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# Controlled-release liquid suspensions based on ion-exchange particles entrapped within acrylic microcapsules

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**Abstract**

Eudragit® RS/RL polymers were used to prepare microcapsules containing terbutaline-loaded ion-exchange resins, with the final aim of formulating this anti-asthmatic drug in a controlled-release liquid form. Oil-in-oil (o/o) and oil-in-water (o/w) solvent evaporation procedures were conveniently modified in order to encapsulate the resin cores. The microcapsules were then suspended in a hydroxypropylmethylcellulose solution of adequate viscosity and palatability, and stored at 20°C and ambient humidity conditions for a 6-month period. Stability studies of the dispersed microparticles were performed in order to evaluate the changes occurred in the diffusion of the drug to the suspending medium and in the dissolution behaviour during storage. The morphological alterations of the stored microcapsules were followed throughout the duration of the study by scanning electron microscopy. The polymer coatings of microcapsules prepared by the o/o method broke up on the first day of storage, while those made by the aqueous procedure remained intact during all the storage period. This agreed with the modification observed in the controlled-release profiles of terbutaline in the case of microcapsules prepared by the o/o method, which completely changed after the first week of storage. On the contrary, the microcapsules prepared by the aqueous method showed identical controlled-release profiles for all the stability study. The different behaviour of both types of microcapsules was attributed to the swelling suffered by the resin particles in contact with the aqueous suspending medium, which was higher in the microcapsules prepared by the o/o technique. In fact, in the anhydrous procedure, the microencapsulation was carried out on the shrunken resin particles, whereas in the o/w method, the presence of water during the microencapsulation process allowed the coating of the swollen particles, thus avoiding the further problem of rupture of the polymer coating. 

*Keywords:* Controlled-release suspensions; Physical stability; Microcapsules; Ion-exchange resins; Eudragit® RS and RL; Terbutaline

## 1. Introduction

Much of the research effort in developing novel drug delivery systems has been focused on oral controlled-release dosage forms. Among them, in the last decade, multiple-unit dosage forms, such

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as beads or microparticles, have gained in popularity for different reasons when compared to non-disintegrating single-unit dosage forms. They distribute more uniformly in the gastrointestinal tract, resulting in more uniform drug absorption and reduced local irritation, and also avoid the unwanted intestinal retention of the polymeric material. In addition, multiparticulate dosage forms offer the possibility of being formulated as liquid suspensions, which constitute the ideal administration form for pediatric and geriatric patients, because of their ease of swallowing and flexibility in the dosification (Sagraves, 1994; Danish and Kottke, 1996). However, despite the evident advantages of these liquid dosage forms, due to the difficulties associated to their development, there are, to date, few suitable liquid oral controlled-release suspensions on the market. These difficulties deal essentially with the diffusion or release of drug into the suspending vehicle during storage, and the interactions between the suspending vehicle and the multiparticulates, often resulting in unwanted changes in the original properties.

The loss of drug into the storage vehicle will be mainly determined by the solubility of drug in this vehicle. Therefore, multiparticulates containing water-insoluble drugs can be suspended into aqueous vehicles without significant drug leaching during storage (Bodmeier and Chen, 1989; Kawashima et al., 1991; Lewis et al., 1998). In contrast, encapsulated water-soluble drugs would diffuse rapidly into aqueous suspending vehicles. To overcome this problem, water-soluble drugs can be bound to ion-exchange resins, offering one of very few usable systems for achieving ready made aqueous liquid products with prolonged release (Borodkin, 1993). The main advantage, which the ionic complexes offer, is their ability to prevent the diffusion of drug when suspended in a non-ionic medium, because drug release will be only promoted by the presence of competing ions, such as occurs in the gastrointestinal tract upon oral administration (Helfferich, 1962; Schacht, 1983; Deasy, 1984). The release rate from the drug–resin complex can be further controlled by coating the drug–resin beads using a variety of microencapsulation or coating processes (Raghunathan et al., 1981; Motycka et al., 1985; Sprockel and Price, 1989; Pongpaibul et al., 1990).

There are comparatively few reports which deal with the study of the physical stability of liquid oral controlled-release products, despite the fact that suspensions containing controlled-release dispersed microparticulates are more complex than solid dosage forms because of interactions that can occur. In most cases, insufficient information is available about changes in the dissolution characteristics, frequently related with alterations in the morphological characteristics of the microparticulates or in the physicochemical properties of the polymeric constituents or of the active drug. Therefore, the present work is aimed at studying the stability during the storage of controlled-release suspensions of an anti-asthmatic drug highly soluble in water, the terbutaline, for which the design of a ready-made liquid controlled-release product offers great interest, especially for asthmatic pediatric and geriatric populations. The suspensions were based on ion-exchange resins microencapsulated within a mixture of the acrylic polymers Eudragit® RS and RL using the oil-in oil (o/o) and oil-in-water (o/w) solvent evaporation procedures.

## 2. Materials and methods

### 2.1. Materials

The following chemicals were obtained from commercial sources and used as received: Eudragit® RS and RL (Röhm Pharma, Weiterstadt, Germany); sulphonic acid cation-exchange resins in the $H^+$ form (Dowex® 50W-x4, 200–400 mesh), terbutaline hemisulphate, silicone (Antifoam A concentrate) and poly(vinylalcohol) (PVA) ($M_w = 30\,000–70\,000$) (Sigma, St. Louis, MO); acetone, methylene chloride and *n*-hexane of HPLC grade (Romil, Cambridge, UK); liquid paraffin (viscosity 110–230 mPa) (Merck, Darmstadt, Germany); sorbitan trioleate (Span® 85, Fluka, Madrid, Spain); polysorbate 20 (Tween® 20, Massó, Barcelona, Spain); hydroxypropyl-

methylcellulose (HPMC) (Methocel® K15M, Dow, Stade, Germany); polyethylene glycol 4000 (Fluka, Madrid, Spain).

### 2.2. Purification of ion-exchange resins

The resins were purified by rinsing ~10 g of wet resin with 3 × 5 ml portions of deionized 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 protonated and the sodium 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 deionized water and dried to constant weight at 50°C in an electronic moisture balance (Shimadzu EB-280 MOC, Kyoto, Japan).

### 2.3. Loading of the resins

The terbutaline–resin complex (TRC) was formed by a bath 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 1 l of acidic buffer (HCl/NaCl, pH 1.2, $\mu = 0.1$) and rotated at 1000 rpm (IKA RW DZM, IKA-Labortechnik, Staufen, Germany) at 37°C. The acidic medium was replaced every hour until the concentration of terbutaline was negligible. The samples were analyzed by spectrophotometry at 227 nm.

From the amount of terbutaline that was eluted from each batch of TRC, the actual drug loading (%) was calculated as the (amount of drug/amount of TRC) × 100.

### 2.4. Microencapsulation process

The terbutaline-loaded resins were encapsulated with Eudragit® RS/RL in proportion 70:30, using the o/o and the o/w solvent evaporation methods.

o/o method: the resin particles were suspended in 10 ml of 20% w/v acetonic solution of the polymers, using an initial coat to core ratio of 5:1. This suspension was emulsified into an external phase constituted by 100 ml of liquid paraffin containing 1% w/w Span® 85. The system was agitated at 1000 rpm with a propeller stirrer until the complete evaporation of acetone was accomplished (3 h). After that, the microcapsules were isolated by vacuum filtration, washed with 200 ml of *n*-hexane and air dried for 24 h.

o/w method: the TRC particles (coat to core ratio: 5/1) were suspended in 10 ml of a 20% w/v solution of the Eudragit® RS/RL mixture in methylene chloride, followed by the emulsification in 1 l of a 0.1% w/v aqueous solution of Tween® 20, using a propeller stirrer at 500 rpm. After agitation for 3 h, the microcapsules were isolated by vacuum filtration, washed with destilled water and air-dried for 24 h.

All the formulations were made in duplicate. The terbutaline content of the microcapsules was determined in duplicate for each batch formulation after dissolving the polymer coat of microcapsules (50 mg) in 10 ml of acetone and weighing the dry remaining resins, in order to estimate the final content using the value obtained previously for the TRC.

### 2.5. Morphological and particle size of microcapsules

The surface and the cross-section of the microcapsules were examined by scanning electron microscopy (SEM) (Jeol JSM-6400, Tokyo, Japan). Samples were gold sputter coated (BAL-TEC SCD 004, Liechtenstein) for 165 seconds at 15 mA under 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 microcapsules was measured by a Coulter® Counter apparatus (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

Terbutaline release was determined using a continuous flow-through apparatus (Sotax, Basel, Switzerland). The dissolution medium (HCl/NaCl, pH 1.2, $\mu = 0.1$) was pumped at 20 ml/min and the system was maintained at 37°C. Samples were taken out by an automatic fraction collector (Gilson FC 204, Middleton, WI) at specified time intervals for 12 h and the samples were analyzed by spectrophotometry at 277 nm. Two replicates were performed for each batch of terbutaline-loaded resins or microcapsules.

### 2.7. Preparation of suspensions

The suspensions were made by adequately dispersing 600 mg of Eudragit® microcapsules in 20 ml of 0.75% w/w hydroxypropylmethylcellulose (HPMC) solution. The samples were stored in closed glass vessels at 20°C and ambient humidity conditions, for a 6-month period.

### 2.8. Stability of suspensions

The following assays were made after 1, 7, 15, 30, 90 and 180 days of storage

- Microscopic evaluation of microcapsules: SEM was used to examine the surface morphology of the aged microcapsules. The suspended microcapsules were isolated by vacuum filtration, freeze-dried and sputter gold coated.

Table 1
Formulation parameters of resin-containing Eudragit® RS/RL microcapsules (mean ± S.D., $n = 4$)

| Method | Drug loading (%) | Particle size (μm) |
|---|---|---|
| o/o | 8.61 ± 0.05 | 198 ± 14 |
| o/w | 9.36 ± 0.14 | 212 ± 10 |

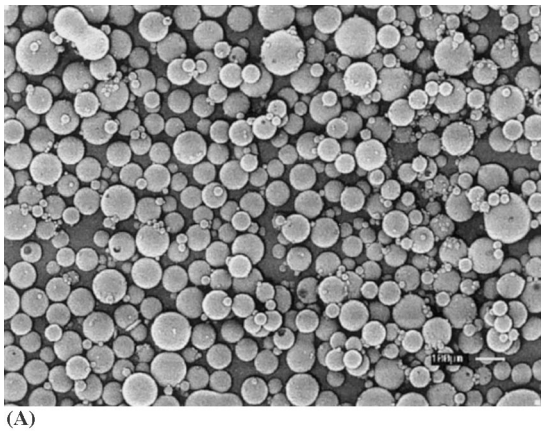
- In vitro release of microcapsule suspension: samples were isolated by vacuum filtration and drug release was determined using the conditions described previously.
- Redispersability: was measured by rotating a test tube of 25 ml at 20 rpm. The test tube was filled with 20 ml and the time necessary to restore homogeneity was recorded.
- Drug leaching into the suspending medium: was calculated after filtrating the suspension by assaying the suspending vehicle spectrophotometrically for terbutaline content.

### 2.9. Statistical analysis

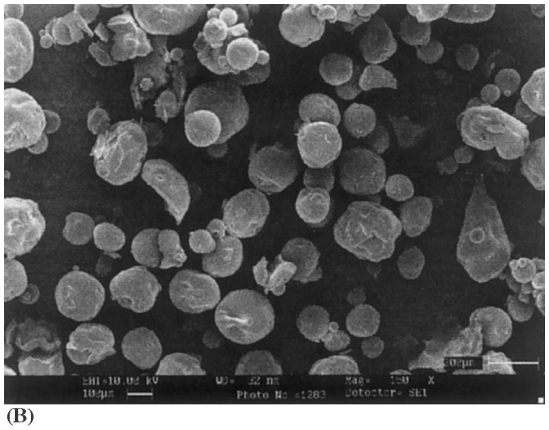
The statistical significance of the found differences between parameters at the different storage periods was tested by the analysis of the variance (ANOVA) or the non-parametric Kruskall–Wallis test. The least significant difference (LSD) test (Dixon and Massey, 1965) or Siegel and Castellan test (Siegel and Castellan, 1988) 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

The percentage of terbutaline fixed to the ion-exchange resins was 50.72 ± 2.57%, and the final loading of the resulting Eudragit® microcapsules was ~9%, irrespective of the method applied (Table 1), this being related to the coat to core ratio (5:1) which was necessary in order to obtain a complete encapsulation of the resin particles. The size of the microparticle formulations was reduced to 200 μm (Table 1), a size which allow the particles to be easily dispersed in a liquid suspension without leading to a gritty sensation during administration. Eudragit® microcapsules, prepared by both the o/o and o/w methods resulted in multinucleated spherical structures, more irregular when using the aqueous procedure (Fig. 1A,B). This irregular form was attributed to the prolonged contact of the polymers, mainly the more permeable Eudragit® RL, with the aqueous phase during the microencapsulation process. In



(A)



(B)

Fig. 1. Scanning electron micrographs of resin-containing Eudragit® RS/RL microcapsules prepared by the (A) o/o and (B) o/w solvent evaporation methods.

fact, it was shown that the more irregular microcapsules were formed when the percentage of this variety in the polymer mixture was increased, due to its high capacity of swelling and hydration (results not shown). It can be appreciated from the terbutaline release profiles (Fig. 2) that the release was efficiently controlled by the developed microcapsules, irrespective of the method applied, in comparison to the immediate release shown by the ionic complex.

Suspensions were prepared by dispersing the microparticles in a 0.75% w/w solution of hydroxypropylmethylcellulose of nominal viscosity 15 000 cps, which allowed an adequate viscosity for oral administration, and also a good redispersability and high sedimentation time (Boado, 1996). The suspensions were stored at 20°C and ambient humidity conditions for 6 months and at scheduled time intervals, samples were withdrawn and tested for their physical stability. The morphological analysis of the stored microcapsules showed that those produced by the o/o method broke up on the first day of storage (Fig. 3A), while the o/w solvent evaporation method led to microparticles which remained intact for 6 months of storage (Fig. 3B).

The rupture of the Eudragit® microcapsules prepared in oily phase may be attributed to the swelling shown by the resin particles after the contact with the suspending aqueous vehicle. The microscopical observation of the same microcapsules prepared without resins, after 30 days of storage, showed that they maintained their integrity (Fig. 4). This indicated that when the non-aqueous method was applied, the microencapsulation was carried out on the shrunken particles, whereas the presence of water in the o/w method allowed the microencapsulation of the swollen particles, thus avoiding the further problem of rupture of the polymer coating.

A possible alternative to overcome the problem of fracture in the coatings could be the pre-treat-

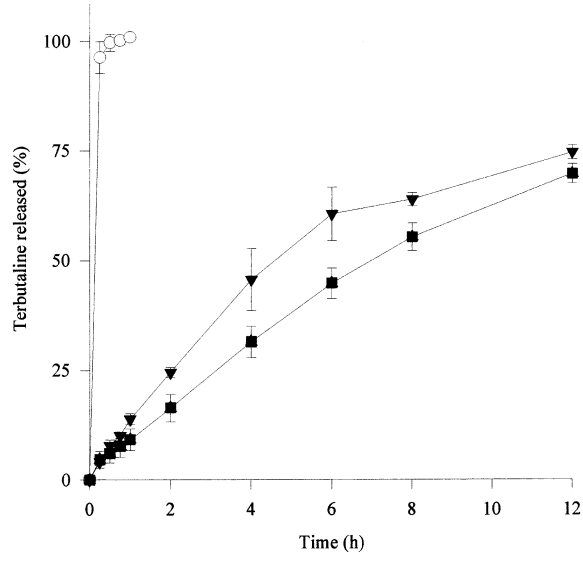
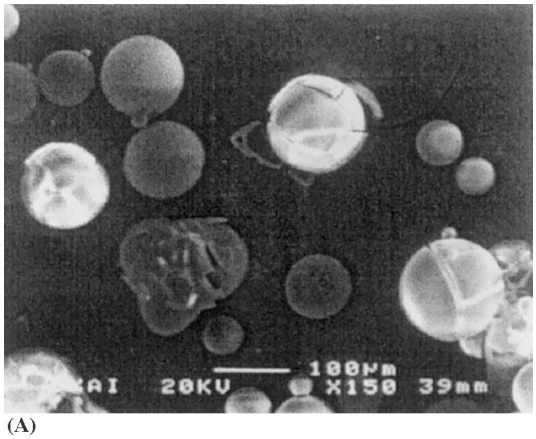
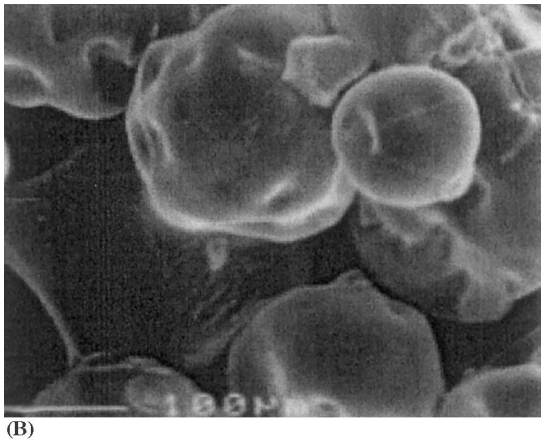



Fig. 2. Terbutaline release profiles of drug–resin complex and Eudragit® RS/RL microcapsules prepared by the different solvent evaporation methods.




(A)



(B)

Fig. 3. Scanning electron micrographs of resin-containing Eudragit® RS/RL microcapsules prepared by the (A) o/o and (B) o/w solvent evaporation methods, after 1 and 180 days, respectively, of storage in HPMC suspensions.

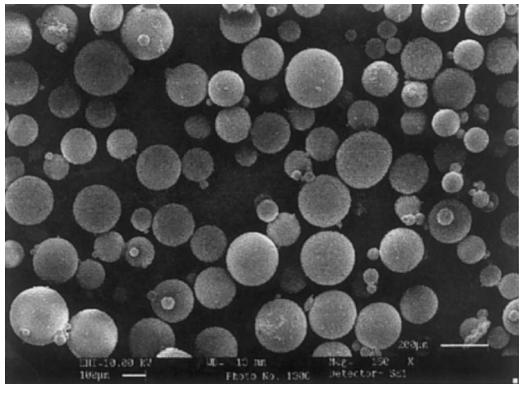


Fig. 4. Scanning electron micrograph of Eudragit® RS/RL microcapsules prepared by the o/o solvent evaporation method, not including resin particles.

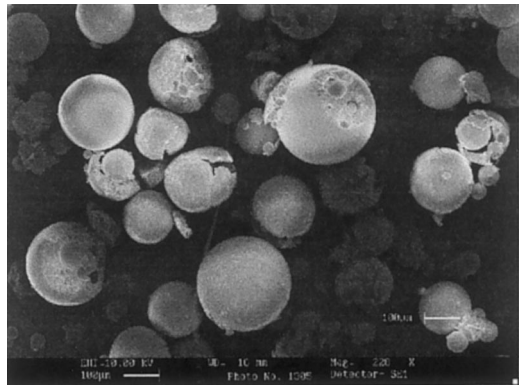


Fig. 5. Scanning electron micrograph of Eudragit® RS/RL microcapsules containing resins pretreated with PEG 4000 (method of preparation: o/o solvent evaporation).

ment of the resin particles with polyethylene glycol (PEG 4000). This excipient acts as an impregnating agent, and has an essential role in retaining the geometry of the particles when coating by air suspension techniques (Raghunathan, 1980). Nevertheless, this approach resulted ineffective in our case, since the microcapsules containing resin particles pre-treated with PEG 4000 appeared identically fractured after 1 day of storage (Fig. 5). This evidenced that this alternative was not suitable for in-liquid drying microencapsulation methods but only for the air suspension coating procedures.

Drug release studies of the aged microparticles agreed with that observed in the microscopical examination, since the microcapsules prepared by the non-aqueous method did not maintain the initial terbutaline controlled-release profile, which changed slightly on the first day of storage and substantially after 1 week (Fig. 6a). The suspensions of Eudragit® microcapsules obtained by the aqueous procedure showed, however, almost superimposable release profiles at the different time intervals (Fig. 6b). In fact, the statistical analysis evidenced in this case that there was no influence of the storage time over the parameter dissolution efficiency (Khan and Rhodes, 1975) (Table 2).

The terbutaline leaching to the suspending medium from the microcapsules in the suspension on storage for 6 months was practically negligible,

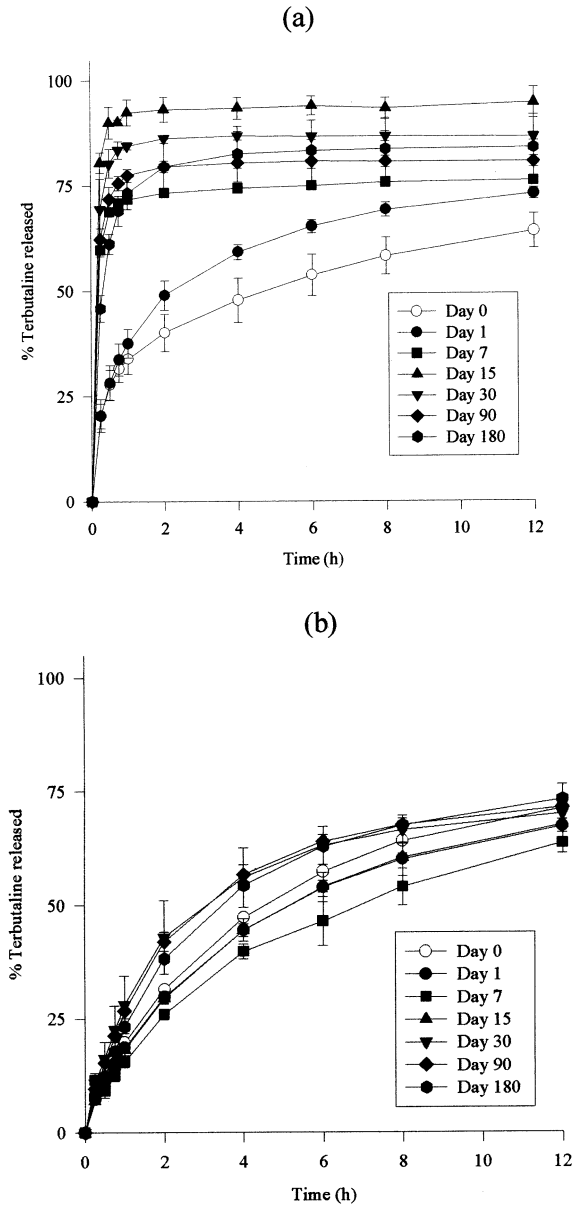



Fig. 6. Effect of storage time on the terbutaline release from suspensions of Eudragit® RS/RL microcapsules prepared by the (a) o/o and (b) o/w solvent evaporation methods.

irrespective of the method of preparation. In fact, this value was below 6% at the end of the stability study, although since the first day of storage the microcapsules obtained by the o/o method showed a higher leakage of drug, possibly related to the rupture of the microcapsules in suspension.

In relation to the redispersability time, this parameter showed practically no changes throughout the study for the Eudragit® microcapsules made in aqueous phase ( $< 2$ min), whereas in the case of those prepared by the anhydrous method, this value was increased over the storage time (Table 3). The macroscopical observation of the sedimentation process of the suspensions before storage revealed that the Eudragit® microcapsules (o/w method) tended to form agglomerates which settled more rapidly but were easily redispersed, while in the non-aqueous procedure, the microcapsules showed a more hydrophobic surface that promoted the adsorption of the suspending polymer, thus avoiding their agglomeration and stabilizing the suspension. This may explain why the time to redisperse the micro-

Table 2
Dissolution efficiency values of the suspensions of Eudragit® RS/RL microcapsules at different storage times (mean ± S.D., $n = 2$)

| Storage time (days) | Dissolution efficiency (12 hours) | |
|---|---|---|
| | o/o Method | o/w Method |
| 0 | 0.50 ± 0.04 | 0.51 ± 0.00 |
| 1 | 0.60 ± 0.02 | 0.48 ± 0.03 |
| 7 | 0.74 ± 0.00 | 0.43 ± 0.03 |
| 15 | 0.92 ± 0.03 | 0.48 ± 0.01 |
| 30 | 0.85 ± 0.00 | 0.56 ± 0.04 |
| 90 | 0.79 ± 0.01 | 0.56 ± 0.01 |
| 180 | 0.80 ± 0.06 | 0.55 ± 0.01 |

Table 3
Redispersability time values of the suspensions of Eudragit® RS/RL microcapsules at different storage times (mean ± S.D., $n = 2$)

| Storage time (days) | Redispersability time (min) | |
|---|---|---|
| | o/o Method | o/w Method |
| 0 | 6 ± 2 | <2 |
| 1 | 10 ± 2 | <2 |
| 7 | 17 ± 1 | <2 |
| 15 | 20 ± 8 | <2 |
| 30 | 29 ± 1 | <2 |
| 90 | 50 ± 1 | <2 |
| 180 | 88 ± 12 | <2 |

capsules was initially slightly higher in the case of those prepared by the anhydrous method, which formed a more stable suspension. However, this time was considerably increased throughout the stability study, as a consequence of the rupture of the coatings which probably led to more cohesive forces and changes in the settling and redispersability of the suspension.

To summarize, the present study shows that the nature of the external phase used in the microencapsulation method has a crucial role in determining the behaviour of the resin-containing acrylic microcapsules when formulated in suspension. Whereas the microcapsules made by the o/w solvent evaporation technique showed good dissolution stability during storage for 6 months, the o/o method led to microcapsules whose drug controlled-release profiles drastically changed after 1 week of storage. These changes were attributed to the rupture of the polymer coating, which occurred as a consequence of the swelling of resin particles after the contact with the aqueous suspending vehicle.

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