The Physical Mechanism for the Production of Hydrophilic Polymer Microparticles from Aqueous Suspensions

ALEC B. SCRANTON,† ANTONIOS G. MIKOS,* LISA C. SCRANTON, and NIKOLAOS A. PEPPAS,‡ *School of Chemical Engineering, Purdue University, West Lafayette, Indiana 47907*

Synopsis

A previously reported method of producing spherical, hydrophilic microparticles by aqueous suspension polymerization is experimentally investigated. The phase separation is the result of a salting-out phenomenon. Characteristics of the salting-out effect between the monomer and suspending phase of aqueous NaCl solution are studied. The size and shape of the produced particles are characterized. It is concluded that the mechanism of polymerization is actually a combination of suspension and solution polymerization, and that the water content in the monomer phase is low enough to produce structurally homogeneous particles.

INTRODUCTION

Production of hydrophilic polymeric microspheres has been a subject of significant interest, especially in the field of biomedical and pharmaceutical engineering. For example, polymer microspheres have been used as hemoperfusion systems,[1] as sorbents,[2] in chemoembolization,[3] and for controlled release applications.[4]

Of particular interest to us is the production of porous and nonporous microspheres of poly(2-hydroxyethyl methacrylate), henceforth designated as PHEMA, which has been shown to be a promising biomedical polymer.[5] Such microparticles have been prepared by various techniques.

For example, Horák et al.[6,7] used a suspension polymerization method in decaline to produce PHEMA microparticles crosslinked with ethylene glycol dimethacrylate (EGDMA). Skelly and Tighe[1] and Denizli et al.[8] produced PHEMA beads by introducing a stream of monomer into a supercooled nonsolvent. Finally, Shirahama and Suzawa[9] and Chang et al.[10] have reported methods of emulsion polymerization for the production of such particles.

A technique of major importance in the pharmaceutical field is the suspension polymerization method of Mueller et al.,[11,12] which has been applied by us[4,13] for the production of hydrophilic microparticles. This technique is preferred because it provides spherical particles while avoiding the use of potentially

* Present address: Dept. of Chemical Engineering, M.I.T., Cambridge, MA 02139.

† Present address: Department of Chemical Engineering, Michigan State University, East Lansing, MI 48824.

‡ Author to whom all correspondence should be addressed.

Journal of Applied Polymer Science, Vol. 40, 997–1004 (1990)
 CCC 0021-8995/90/5-60997-08$04.00

toxic organic suspending phases. Briefly, the monomer HEMA is suspended in an aqueous phase that includes dissolved sodium chloride and magnesium hydroxide precipitate, under controlled agitation. Initiation is done by classical free-radical techniques and crosslinking agents are added as necessary. Although the monomer HEMA is soluble in water, the presence of the sodium chloride in the aqueous suspending phase reduces the monomer solubility and allows the suspension to be formed. The magnesium hydroxide precipitate acts as a suspending agent.

The decrease in the solubility of nonaqueous solvents in water upon addition of an electrolyte is known as the "salting-out effect."[14,15] Many theoretical models have been proposed to interpret the phenomenon in terms of selective solvation of ions. When selective solvation occurs, the concentration of the solvent around the ions is different than the overall composition of the system. For instance, electrostatic models predict that the concentration of the solvent component with the highest dielectric constant increases around the electric charge. At high ion concentrations, this effect may be strong enough to cause phase separation. Hydration, electrostatic, and thermodynamic theories have been proposed to explain the salting-out effect.

In this contribution, we present an experimental analysis of a technique to produce hydrophilic microparticles by an aqueous suspension polymerization. The characteristics of the salting-out phenomenon responsible for the reduction in solubility of the monomer in the aqueous suspending phase are investigated by measuring the compositions of the two phases that are formed. These compositions are important because they influence the characteristics of the reaction and the produced particles.

EXPERIMENTAL

Materials

The monomer 2-hydroxyethyl methacrylate (HEMA) (Aldrich Chemical Co., Milwaukee, WI) was purified by vacuum distillation and was stored at a temperature of 5°C until use. Ethylene glycol dimethacrylate (EGDMA) (Aldrich Chemical Co., Milwaukee, WI) was used without any purification as a crosslinking agent. The polymerization initiator was 2,2′-azobis(2-methyl propionitrile) (AIBN) (Aldrich Chemical Co., Milwaukee, WI). Aqueous solutions of NaCl and NaOH were made by dissolving NaCl crystals and NaOH pellets, respectively, in distilled-deionized water.

Salting-Out Studies

Although the monomer HEMA is soluble in pure water, phase separation occurs when it is mixed with NaCl solutions. To investigate the salting-out effect of NaCl on HEMA, several qualitative and quantitative studies were performed. The monomer HEMA was mixed with water containing 5, 10, 15, 20, or 25 wt % NaCl with various volumetric ratios of monomer to salt water, and the volume fraction of the resulting monomer-rich phase, ϕ_m, was measured. The extent of phase separation was investigated qualitatively using infrared spectroscopy. The aqueous phase was isolated, placed in the IR sample cell,

and its spectrum was obtained using an infrared spectrometer (Model 180, Perkin Elmer, Norwalk, CT).

The composition of the HEMA-rich phase was investigated quantitatively using ^1H nuclear magnetic resonance (NMR) spectroscopy. The HEMA phase was isolated, placed in the NMR tube, and the spectrum was obtained using a Fourier transform spectrometer (Model A-200, Chemagnetics, Fort Collins, CO). Sixteen 90° pulses were accumulated before the free induction decay was Fourier-transformed. The composition of the HEMA phase was determined by comparing the integration of the hydroxyl proton peak after the HEMA contribution had been subtracted to the integrations of the peaks corresponding to HEMA protons. The amount of HEMA present in the salt-water phase was analyzed quantitatively using high performance liquid chromatography (HPLC). The analysis was performed using a solvent delivery system (Spectroflow Model 400, Kratos, Ramsey, NJ), a reverse-phase column (Partisil ODS-3, Alltech, Deerfield, IL), and an absorbance detector (Waters Model 440, Milford, MA) operating at a wavelength of 254 nm. The active chromophore at this wavelength was the ester–carbonyl double bond. The amount of HEMA present in the sample was determined by comparing the area of the HEMA peak to the area of a peak corresponding to an internal standard of EGDMA of known concentration.

Production of Hydrophilic Polymer Microparticles

The Mueller suspension polymerization technique[11–13] was used for the production of PHEMA microparticles from aqueous dispersions. A 500-mL three-neck flask, equipped with a reflux condenser, was employed for the suspension polymerization reaction. The flask was immersed in a temperature-regulated water bath. The temperature at the water bath was set at 70°C. The agitation was performed with a polypropylene stirring paddle driven by a variable speed motor (Model 102, Talboys Engineering Corp., Emerson, NJ). The width of the two extended swing-out blades was 56 mm.

The suspending phase solution, consisting of 180 g of a 20 wt % NaCl solution together with 11.5 g $MgCl_2 \cdot 6H_2O$ (Mallinckrodt Chemical, St. Louis, MO), was added to the flask and the solution was agitated at 250 rpm. The polymerizing phase solution was poured into the flask afterwards. It comprised 50 g HEMA and the appropriate amounts of EGDMA and AIBN. The quantity of EGDMA was determined based on the desired crosslinking ratio. The mole fraction of AIBN was kept at 0.002. After 15 min, a sample of 61.5 mL of a 1*N* NaOH solution was added dropwise to form a fine gel-like precipitate of $Mg(OH)_2$, which served as a suspending agent preventing droplet coalescence. The ratio of the organic to the aqueous phase was approximately 1 : 5.

The polymerization reaction was carried out at 70°C for 3 h. Then, the temperature was raised to 90°C and the polymerization was continued for two more hours. In the end of this period 5 mL of a 37.8 wt % HCl solution (Baker Chemical Co., Phillipsburg, NJ) were added to the flask to dissolve the $Mg(OH)_2$ and the system was cooled under agitation for 5 min.

The produced microparticles were filtered using a qualitative filter paper and were washed with water. They were dried at room temperature for a day and in a vacuum oven at 40°C and 150 mm Hg for 3 days. The dried particles

were sieved using ASTM sieves of 40, 60, 80, and 100 mesh size, corresponding to meshes of 425, 250, 180, and 150 μm, respectively.

RESULTS AND DISCUSSION

The change in the equilibrium volume fraction of the monomer-rich phase, ϕ_m, with NaCl concentration is shown in Figure 1. Experiments were performed with initial volume ratios of monomer phase (HEMA) to water phase of 1 : 1, 1 : 2, and 1 : 4. For the isovolumetric mixing, phase separation occurred when HEMA was mixed with a NaCl solution of concentration as low as 5 wt %. However, the monomer phase appeared to contain a significant amount of water, especially for the lowest salt concentrations, since the value of ϕ_m was larger than the initial volume fraction of the monomer-rich phase (which was 0.5). Besides, ϕ_m decreased as the salt concentration increased. Salt precipitated from the 25 wt % NaCl solution upon mixing with the monomer. Similar results were obtained for the systems with initial monomer volume fractions of 0.33 and 0.2 (see Fig. 1).

The infrared spectra of a 20 wt % aqueous NaCl solution, the monomer HEMA, and the aqueous phase which results from their isovolumetric mixing are presented in Figure 2. This figure illustrates that the spectrum of the aqueous phase resembled the spectrum for the salt water much more than that of the HEMA monomer. However, the small peaks observed between 950 and 1450 cm^{-1} indicate that a small amount of HEMA is present in the aqueous phase, since such peaks appear only in HEMA [viz. Fig. 2(b)]. From these qualitative experiments, we can conclude that when HEMA monomer is dispersed in an aqueous NaCl solution, a substantial amount of water is contained in the monomer-rich phase, whereas the aqueous phase includes a small quantity of

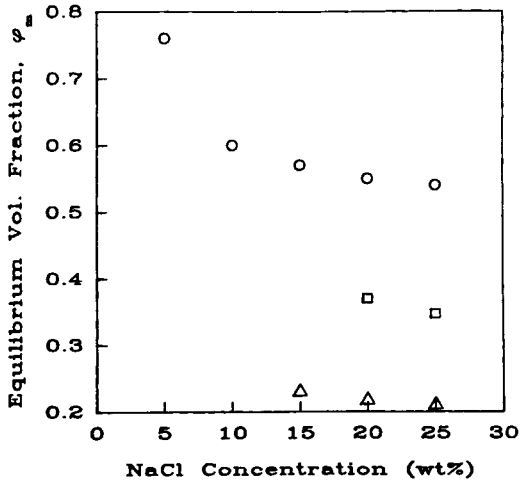

Fig. 1. Variation of the equilibrium volume fraction of the monomer-rich phase, ϕ_m, with the NaCl concentration in the salt water. Volumetric ratios of monomer to salt water before mixing are: (○) 0.5; (□) 0.33; (△) 0.2.

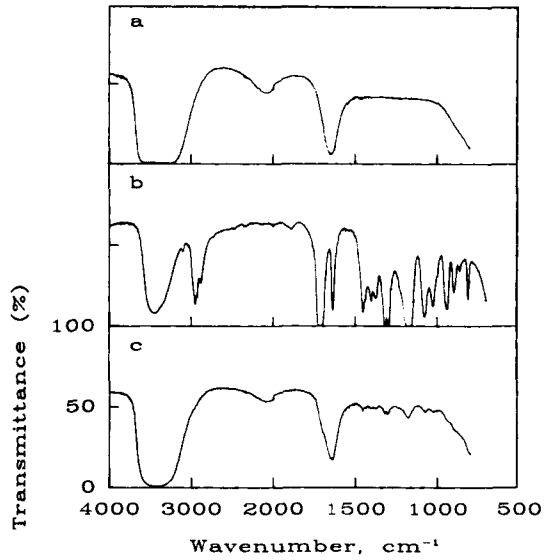

Fig. 2. Infrared spectra of a 20 wt % aqueous NaCl solution (a), 2-hydroxyethyl methacrylate (b), and the aqueous phase resulting from the isovolumetric mixing of the above (c).

HEMA. These conclusions were further tested by more quantitative experiments.

The HEMA-rich phase was analyzed by ^{1}H-NMR spectroscopy to determine the quantity of water present. The NMR spectra of pure HEMA and of the HEMA-rich phases produced by isovolumetric mixing with water containing 20 and 25 wt % NaCl are shown in Figure 3. The hydroxyl protons of water and of the monomer appear as one peak because they exchange rapidly relative to the NMR time scale.[16] The amount of water in the sample was determined quantitatively by comparing the area under the peak of the hydroxyl proton (after the HEMA contribution had been subtracted) to the areas of the other peaks. This analysis revealed that when equal volumes of HEMA and water containing 15, 20, and 25 wt % NaCl were mixed, the resulting HEMA phase contained 60.0 mol % (17.2 wt %), 52.9 mol % (13.5 wt %), and 45.9 mol % (10.5 wt %) water, respectively. This quantitative analysis showed that, as the amount of salt in the water phase increased, the amount of water in the HEMA phase decreased.

The amount of HEMA present in the aqueous phase was evaluated quantitatively using HPL chromatography. Comparison of the resulting HEMA peak to the peak of an internal standard of known concentration revealed that the concentration of HEMA in the water phase was 0.189 mol % or 1.09 wt %. Therefore, the water phase contained very little HEMA, as was determined qualitatively earlier using IR spectroscopy.

This experimental characterization of the salting-out effect that occurs between the monomer HEMA and NaCl in water reveals that the resulting monomer-rich phase contains a significant amount of water while the aqueous salt solution contains only a little monomer. Therefore, the reaction is mechanistically both a suspension and a solution polymerization.

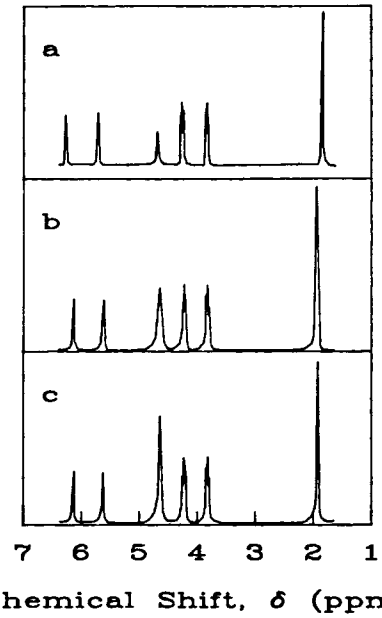

Fig. 3. ^{1}H-NMR spectra of pure HEMA (a), the HEMA phase after the isovolumetric salting-out process with 25 wt % NaCl solution (b), and the HEMA phase after the isovolumetric salting-out process with 20 wt % NaCl solution (c).

These results have important manifestations in the properties of the particles produced by the suspension polymerization technique. The amount of water in the monomer phase is important because it determines the pore structure of the particles that are produced. If the water content were above about 40 wt %, the particles would be heterogeneous in structure[17,18] (therefore macroporous) and would be unsuitable for use in applications in which diffusion out of the particles rather than absorption and desorption is the working mechanism. Our experiments show that the water content is well below this threshold value if the salt content of the suspending phase is above 15 wt %. Since the amount of HEMA in the aqueous phase is very small, the effect of mass transfer of monomer from the suspending phase to the polymer particles during the reaction will be very small.

Using the previous conclusions from the salting out studies, crosslinked PHEMA microparticles were produced for crosslinking ratios X of 0.002, 0.005, 0.010, 0.020, and 0.050 mol EGDMA/mol HEMA. A solution of 20 wt % NaCl was selected to salt-out HEMA. The particles were spherical and polydisperse with an average particle diameter of approximately 100 μm (see Fig. 4). These particles were much smaller than those produced by Robert et al.[4] and Barr-Howell and Peppas[13] due to modifications in the suspension polymerization technique. These modifications included changes in the agitation rate, and a change in the time of formation of the suspending agent. The formation of the $Mg(OH)_2$ was delayed 15 min, until a stable dispersion of monomer droplets had been formed.

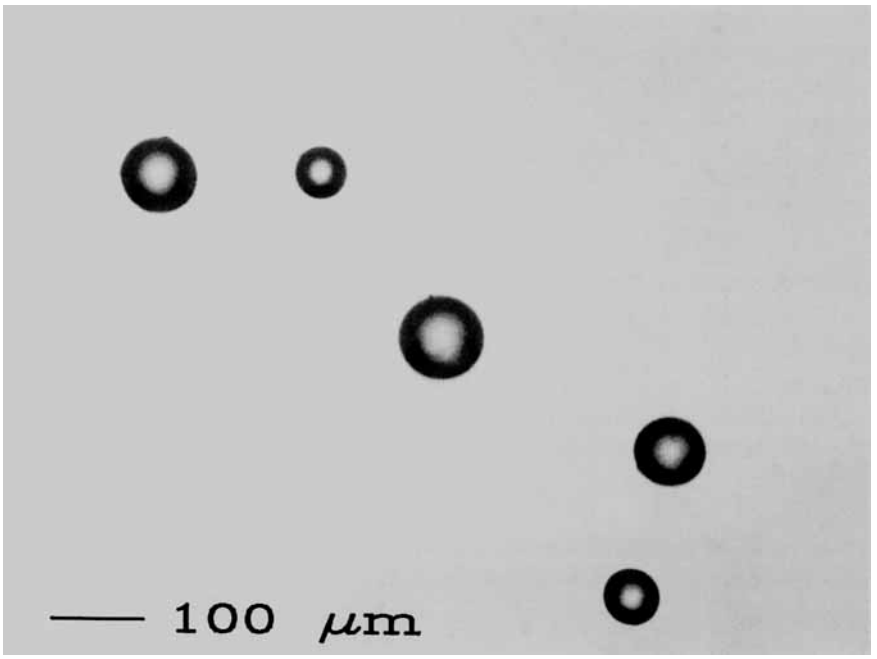

Fig. 4. Photomicrograph of a sample of dry poly(2-hydroxyethyl methacrylate) microparticles of crosslinking ratio of 0.05.

CONCLUSIONS

A method of producing hydrophilic polymer microparticles by aqueous suspension polymerization was investigated experimentally. The solubility of the monomer in the aqueous suspending phase was decreased as the NaCl concentration was increased indicating a salting-out effect. Quantitative analysis of the salting-out effect revealed that a significant amount of water was present in the monomer phase while very little monomer was present in the aqueous phase. These results suggest that the polymerization reaction is really a combination of suspension polymerization with the reaction taking place in the droplets of the dispersed monomer phase and solution polymerization inside the droplets, since there is a significant amount of solvent in the monomer droplets. Since the amount of water present is below 40 wt %, the reaction will produce structurally homogeneous networks. The particles formed by the suspension polymerization process were spherical and had an average diameter of about 100 μm.

This work was supported by National Science Foundation Grant No. CBT-86-17719. In addition, ABS was the recipient of a National Science Foundation fellowship and AGM was the recipient of a David Ross Fellowship.

References

1. P. J. Skelly and B. J. Tighe, *Polym. Commun.*, **20,** 1051 (1979).
2. E. Piskin, *Int. J. Artif. Org.*, **9,** 401 (1986).

3. D. Horák, F. Svec, J. Kálal, A. Adamyan, N. Skuba, M. Titova, V. Dan, B. Varava, N. Trostenyuk, O. Vorankova, K. Gumargalieava, and V. Timochina, *Biomaterials,* **9,** 367 (1988).

4. C. C. R. Robert, P. A. Buri, and N. A. Peppas, *J. Appl. Polym. Sci.,* **30,** 301 (1985).

5. N. A. Peppas, Ed., *Hydrogels in Medicine and Pharmacy,* CRC Press, Boca Raton, FL, 1987, Vol. 2.

6. D. Horák, F. Sveč, J. Kálal, K. Gumargalieva, A. Adamyan, N. Skuba, M. Titova, and N. Trostenyuk, *Biomaterials,* **7,** 188 (1986).

7. D. Horák, M. Metalová, F. Sveč, J. Drobník, and J. Kálal, M. Borovicka, A. A. Adamyan, O. S. Voronkova, and K. Z. Gumargalieva, *Biomaterials,* **8,** 142 (1987).

8. A. Denizli, M. Kiremitci, and E. Piskin, *Biomaterials,* **9,** 363 (1988).

9. H. Shirahama and T. Suzawa, *J. Appl. Polym. Sci.,* **29,** 3651 (1984).

10. M. Chang, M. Colvin, and A. Rembaum, *J. Polym. Sci., Polym. Lett.,* **24,** 603 (1986).

11. K. F. Mueller and S. J. Heiber, *J. Appl. Polym. Sci.,* **27,** 4043 (1982).

12. K. F. Mueller, S. J. Heiber, and W. L. Plankl, U.S. Pat. 4,224,427 (1980).

13. B. D. Barr-Howell and N. A. Peppas, *Eur. Polym. J.,* **23,** 591 (1987).

14. J. H. Hildebrand, *Solubility,* Reinhold, New York, 1936.

15. H. Schneider, in *Solute–Solvent Interactions,* J. F. Coetzee and C. D. Ritchie, Eds., Dekker, New York, 1969.

16. J. K. M. Sanders and B. K. Hunter, *Modern NMR Spectroscopy,* Oxford University Press, New York, 1987.

17. K. Dušek and B. Sedlaček, *Coll. Czech. Chem. Commun.,* **36,** 1569 (1971).

18. M. F. Refojo and H. Yasuda, *J. Appl. Polym. Sci.,* **9,** 2425 (1965).

Received March 7, 1989
Accepted April 6, 1989