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Organic solvent-free polymeric microspheres prepared from aqueous colloidal polymer dispersions by a w/o-emulsion technique

Chin-Ming Chang[a], Roland Bodmeier[b,*]

[a]*College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, USA*
[b]*Institut für Pharmazie, Freie Universität Berlin, Kelchstr. 31, 12169 Berlin, Germany*

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Abstract

Polymeric microspheres were prepared from water-insoluble polymers by a novel technique without the use of organic solvents. Aqueous colloidal polymer dispersions (latexes or pseudolatexes) were emulsified into a heated external oil phase to form a w/o emulsion. The colloidal polymer particles fused (coalesced) into homogeneous polymeric microspheres at temperatures above the minimum film formation temperature upon removal of water. The formation of the microspheres was affected by the glass transition temperature of the polymer, the type of oil and surfactant, the heating temperature and time, and the addition of plasticizers. Plasticizers had to be added to colloidal dispersions with high minimum film formation temperatures. The resulting microspheres were spherical with a smooth surface and non-agglomerated. The particle size could be varied between 5 and 250 μm. Water-soluble compounds such as propranolol HCl could be entrapped with drug loadings up to 40% within the microspheres by dissolving the drug in the aqueous polymer dispersion prior to the emulsification step. The drug release was sustained over a 6-h period with microspheres prepared with the acrylic pseudolatex, Eudragit RS 30D.

Keywords: Aqueous colloidal polymer dispersion; Latex; Microencapsulation; Microsphere; Polymer; Sustained release

1. Introduction

Microparticles can be formed by a variety of microencapsulation techniques (Kondo, 1979; Deasy, 1984). The choice of one particular method is determined to a large extent by the solubility characteristics of the active compound and the carrier material. Although various carrier materials (e.g., water-soluble and -insoluble polymers or waxes) are available, water-insoluble polymers such as ethyl cellulose, cellulose acetate butyrate, poly(lactides), and various acrylic and vinyl polymers have been primarily used for the

* Corresponding author. Tel.: 49 30 77000443; Fax: 49 30 77000492.

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preparation of sustained release microparticles. Microencapsulation methods using these polymers include organic phase separation (Kondo, 1979; Deasy, 1984), aqueous and non-aqueous solvent evaporation (Huang and Ghebre-Sellassie, 1989; Bodmeier et al., 1991), and spray-drying techniques (Bodmeier and Chen, 1988).

Water-soluble drugs can be encapsulated by organic phase separation or non-aqueous solvent evaporation techniques; the drugs are insoluble in the organic solvents or oils used as external phases in these methods. In the non-aqueous solvent evaporation method, the drug is dissolved in an organic polymer solution followed by emulsification of this phase into an external oil phase and solvent evaporation to form the microspheres (Beyger and Nairn, 1986; Kawata et al., 1986; Huang and Ghebre-Sellassie, 1989; Bodmeier et al., 1994). The major disadvantage of these microencapsulation methods is the use of organic solvents, which are required to dissolve the water-insoluble polymers. Safety and toxicity concerns make the development of solvent-free microencapsulation methods desirable.

The objective of this study was therefore to prepare microparticles from water-insoluble polymers without the use of organic solvents. This was achieved with a novel water-in-oil emulsification method based on aqueous colloidal polymer dispersions. Instead of emulsifying an organic polymer solution into an oil phase, a drug-containing colloidal polymer dispersion was used to form the microparticles. Colloidal polymer dispersions (latexes or pseudolatexes) have found widespread applications in the painting and coating industry where they have replaced coating with organic solvents (Lehmann, 1986; Steuernagel, 1989). Water-insoluble films are formed through the coalescence of the colloidal polymer particles upon water evaporation in a completely aqueous environment. The principle of coalescence of the colloidal polymer particles (not into films but into spherical particles) was used in this study to form microspheres from an emulsion of the aqueous colloidal polymer dispersions in an external oil phase.

2. Materials and methods

2.1. Materials

The following materials were used as received from commercial suppliers: propranolol HCl (Sigma Chemical Co., St. Louis, MO), dibutyl sebacate (Eastman Kodak Co., Rochester, NY), triacetin, tributyl citrate, triethyl citrate (Morflex, Inc., Greensboro, NC), Aquacoat (ethyl cellulose dispersion, FMC Corporation, Newark, DE), Surelease (ethyl cellulose dispersion, Colorcon Inc., West Point, PA), Eudragit NE 30D (polyethylacrylate, methylmethacrylate dispersion), Eudragit RS 30D and RL 30D (polyethylacrylate–methyl methacrylate–trimethylammonioethyl methacrylate chloride dispersions) (Röhm Pharma, Darmstadt, Germany), cottonseed oil (Sigma Chemical Co., St. Louis, MO), corn oil, sesame oil, soybean oil (Fisher Scientific, Fair Lawn, NJ), mineral oil (Sigma Chemical Co., St. Louis, MO), methanol (Baxter Healthcare Co., McGaw Park, IL), *n*-hexane (J.T. Baker Inc., Phillipsburg, NJ).

2.2. Methods

2.2.1. Preparation of microspheres

A schematic diagram of the preparation method is shown in Fig. 1. The colloidal polymer dispersions (2 g, 30% w/v solids content) were

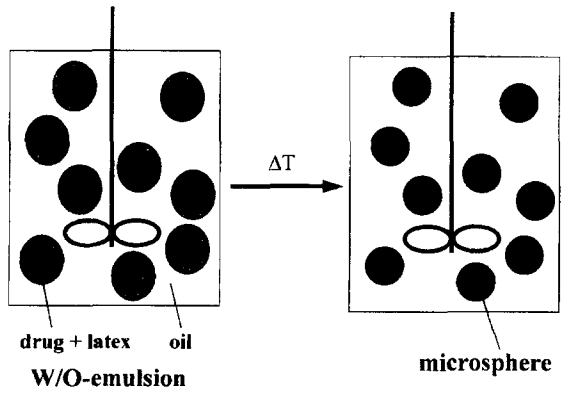

Fig. 1. Schematic diagram of the preparation of the microspheres by a w/o-emulsion technique using aqueous colloidal polymer dispersions (latexes).

emulsified into an external cottonseed oil phase (30 ml) with a magnetic or propeller stirrer. The resulting w/o emulsion was heated and agitated in a water bath at 60°C for 30 min to evaporate water and to induce fusion of the colloidal polymer particles into larger microspheres. After cooling the microparticle/oil suspension to room temperature, the microspheres were collected by filtration, washed with *n*-hexane to remove excess oil from the microsphere surface, and dried under vacuum in a desiccator overnight.

The following formulation and process variables were investigated: theoretical propranolol HCl loading (10–40%), type of oil (cottonseed, corn, mineral, sesame and soybean oil), volume of Eudragit RS30D (2–20 ml, into 60 ml cottonseed oil), type of colloidal polymer dispersion (Aquacoat, Surelease, Eudragit NE 30D, RS 30D, RL 30D), solids content of Eudragit RS30D (10–30%, 5% interval), temperature of cottonseed oil (26–70°C).

2.2.2. Determination of drug loading

The propranolol HCl content of the microspheres (10 mg, 150–250 μm) was determined by UV-spectrophotometry after extraction in methanol (20 ml). Encapsulation efficiency is the ratio of the actual drug content to the theoretical drug content, expressed in %.

2.2.3. Drug release study

The dissolution profiles were obtained by a horizontal shaker-water bath method. The microspheres (150–250 μm) were placed into dialysis bags (molecular weight cut-off 6000–8000; Spectrum Medical Industries, Inc., Los Angeles, CA), then placed into glass vials containing 20 ml of 0.1 M phosphate buffer, pH 7.4, and shaken in a horizontal shaker-water bath (70 strokes/min, 37°C, $n = 3$). The vials were removed from the water bath at predetermined time intervals and the amount of drug released was determined by circulating the dissolution medium through a UV sipper cell.

2.2.4. Scanning electron microscopy

Scanning electron microscopy (SEM) was used to characterize the surface and cross-section of the microparticles. The samples were coated for 70 s under an argon atmosphere with gold-palladium (Pelco Model 3 Sputter Coater) and examined with a scanning electron microscope (Jeol JSM 35C). Cross-sections were obtained by dispersing and drying the microparticles in a glue (Testor Corporation, Rockford, IL), followed by cutting the dried matrix with a razor blade.

3. Results and discussion

Microspheres of water-soluble carriers such as albumin have been prepared by emulsifying aqueous drug-carrier solutions into an external oil phase to form a w/o emulsion; the microparticles were formed after water removal (Tomlinson et al., 1984). With water-insoluble polymers, drug-containing microparticles have been prepared by emulsifying solutions of the drug and polymer in an organic solvent into an external oil phase, followed by solvent evaporation (Huang and Ghebre-Sellassie, 1989).

In this study, instead of emulsifying aqueous or organic polymer solutions, aqueous colloidal polymer dispersions were emulsified into an external oil phase to form a w/o emulsion. The emulsion was heated to evaporate the water and to form the microspheres through coalescence of the colloidal polymer particles within the individual emulsion droplets.

Various colloidal polymer dispersions used in the coating of pharmaceutical dosage forms were evaluated using this microencapsulation method. The polymer dispersions were based on either cellulosic (ethyl cellulose, Aquacoat and Surelease) or acrylic (poly (ethylacrylate, methylmethacrylate), Eudragit NE 30D; poly (ethylacrylate–methyl methacrylate–trimethylammonioethyl methacrylate chloride, Eudragit RS 30D and RL 30D; poly (methacrylic acid, ethylacrylate), Eudragit L 30D) polymers. The coalescence or fusion of the colloidal polymer particles into a homogeneous polymer film or matrix depends on the glass transition temperature of the polymer and the minimum film formation temperature of the colloidal polymer dispersion. The minimum film formation temperature is the tem-

perature at which coalescence of the polymer particles occurs. A fine polymer powder or only partially coalesced particles were obtained if drying occurred at temperatures below this temperature. With polymers having high glass transition temperatures, plasticizers had to be added to the polymer dispersions to reduce the film formation temperature below the drying temperature.

Aquacoat and Eudragit RS or RL 30D required the addition of plasticizers to induce/enhance the coalescence of the colloidal polymer particles. Both water-insoluble (dibutyl sebacate and tributylcitrate) and -soluble (triethyl citrate and triacetin) plasticizers gave free-flowing, individual microparticles. Although the water-insoluble plasticizers were miscible with the external oil phase, the resulting microparticles were nonagglomerated at the plasticizer levels (20–30% w/w based on the polymer) investigated. Microspheres could also be formed with Surelease which is an ethylcellulose pseudolatex already plasticized with dibutyl sebacate. Eudragit NE 30D could be emulsified into the oil phase to form a w/o-emulsion, however, the particles agglomerated upon evaporation of water. This could be explained with the low glass transition temperature of the polymer, the polymer being in the rubbery state during microparticle preparation and cooling. Another important consideration is the interaction between the oil phase and the polymer. Sticking could result from partial swelling of the polymer by the external oil phase. The polymer therefore should be insoluble and should not swell in the oil used.

One advantage of colloidal polymer dispersions is their low viscosity at a high polymer solids content when compared with organic polymer solutions. The latexes or pseudolatexes typically have a solids content of 30% or more while organic polymer solutions used in the microencapsulation of drugs generally have a polymer content of less than 10%. More concentrated polymer systems can therefore be processed with colloidal polymer dispersions.

Various drugs were evaluated with this microencapsulation method. As with most microencapsulation techniques, partitioning between two immiscible phases needs to be minimized in order to maximize the drug loading of the microspheres. This w/o-microencapsulation technique is most suitable for water-soluble drugs being soluble in the internal aqueous and insoluble in the external oil phase. A solvent- and oil-free method for the encapsulation of lipophilic drugs based on aqueous colloidal polymer dispersions has been recently developed (Bodmeier and Wang, 1993).

A prerequisite for the successful preparation of the microparticles was the compatibility between the colloidal polymer dispersion and the drug. Colloidal polymer dispersions are stabilized against premature flocculation and coalescence or settling during storage by either anionic or nonionic surfactants or by charged groups present in polymer sidechains. The ethyl cellulose dispersions, Aquacoat and Surelease, are stabilized with the anionic surfactants, sodium lauryl sulfate and ammonium oleate, respectively. The addition of cationic drugs such as chlorpheniramine maleate, pseudoephedrine HCl, or propranolol HCl to these pseudolatexes resulted in immediate flocculation or precipitation and no particle formation after injection of this dispersion into the oil. Eudragit RS and RL 30D pseudolatexes are stabilized by quaternary ammonium groups present on the polymer sidechain; the cationic drugs can be dissolved in these dispersions without causing flocculation.

Various formulation and process variables were investigated in order to understand and characterize the formation of the microparticles. The encapsulation efficiencies with Eudragit RS 30D were close to 100% for theoretical propranolol HCl loadings up to 40%. Propranolol HCl was insoluble in the oil and therefore did not partition into the external oil phase. The encapsulation was not affected by the solids content of the polymer dispersion (10 vs. 30% w/w). Scanning electron micrographs of the surface and a cross-section of the microparticles are shown in Fig. 2. The microparticles were spherical and non-agglomerated, the cross-section revealed a homogeneous, dense matrix structure without visible drug crystals at a drug content of 30%.

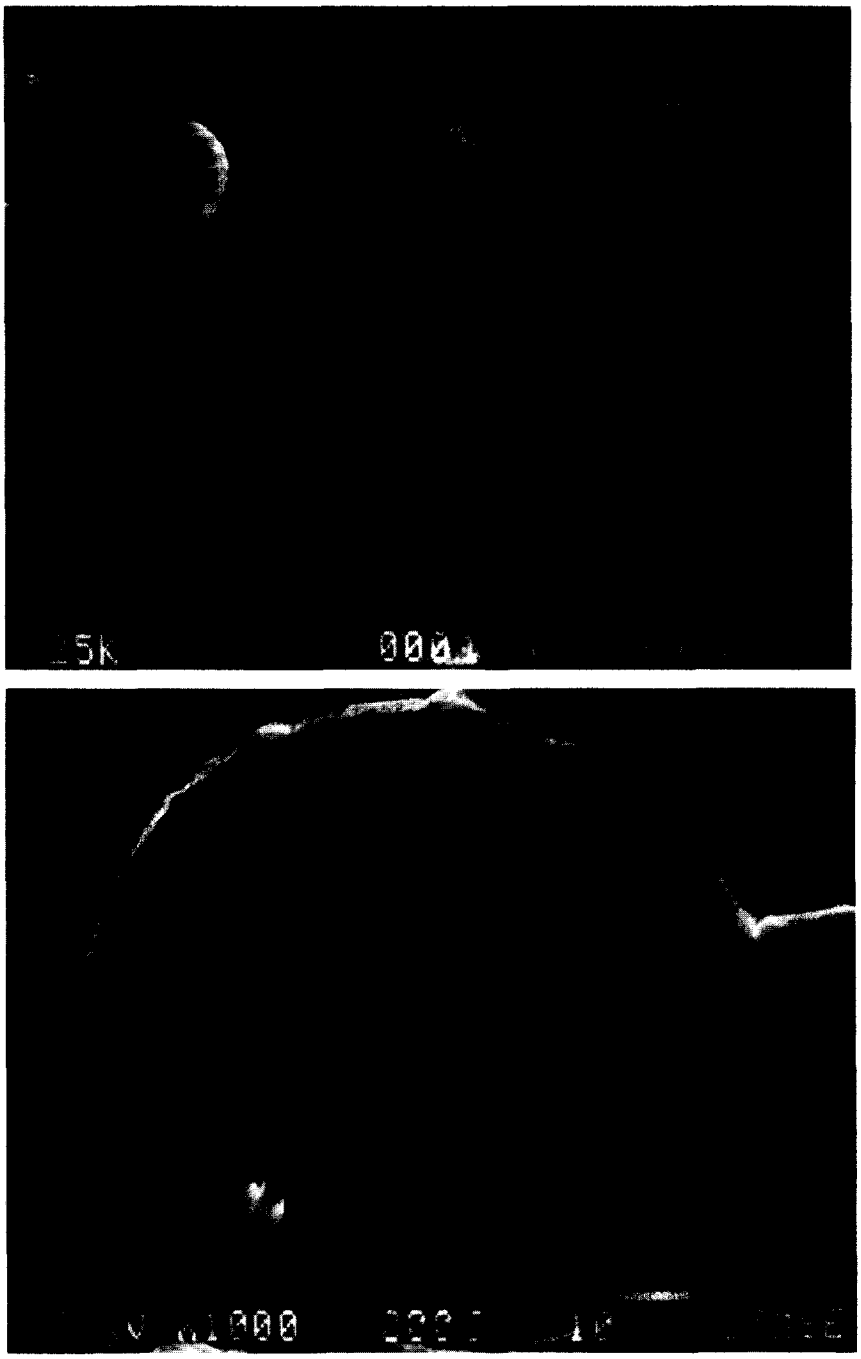

Fig. 2. Scanning electron micrographs of propranolol HCl (30% w/w)-Eudragit RS microspheres. (A) surface, (B) cross-section.

Table 1
Effect of type of oil on the propanolol hydrochloride loading of Eudragit RS 30D microspheres

Oil	Theoretical drug loading (%)	Actual drug loading (%)	Encapsulation efficiency (%)
Corn oil	25.53	25.33	99.21
Cottonseed oil	25.53	23.88	93.53
Sesame oil	25.53	25.21	98.74
Soybean oil	25.53	23.39	91.61

Table 2
Effect of the temperature of the cottonseed oil phase on the propanolol hydrochloride loading of Eudragit RS 30D microspheres

Temperature (°C)	Theoretical drug loading (%)	Actual drug loading (%)	Encapsulation efficiency (%)
26	16.67	16.53	99.16
40	16.67	16.74	100.42
50	16.67	16.36	98.14
60	16.67	16.84	101.02
70	16.67	16.34	98.02

Table 3
Effect of the volume of the internal phase on the propranolol hydrochloride loading of Eudragit RS 30D microspheres

Internal phase (ml)[a]	Theoretical drug loading (%)	Actual drug loading (%)	Encapsulation efficiency (%)
2	22.65	21.55	95.15
5	22.65	22.01	97.18
10	22.65	23.80	105.08
15	22.65	22.82	100.75
20	22.65	22.04	97.31

[a]In 60 ml of cottonseed oil.

The propranolol HCl content of the microparticles was not affected by type of oil used, the temperature of the external phase and volume of internal phase in the ranges investigated as shown in Tables 1–3. The solubility of the drug in the external phase was minimal at all temperatures and therefore was not a significant factor. The encapsulation efficiencies were close to 100% in most cases. Higher temperatures are preferred because of shorter stirring times and faster coalescence of the colloidal polymer particles. From a scale-up point of view, a higher internal to external phase ratio will result in higher product yields.

The coalescence and hence solidification and formation of the microparticles was primarily affected by the solids content of the polymer dispersion, the amount of internal phase emulsified, and the temperature of the external oil phase. The solidification time (the time necessary to obtain individual, non-agglomerated microspheres after filtration) decreased with increasing solids content because less water had to be evaporated (Fig. 3). Increasing the amount of polymer dispersion emulsified increased the time necessary prior to separation of the microspheres (Fig. 4). The stirring time also decreased with increasing temperature of the oil phase because of a more

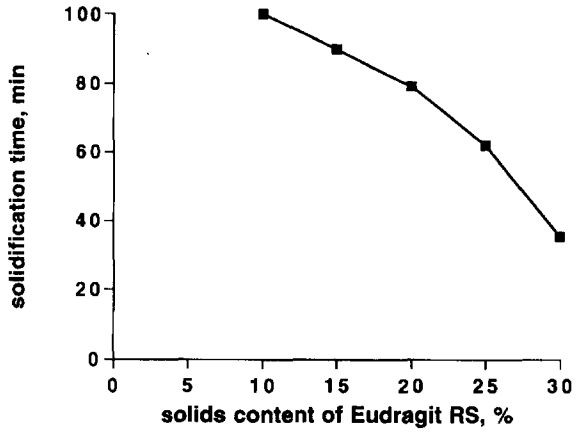

Fig. 3. Effect of the Eudragit RS30D solids content on the solidification time.

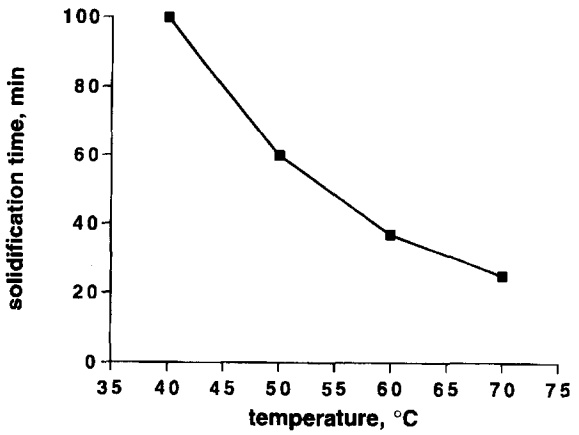

Fig. 5. Effect of the temperature of the cottonseed oil phase on the solidification time.

rapid evaporation of water (Fig. 5). Microparticles could be formed with various oils including cottonseed, corn, and sesame oil, but not with mineral oil after stirring at 60°C for 24 h. In order to form microparticles, water had to be removed and the colloidal polymer particles had to fuse into a homogeneous matrix. During microparticle formation, water diffused into the oil phase and then evaporated at the oil/air interface. Because of the hydrophobic character of mineral oil and hence a low water solubility in mineral oil, the water diffusion into mineral oil was probably slower when compared to the other oils.

The propranolol HCl release from microspheres prepared from Eudragit RS 30D could be sustained over a 6-h period as shown in Fig. 6. Eudragit RS contains quaternary ammonium groups which are responsible for the hydration of and drug release from the microparticles. A further retardation of the drug release could possibly be achieved with more hydrophobic polymers.

In conclusion, microspheres in the μm size range were prepared from water-insoluble polymers by a novel technique without solubilization of the polymer in organic solvents. The microspheres were formed by a w/o-emulsion technique

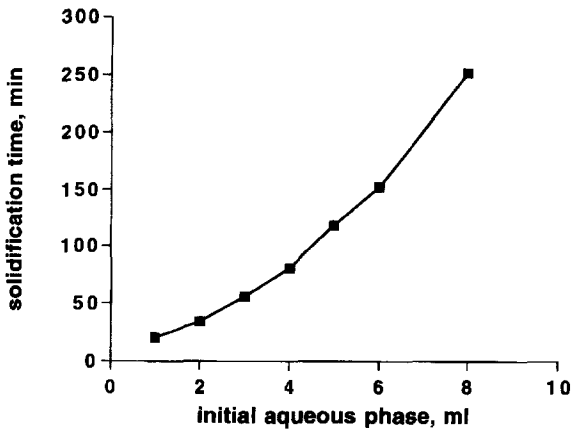

Fig. 4. Effect of the amount of the internal aqueous phase (Eudragit RS30D) on the solidification time.

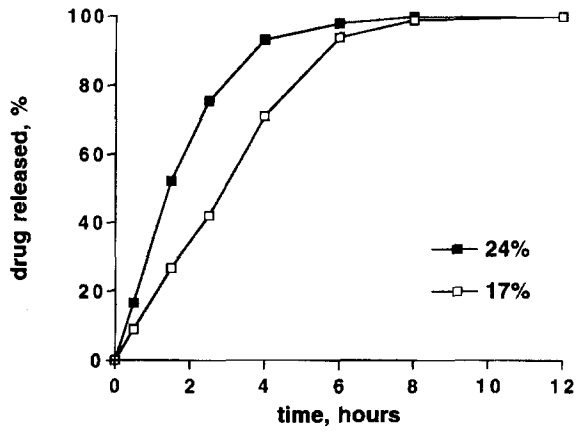

Fig. 6. Drug release from propranolol HCl-Eudragit RS30D microspheres with drug loadings of 17 and 24%.

through the coalescence of colloidal polymer particles within the internal aqueous phase into larger polymeric microparticles.

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