **14**(1), 5
- 2 Hunkeler, D., Candau, F., Pichot, C., Hemielec, A. E., Xie, T. Y., Barton, J., Vaskova, V., Guillot, J., Dimonie, M. V. and Reichert, K. H. *Adv. Polym. Sci.* 1994, **112**, 115
- 3 Kim, C. *Chemtech* 1994, August, 36
- 4 Yarmush, M. L., Weiss, A. M., Antonsen, K. P., Odde, D. J. and Yarmush, D. M. *Biotech. Adv.* 1992, **10**, 413
- 5 Eury, R., Patel, R., Longe, K., Cheng, T. and Nacht, S. *Chemtech* 1992, January, 42
- 6 Buchholz, F. L. *Chemtech* 1994, September, 38