Polymerization of 2-hydroxyethyl methacrylate as large size spherical beads

A. Jayakrishnan*, M. C. Sunny and B. Chithambara Thanoo
Polymer Chemistry Division, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Satelmond Palace Campus, Trivandrum 695012, India
(Received 10 August 1989; accepted 16 August 1989)

Poly(2-hydroxyethyl methacrylate) (PHEMA) beads of fairly large size (more than 2.0 mm in diameter) crosslinked with ethyleneglycol dimethacrylate (EGDM) were prepared by the suspension polymerization of 2-hydroxyethyl methacrylate (HEMA) in the presence of benzyl alcohol (BA) in 35% sodium chloride solutions using 2,2'-azobis isobutyronitrile (AIBN) as the polymerization initiator. Magnesium hydroxide formed *in situ* served as the suspension stabilizer during polymerization. The presence of BA afforded the preparation of clear, large size spherical beads whereas many other inert solvents such as toluene, hexane, isopropanol or cyclohexanol either yielded beads of very small size or particles of irregular shape. The effect of concentration of EGDM, $Mg(OH)_2$ and the stirring speed on the stability of the suspension and particle size was investigated.

(Keywords: Poly(2-hydroxyethyl methacrylate); ethyleneglycol dimethyacrylate; crosslinking)

INTRODUCTION

Hydrogels are an important class of materials for biomedical applications[1-3]. Among hydrogel materials, PHEMA has attracted considerable attention and interest because of its non-toxicity, non-irritability and biocompatibility with the living tissues[4,5]. Contact lenses[6], liver resection supporting materials[7] and blood contacting surfaces[8], are a few of its applications. In the form of microspheres, PHEMA is used for the immobilization of enzymes[9], for the controlled release of pharmaceutical agents[10], for the encapsulation of mammalian cells[11], for immunochemical studies[12], and as sorbents in various types of chromatography[13,14]. Microspheres are usually prepared by the suspension polymerization of the monomer in a non-solvent using suitable stabilizing agents to prevent the agglomeration of the monomer droplets during polymerization[15]. Preparation of microspheres of large size (>1 mm) is usually difficult with monomers such as HEMA or methacrylic acid which are highly soluble in an aqueous medium. PHEMA beads of large size (>1 mm) are used for the controlled release of pharmaceutical agents[16] and as artificial emboli in endovascular embolization[17,18]. Methods resorted to for preparing beads of large size include gamma irradiation polymerization of a frozen dispersion of HEMA in petroleum ether (up to 3 mm diameter)[16] and suspension polymerization of the monomer using decalin as the dispersion medium (up to 2 mm diameter)[17]. In the latter case stabilization of the monomer droplets was achieved using poly(1-dodecyl methacrylate) having a molecular weight of 4×10^6, which was specifically made for this purpose. Many other stabilizing systems such as cetyl alcohol, Span 85 and butyl rubber have been reported to be unsuitable. A US patent disclosure describes the preparation of PHEMA beads of average diameter 1.03 ± 0.3 mm by polymerization and crosslinking of HEMA using poly(tetramethylene glycol) endcapped with isophorene diisocyanate in a sodium chloride solution[19]. We have recently devised a method of producing highly porous beads of PHEMA having diameters up to 1.00 mm by the suspension polymerization of HEMA in the presence of polymeric diluents such as poly(methyl methacrylate) in toluene or poly(tetramethylene glycol)[20]. Washing off the polymeric diluent after polymerization yields beads of very high porosity.

It is thus evident that preparation of PHEMA beads of large size in the laboratory is not a simple procedure. Preparation of beads using polymeric stabilizers has the disadvantage that the adsorbed stabilizers are often difficult to remove after the polymerization, thus contaminating the product particularly when it is intended for biomedical use. Gamma radiation polymerization, though a clean procedure, cannot be adopted in laboratories where such facilities do not exist. In this paper we report a procedure for the suspension polymerization of HEMA to give beads more than 2 mm in diameter.

MATERIALS AND METHODS

HEMA and EGDM (Aldrich, USA) were purified by distillation under reduced pressure. AIBN was recrystallized twice from methanol before use. All other reagents employed were of analytical grade. Single distilled water was used throughout.

PHEMA beads were prepared by suspension polymerization of the monomer in NaCl solutions containing $Mg(OH)_2$ as the suspension stabilizer. $Mg(OH)_2$ was formed *in situ* by precipitation from $MgCl_2$ using NaOH. A typical polymerization was carried out as follows. Into a 250 ml round bottomed flask fitted with a thermometer, condenser and a stainless steel half-moon paddle stirrer

* To whom correspondence should be addressed

0032-3861/90/071339-04

was introduced 47 ml of a 35% solution of NaCl in water, 1.00 g of $MgCl_2 \cdot 6H_2O$ (excess) and 3 ml of NaOH solution (exactly 1N, 2N or 3N). The contents were degassed using oxygen-free nitrogen for 10 min. HEMA mixed with the required amounts of EGDM and benzyl alcohol (BA) and 100 mg of AIBN was separately degassed using nitrogen for 10 min and introduced into the flask. The contents were stirred at 300 rpm at 70°C for 2 h. After 2 h, the temperature was raised to 75°C and the stirring continued for another 2 h, following which the temperature was again raised to 80°C and stirred for another hour to complete polymerization. After the reaction, the flask was cooled to room temperature and the beads were filtered, soaked in methanol, and washed several times with the same solvent to remove the BA completely. They were then washed with dilute HCl to remove the $Mg(OH)_2$ followed by distilled water several times and dried in a vacuum oven. Beads having diameters up to 1.2 mm were then fractionated by sieving in standard test sieves (Filterwel, India). The size distribution of beads having diameters above 1.2 mm was determined by randomly picking 60 beads from the fraction above 1.2 and measuring their diameter using the travelling microscope of a contact angle goniometer (Rame-Hart, USA). The percentage distribution was then plotted using a computer program (Lotus 1-2-3) in a personal computer.

RESULTS AND DISCUSSION

The presence of an inert high boiling solvent such as BA was found to be essential for the formation of PHEMA beads of large size. Inert solvents like toluene, hexane, cyclohexanol and isopropanol failed to generate beads of large size. With cyclohexanol and isopropanol, particles of spherical geometry could not be obtained and the suspension was found to aggregate on polymerization. The reason why BA alone could give rise to large size beads is not clear. Increasing the amount of BA in the dispersed phase also increased the bead size. *Figure 1* shows the particle size distribution of beads having diameters up to 1.2 mm. *Figure 2* shows the distribution of particles above 1.2 mm in diameter when three different concentrations of BA are employed in the dispersed phase. When HEMA was polymerized in the presence of an equal volume of BA, it was found that only beads of small size, aggregatory in character and irregular in shape could be obtained. Thus an optimum concentration of BA in the dispersed phase is essential for the formation of large non-aggregatory spherical beads.

Change in concentration of the cross-linking agent EGDM also influenced the particle size and distribution. When the amount of HEMA and BA in the dispersed phase was held constant and the concentration of EGDM varied, it was found that there was an optimum concentration of the crosslinking agent at which formation of spherical non-aggregatory beads resulted. *Table 1* illustrates these observations. However, it was possible to employ higher concentrations of EGDM in the monomer phase to obtain highly crosslinked PHEMA beads when the amount of BA in the dispersed phase was also correspondingly increased. When the EGDM concentration

Table 1 Effect of EGDM concentration on the particle size and shape of PHEMA beads. The dispersed phase contained 4 ml HEMA, 6 ml BA and various amounts of EGDM. $Mg(OH)_2$ was precipitated using 3 ml of 1N NaOH

Volume of EGDM (ml)	Nature of PHEMA beads formed
0.2	Spherical beads, up to 1 mm, aggregatory
0.5	Spherical beads, up to 2 mm, non-aggregatory
1.0	Non-spherical, non-aggregatory particles

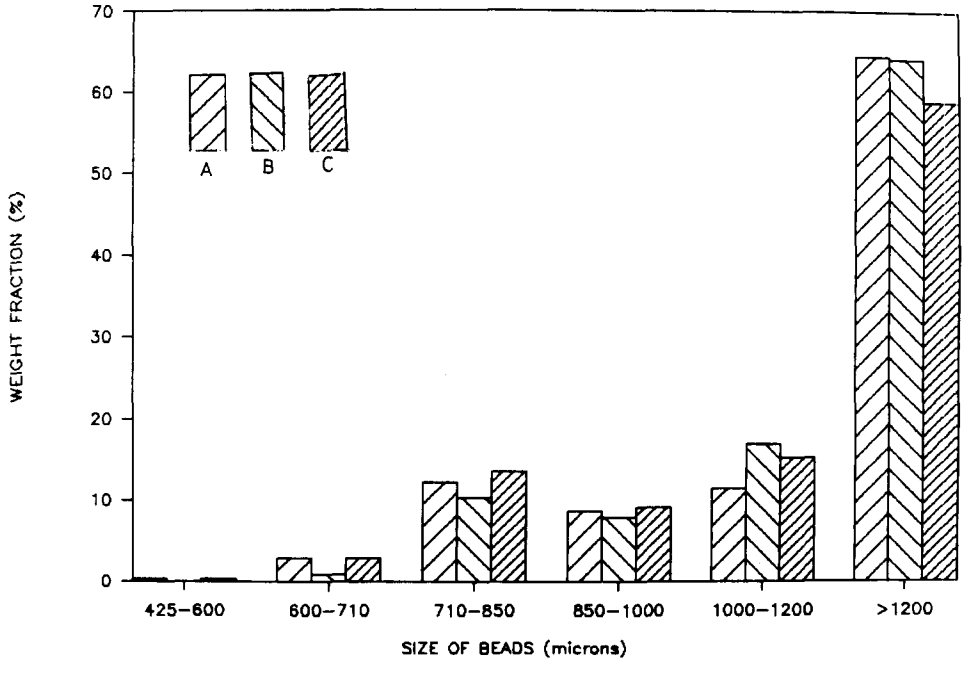

Figure 1 Particle size distribution of PHEMA beads up to 1.2 mm in diameter prepared using three different concentrations of benzyl alcohol (BA) in the dispersed phase. The dispersed phase contained 4 ml HEMA, 0.5 ml EGDM and 10 ml BA (A), 8 ml BA (B) and 6 ml BA (C). $Mg(OH)_2$ was precipitated in the dispersion medium using 3 ml of 1N NaOH

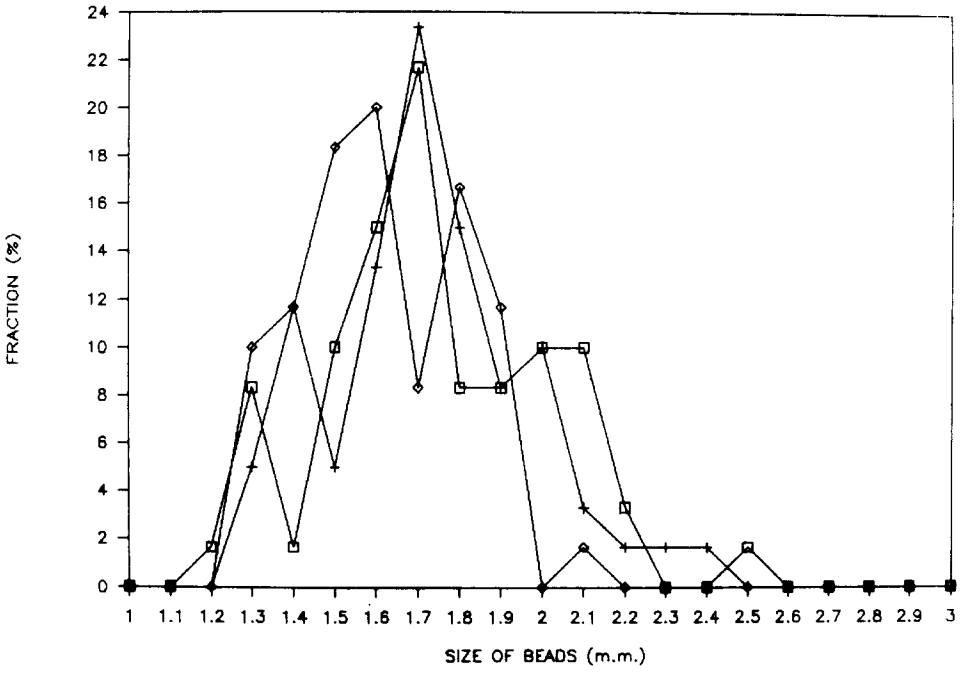

Figure 2 Particle size distribution of PHEMA beads having more than 1.2 mm diameter at three different benzyl alcohol concentrations. Composition: □, A; +, B; ◇, C, as in *Figure 1*

was 25% of the HEMA monomer, use of higher concentrations of BA gave rise to beads of large size. Thus when 8, 10 or 12 ml of BA was employed in combination with 4 ml of HEMA, beads obtained in all cases were spherical, non-aggregatory and large in size.

Variation of the amount of $Mg(OH)_2$ present in the dispersion medium also showed interesting results. An optimum concentration of $Mg(OH)_2$ was found to be essential for the formation of large, spherical, non-aggregatory beads. *Table 2* illustrates the data. As expected, a lower concentration of the stabilizer produced spheres of larger size. Increase in concentration up to a certain extent led to decrease in the size of beads. Beyond a certain concentration, however, no polymerization took place even at 80°C. Moreover, polymerization did not take place at all when a fine powder of $Mg(OH)_2$ precipitate was employed as the stabilizer instead of the same precipitated *in situ*, irrespective of the concentrations employed.

Change in stirring speed also influenced the formation and stability of the suspension. Increase in stirring speed from 300 rpm to 600 rpm under identical conditions produced smaller beads which agglomerated towards the completion of polymerization. This is possibly due to the fact that at higher stirring speeds, the dispersed phase breaks up into very small droplets thereby increasing the total surface area. The amount of stabilizer present in the system may thus become insufficient to cover the surface of the droplets effectively to prevent agglomeration. Stopping the stirring during the polymerization process was also found to influence the rate of polymerization and the particle size of the final product. After stirring the polymerization recipe for 2 h at 300 rpm, when the stirring was stopped for 10 min during which the temperature was raised to 75°C, polymerization of the monomer into small size beads having diameter below 0.5 mm could be seen immediately on resumption of stirring. With uninterrupted stirring, the temperature has to be above 75°C before the formation of polymer beads could be observed. This indicated that $Mg(OH)_2$ exerts an inhibitory effect on the polymerization reaction. It is already seen that beyond a certain concentration of the metal hydroxide stabilizer, the polymerization never took place even at 80°C. When the stirring is stopped, the dispersed phase separates into a layer while the $Mg(OH)_2$ remains in the dispersion medium. When dispersed into droplets, adsorption of $Mg(OH)_2$ on the surface of the monomer droplets inhibits their polymerization by possibly interacting with the free radicals generated by the decomposition of the initiator in some way. The inhibitory effect of the metal hydroxide stabilizer was further confirmed by conducting the polymerization reaction in the absence of $Mg(OH)_2$. Rapid polymerization took place giving rise to an agglomerated product. The precise nature of this inhibitory effect is not clear and to the best of our knowledge, there are no references in the literature on the inhibitory effect produced by particulate stabilizers such as metal hydroxides in suspension polymerization.

Table 2 Effect of magnesium hydroxide on the formation of PHEMA beads. The dispersed phase contained 4 ml HEMA, 6 ml BA and 0.5 ml EGDM. $Mg(OH)_2$ was precipitated using 3 ml of 1, 2 and 3N NaOH

$Mg(OH)_2$ in the dispersed phase (g)	Nature and size of beads formed
0.0875	Non-aggregatory, spherical, >2 mm
0.1749	Non-aggregatory, spherical, up to 1 mm
0.2624	No polymerization took place

The scanning electron micrographs of the PHEMA beads obtained are shown in *Figure 3*. The prevalently spherical shape of the beads can be ascertained from the photomicrographs.

Though the method reported here would prove to be useful for the preparation of PHEMA beads of large size, several questions remain unanswered. Of the three

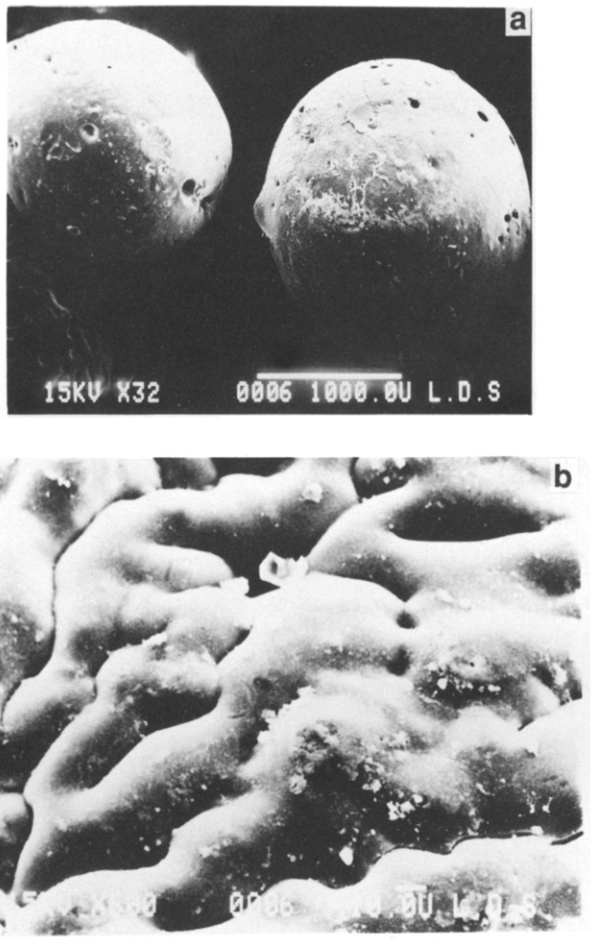

Figure 3 Scanning electron micrographs of PHEMA beads prepared using benzyl alcohol as the diluent (a) in the dispersed phase and (b) surface morphology of the same phase at higher magnification

different alcohols investigated, why BA alone was capable of producing large beads whereas alcohols such as cyclohexanol and isopropanol failed to produce spherical beads is not clear. The possibility that the polarity, hydrophobicity and viscosity of the diluent in the dispersed phase has a significant effect in determining the stability of the dispersion, particle size, and shape cannot be ruled out. Theoretical understanding of the stabilization action of particulate stabilizers in suspension polymerization is limited[21]. At present there is no concrete explanation for the fact that while $Mg(OH)_2$ precipitated *in situ* was capable of producing spherical particles of large size, $Mg(OH)_2$ introduced as a fine precipitate completely inhibited the polymerization at all concentrations in this system. It has been reported[22] that drop stability in suspension polymerization is enhanced if the contact angle between the powder and the dispersed phase exceeds 50°. If this angle is less than 50°, then drop stability is decreased resulting in the breakdown of the dispersion. However, this does not explain why the polymerization is completely inhibited in the present case in the presence of added $Mg(OH)_2$ precipitate. The beneficial effects of precipitating particulate stabilizers *in situ* has been recorded in the patent literature[23–25]. A combination of producing smaller particles, an electrolyte effect and the crystalline nature of the particles, all seem to be important.

CONCLUSIONS

PHEMA beads of more than 2 mm in diameter were prepared by polymerization of HEMA monomer in the presence of benzyl alcohol as the diluent. The beads obtained were clear and prevalently spherical in shape. While $Mg(OH)_2$ precipitated *in situ* up to certain concentrations effectively stabilized the monomer droplets during polymerization, $Mg(OH)_2$ added as a fine precipitate was found to inhibit the polymerization completely. The reason for this behaviour is not clear. Other alcohols such as cyclohexanol and isopropanol were found to be ineffective in producing spherical non-aggregatory beads possibly due to polarity, hydrophobicity or viscosity factors.

ACKNOWLEDGEMENTS

The authors thank Professor M. S. Valiathan, Director, SCTIMST for permission to publish this manuscript and Dr R. Williams of the University of Liverpool, UK, for the electron micrographs.

REFERENCES

1 Andrade, J. D. (Ed.) 'Hydrogels for Medical and Related Applications', American Chemical Society: Washington DC (1976), ACS Symp. Ser. No. 31
2 Peppas, N. A. (Ed.) 'Hydrogels in Medicine and Pharmacy', Vols 1, 2, 3, CRC Press, Boca Raton, FL (1987)
3 Ratner, B. D. in 'Biocompatibility of Clinical Implant Materials' (Ed. D. F. Williams), CRC Press, Boca Raton, FL, 1981, p. 145
4 Hoffman, A. S. and Harris, C. *Am. Chem. Soc., Div. Polym. Chem., Polym. Prepr.* 1972, **13**, 740
5 Bruck, S. D. *J. Biomed. Mater. Res.* 1972, **6**, 173
6 Tighe, B. J. in 'Hydrogels in Medicine and Pharmacy', Vol. 2, (Ed. N. A. Peppas), CRC Press, Boca Raton, FL, 1987, p. 53
7 Michnevie, I. and Kliment, K. *J. Biomed. Mater. Res.* 1971, **5**, 17
8 Ratner, B. D., Hoffman, A. S., Hansen, S. R. *et al., J. Polym. Sci., Polym. Symp.* 1979, **66**, 363
9 Chang, M., Colin, M. and Rembaum, A. *J. Polym. Sci., Polym. Lett. Edn.* 1986, **24**, 603
10 Robert, C. C. R., Buri, P. A. and Peppas, N. A. *J. Control. Rel.* 1987, **5**, 151
11 Stevenson, W. T. K. and Sefton, M. V. *Biomaterials* 1987, **8**, 449
12 Rembaum, A., Yen, S. P. S., Cheong, E. *et al., Macromolecules* 1976, **9**, 328
13 Kahovec, J. and Coupek, J. *Reactive Polymers* 1988, **8**, 105
14 Mohr, M., Pommerening, K., Kuhn, M. *et al.* in 'Affinity Chromatography: Proceedings of an International Symposium held at Austria' (Eds O. Hoffmann-Ostenhof, M. Breitenbach, F. Koller *et al.*), Pergamon Press, Oxford, 1978, p. 129
15 Munzer, M. and Trommsdorff, E. in 'Polymerization Processes' (Eds C. E. Schildknecht and I. Skeist), Wiley-Interscience, New York, 1977, p. 106
16 Denizli, A., Kiremitci, M. and Piskin, E. *Biomaterials* 1986, **7**, 363
17 Horak, D., Svec, F., Kalal, J. *et al., Biomaterials* 1986, **7**, 188
18 Horak, D., Svec, F., Kalal, J. *et al., Biomaterials* 1986, **7**, 467
19 Muller, K. F., Heiber, S. J. and Plankl, W. L. US Patent 4 224 427. *Chem. Abstr.* 1981, **94**, 16568t
20 Jayakrishnan, A. and Chithambara Thanoo, B. *J. Biomed. Mat. Res.* in press
21 Brooks, B. W., Bygate, F. and Lane, A. C. *Br. Polym. J.* 1988, **20**, 19
22 Wenning, H. *Makromol. Chem.* 1956, **20**, 196
23 Wenning, H. *Makromol. Chem.* 1956, **22**, 41
24 Rohm, O. and Trommsdorff, E. US Patent 2 171 765 (1940)
25 Muller-Tamm, H. German Patent 1 007 061 (1957)