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Entrapment of drug-loaded ion-exchange particles within polymeric microparticles

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Abstract

The cationic water soluble drugs (chlorpheniramine maleate, pseudoephedrine HCl and propranolol HCl) were bound to a cation-exchange resin (Amberlite® IRP 69) and microencapsulated with an aqueous solvent evaporation method, whereby the resin particles were dispersed in an organic polymer solution [ethylcellulose, poly(methyl methacrylate), Eudragit RS 100] followed by emulsification into an external aqueous phase. A key variable for the successful encapsulation was the preferred wettability of the resin particles by the polymer phase. High encapsulation efficiencies were obtained, at high drug loading capacity of the resin, with drugs with high binding affinity and with a wetting agent. Phosphatidyl choline was the preferred wetting agent in order to avoid the partitioning of the resin into the external phase. With Eudragit RS 100, a cationic polymer with quaternary ammonium, all resin particles were encapsulated and the drug release was negligible when compared to the other polymers. This was attributed to the interactions of the polymer with the oppositely charged resin particles, which prevented hydration and swelling of the resin. The drug release depended strongly on the type of polymer used, the microstructure of the microparticles and the binding affinity of the drug to the resin. © 1997 Elsevier Science B.V.

Keywords: Controlled release; Ion-exchange resins; Microencapsulation; Microspheres; Solvent evaporation method

1. Introduction

In the area of oral controlled drug delivery, most systems are solid dosage forms with multiparticulate systems (e.g. microparticles, pellets) becoming more popular (Lippold, 1990). For certain patient groups (e.g. children, elderly) or applications, it could be advantageous to develop liquid rather than solid controlled release delivery systems. Several challenges have to be addressed when formulating multiparticulates into liquid dosage forms. Besides physical and chemical stability problems associated with a dispersed system, the major problems are the leaching of the drug from the microparticles into the liquid vehi-

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cle and possible interactions of the carrier or coating material with the vehicle during storage (Bodmeier and Paeratakul, 1994).

A dry multiparticulate preparation, which is dispersed in water just prior to use, could overcome these problems (Sorenson et al., 1991). If a liquid is the desired final dosage form, two approaches could be taken. First, a vehicle could be selected in which the drug is not soluble or which does not diffuse through the polymer membrane in order for the drug not be released during storage (Bodmeier et al., 1991). For example, microparticles containing a water-soluble drug could be dispersed in an oily vehicle. Another approach, which allows the use of more preferred aqueous vehicles, is based on ion-exchange resins.

Ion-exchange resins are used in various pharmaceutical applications including taste masking (Borodkin and Sundberg, 1971) or controlled drug release for ocular (Jani and Harris, 1990) and primarily oral applications. For liquid controlled release preparations, the charged drug is bound to oppositely charged resin particles. The drug is not released in ion-free media, but after oral use, it is released through displacement of ions of same charge being present in gastrointestinal fluids. Since the drug is released quite rapidly, the drug-resin complexes are coated with polymers, like ethylcellulose, to retard the release (Raghunathan, 1980, 1989). The coated particles are then suspended into an ion-free aqueous phase to form a liquid dosage form. Liquid controlled release preparations of ion-exchange resins are therefore based on two principles: (1) the binding of the drug to the resin in order to prevent leaching during storage; and (2) coating of the drug-loaded resin particles to retard the drug release once the particles are in contact with body fluids. Besides polymers, waxes have also been used as coating materials (Kogan et al., 1991). Recently, a multiparticulate floating system based on ion-exchange resins with bound bicarbonate has been developed (Atyabi et al., 1996).

Besides coating techniques, various microencapsulation techniques have been used to form drug-resin containing microparticles. These methods include organic phase separation (Motycka et al., 1985), aqueous and non-aqueous solvent evaporation (Sprockel and Prapaitrakul, 1988; Torres et al., 1995) and interfacial polymerization (Torres et al., 1990) methods.

The objective of this study was to encapsulate drug-resin complexes with polymers by the solvent evaporation method with emphasis on achieving high encapsulation efficiencies. In particular, parameters affecting the wettability of the resin particles were key factors for their successful entrapment.

2. Experimental

The following chemicals were obtained from commercial suppliers and used as received: chlorpheniramine maleate, propranolol HCl, pseudoephedrine HCl (Sigma, St. Louis, MO), ion-exchange resin—Amberlite® IRP 69 (sodium polystyrene sulfonate, USP) (Röhm and Haas, Philadelphia, PA), phosphatidyl choline (Lipoid GmbH, Ludwigshafen, Germany), poly(vinyl alcohol) (88 mol% hydrolyzed, M.W. 125 000), poly(methyl methacrylate) (Polysciences, Worthington, PA), Span 80 (sorbitan oleate), Tween 20 (polyoxyethylene(20)sorbitan monolaurate) (ICI Surfactants, Cleveland, UK), ethylcellulose (Ethocel® STD 10 Premium) (Dow Chemical, Midland, MI), Eudragit® RS 100 (poly(ethylacrylate-methylmethacrylate-trimethylammonioethyl methacrylate chloride, Röhm GmbH, Darmstadt, Germany), ethanol, methylene chloride (Mallinckrodt Chemical Works, St. Louis, MO).

The resin particles were ground and purified prior to drug binding and microencapsulation. An aqueous slurry of the Amberlite® IRP 69 resin was transferred into a ball mill (US Stoneware, East Palestine, OH) and milled for 24 h. The ground resin particles were recovered by centrifugation (Beckman centrifuge model TJ-6, Spinco Division, Palo Alto, CA) and then washed 2 × 300 ml 95% ethanol, 2 × 300 ml deionized water, 2 × 300 ml 1.0 N HCl, 1 × 300 ml deionized water, 2 × 300 ml 1.0 N NaOH followed by washing with deionized water until the supernatant was neutral. The resin was then recovered after centrifugation and dried in a desiccator. The particle size distribution of ground Amberlite® IRP 69

was determined with a particle size analyzer (Malvern Mastersizer Model E, Herrsching, Germany). 65 vol% of the ground resin particles were smaller than 10 μm, 97 vol% < 30 μm and 99 vol% < 38 μm.

The drug-resin complex was formed by a batch process, whereby the ground resin particles (100 mg) were added to an aqueous drug solution (2% w/v, volumes between 1 and 12 ml, depending on the loading capacity, standard formulation = 5 ml) and shaken in a horizontal shaker at room temperature for 48 h. The drug-resin particles were separated from the supernatant by centrifugation, washed with deionized water to remove unbound drug and counterions and dried in a desiccator at room temperature. To determine the actual loading capacity, the supernatant was assayed spectrophotometrically (Shimadzu UV-2101 PC, Shimadzu Europa GmbH, Germany; chlorpheniramine maleate, $\lambda = 262$ nm; propranolol HCl, $\lambda = 290$ nm; pseudoephedrine HCl, $\lambda = 254$ nm). The amount of drug bound to the resin was calculated as the difference between the initial and the remaining amount of drug in the supernatant. The loading capacity was: the amount of drug bound to the resin, mg/amount of resin, mg $\times$ 100%.

The drug-resin particles were encapsulated by the O/W- or W/O/W-solvent evaporation methods. In the O/W-method, the drug-resin particles (100 mg) were suspended in a solution of the polymer (200 mg) in methylene chloride (2.0 ml) followed by emulsification of this phase into an external aqueous phase (200 ml, 0.25% w/v poly(vinyl alcohol)). In the W/O/W-method, 0.2 ml water was added to the organic phase in addition to the resin particles. If used, the wetting agents, phosphatidyl choline (5, 10 or 20 mg), Span 80 or Tween 20 (10, 20, 50 or 100 mg) were added to the resin-polymer phase at least 3 h prior to emulsification in the external aqueous phase. The microspheres were removed after 60 min by filtration and dried in a vacuum desiccator for at least 48 h. The microspheres within the size range of 40–160 μm (unencapsulated resin particles were smaller than 40 μm) were used for further experimentation. The standard formulation corresponded to a theoretical drug-resin content of 33.3% and to a theoretical drug content of 15–17%.

The particle size distribution of the drug-loaded resin particles and the microspheres was measured by a particle size analyzer (Mastersizer Model E, Herrsching, Germany). After emulsification of the resin-containing polymer phase into the aqueous phase (200 ml, 0.25% poly(vinyl alcohol)), the emulsion was poured into the sample cell of the machine. A lens with a diameter of 300 mm, which is suitable for a size range of 0.5–600 μm, was used. An aqueous solution of 0.25% poly(vinyl alcohol) was used as a blank.

The drug loading of the polymeric microspheres was determined spectrophotometrically (chlorpheniramine, $\lambda = 262$ nm) after dissolving the microspheres (10–50 mg, 45–105 μm) in 2 ml methylene chloride and extraction with 50 ml 0.2 M $CaCl_2$ solution. The actual drug loading was calculated as: the amount of drug, mg/amount of microspheres, mg $\times$ 100% and the encapsulation efficiency as: the actual drug content/theoretical drug content $\times$ 100%. The amount of drug leached into the external phase during microsphere preparation was obtained by analyzing the external phase spectrophotometrically after filtration through a 0.45 μm filter.

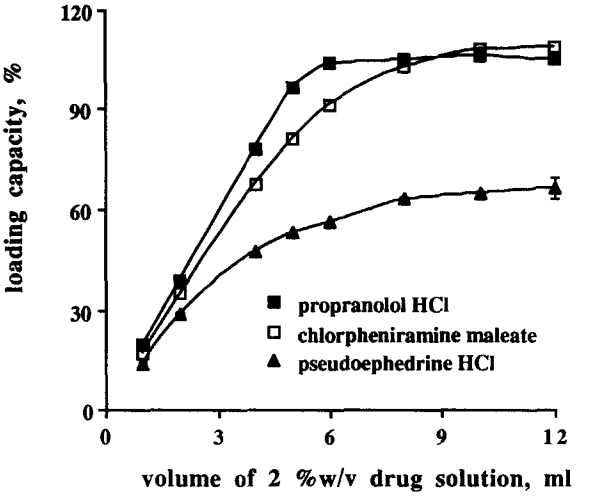

Fig. 1. Effect of volume of 2% w/v aqueous drug solution on the binding capacity of Amberlite® IRP 69 with three cationic drugs.

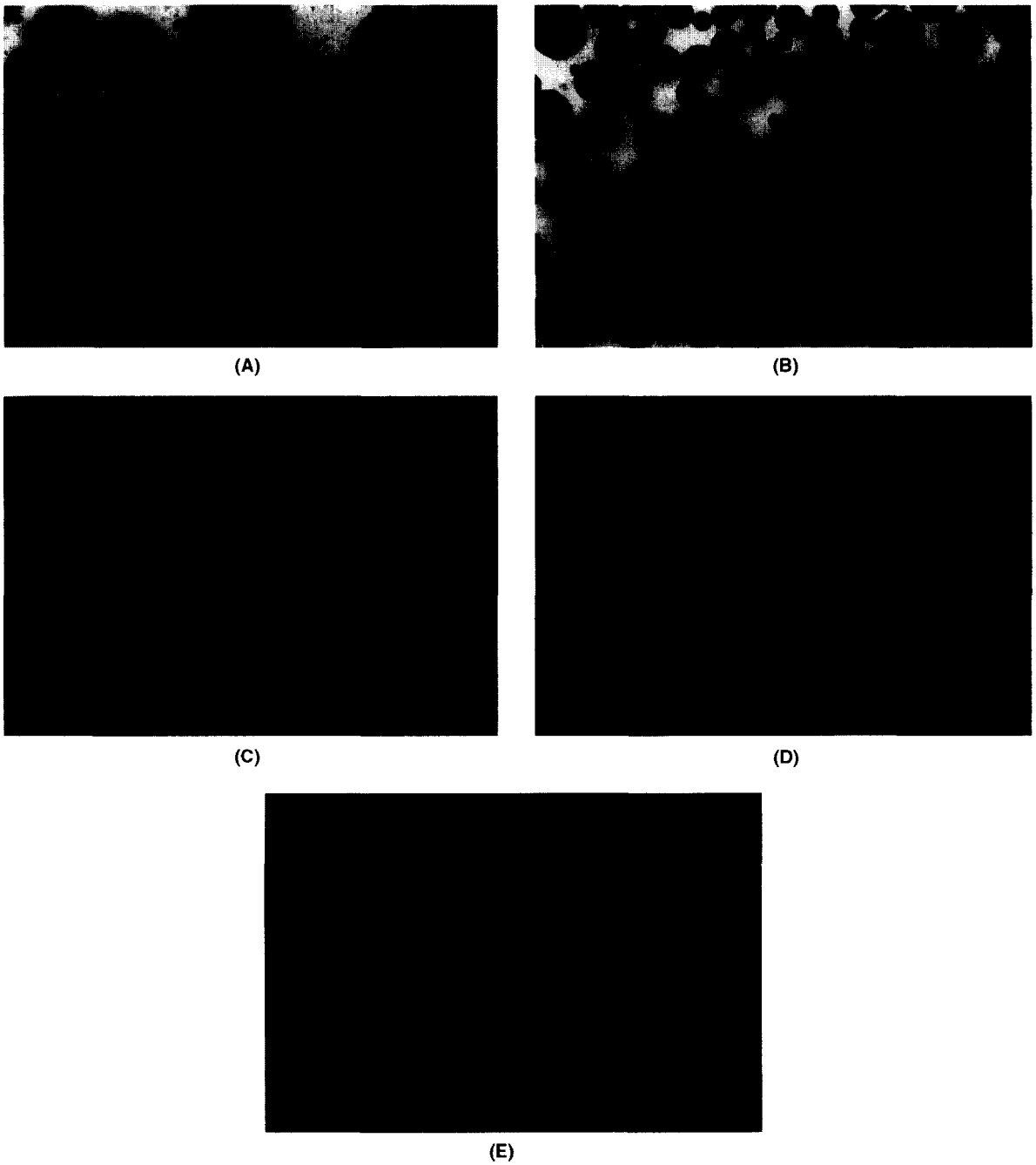

Fig. 2. Photomicrographs of microspheres containing chlorpheniramine-Amberlite® IRP 69 resin particles prepared with different polymers and by different methods: (a) ethyl cellulose—W/O/W-method; (b) ethyl cellulose—W/O/W-method (with phosphatidyl choline); (c) poly(methyl methacrylate)—W/O/W-method; (d) poly(methyl methacrylate)—W/O/W-method (with phosphatidyl choline); (e) Eudragit RS100—W/O/W-method.

In vitro drug release was determined with a horizontal shaker method, whereby the microspheres (10–50 mg, 45–105 μm) were placed into bottles containing 0.1 M pH 7.4 phosphate buffer (250 ml for chlorpheniramine and propranolol, 50 ml for pseudoephedrine, 37°C, $n = 2$) followed by shaking in a horizontal shaker at 80 rpm (Gesellschaft für Labortechnik GmbH, Burgwedel, Germany). The samples were withdrawn at predetermined time intervals and assayed spectrophotometrically (chlorpheniramine, $\lambda = 262$ nm; propranolol, $\lambda = 290$ nm; pseudoephedrine, $\lambda = 254$ nm)

In order to observe unencapsulated resin in the aqueous phase during the microsphere preparation, samples were taken from the aqueous phase, observed with a Zeiss Phase Contrast Microscope and photographed with a Contax 167 MT camera. The surface and cross-section of the microspheres were examined by scanning electron microscopy (S.E.M.). The cross-sections of the microspheres were obtained by dispersing and drying the microspheres in a glue (Testor Corporation, IL), followed by cutting the dried matrix with a razor blade. The dried microspheres were mounted onto the stage prior to coating for 70 s under an argon atmosphere with gold-palladium (Pelco Model 3 Sputter Coater). The coated samples were then examined with an S.E.M. (Jeol JSM 35C).

3. Results and discussion

The drug-resin particles were encapsulated by the solvent evaporation method, whereby the resin particles were first suspended in the organic polymer solution followed by emulsification of this phase into an external aqueous phase. The microspheres were then obtained by filtration after solvent evaporation and solidification of the polymer droplets. During initial trials with ethyl cellulose, it was observed that under certain conditions, large amounts of resin particles were unencapsulated because of a redistribution from the inner organic phase to the external aqueous phase after emulsification. The preferential wettability of the particles by the organic phase and not by the aqueous phase was a key factor for the successful encapsulation of the resin particles. Microscopic observations of the aqueous phase during microsphere preparation revealed qualitatively, that the amount of resin particles encapsulated depended

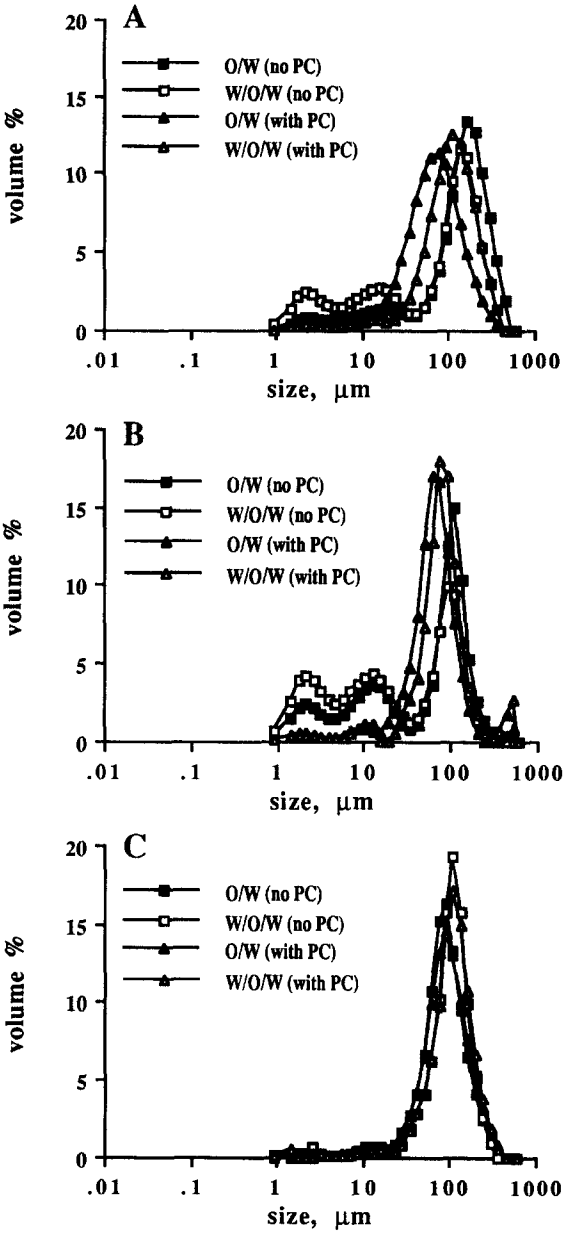

Fig. 3. Size distribution of microspheres prepared with different methods and polymers: (a) ethylcellulose; (b) poly(methyl methacrylate); and (c) Eudragit® RS 100.

Table 1
Effect of the polymer, the method of preparation and the use of phosphatidyl choline on the presence of unencapsulated resin particles in the external phase, on the encapsulation efficiency and on drug leaching during microsphere preparation

Polymer	Phosphatidyl choline (mg)	Resin particles in external phase	Encapsulation efficiency, %	Drug leached, %
Ethylcellulose				
Method				
O/W	—	Some outside	90.9	1.3
W/O/W	—	Some outside	42.9	1.1
O/W	5	All inside	104.0	1.0
W/O/W	5	All inside	105.9	1.3
Poly(methyl methacrylate)				
Method				
O/W	—	Some outside	74.8	1.1
W/O/W	—	Many outside	6.2	1.1
O/W	5	All inside	99.2	0.8
W/O/W	5	All inside	96.1	0.9
Eudragit® RS100				
Method				
O/W	—	All inside	94.7	6.0
W/O/W	—	All inside	98.5	4.5
O/W	5	All inside	98.5	5.7
W/O/W	5	All inside	96.3	5.5

on the loading capacity of the resin particles and the type of drug. Drug-free resin particles (in the Na-counterion form) hydrate rapidly when in contact with water, they were almost completely found in the external aqueous phase. Resin particles with different loading capacities were prepared by equilibrating the resin particles with different volumes of drug solution. The loading capacity increased with increasing amount of drug in the external phase during loading and then levelled off (Fig. 1). Microparticles were then prepared with resin particles having different loading capacities and observed microscopically for resin loss during microparticle preparation. Resin particles were found outside the microspheres at low loading capacities, irrespective of the drug. This could be explained with the higher amount of sodium counterions in the resin phase at lower loading capacities resulting in more water uptake upon dispersion into the external aqueous phase. Therefore, the resin particles preferably partitioned in the aqueous phase rather than remaining in the polymer phase. The encapsulation of the drug-loaded resin particles increased with increasing loading capacity of the resin and increased binding affinity of the drug to the resin. While a considerable amount of pseudoephedrine-Amberlite® IRP 69 complex was found outside even at high loading capacities, less chlorpheniramine-Amberlite® IRP 69 complex and no propranolol-IRP 69 Amberlite® complexes were visible in the aqueous phase at loading capacities in excess of 75%. This correlated well with the binding affinity of the drugs to the resin which increased in the order of pseudoephedrine HCl < chlorpheniramine maleate < propranolol HCl (Sriwongjanya, 1996). In general, the resin particles became more hydrophobic with increasing loading capacity and binding affinity of the drug, thus being preferentially wetted by the organic polymer phase.

In order to improve the wettability of the resin particles by the polymer phase and therefore the encapsulation efficiency, different wetting agents (phosphatidyl choline, Span 80 or Tween 20), different polymers [ethylcellulose, poly(methyl methacrylate) or Eudragit® RS 100] and two modifications of the solvent evaporation methods (O/W- or W/O/W-methods) were evaluated. Photographs of the microparticles were taken to illustrate the presence of the drug-resin complexes

outside the microspheres (Fig. 2). Among the wetting agents, only phosphatidyl choline was effective, no chlorpheniramine-Amberlite® IRP 69 resin particles were visible in the aqueous phase

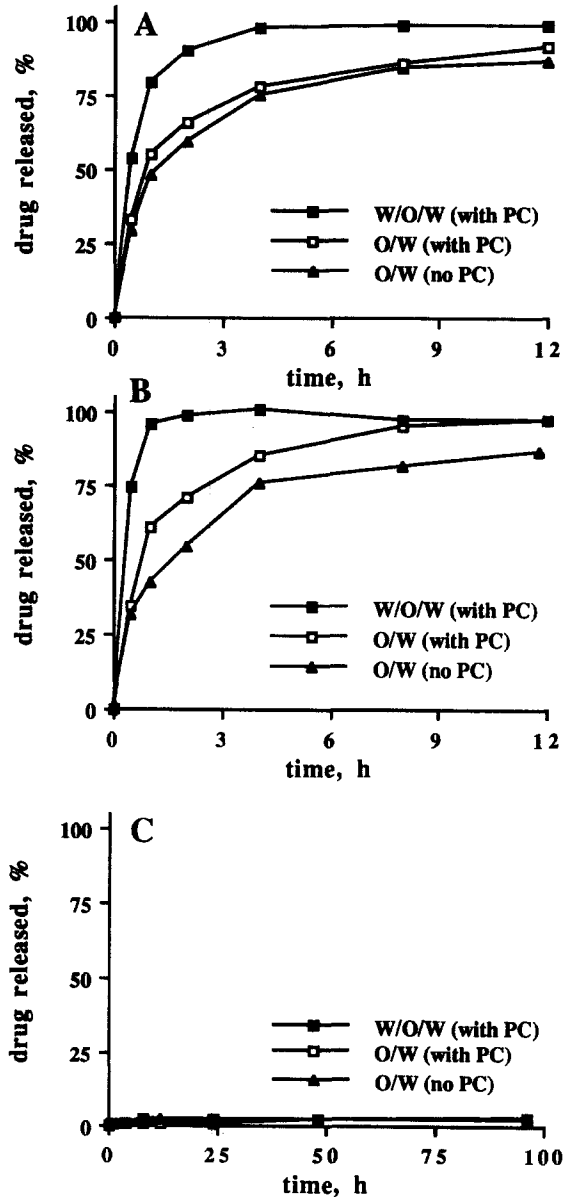

Fig. 4. Chlorpheniramine release from microspheres containing drug-Amberlite® IRP 69 resin particles prepared by different methods in 0.1 M pH 7.4 phosphate buffer: (a) ethylcellulose; (b) poly(methyl methacrylate); and (c) Eudragit® RS 100.

for all polymers and for both the O/W- and W/O/W-methods (Fig. 2b and d, only microparticles prepared with W/O/W-method shown). The drug-resin complex became more hydrophobic by the adsorption of phosphatidyl choline, an amphiphilic lipid with a zwitterionic polar head group. The quaternary ammonium groups probably interacted with the sulfonate groups of Amberlite® IRP 69, resulting in an increase in the hydrophobicity of the drug-resin complex, a decreased tendency to take up water and better wetting by the polymeric phase. Irrespective of their concentration, Tween 20 or Span 80, which are nonionic surfactants did not improve the encapsulation of the resin. Without phosphatidyl choline, chlorpheniramine-Amberlite® IRP 69 complexes were noticeable outside ethylcellulose (Fig. 2a) and poly(methyl methacrylate) (Fig. 2c) microspheres prepared by both the O/W- and the W/O/W-methods. Interestingly, with Eudragit® RS 100, a cationic polymer with quaternary ammonium groups, all resin particles were inside the microspheres regardless of the use of phosphatidyl choline or the method (Fig. 2e). This was attributed to the ionic interactions between the positive charges of Eudragit® RS 100 and the sulfonate groups of the anionic resin, Amberlite® IRP 69.

The presence of unencapsulated resin particles was also evident after measuring the particle size distribution of the microparticles (Fig. 3). With ethylcellulose (Fig. 3a) and poly(methyl methacrylate) (Fig. 3b) microspheres prepared without phosphatidyl choline, particles with a size below 30 μm, corresponding to the size of the drug-resin complex, were visible. The fraction of particles in this size range was higher with the W/O/W-method than with O/W-method, especially for poly(methyl methacrylate) microspheres. Initially, it was thought that the resin particles could possibly be associated with the internal aqueous phase and therefore stay within the microparticles by adding water to the organic phase (W/O/W-method). However, the resin particles hydrated with the internal water, became more hydrophilic and partitioned into the external phase. Unencapsulated resin particles were absent after the inclusion of phosphatidyl choline, the microparticles

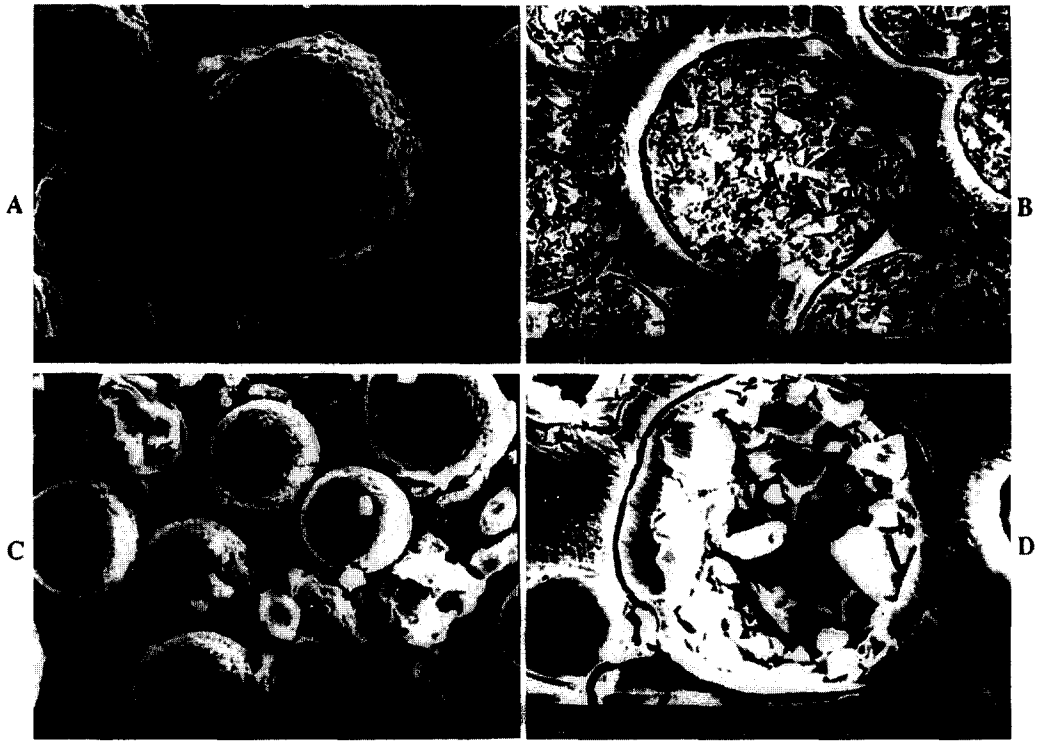

Fig. 5. Scanning electron micrographs of the surface and cross-section of ethylcellulose microspheres prepared by: (A–B) O/W-method; and (C–D) W/O/W-method.

were also smaller, probably because of the reduction of the interfacial tension between the organic polymer phase and the aqueous phase. Increasing the viscosity of the organic phase also enhanced the microencapsulation of the resin particles. For example, more resin particles were found outside poly(methyl methacrylate) microspheres than with ethylcellulose microspheres because the viscosity of the PMMA solution was lower than that of the ethylcellulose solution at the same concentration. Unencapsulated resin particles were absent with Eudragit® RS 100 microspheres (Fig. 3c). As already described above, this could be attributed to the interaction between the cationic groups of the polymer and the anionic groups of the exchanger reducing the hydration of the ion-exchange resin. The particle size of the microparticles was not affected by the inclusion of phosphatidyl choline. The polymer with its quaternary ammonium groups is surface active on its own.

The drug content and the encapsulation efficiency were determined by adding a known amount of microspheres to 2 ml of methylene chloride to dissolve the polymer followed by extraction with 50 ml of 0.2 N $CaCl_2$ to replace the drug from the resin. The results confirmed the findings mentioned above. High encapsulation efficiencies were obtained when phosphatidyl choline was used and with Eudragit® RS 100 microspheres (Table 1). Without phosphatidyl choline, the W/O/W-method resulted in lower encapsulation efficiencies than the O/W-method because of more resin particles being lost to the external aqueous phase.

In order to keep the drug bound to the resin during the microsphere preparation, ions which could replace the drug have to be avoided. The amount of drug released during the microsphere preparation (free drug in the external phase, does not include unencapsulated drug-resin particles) was determined by assaying the external aqueous

phase. While only small amounts of drug (≈ 1%) leached from the resins when ethylcellulose or poly(methyl methacrylate) were used, between 4–6% drug was found in the external phase for

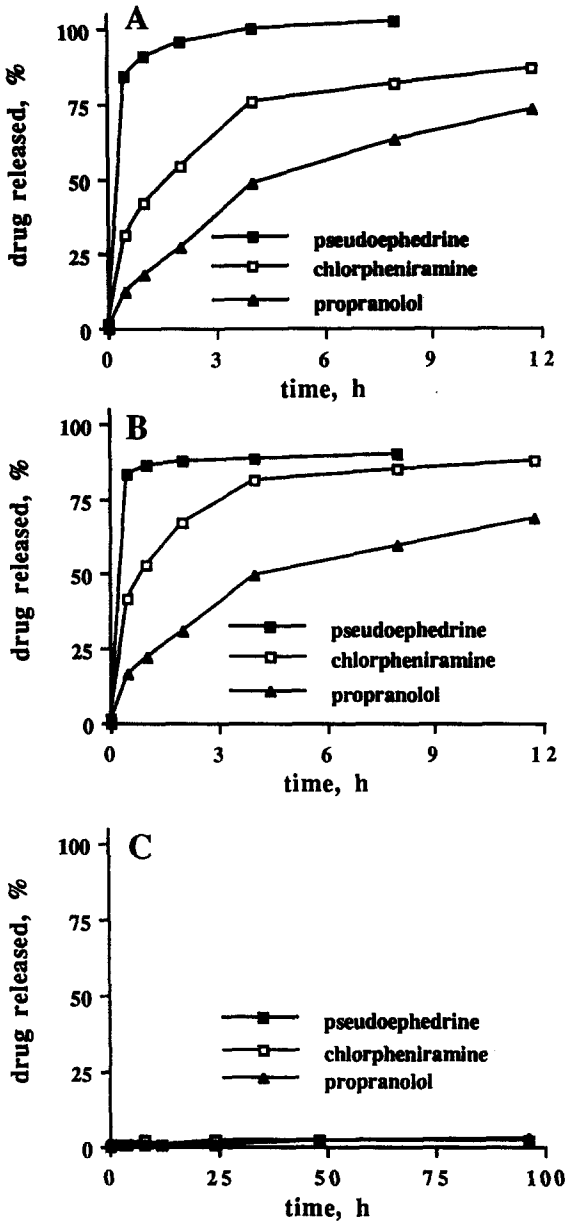

Fig. 6. Release of drugs from: (a) ethylcellulose; (b) poly(-methyl methacrylate); and (c) Eudragit® RS 100 microspheres (O/W-method with phosphatidyl choline) containing drug-Amberlite® IRP 69 resin particles in 0.1 M pH 7.4 phosphate buffer.

Eudragit® RS 100 (Table 1). The cationic drug was replaced by the quaternary ammonium groups of Eudragit RS 100 during the microsphere preparation. The amount of drug released during microsphere preparation also increased with increasing concentration of poly(vinylalcohol), the polymer used to stabilize the emulsion. Increasing the poly(vinylalcohol) concentration from 0.25 to 2% increased the drug loss with ethylcellulose micropheres from ≈ 1 to 9%. This was due to ionic impurities present in the poly(vinylalcohol). Raw materials with low amounts of ionic impurities should be used.

The release of chlorpheniramine from unencapsulated resin particles was complete within 1 h (Sriwongjanya, 1996). The release of drug from ethylcellulose and poly(methyl methacrylate) microspheres containing chlorpheniramine-Amberlite® IRP 69 particles was fastest from microspheres prepared by the W/O/W-method, followed by microspheres prepared by the O/W-method with phosphatidyl choline and microspheres prepared by the O/W-method without wetting agent (Fig. 4a, b). Scanning electron micrographs of the surface and cross-sections of ethylcellulose microspheres revealed a dense structure with dispersed resin particles for microspheres prepared by the O/W-method (Fig. 5a, b) and a more porous stucture for microspheres prepared with the W/O/W-method (Fig. 5c, d), thus explaining the faster release from the microparticles prepared with an internal aqueous phase. The faster release from the microspheres prepared with phosphatidyl choline was probably due to their better wettability by the dissolution medium. Surprisingly, the drugs were not released from Eudragit® RS 100 microspheres (Fig. 4c). This could be a result of the strong interaction between the quaternary ammonium groups of polymer and the sulfonic groups of Amberlite® IRP 69, preventing hydration and swelling and therefore drug release from the microparticles. The drug release correlated well with the binding affinities of the drugs for the resin, with pseudoephedrine (lowest binding affinity) being released faster than chlorpheniramine or propranolol (Fig. 6).

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