Formation of encapsulated hydrophilic polymer beads by combined techniques of bead polymerization and phase separation

H. SURYAKUSUMA*† AND H. W. JUN*

Department of Pharmaceutics, College of Pharmacy, †University of Georgia, Athens, GA 30602, USA

A novel and rapid procedure for the preparation of hydrophilic polymer beads coated with ethyl cellulose has been developed. The coated polymer beads were prepared by combining techniques of bead polymerization and phase separation into a single step procedure. The final product has a size range of 200–1000 µm and consists of the core copolymer of 2-hydroxyethyl methacrylate—acrylamide and the barrier membrane of ethyl cellulose. Examination of beads in which amaranth dye was used as a model of active ingredient showed the dye to be uniformly distributed throughout the polymer matrix. Microscopic examination indicated that ethyl cellulose coated the core matrix. The effects of ethyl cellulose concentration, degree of agitation and molar ratio of monomers on the size of coated beads were investigated.

The use of hydrophobic and hydrophilic polymers in drug delivery systems in which drugs are homogeneously dispersed throughout the polymer network has been reported (Chien et al 1975; Chien & Lau 1976; Song et al 1981). The rate of drug release from such systems depends on the physicochemical properties of the polymer and the drug itself.

A system exists where a drug dispersed in a polymer matrix is encapsulated with a polymer membrane of lower permeability. In this case, the core matrix serves as a reservoir for constant release (Borodkin & Tucker 1975; Cowsar et al 1976; Olanoff et al 1979). The fabrication of these systems requires several processes, such as dispersing the drug in the core matrix and laminating it with the polymer membrane, and thus, the surface area available for releasing the active ingredient is often limited in size.

Microcapsules are an example of drug delivery systems that have a relatively large surface area. The active agent is either contained within an envelope of polymer material or dispersed in the network of polymer (microspheres). Various microencapsulation processes such as air suspensions, coacervation-phase separation, spray drying and congealing, pan coating techniques and microencapsulation by interfacial polymerization have been reviewed (Luzzi 1970). However, the encapsulation of hydrophilic microspheres in which the coating material has lower permeability than the core has not been reported.

† Correspondence.
* Present address: College of Pharmacy, Northeastern University, Boston, MA 02115, USA.

We describe a novel method of preparing encapsulated microspheres (beads) by a single step procedure. The encapsulated microspheres are composed of a hydrophilic copolymer of 2-hydroxyethyl methacrylate—acrylamide and a hydrophobic barrier membrane of ethyl cellulose. The coated beads were prepared by combining methods of bead polymerization and phase separation. Amaranth, because of its visibility, was used as a model of active ingredient.

GENERAL APPROACH

The basic procedure involves the combination of two steps carried out under continuous agitation. The first step is the formation of a core matrix containing active ingredient by bead polymerization. In bead polymerization (Farber 1970), a monomer, or mixture of monomers containing an initiator, is dispersed as liquid droplets by strong mechanical agitation in a second liquid phase in which monomer(s) and polymer formed are essentially insoluble. Protective colloids or suspension stabilizer may be added to the suspending medium to hinder coalescence of the droplets during polymerization. Polymerization takes place in the individual monomer droplets to form beads. The second step is the deposition of the coating material upon the beads by phase separation. This can be accomplished by temperature change. Ethyl cellulose in cyclohexane is an example of this system (Miller et al 1967). At high temperature, ethyl cellulose is completely soluble in cyclohexane; upon cooling, the ethyl cellulose precipitates from the solution. Under proper conditions of concentration, temperature and

agitation, ethyl cellulose coalesces around the dispersed core particles.

In this study, 2-hydroxyethyl methacrylate and acrylamide were used as monomers because they polymerize to form a hydrophilic polymer. The monomers were dispersed and polymerized in hot cyclohexane containing ethyl cellulose. Ethyl cellulose was initially used as a protective colloid to prevent the coalescence of the droplets during polymerization. Hence, a protective film of ethyl cellulose was formed around the monomer droplets (Fig. 1a). When the formation of beads was complete, the temperature of the system was allowed to fall. During this period the ethyl cellulose precipitated on the surface of the beads to form a coating (Fig. 1b). The active ingredient was entrapped in the core matrix during the formation of the beads.
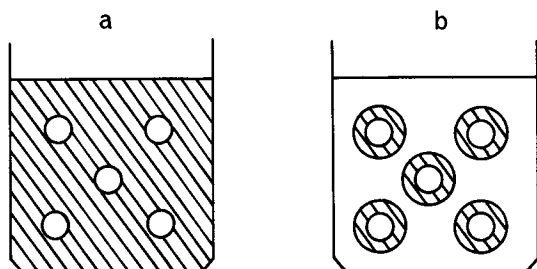

FIG. 1. Formation of encapsulated hydrophilic polymer beads, (a) during polymerization reaction: ▨▨▨, ethyl cellulose, ○, monomer droplets, (b) after polymerization reaction and phase separation: ▨▨▨. ethyl cellulose, ○, hydrophilic copolymer. '

MATERIALS AND METHODS

Materials
2-Hydroxyethyl methacrylate and acrylamide (Aldrich Chemical Co., Milwaukee, Wis.) were used without purification. Ethyl cellulose (Sigma Chemical Co., St Louis, Mo, viscosity 45 cps); sodium persulfate (J. T. Baker Chemical Co., Phillisburg, N.J.); amaranth dye (Fisher Scientific Co., Fair Lawn, N.J.); and cyclohexane (J. T. Baker Chemical Co., Phillisburg, N.J.) were used as received.

Methods
2-Hydroxyethyl methacrylate, acrylamide, amaranth and sodium persulfate as initiator were dissolved in 10 ml of water. This solution was placed in a 500 ml three-neck round bottom flask equipped with Teflon stirrer, reflux condenser and nitrogen inlet. In a

separate vessel, ethyl cellulose was dissolved in 200 ml cyclohexane and heated to 80 °C. The ethyl cellulose solution was then added to the aqueous monomer solution with vigorous agitation. The flask was immediately immersed in a thermostatically controlled water bath at 80 °C. While continuously agitated, the mixture was left for 1 h to complete the polymerization reaction. The different formulae prepared are given in Table 1.

Table 1. Composition of coated beads formulations.

| Materials | Formulations[a] | | | | | |
	1	2	3	4	5	6
2-Hydroxyethyl methyacrylate (g)	12·3	12·0	11·6	11·0	15·2	6·8
Acrylamide (g)	6·7	6·5	6·4	6·0	2·8	11·2
Sodium persulfate (g)	0·5	0·5	0·5	0·5	0·5	0·5
Water (ml)	10·0	10·0	10·0	10·0	10·0	10·0
Amaranth (g)	0·5	0·5	0·5	0·5	0·5	0·5
Ethyl cellulose (g)	1·0	1·5	2·0	3·0	2·0	2·0
Cyclohexane (ml)	200	200	200	200	200	200

[a] 1:1 Molar ratio of 2-hydroxyethyl methacrylate—acrylamide was used in formulations 1–4. 3:1 Molar ratio of 2-hydroxyethyl methacrylate—acrylamide was used in formulation 5. 1:3 Molar ratio of 2-hydroxyethyl methacrylate—acrylamide was used in formulation 6.

After polymer beads were formed, the temperature of the system was brought down slowly to 35 °C. Ice was then added to the water bath to accelerate cooling to 5 °C. At the same time, 100 ml of n-hexane was added to the system to lower the freezing point of cyclohexane and to accelerate the solidification of ethyl cellulose. The cooling was continued for another 30 min. The resulting encapsulated microspheres were filtered, washed with 250 ml of n-hexane and dried overnight at room temperature (ca 20 °C).

RESULTS AND DISCUSSION
Previous studies utilizing the suspension polymerization technique for the formation of polymer beads (Khanna et al 1970; Croswell & Becker 1974) showed that protective colloids in the suspending medium helped to prevent coalescence and agglomeration of the polymer beads formed. Ethyl cellulose was initially used as a protective colloid for the bead polymerization reaction. However, it was later found that the ethyl cellulose precipitated on the surface of the polymer beads during the cooling process. Preliminary studies showed that when the concentration of ethyl cellulose used was less than

5% (w/w) the beads were not formed. Instead the polymer became a large rubbery mass. When the concentration of ethyl cellulose used was between 5% (w/w) to 15% (w/w), the beads were formed and the size of the beads was in the range of 250–1000 µm (Table 2).

finding further demonstrates that the beads were coated with ethyl cellulose. Hence, upon cooling, the ethyl cellulose, which was added as a protective colloid, encapsulated the polymer beads. The use of ethyl cellulose thus facilitated the formation of the polymer beads as well as the coating of the beads in a single continuous procedure.

Table 2. Size distribution of coated beads of different formulations.

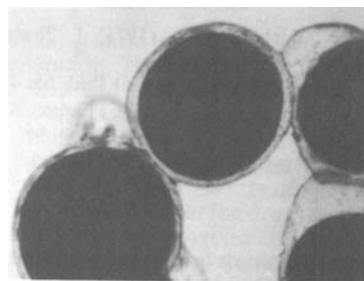| Mean size diameter (µm)	% Sieve fraction for formulation					
	1	2	3	4	5	6
>1000	6·1	2·4	4·7	3·1	0·0	48·9
920	3·4	4·7	3·1	1·9	0·0	20·8
715	11·8	13·3	10·3	10·1	0·8	19·6
505	38·8	38·1	22·9	22·5	9·6	7·2
359	33·4	30·5	43·1	41·4	54·8	3·5
<297	6·5	11·1	15·9	21·1	34·8	0·0
Yield of coated beads (%)	91	93	91	93	87	92

FIG. 2. Photomicrograph of encapsulated beads with 15% ethyl cellulose and containing amaranth dye, mean size 500 µm (×50).

The speed of agitation was also a factor in producing coated beads. It was found that an agitation speed between 250–300 rev min⁻¹ gave optimum results in terms of yield, particle size and coating efficiency. The % yield of the beads was obtained from the weight of the beads after washing and drying divided by the total weight of the starting materials. Agitation speeds of less than 200 rev min⁻¹ were not fast enough to disperse the monomer droplets in the medium. On the other hand, speeds above 350 rev min⁻¹ gave a yield of less than 75%. This was probably due to the high turbulence of the system which led to the adhesion of the beads to the walls of the flask. Such losses were minimal when agitation was maintained at 300 rev min⁻¹, and the average yield of the preparations was about 91% (Table 2).

The final products obtained after washing and drying were found to be spherical, rigid and free-flowing. Amaranth was distributed homogenously in the network of core matrix. Photomicrographs of the coated beads in cyclohexane (Fig. 2) show that the beads were coated with ethyl cellulose. In addition, the coated beads were also examined after washing with hot cyclohexane. After washing the beads the ethyl cellulose coating was completely removed. This

The size distribution of the coated beads was determined by the method of sieve analysis. Table 2 shows the effect of the amount of ethyl cellulose and of the molar ratio of monomers on the size of the beads. As shown in Table 2, most of the beads fell in the size range of 300–700 µm. Khanna et al (1970) reported that higher concentration of protective colloids used during polymerization produced beads of smaller size. The present study shows that the minimum concentration of ethyl cellulose needed for the formation of beads was 5% (w/w). Increasing the concentration of ethyl cellulose to 15% (w/w) produced smaller particles. When different molar ratios of monomers were used, the average particle size of the beads was also different (Table 2). It was found that when higher percentages of acrylamide were used, larger beads were formed.

Active ingredients, such as drugs and pesticides, initially dispersed in the monomer solution can be entrapped in the network of polymer beads formed and can be simultaneously coated with ethyl cellulose. Since the coated membrane has a lower permeability to water than the core matrix, it is expected that the membrane will serve as a rate limiting barrier for the release of active ingredients. By varying the amount of coating material and the ratio of the monomers used, different rates of drug release may be obtained.

REFERENCES

Borodkin, S., Tucker, F. E. (1975) J. Pharm. Sci. 64: 1289–1294

Chien, Y. W., Lau, E. P. K. (1976) Ibid. 65: 488–492

Chien, Y. W., Mares, S. E., Berg, J., Huber, S., Lambert, H. J., King, K. F. (1975) J. Pharm. Sci. 64: 1776–1781

Cowsar, D. R., Tarwater, O. R., Tanguary, A. C. (1976) in: Andrade, J. D. (ed.) Hydrogels for Medical and Related Applications. ACS Symp. Series No. 31, American Chemical Society, Washington, D.C., pp 180–197

Croswell, R. W., Becker, C. H. (1974) J. Pharm. Sci. 63: 440–442

Farber, E. (1970) in: Encyclopedia of Polymer Science and Technology. Intersciences Publishers, Vol. 13, New York, pp 552–571

Khanna, S. C., Jecklin, T., Speiser, P. (1970) J. Pharm. Sci. 59: 614–618

Luzzi, L. A. (1970) Ibid. 59: 1367–1376

Miller, R. W., Fanger, G. O., McNiff, R. G. (1967) Union of South Africa Patent 4211–4266

Olanoff, L., Koinis, T., Anderson, J. M. (1979) J. Pharm. Sci. 68: 1147–1150

Song, S. Z., Cardinal, J. R., Kim, S. H., Kim, S. W. (1981) Ibid. 70: 216–219