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Comparison between aqueous and non-aqueous solvent evaporation methods for microencapsulation of drug–resin complexes

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Abstract

Terbutaline-loaded ion-exchange resins were entrapped within cellulose acetate butyrate (CAB) microcapsules using either an aqueous (O/W) or a non-aqueous (O/O) solvent evaporation method. Scanning electron micrographs of the cross-sections of microcapsules prepared by both techniques revealed that the degree of multinucleation was dependent on the polymer concentration. A low polymer concentration led to a typical mononucleated reservoir structure whereas more multicore microcapsules were formed at high polymer concentrations. These differences on the inner structure affected the in vitro terbutaline release profiles. Terbutaline released very rapidly from the mononucleated microcapsules, however its release was controlled from the multinucleated systems. In addition, terbutaline release was influenced by the microencapsulation method. Using the higher CAB concentrations, the O/O technique produced microcapsules which adequately controlled the release of terbutaline; in contrast, microcapsules obtained by the O/W method showed a biphasic behaviour, with an initial burst effect followed by stabilization of the drug release, which became finally incomplete. With the aim of elucidating the main causes which were responsible for the differences in drug release, CAB films were obtained by casting the polymeric solutions prepared with the solvents used in each encapsulation procedure, acetone and methylene chloride for O/O and O/W methods, respectively. Thermal properties of the polymer in films and microcapsules were compared, and terbutaline diffusion studies through the films were performed. Results revealed that the polymer solvent was a key factor that determined the structure of the polymer wall formed, and thereby the in vitro release properties of the polymer films. After an initial rapid permeation step in both films, the CAB film cast from acetone allowed a faster permeation of terbutaline by diffusion through the pores, whereas the diffusion through the polymer chains was probably the only possible mechanism of drug release in the dense film formed from methylene chloride polymer solutions, this process being extremely slow for terbutaline.

Keywords: Microencapsulation; Ion-exchange resins; Controlled release; Solvent evaporation method; Cellulose acetate butyrate; Terbutaline

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1. Introduction

Most of the oral controlled-release products are available as solid forms, however, liquid suspensions are especially preferred in particular situations, for example in the pediatric or geriatric populations, because of their ease of swallowing and the flexibility of adjusting dosages. Attempts to develop liquid oral controlled-release formulations are generally based on multiparticulates, such as coated pellets or microparticles, but due to the drawbacks associated to their development, there are to date few suitable suspensions available on the market. These difficulties deal essentially with the leaching of the drug into the aqueous suspending medium and the interactions with the liquid contents, often changing the original properties during storage.

Ion-exchange resins offer one of very usable systems for achieving ready-made liquid products with prolonged release properties. The drug–resin complexes can be suspended in an ion-free aqueous medium without any appreciable drug leaching occurring during storage, whereas the drug release will be only promoted upon administration by the presence of competing ions in the gastrointestinal fluids. If the properties of the drug–resin complex do not give the desired sustained-release rate, coating the particles with a rate-controlling membrane often achieves the targeted bioavailability. With this aim, different polymers, mainly hydrophobic compounds, and coating or microencapsulation processes have been used to encapsulate drug–resin beads. In addition to the typical air coating methods as is described in the most common application of this technology—the Pennkinetic system, developed by the Pennwalt Corporation (Raghunathan, 1980)—a variety of microencapsulation methods have been applied to obtain resin containing hydrophobic microparticles. Organic phase separation methods, such as the solvent/non solvent evaporation method (Motycka et al., 1985; Moldenhauer and Nairn, 1990, 1991), were used to explore the possibilities of ethylcellulose in the microencapsulation of resin cores. Taking into account some of the critical steps involved in the microencapsulation of resin beads, such as the dispersion of the solid cores in the coating medium or the rate of polymer precipitation, the above mentioned authors concentrated their work on the study of the main factors related to these steps, allowing mononucleated and uniformly coated microcapsules to be formed. The protective colloid polyisobutylene was considered essential in the microencapsulation process in order to prevent microcapsule multinucleation by altering phase changes in the ethylcellulose solution. Also the rate of solvent evaporation was found to be an important factor to be controlled, as it affects the type of coat formed.

Drug–resin complexes were also microencapsulated with water-insoluble polymers, such as cellulose acetate butyrate and polymethyl metacrylate, using emulsion-solvent evaporation methods in an oily phase (Sprockel and Price, 1989, 1990). However, the resulting microparticles prepared by these techniques presented some problems, such as their large particle size distribution or the long time required for manufacture. The inclusion of emulsion stabilizers in the external phase (i.e. magnesium stearate), allowed to some extent the reduction of the particle size although the technique continued to be a time-consuming process.

Whereas, the non-aqueous phase methods have generally been applied for encapsulating drug–resin complexes, the use of typical solvent evaporation methods in an aqueous phase has not yet been reported for this purpose. The present work deals with the comparison of aqueous and non-aqueous solvent evaporation techniques for microencapsulation of drug–resin complexes with cellulose acetate butyrate. In addition to the type of method, several formulation variables were included in the study to disclose their influence on microcapsule structure and coat characteristics. The anti-asthmatic terbutaline, a highly water soluble drug, was chosen to evaluate the feasibility of the two types of microencapsulation methods to obtain a liquid controlled-release product.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial sources and used as received: cellulose acetate butyrate (CAB 171-15S: 29.5% w/w acetyl, 17% w/w butyryl and 1.5% w/w hydroxyl content; MW = 65000) (Eastman Chemical, Kingsport, TN); poly(ξ-caprolactone) (PξCL) (Aldrich, Madrid, Spain); sulfonic acid cation-exchange resins in the H^+ form (Dowex® 50W-X4, 200–400 mesh), terbutaline hemisulphate, silicone (antifoam A concentrate), poly(vinyl alcohol) (PVA) (MW = 30000–70000) and propylene glycol (PG) (Sigma, St. Louis, MO); liquid paraffin (viscosity = 110–230 mPa; Merck, Darmstadt, Germany); sorbitan trioleate (Span® 85) and polyethylene glycol 400 and 4000 (PEG 400 and PEG 4000) (Fluka, Madrid, Spain); acetone, methylene chloride and n-hexane of HPLC grade (Romil, Cambridge, UK). All other chemicals were of analytical grade.

2.2. Purification of the ion-exchange resins

The resins were purified by rinsing about 10 g of wet resin with 3×50 ml portions of deionizated water, 1×50 ml of 95% ethanol, 1×50 ml of 50% ethanol and 1×50 ml of deionized water. Each stage of treatment lasted 1 h under magnetic stirring. The resin was then conditioned by recycling the ion exchanger twice between the H^+ and the Na^+ form, with 60 ml of 2 M NaOH and 60 ml of 2 M HCl, and washing with deionized water after each treatment. Finally, the resin in the Na^+ form was recovered by vacuum filtration, washed thoroughly with deionizated water and dried to constant weight at 50°C in an electronic moisture balance (Shimadzu model EB-280 MOC, Kyoto, Japan).

2.3. Loading of the resins

The terbutaline–resin complex (TRC) was formed by a batch process, in which the previously purified resin (5 g dry weight) was suspended in a 0.1 M solution of terbutaline sulphate (250 ml) and stirred at room temperature for 1 h. The complex was separated from the supernatant by vacuum filtration, washed with deionized water to remove any unreacted drug, dried to constant weight and placed in a dessicator. Two batches of TRC were prepared.

The terbutaline content of the complex was determined in duplicate by placing 25 mg of the dry complex into centrifugal basket stirrers with 400 mesh wire screens, which were introduced into 1000 ml of acidic buffer (HCl/NaCl, pH 1.2, $\mu = 0.1$), and rotated at 1000 rpm (IKA stirring motor RW DZM, IKA Labortechnik, Staufen, Germany) at 37°C. The acidic medium was replaced every hour until the concentration of terbutaline was negligible (< 0.01 μg/ml). The solutions from each sample were accumulated and analyzed by HPLC for terbutaline (HPLC conditions are below described). From the amount of terbutaline that was eluted from each batch of TRC, the actual drug loading (%) was calculated as the (amount of drug (mg)/amount of TRC (mg)) $\times$ 100. The value for this parameter was 55.57 ± 2.57.

2.4. Microencapsulation process

The terbutaline-loaded resins were encapsulated by the O/O or O/W solvent evaporation methods. In the O/O method, the resin particles (coat to core ratio: 2:1 or 3:1) were suspended in 15 ml of a solution of the polymer (0.6, 0.9 or 1.2 g) in acetone followed by emulsification of this phase in 100 ml of liquid paraffin containing 1% w/w Span 85 and 0.1% w/w silicone. The resulting emulsion was maintained at 25°C and agitated at 1300 rpm with a propeller stirrer (IKA stirring motor RW DZM, IKA Labortechnik, Staufen, Germany) until the complete evaporation of acetone was accomplished (3 h). After that, the microcapsules were collected by vacuum filtration, washed with three portions of 75 ml of n-hexane and air dried for 24 h. In the O/W method, the resin particles (coat to core ratio: 2:1) were suspended in 10 ml of a solution of the polymer (0.3 or 0.6 g) in methylene chloride followed by emulsification in 100 ml of a 0.25% w/v aqueous solution of poly(vinyl alcohol). The emulsion was stirred at

700 rpm (25°C, 3 h) to evaporate the solvent. The microcapsules were recovered by vacuum filtration, washed with 200 ml of deionized water and dried at 50°C in oven for 24 h. Two batches were made for each formulation.

The terbutaline content of the microcapsules was determined in duplicate for each batch formulation after dissolving the polymer coat of the microcapsules (50 mg dry weight) in 10 ml of acetone. The remaining resin particles were then vacuum filtered, dried to constant weight and placed (25 mg) into centrifugal basket stirrers to determine the drug content by allowing the complete elution of terbutaline as previously described for the terbutaline–resin complex.

2.5. Morphological and particle size analysis of CAB microcapsules

The surface and the cross-section of the microcapsules was examined by scanning electron microscopy (Jeol model JSM-6400, Tokyo, Japan). Samples were gold sputter coated (BAL-TEC SCD 004, Lichenstein) for 165 s at 15 mA under an argon atmosphere. The cross-sections of the microcapsules were obtained by cryofracture. The microcapsules were suspended in water, frozen and cross-sectioned using an ultra-microtome (Ultracut Reichert-Jung, Austria).

The particle size distribution of the resin particles and the microcapsules was measured by a Coulter counter (Multisizer II, Coulter Electronics, Northwell, UK). The particle size was expressed as the equivalent volume diameter and two replicates were performed for each batch of microcapsules.

2.6. Drug release studies

In vitro terbutaline release was determined with a continuous flow-through apparatus (Sotax, Basel, Switzerland), where 25 mg of dry resin complex or microcapsules were placed in the sample cells. The dissolution media (HCl/NaCl, pH 1.2, $\mu = 0.1$; or NaH_2PO_4/Na_2HPO_4, pH 6.8, $\mu = 0.1$) were pumped at 20 ml/min and the system was maintained at 37°C. Samples were taken out by an automatic fraction collector (Model FC 204, Gilson, Middleton, WI) at specific time intervals for 12 h and then assayed by HPLC for terbutaline content. Two replicates were performed for each batch of terbutaline–resin complex or microcapsules ($n = 4$).

2.7. X-ray diffraction studies

X-ray diffraction experiments were performed in a Philips PW 1710 X-ray diffractometer (Philips Export; Eindhoven, The Netherlands) using Cu $K\alpha_2$ rays with a voltage of 40 kV and a current of 30 mA. Samples were scanned from 5 to 80° 2θ at a scanning rate of 1.5° 2θ/min. Diffraction patterns for polymer and both types of CAB microcapsules were obtained.

2.8. Films preparation

Cast films were prepared from 6% w/v CAB solutions in acetone and methylene chloride. A 5-ml sample of solution was poured onto an aluminium dish (63 mm diameter × 17.5 mm height; Fisher Scientific and Pacisa, Madrid, Spain) and the solvent was allowed to evaporate at room temperature for 48 h. Following the complete evaporation of the solvent, the films were carefully removed and stored in a desiccator for at least 24 h (approximate dry film thickness = 77 μm).

2.9. Thermal analysis

Thermograms of the CAB films and microcapsules were obtained using a Shimadzu differential scanning calorimeter (DSC-50 model, Kyoto, Japan). Samples (5 mg) were scanned in aluminium pans over the temperature range between 30–250°C (first run) and 100–200°C (second run) at a scanning rate of 10°/min. The glass transition temperature (T_g) of the polymeric samples was determined after a repeat run from the onset temperature values. All tests were carried out in duplicate.

2.10. Terbutaline diffusion from the films

Diffusion experiments were performed using a

horizontal side-by-side diffusion cell (Crown Glass, Somerville, NJ). CAB films were clamped between two compartments of equal volume (3 ml; 37°C; diffusion area 78 cm^2). A saturated solution of terbutaline in acidic medium (HCl/NaCl, pH 1.2, $\mu = 0.1$) was placed in the donor compartment while acidic medium was placed in the receptor. Samples of 500 μl were taken from the receptor cell and replaced with fresh medium at predetermined time intervals. The amount of terbutaline diffused through the films was determined by HPLC and each experiment was repeated twice.

2.11. HPLC conditions

The HPLC system consisted of a solvent delivery pump (Model P 1500, Spectra Physics, San José, CA), a variable UV absorbance detector (Model UV 1000, Spectra Physics, San José, CA) and an automatic injector (Kontron autosampler 460, Zurich, Switzerland). The detection wavelength was set at 276 nm and the separation was achieved using a reverse phase column (Spherisorb ODS 2, 10 μm particle size, 15×0.46 cm; Tecknokroma, Barcelona, Spain) at 35°C. The mobile phase consisted of an acetonitrile/0.15% v/v *o*-phosphoric acid aqueous solution (12:88 v/v; pH 2.5) and the flow rate was 1 ml/min.

2.12. Statistical analysis

The statistical significance of the differences between formulations was tested by the analysis of the variance (ANOVA) or the non-parametric Kruskal-Wallis test. The least significant difference (LSD) test or Siegel and Castellan (1988) test were applied for multiple comparison between formulations. Reference to a significant difference in the subsequent test refers to a level of $p < 0.01$.

3. Results and discussion

Cellulose acetate butyrate (CAB) microcapsules containing terbutaline-loaded resins were obtained by aqueous and non-aqueous solvent evaporation methods. Differences between the microcapsules in their surface porosity, inner structure and particle size were evaluated and related to the drug release profiles. The modified O/O solvent evaporation technique presented here led to discrete microcapsules of less than 200 μm in diameter, adequate to be suspended in an aqueous medium. The time required to form the microparticles was reduced from 12 to 3 h by adjusting the viscosity of the external phase, the stirring rate and by adding silicone and Span® 85 to the external phase. As an alternative, in this report, the use of the O/W solvent evaporation method for the microencapsulation of resin particles is also presented. This procedure is more economical and desirable, since the oil phase is replaced by an aqueous solution, and the use of solvents in the final cleaning-up step is eliminated.

3.1. Morphological and physicochemical characterization of CAB microcapsules containing terbutaline-loaded resins

The effect of the preparation method, coat/core ratio and polymer concentration on terbutaline loading and particle size of the resin containing microcapsules is shown in Table 1. The drug loading was closely related to the initial coat/core ratio, and ranged from 17–19% when the coat/core ratio was 2:1, to 12–13% when it was 3:1 (encapsulation efficiency: between 92–103% and 86–94%, respectively). The mean particle size of microcapsules prepared by the O/O method was mainly determined by the polymer concentration (Fig. 1a, b). As the viscosity increased (Fig. 2), the difficulty in obtaining a good dispersion of the resin particles before the polymer deposition become more difficult, thus producing more multinucleated particles and a less homogeneous population in size. This fact was also corroborated by the examination of the inner structure of the microparticles. Scanning electron micrographs of cross-sections of microcapsules (Fig. 3c, d; Fig.

Table 1
Mean values ± standard deviations of drug loading and particle size ($n = 4$) of CAB microcapsules containing terbutaline-loaded resins prepared by different solvent evaporation methods

Method	CAB conc. (% w/v)	Coat/core ratio	Drug loading (%)	Particle size (μm)
O/O	4	2:1	18.15 ± 1.68	114.72 ± 7.94
	4	3:1	13.07 ± 0.69	112.52 ± 6.59
	6	2:1	19.40 ± 1.11	145.42 ± 3.06
	6	3:1	11.97 ± 0.82	138.85 ± 2.98
	8	2:1	16.96 ± 1.20	191.20 ± 10.95
	8	3:1	12.84 ± 0.20	172.07 ± 10.73
O/W	3	2:1	17.40 ± 0.04	53.17 ± 0.72
	6	2:1	19.15 ± 1.65	143.48 ± 6.75
	6[a]	2:1	18.74 ± 2.17	125.05 ± 15.75
	6[b]	2:1	18.41 ± 0.95	149.71 ± 9.66

[a] CAB/PξCL (50:50) polymer mixture.
[b] CAB/PξCL (25:75) polymer mixture.

4c, d) revealed that the multinucleation degree increased with increasing polymer concentrations, this trend being more pronounced for the aqueous method. At the lower CAB concentration, the microcapsules formed a very homogeneous population, the mean particle size being fairly similar to that the resin particles (theoretical particle size: 37–74 μm, data from the supplier), which evidenced the existence of a uniform population of mononucleated microcapsules with a typical reservoir structure (Fig. 4c).

The scanning electron micrographs of the microparticles prepared by both the O/O and O/W methods (Fig. 3a, b; Fig. 4a, b) evidenced the higher porosity of the microcapsules prepared in an aqueous medium.

3.2. In vitro release studies of CAB microcapsules containing terbutaline-loaded resins

The dissolution profiles of terbutaline from the resin containing CAB microcapsules prepared by both the O/O and the O/W methods are depicted in Fig. 5a–c. It can be noted that terbutaline released immediately from the uncoated complex, while the CAB coating effectively retarded the drug release in most of the formulations. CAB microcapsules made using the O/O method exhibited adequate controlled-release profiles when higher CAB concentrations (6 and 8%) were used, however the lowest concentration hardly showed any additional control on the drug release from the resin complex, particularly for the 2:1 coat/core ratio. CAB concentration and coat/core ratio were found to be significant factors when the parameter dissolution efficiency was statistically analyzed ($F_{(2,18)} = 38.97$ and $F_{(2,18)} = 21.55$; $p < 0.01$), the multiple comparison test distinguishing for each coat/core ratio the formulation prepared at the lowest polymer concentration from the others. The microcapsules made using the O/W method, in contrast, did not adequately control the release of terbutaline from the ionic complex. They showed quite different biphasic release profiles, with an initial burst effect depending on the concentration of CAB, followed by a very slow release of drug until the end of the dissolution study. This led finally to an incomplete drug release, especially for the microcapsules made of the higher CAB concentration, which only released about 35% of drug fixed onto the resin complex after 12 h. This slow release rate did not agree well with the higher porosity of these microcapsules evidenced in the scanning electron micrographs.

3.3. CAB-PξCL microcapsules containing terbutaline-loaded resins

With the objective of increasing drug release

from the microcapsules made in the aqueous medium, two formulations were prepared at the higher polymer concentration by combining CAB with a more permeable polymer, the poly(ξ-caprolactone) (PξCL), in the proportions 50:50 and 25:75 (CAB/PξCL). Neither particle size nor terbutaline loading of the formulations (Table 1) were affected by the incorporation of PξCL (drug loading efficiency was about 100%). These results were a contrast to the important decreases in drug loading efficiencies described in similar formulations, such as those of diltiazem pectate-loaded CAB microcapsules, when CAB was partially substituted by PξCL (Shah and Chafetz, 1994); increasing PξCL proportions increased the drug loss (about 34–42%) due to the partition to the external aqueous phase, even in this particular case where diltiazem was formulated as pectate, a sparingly soluble salt. This drug loss, attributed to a slower precipitation rate of PξCL during processing, did not occur in our case when the terbutaline was fixed on the ion-exchange resins, because the drug leaching was avoided in an ion-free medium. Drug release profiles for CAB-PξCL microcapsules (Fig. 6) revealed a significant difference in the burst effect followed by similar dissolution rates, when compared to the same formulation made of CAB. The higher burst effect was correlated to the increased porosity and irregularity of the surface of the microcapsules, as seen in the scanning electron micrograph (Fig. 7). Therefore, the combination of CAB with PξCL did not permit an adequate control of terbutaline release.

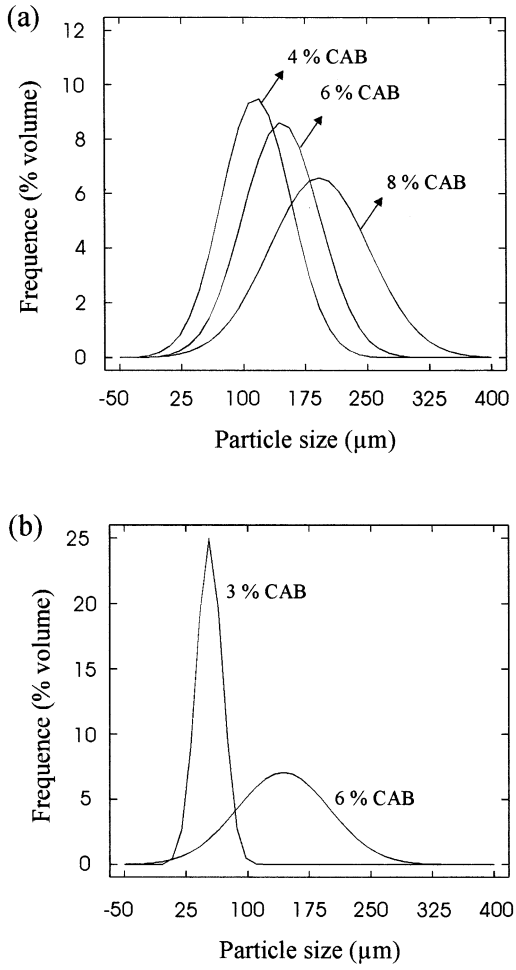

Fig. 1. Effect of polymer concentration on the particle size distribution of CAB microcapsules prepared by the (a) O/O and (b) O/W solvent evaporation methods.

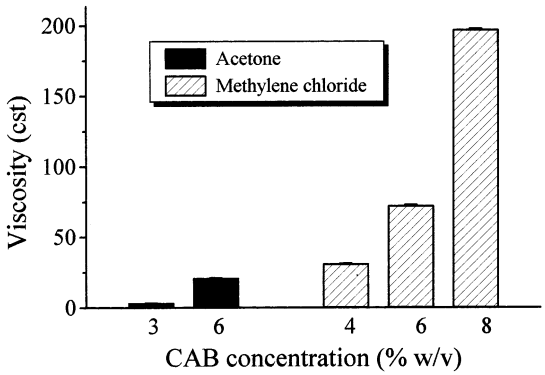

Fig. 2. Viscosity of the acetone and methylene chloride CAB solutions used in the microencapsulation procedures.

3.4. Global comparison of methods by using CAB films and microcapsules

From the comparison of both the O/O and O/W methods at higher polymer concentrations, it can be appreciated that the first method allows an adequate control of terbutaline release, whereas the microcapsules made in aqueous medium led to a very slow and incomplete drug

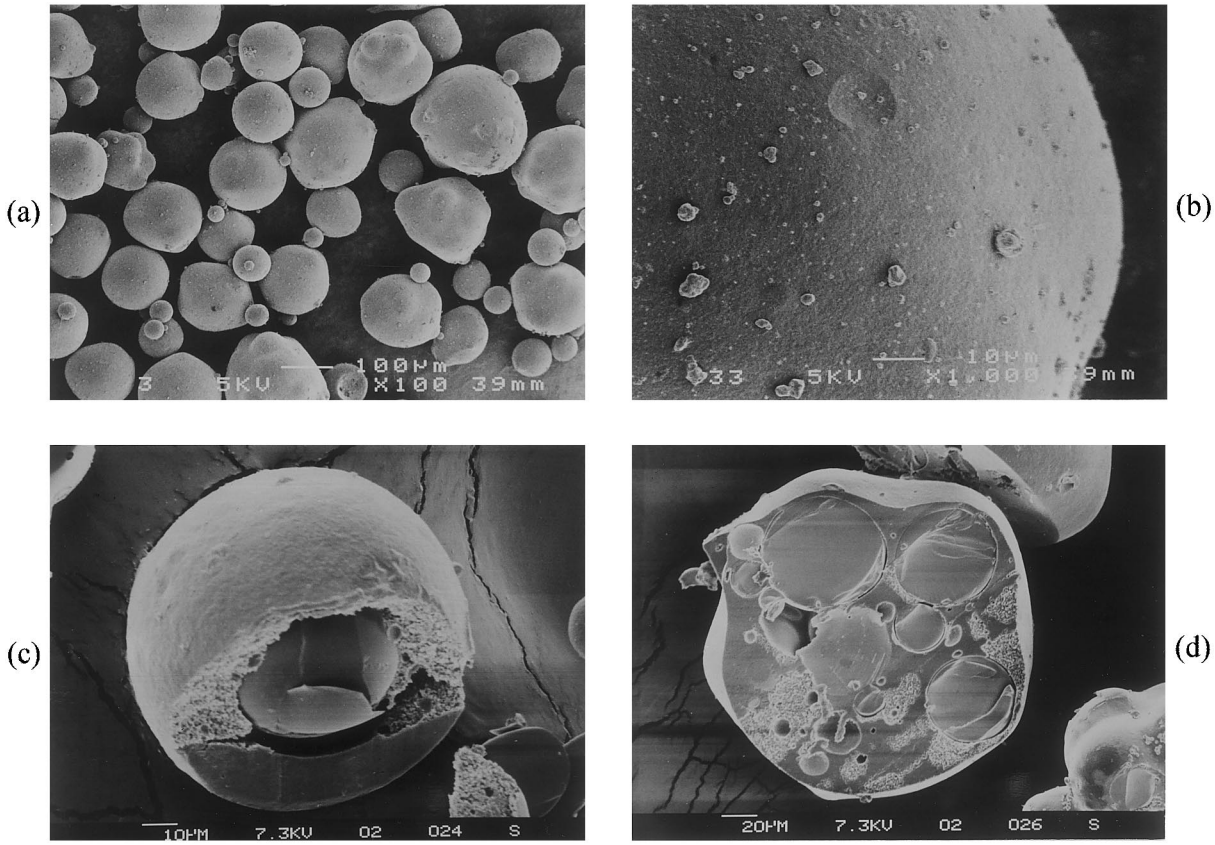

Fig. 3. Scanning electron micrographs of CAB microcapsules prepared by the O/O solvent evaporation method (coat to core ratio: 2:1). (a) General view; (b) detail of the surface, and (c, d) cross-sections of those prepared at 4 and 8% CAB concentration, respectively.

release. These differences in the release behaviour could not be explained on the basis of the differences in their inner structure—as it was very similar—or in their wall porosity, as the morphological characteristics suggested exactly the opposite result. Therefore, with the aim of obtaining additional information about the microcapsules wall characteristics while avoiding other factors related to the microencapsulation methods (i.e. nature of external phase, solvent diffusion rate or presence of additives), CAB films were prepared by solvent casting (Nixon and Wong, 1990). The terbutaline diffusion through the films prepared at the same polymer concentration (6% w/v) was evaluated, and the thermal properties of the CAB films and microcapsules were analyzed in order to elucidate the possible structural changes caused by the solvent or the method used.

The thermal properties, determined by differential scanning calorimetry, were the glass transition temperature (T_g) and the melting temperature (T_m). It has been reported that repeated differential runs are recommended to minimize erratic results caused by the appearance of broad endotherms (Sakellariou et al., 1985), usually due to the water or typically seen with some polymers such as the cellulose esters. In this study, a second run was necessary to clearly distinguish the T_g of CAB samples. The results (Table 2) showed that the T_g values of the polymer were very similar for microcapsules and films made with the same solvent. However, significant differences between groups were observed when formulations made using acetone were compared with those made

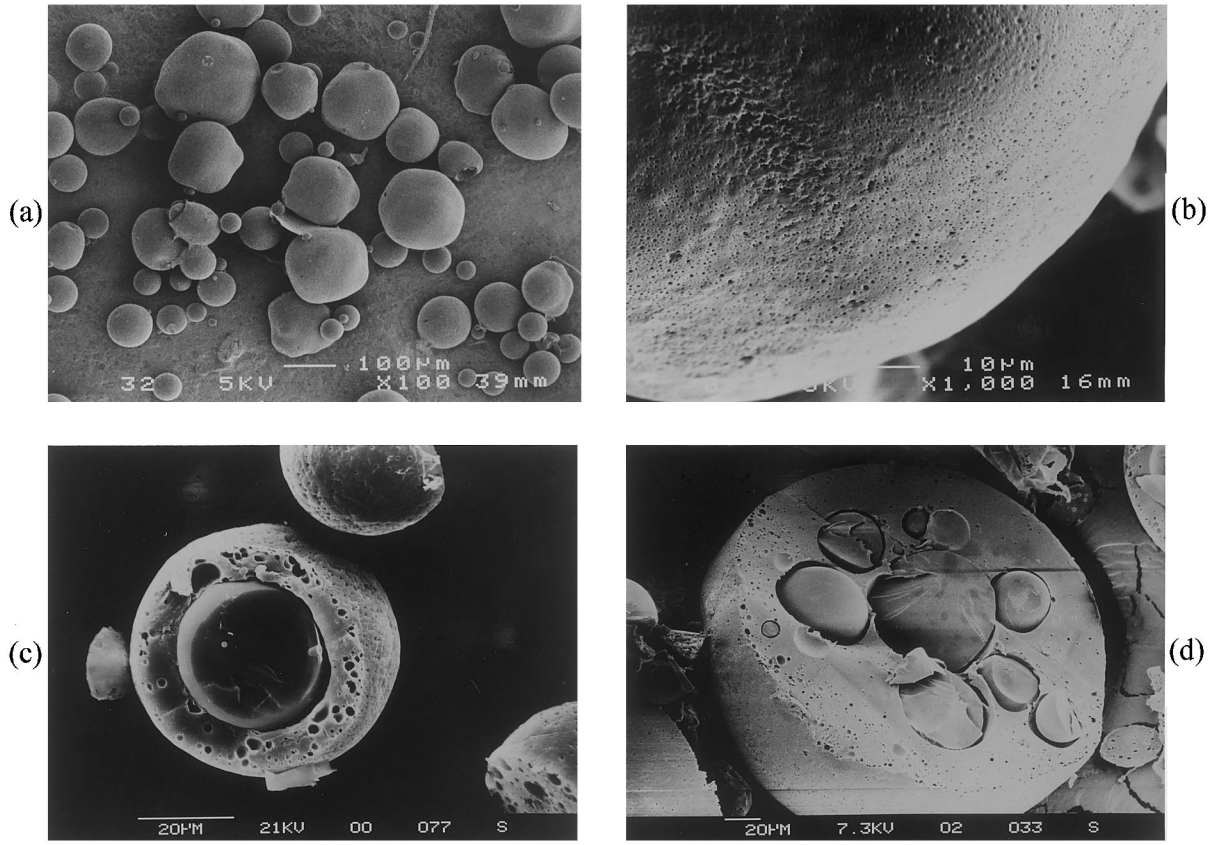

Fig. 4. Scanning electron micrographs of CAB microcapsules prepared by the O/W solvent evaporation method. (a) General view; (b) detail of the surface, and (c, d) cross-sections of those prepared at 3 and 6% CAB concentration, respectively.

from methylene chloride solutions ($F_{(1,4)} = 44.57$, $p < 0.01$). Additionally, it was observed that the T_m values were significantly higher when acetone was the polymer solvent employed, either for microcapsules or films ($F_{(1,4)} = 7730.90$, $p < 0.01$). As both products, microcapsules and films, showed similar changes, the possibility that some additive included in the microencapsulation process was responsible for the observed variations, was immediately excluded. Therefore, it was thought that the T_g and T_m changes recorded could be related to some physicochemical change occurring in the polymer during solvent evaporation from the two different CAB solutions. These changes could have had effects on the crystallinity degree of the polymer, but no modifications were found after examining the X-ray diffractograms of the raw polymer and microcapsules prepared by the two microencapsulation methods (Fig. 8). They did not show any appreciable change when these products were compared, thus indicating that the solvent evaporation process did not modify the crystallinity of polymer.

Finally, the terbutaline permeation through different CAB films was evaluated (Fig. 9). The information from this study on the particular diffusion characteristics of the drug through each film was in agreement with some previous reports which indicated the important role of the solvent on the film properties (Narisawa et al., 1994; Jones and Medlicott, 1995). The present data indicated that terbutaline permeated faster through the CAB film cast from acetone, whereas the drug diffusion through the film cast from methylene chloride was very slow. The initial rapid permeation rate observed in both films de-

creased with time as the films became saturated with the drug. However, after a few hours, the terbutaline continued to diffuse progressively through the CAB film cast from acetone but no

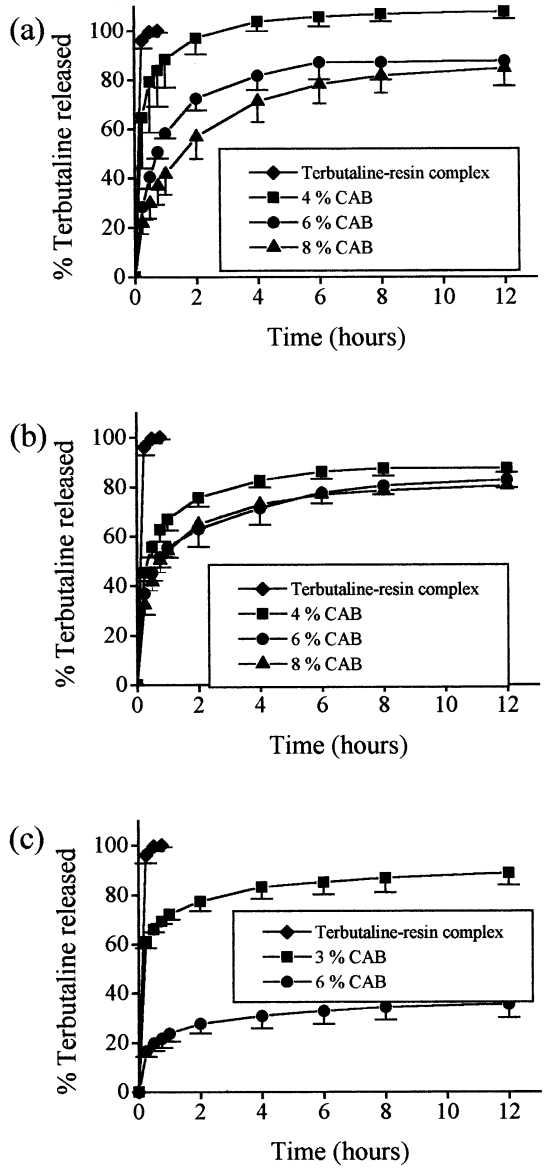

Fig. 5. Effect of polymer concentration on the terbutaline release from the CAB microcapsules prepared by the different solvent-evaporation methods. (a) O/O method, coat/core: 2:1; (b) O/O method, coat/core: 3:1 and (c) O/W method, coat/core: 2:1. (Data shown are the mean ± standard deviation, $n = 4$).

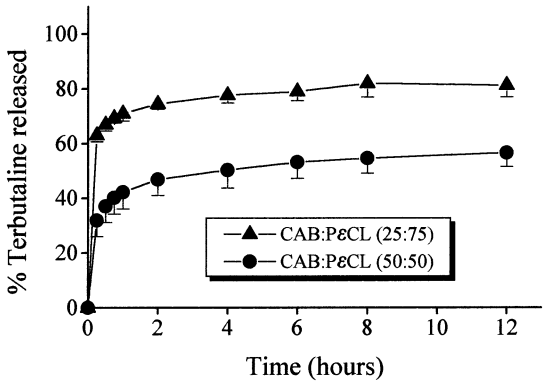

Fig. 6. In vitro terbutaline release profiles of microcapsules prepared from CAB/PξCL blends by the O/W method. (Data shown are the mean ± standard deviation, $n = 4$).

diffusion was observed through the CAB film cast from the methylene chloride solution. These results suggest that drug transport through the CAB film produced from the methylene chloride solution occurs principally by simple molecular diffusion, whereas in the film cast from the acetonic solution, the drug diffusion occurs through the liquid-filled pores rather than by partitioning into the polymeric membrane.

These discrepancies in permeability are attributable to differences in the density/porosity of the CAB films resulting from the two casting solvents. When methylene chloride was the solvent used, the resulting film was nearly transpar-

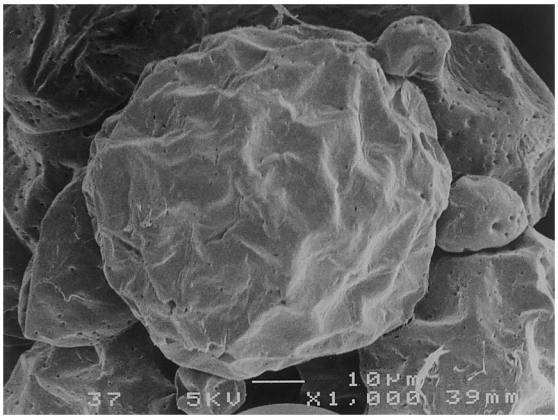

Fig. 7. Scanning electron micrograph of CAB/PξCL (25:75) microcapsules prepared by the O/W method.

Table 2
Mean values ± standard deviations ($n = 2$) of glass transition (T_g) and melting (T_m) temperatures of raw polymer, and CAB microcapsules and films prepared from polymer solutions in acetone and methylene chloride

Polymer solvent	Formulation	T_g (°C)	T_m (°C)
	Raw polymer	151.33 ± 1.34	190.24 ± 0.88
Acetone	Microcapsules	148.00 ± 1.38	227.86 ± 0.47
	Film	143.46 ± 0.30	238.57 ± 0.36
Methylene chloride	Microcapsules	158.54 ± 2.36	190.43 ± 0.24
	Film	151.26 ± 2.59	189.72 ± 1.12

ent and flexible, suggesting that a very homogeneous film was formed. In contrast, the film prepared from the acetonic solution was opaque, slightly whitish and brittle, corresponding to a more heterogeneous and porous structure. These differences in the film structures may be explained by the conformation of the polymer in the solution prior to the casting process (Banker, 1966; Isihara and Guth, 1968). When thermodynamically good solvents are used, upon solvent evaporation, the intermolecular forces between chain segments of the polymer molecule and also between chain segments of neighbouring polymer molecules become increasingly effective and, thus, the resulting film is a homogeneous dense structure with strong interpenetrating chains (methylene chloride case). In dilute solutions of poor solvents, the polymer coils are compact and only superficially interact when the solvent evaporates. The resulting film is distinctly heterogeneous in structure due to the presence of microvoids (acetone case).

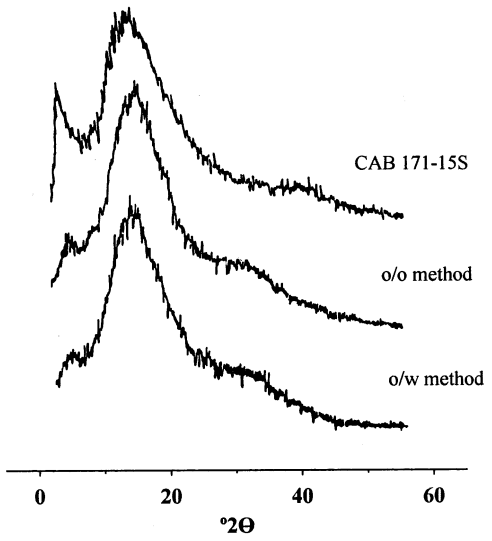

Fig. 8. X-ray diffraction patterns of raw polymer and CAB microcapsules prepared by the O/O and O/W solvent evaporation methods.

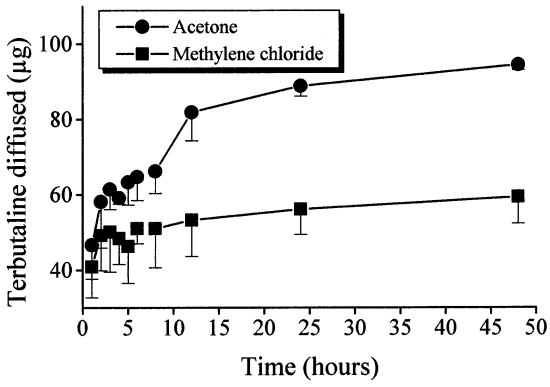

Fig. 9. Diffusion of terbutaline through CAB films prepared by casting from acetone and methylene chloride solutions. (Data shown are the mean ± standard deviation, $n = 2$).

Although these results do not exactly describe the case of microcapsules, they could explain, to a certain degree, the differences observed between microcapsules prepared by the O/O and O/W methods. Therefore, it could be interpreted that the structure of the polymer wall obtained by the O/O method allows a rapid exchange between terbutaline and ions present in the dissolution medium whereas the density of the coat produced in the O/W method hinders the penetration or ions, and thus the release of terbutaline. The higher apparent porosity of the microcapsules prepared by this latter method is only related to the observed burst effect (resin particles entrapped near the surface), however the diffusion studies indicate that the drug release process was definitely conditioned by the dense structure of the polymer wall formed.

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