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Ketoprofen Spray-dried Microspheres Based on Eudragit® RS and RL: Study of the Manufacturing Parameters

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The preparation of ketoprofen spray-dried microspheres can be affected by the long drug recrystallization time. Polymer type and drug–polymer ratio as well as manufacturing parameters affect the preparation. The purpose of this work was to evaluate the possibility to obtain ketoprofen spray-dried microspheres using the Eudragit® RS and RL; the influence of the spray-drying parameters on morphology, dimension, and physical stability of microspheres was studied. Ketoprofen microspheres based on Eudragit® blend can be prepared by spray-drying and the nebulization parameters do not influence significantly particle properties; nevertheless, they can be affected by drying and storage methods. No effect of the container material is found.

Keywords ketoprofen; spray-drying parameters; microspheres; Eudragit®.

INTRODUCTION

Ketoprofen is a nonsteroidal anti-inflammatory drugs (NSAIDs) drug widely formulated in microspheres and microcapsules as oral controlled release systems owing to its short half-life, the irritation in the gastrointestinal mucosa, and its unpleasant taste (Caruso et al., 1982; Giunchedi, Maggi, Conte, & Caramella, 1991; Habib & Meuse, 1995; Houghton, Dennis, Rigler, & Parsons, 1984; Houghton, Dennis, Templelon, Calvert, & Cresswell, 1984; Khan, Dib, & Reedy, 1996; Le Liboux, Teule, Frydman, Osterhuis, & Jonkman, 1994; Marcolongo et al., 1984; Morley et al., 1984; Palmieri, Bonacucina, Di Martino, & Martelli, 2002a, 2002b; Parejo, Gallardo, & San Roman, 1998; Roda, Sabatini, Mirasoli, Baraldini, & Roda, 2002; Vergote et al., 2001; Vueba, Batista de Carvalho, Veiga, Sousa, & Pina, 2004).

In the last 10 years, a large number of procedures have been used for the encapsulation of ketoprofen, such as emulsification and solvent evaporation technique (El-Kamel, Sokar, Al Gamal, & Naggar, 2001; Gabor, Ertl, Wirth, & Mallinger, 1999; Mateovic-Rojnik, Frlan, Bogataj, Bukovec, & Mrhar, 2005; Ré & Biscans, 1999; Ricci et al., 2005), dry-in-oil multiple emulsion method (Genta, Perugini, Conti, & Pavanetto, 1997), ionotropic gelation (El-Gibaly, 2002), and coacervation techniques (Palmieri, Martelli, Lauri, & Wehrle, 1996).

Spray-drying is an important and widely used microencapsulation method. Compared with the other techniques, it has many advantages, including the shorter duration, reliability and reproducibility, cost-effectiveness of the process preparation, particle size control, good yield of production, and higher encapsulation efficiency (Giunchedi & Conte, 1995). The properties of spray-dried powders are controlled by both the process and formulation parameters (Chan & Chew, 2003), such as inlet and outlet temperatures, spray rate of feed, exhausting concentration, and drug–polymer ratio of the polymeric feed solution (Giunchedi & Conte, 1995).

This technique has not been widely used for producing microparticles containing ketoprofen (Castelli, Conti, Maccarrone, Conte, & Puglisi, 1998; Gavini, Sanna, Juliano, & Giunchedi, 2003; Giunchedi, Conti, Maggi, & Conte, 1994; Moretti, Gavini, Juliano, Pirisino, & Giunchedi, 2001; Palmieri et al., 2002a). In fact, the preparation of ketoprofen microspheres by spray-drying is possible only under certain experimental conditions, and it is affected by the polymer type and by drug–polymer ratio because of the very long ketoprofen recrystallization time (Palmieri, Elisei, Di Martino, & Martelli, 2000; Palmieri et al., 2002b).

Polymers such as poly(lactide-co-glycolide) (PLGA) (Gavini et al., 2003), cellulose acetate butyrate (CAB), and hydroxypropylmethyl cellulose phthalate (HPMCP) (Moretti et al., 2001), poly(epsilon-caprolactone) (PCL) (Giunchedi et al., 1994), cellulose acetate trimellitate (CAT), HPMCP, and Eudragit® S or L (Palmieri et al., 2002a) are able to microencapsulate ketoprofen by spray-drying using an excess of polymer: the drug–polymer ratio must be equal to or greater than 1:3 (Gavini et al., 2003; Moretti et al., 2001; Palmieri et al., 2000).

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Considering the difficulty of ketoprofen microencapsulation by spray-drying and the many advantages of this method, the aim of this work was (a) to verify the possibility of obtaining spray-dried microspheres of ketoprofen employing a mixture of Eudragit® RS 100 and RL 100, as well as (b) to study the influence of the spray-drying technological parameters on the morphology, dimension, and stability of ketoprofen microspheres and on the yield of production and encapsulation efficiency. The air aspirator capacity, the peristaltic pump capacity, and the inlet temperature were the considered parameters. Air aspirator significantly influences the transformation of nebulized droplets in solid particles (Esposito, Roncarati, Cortesi, Cervellati, & Nastruzzi, 2000; Masters, 1991). The peristaltic pump influences the time and efficacy of the drying process as well as the particle dimensions (Esposito et al., 2000; Giunchedi & Conte, 1995; Masters, 1991). The inlet temperature is an important parameter for both particle dimensions and recovery; it must be compatible with the material (drug and polymer) and solvent utilized (Esposito et al., 2000; Giunchedi & Conte, 1995).

Eudragit® polymers are interesting candidates for the production of microparticles by spray-drying because of their inertness and solubility properties. Eudragit® RL 100 and RS 100 were chosen as polymers. They are biocompatible copolymers synthesized from acrylic and methacrylic acid esters with some hydrophilic properties due to the presence of quaternary ammonium groups (Omari, Sallam, Abd-Elbary, & El-Samaligy, 2004). Eudragit® RL has a greater proportion of these groups, and thus it is more permeable than Eudragit® RS (Haznedar & Dortunç, 2004). They are insoluble in water but swell in digestive fluid independently of the pH value (Omari et al., 2004), thus representing a valid material for oral controlled drug delivery (Castelli, Messina, Sarpietro, Pignatello, & Puglisi, 2002; Esposito et al., 2000; Goto, Kawata, Nakamura, Maekauwa, & Ayoama, 1986; Kawashima, Niwa, Handa, Takeuchi, & Ito, 1991; Kawashima et al., 1989; Kawashima, Toshiyuki, Takeuchi, Hino, & Ito, 1992; Kawata, Nakamura, Goto, & Ayoama, 1968; Khalil & Sallam, 1999; Mateovic-Rojnik et al., 2005) Pignatello, Vandelli, Giunchedi, & Puglisi, 1997).

MATERIALS AND METHODS

Materials

Ketoprofen (K) was purchased from Sigma-Aldrich Chemie Gmbh (Steinheim, Germany) although Eudragit® RS 100 (RS) and Eudragit® RL 100 (RL) were kindly provided by Röhm Pharma Polymers GmbH (Darmstadt, Germany). Dow Corning® 345 volatile silicone fluid was obtained from Dow Corning® Europe (Brussels, Belgium). Dichloromethane (CH_2Cl_2, Riedel-de-Haen, Milan, Italy) and ethanol (A.R.P.I. Society, Rome, Italy) were of analytical grade.

Microsphere Preparation

Ketoprofen microspheres were produced using a Mini Spray Dryer, model B-191 (Büchi Labortechnik AG, Flawil, Switzerland), a co-current spray-dryer apparatus equipped with the high-performance cyclone.

On the basis of literature data and of preliminary experiments carried out, a formulation, called A, was prepared by spraying a 2% (wt/vol) feed solution obtained by dissolving 250 mg of ketoprofen and 750 mg of Eudragit® polymers (375 mg of RS and 375 mg of RL) in 50 mL CH_2Cl_2. The drug–Eudragit® ratio of 1:3 (wt/wt) was employed. The solution was fed into the instrument by a peristaltic pump, set up at 12% of its capacity, at the feed rate of 3.33 mL/min, and sprayed with a 0.7-mm nozzle, by 500 l/h and 2 bar compressed air flow. A flow of heated air (50°C), aspirated by 83% of aspirator capacity, induced the quick evaporation of the solvent and the deposition of the solid microparticles in the cyclone from where they were collected. All spray-drying parameters used are reported in Table 1. This formulation was produced three times for verifying the method reproducibility.

To prove the influence of the manufacturing parameters on microsphere characteristics, air aspirator or peristaltic pump capacity or drying temperature was changed: the formulations obtained and the respective spray-drying conditions used are listed in Table 1. Formulations B and C were produced by spraying the feed solution previously described, setting the air

TABLE 1
Spray-drying Conditions used for Preparing the Ketoprofen Formulations

Formulations	Drying Air Temperature (°C)	Aspirator Capacity (%)	Pump Capacity (%)	Feed Solution Rate (mL/min)	Compressed Air flow (L/h)
A	50	83	12	3.33	500
B	50	70	12	4.00	500
C	50	60	12	4.07	500
D	50	83	8	2.47	500
E	50	83	4	1.48	500
F	50	83	2	0.79	500
G	40	83	12	3.30	500
H	40	70	4	1.23	500

aspirator capacity at 70 and 60% respectively; three different formulations (D–F) were produced decreasing the peristaltic pump capacity. The inlet temperature was reduced from 50 to 40°C for preparing the G formulation.

On the basis of the results obtained from the in vitro characterization of A–G, a new spray-dried microparticle batch, H, was prepared choosing the following parameters: the heating was set at 40°C and the aspirator and pump capacity at 70 and 4%, respectively (Table 1).

Microsphere Characterization

After production, the microspheres A–H were stored for 24 h in a desiccator at 12% relative humidity (RH) and 20 ± 1°C. They were then characterized in terms of yield of production, drug content and encapsulation efficiency, particle size and particle size distribution, and morphological properties.

Yield of Production

Dried microspheres were accurately weighed, and considering the total amount of drug and polymers used for preparing the feed solution, the yield of production (*YP*) was calculated, as a percentage, using the following equation:

$$YP = \frac{MC}{\mathrm{RS} + \mathrm{RL} + \mathrm{K}} \times 100 \quad (1)$$

where *MC* stands for the amount of produced microspheres and (RS + RL + K) for the sum of the amounts of two types of Eudragit® and ketoprofen solubilized for the preparation of microparticles.

Real Drug Content and Encapsulation Efficiency Determination

To determine the exact amount of ketoprofen encapsulated into RS/RL matrix, 4 mg of microspheres were solubilized in 100 mL ethanol. The UV absorbance of the solution was measured using a Hitachi UV-Vis spectrophotometer, model U-2001 (Hitachi Instruments Inc, Tokyo, Japan), at 262 nm. These resulting values were interpolated at the calibration curve of ketoprofen in ethanol, elaborated earlier.

Drug content (DC) and encapsulation efficiency (EE), expressed as percentage, were determined in triplicate for all batches as follows:

$$\mathrm{DC}\ (\%) = \frac{K_\mathrm{r}}{\mathrm{EM}} \times 100 \quad (2)$$

$$\mathrm{EE}(\%) = \frac{K_\mathrm{r}}{K_\mathrm{t}} \times 100 \quad (3)$$

where K_r is the amount (grams) of ketoprofen found in the microspheres, EM is the examined quantity of microspheres, and K_t is the grams of ketoprofen theoretically included into the polymeric matrix.

Particle Size and Particle Size Distribution Analyses

The mean diameter and size distribution of microspheres were determined by laser diffraction (Coulter LS 100Q Laser Sizer, Beckman Coulter, Miami, FL, USA). A sample of microspheres (3.0 mg) was suspended in 0.5 mL volatile silicone fluid and sonicated in ultrasound bath for 5 s before particle size analysis. Because a Gaussian-like distribution of particle size was observed, the particle size is described by the volume/surface mean diameter (d_{vs}) and the standard deviation (*SD*), whereas microparticle size distribution is expressed as SPAN Index (SI) calculated applying the following equation:

$$\mathrm{SI} = \frac{d_{90} - d_{10}}{d_{50}} \quad (4)$$

where d_{10}, d_{50}, and d_{90} indicate the volume percentage of particles (10, 50, and 90% respectively) having a mean diameter lower than the obtained value.

Morphological Analysis

Microsphere morphology was studied by scanning electron microscopy (SEM) (ISI-DS 130 Scanning Electron Microscope, Akashi Beam Technology Corporation, Tokyo, Japan). Completely dried microspheres were mounted on aluminum stubs using double-sided adhesive tape. They were then gold-sputtered and analyzed with accelerating voltage of 20 kV. The resulting images were photographed.

Physical Stability Studies

To investigate the influence of the drying and storage process as well as of the container materials on microparticle stability, morphology and dimension were studied within 1 month. The stability study is schematized in Figure 1.

After production, A–H microspheres were dried in desiccator at 20°C for 24 h, as already described, or in oven (Memmert GmbH + Co. KG, Schwabach, Germany) at 30°C (named A1–H1) along the same time.

H2 formulation, as example, was dried in oven at 25°C for 24 h to verify the effect of the temperature on morphological variations.

Samples (20 mg) of dried powders (A–H, A1–H1, and H2) were then stored both in open *p*olystyrene weighing *d*ishes (A–H, A1–H1, and H2 pd), *s*ealed *p*lastic Eppendorf (A–H, A1–H1, and H2 sp), and sealed *g*lass vials (A–H, A1–H1, and H2 sg); all of these were stored in the desiccator (12% RH and 20 ± 1°C) and their size and morphology were observed after 15 and 30 days.

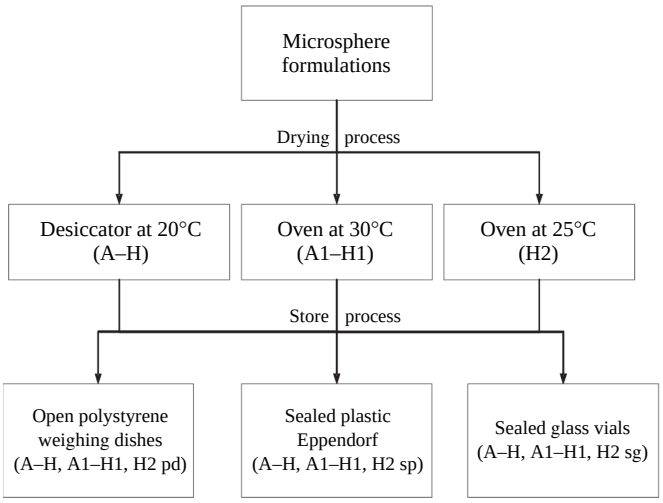

FIGURE 1. Physical stability study procedure.

Differential Scanning Calorimetric Studies

The thermal behavior of ketoprofen in A and C formulations was determined using differential scanning calorimeter (DSC) (DSC Q100 V9.0, TA Instrument, New Castle, DE, USA). Formulation A was used as a reference, whereas formulation C was used on the basis of the results obtained from the stability study. As a comparison, the thermal behavior of pure drug (raw material), polymers, and blank microspheres (prepared using a mixture of RS and RL 100) was studied. Samples of 3 mg were scanned in crimped sealed aluminum pans, under static air atmosphere. An empty pan was used as reference. The heating rate was 10°C/min, and the temperature interval used was –40 to 250°C.

Statistical Analysis

Statistical analysis was performed with GraphPad Prism 4.0 for Windows. Unpaired *t*-test was applied to test the significance of the effect of each spray-drying parameter on the yield of production, the drug content, and the encapsulation efficiency, and particle size of microsphere formulations. The significant level was set at $p < 0.05$.

RESULTS AND DISCUSSION

Microsphere Preparation and Characterization

Ketoprofen microspheres can be produced by spray-drying technique using Eudragit® RS 100 and RL 100 as polymers. The technological parameters employed for A preparation (Table 1) allow to obtain microspheres with good yield of production (59.4 ± 1.5%); drug content (30.2 ± 0.8%) and encapsulation efficiency values (118.6 ± 0.9%) result higher than theoretical values (25 and 100%, respectively). This result can be due to the loss of the smallest particles mainly consisting of polymers (Giunchedi, Conte, Chetoni, & Saettone, 1999); in fact, the spray-dryer is not equipped with a trap to recover lightest and smallest particles, which are exhausted by the aspirator during the process (Giunchedi, Gavini, Bonacucina, & Palmieri, 2000).

The mean diameter and size distribution of microspheres were analyzed by laser diffraction and expressed as d_{vs} and SPAN Index calculated using Equation 4. The A microspheres have 8.7 ± 2.1 μm d_{vs} and narrow size distribution as indicated by SI value (1.4). As shown by SEM analysis, they appear spherical in shape, with surface almost smooth and quite separate from each other (Figure 2). There are no drug crystals outside the particles.

To verify the influence of air aspirator on microsphere characteristics, B and C formulations were prepared reducing the air aspirator capacity to 70 and 60% with respect to A preparation, respectively. It is known that an increase in aspirator rate leads to a decrease of the time for the air to pass throughout the instrument, and consequently it reduces contact time between drying air and droplets affecting the transformation of sprayed droplets in solid particles (Esposito et al., 2000; Masters, 1991).

The reduction to 60% of the air aspirator capacity determines, in case of C formulation, a significant decrease of production yield ($p = 0.013$) caused by the loss of dried particles inside the nebulization chamber. Drug content and encapsulation efficiency of B microspheres ($p < 0.05$) decrease; nevertheless, these values are still higher than theoretical data. Size and size distribution of B and C particles do not undergo changes. All data are reported in Table 2.

SEM analysis shows that the decrease of aspirator capacity does not influence particle morphology: B and C microspheres are spherical but the smallest particles appear partially sticking to each other. Figure 3 shows the micrograph of C, chosen as example.

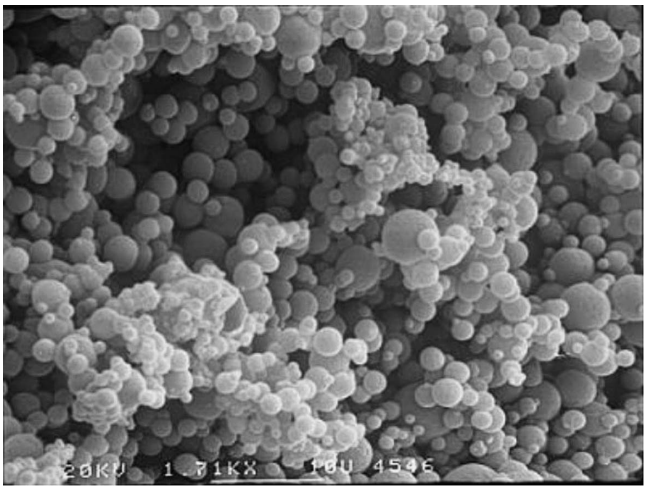

FIGURE 2. SEM picture of A. Magnification: 1,710×.

TABLE 2
Characterization of Microsphere Formulations

Formulations	YP[a](%)	DC[a](%)	EE[a](%)	d_{vs}[a](μm)	*SI*
A	59.43 ± 1.48	30.25 ± 0.76	118.65 ± 0.89	8.73 ± 2.11	1.42
B	55.95 ± 5.00	28.64 ± 0.50[b]	114.30 ± 1.99[b]	7.74 ± 0.02	1.45
C	53.18 ± 2.10[b]	28.71 ± 1.36	110.79 ± 6.46	7.23 ± 0.53	1.45
D	63.50 ± 0.20[b]	29.48 ± 0.12	117.34 ± 1.14	7.08 ± 0.68	1.52
E	57.80 ± 3.20	28.96 ± 0.39	116.84 ± 3.87	7.27 ± 0.06	1.46
F	59.07 ± 2.02	27.76 ± 0.18[b]	113.97 ± 1.13[b]	6.87 ± 0.16	1.43
G	65.43 ± 2.77[b]	28.61 ± 1.45	115.16 ± 0.90[b]	7.23 ± 0.85	1.43
H	58.30 ± 5.70	30.75 ± 2.46	121.39 ± 8.56	7.37 ± 0.42	1.42

[a]Mean ± standard deviation (*SD*).
[b]Mean significantly different from A data.

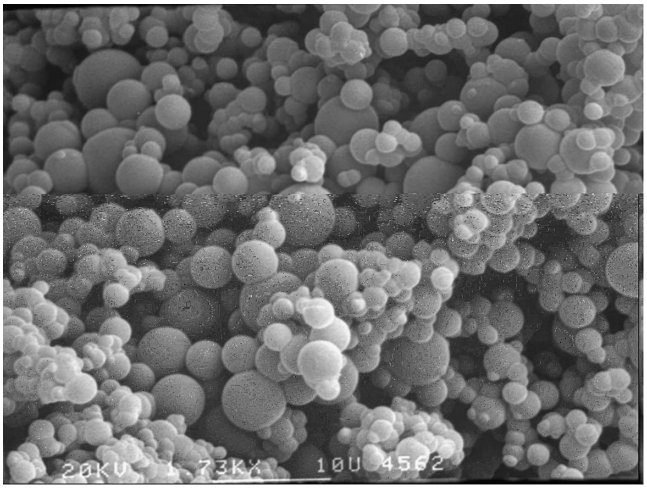

FIGURE 3. SEM picture of C. Magnification: 1,730×.

Because the feed rate of polymeric solution could influence the efficacy of drying process and particle size (Esposito et al., 2000; Giunchedi & Conte, 1995; Masters, 1991), three Eudragit® microparticle formulations, called D, E, and F, were produced changing the peristaltic pump capacity to 8, 4, and 2%, respectively. Compared with A, the use of 8% pump (D) causes a significant increase of the yield production and the particle size distribution, as expressed by the highest SI (1.52), whereas applying 2% pump ratio (F) the DC and EE slightly decrease ($p < 0.05$) (Table 2).

The feed rate does not influence significantly the particle dimensions ($p > 0.05$), even if the lowest pump capacity (2%) produces the smallest particles (6.87 μm): no differences are observed among D–F and A. This could be attributed to the low viscosity of feed solutions and to the high volatility of the solvent used.

The reduction of heating from 50 to 40°C determines a significant increase ($p = 0.03$) of microsphere recovery (YP of G is about 65.43%), confirming literature data (Esposito et al., 2000; Giunchedi & Conte, 1995); furthermore it determines a decrease of EE% ($p < 0.01$), which anyway remains higher than theoretical values. As the temperature reduction increases the particle size, the percentage of particles mainly consisting of polymers sucked up from the aspirator decreases. The dimensions and the shape of G are similar to those of A microspheres.

The H formulation was prepared changing, with respect to A at the same time heating (40°C), aspirator (70%) and pump capacities (4%). In fact the use of a temperature of 40°C allows to obtain the highest YP value, and the aspirator at 70% of its capacity shows DC and EE% significantly different from A; finally, the pump capacity of 4% was chosen for controlling the outlet temperature.

The characterization shows that by these parameters it is possible to produce microspheres with similar properties in terms of yield, drug content, size, and morphology than A. Figure 4 illustrates the size distribution profiles of A, G, and H.

Briefly the in vitro characterization demonstrates that G shows the highest value of yield of production compared with the other formulations; all the microspheres are produced with EE% > 100%. All microparticles present d_{vs} values slightly lower than A, but in any case they range from 6.9 to 7.8 μm; no differences are revealed in size distribution profiles: SI data are between 1.42 and 1.52.

Physical Stability Studies

The stability tests were carried out to evaluate the possible variations of microparticle morphology and dimension both after drying and after storage.

After production, the microspheres were dried for 24 h in oven at 30°C (A1–H1); the microspheres were then studied by SEM and by Coulter laser diffraction. The data obtained were compared with A–H.

As shown in Figure 5, after the thermal treatment at 30°C, the A microspheres loose their integrity and sphericity: mainly

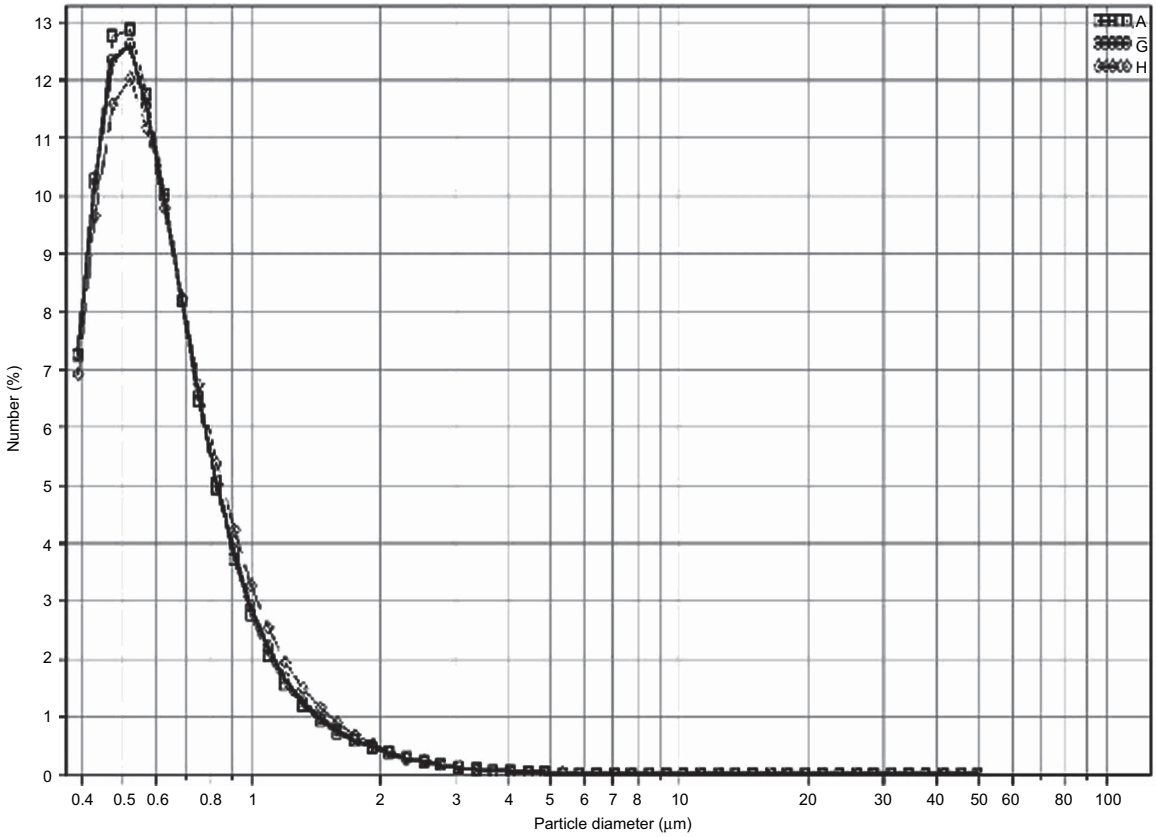

FIGURE 4. Particle size distribution of A, G, and H.

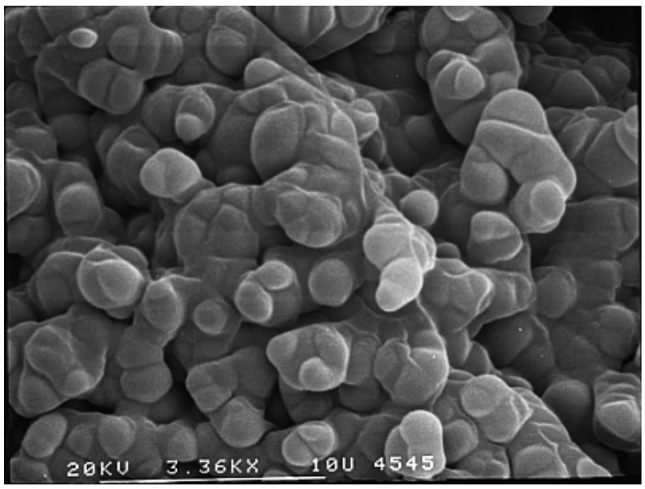

FIGURE 5. Photomicrograph of A1. Magnification: 3,360×.

the small particles are inclined to merge and make aggregates. All other microsphere formulations have similar behavior in the rank order H≈A > B > D > E > G > F > C.

Despite these morphological modifications, SPAN Index values (from 1.42 to 1.52) and particle size do not significantly change. This could be explained with the use of ultrasounds for suspending the particles in silicon oil before laser diffraction analysis that could break the aggregates observed by SEM.

To verify the real influence of temperature on the morphological changes, H microspheres, chosen as an example, were dried for 24 h in oven at 25°C (H2), at a mean temperature between those previously applied (20 and 30°C). In this case, as shown in Figure 6, the particle morphology does not undergo variations; thus, the temperature affects the morphological stability of spray-dried microspheres.

Thus, the drying temperature does not affect the particle physical stability when the drying process was carried out at 20 and 25°C. The exposure of microspheres to a temperature > 25°C causes the collapse of microspheres in the measure dependent on the spray-drying parameters used for their production.

A–H, A1–H1, and H2 were stored in open *p*olystyrene weighing *d*ishes (A–H, A1–H1, and H2 pd), *s*ealed *p*lastic Eppendorf (A–H, A1–H1, and H2 sp), and *s*ealed *g*lass vials (A–H, A1–H1, and H2 sg); for 15 and 30 days to estimate the particles stability according to the time and the conservation method as well as the container materials. Again the shape of microparticles was studied by SEM.

After 15 days, the A sp and A sg microspheres, first dried in desiccator and then stored in sealed container, change the

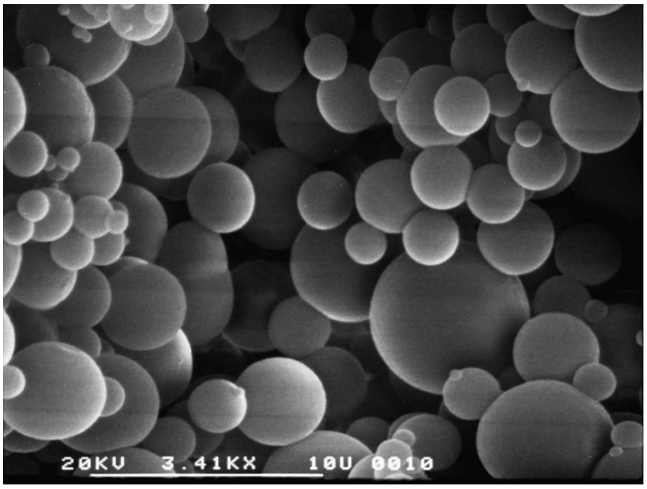

FIGURE 6. Photomicrograph of H2 microspheres. Magnification: 3,410×.

morphology observed earlier: they lose the spherical shape and partially blend making clusters. This phenomenon is accentuated in the microparticles dried at 30°C, A1 sp and sg (Figure 7a): the blending is so greater that the microspheres totally lost their shape and those against the container walls reproduce their form. This behavior is unrelated to the container materials (plastic and glass).

After 30 days, the A1 morphology does not further modify while rarely fragments of material outside the microspheres appear (Figure 7b).

After 15 and 30 days, the SEM analysis of all the other formulations, B–H sp and sg and B1–H1 sp and sg, gave prominence to the morphological inhomogeneity of all samples, independently of the drying method and the container material: owing to the different distribution in the sealed vials, some microspheres appear almost totally melted and others are distinct and in spherical shape except for C sp and sg, stored after production in desiccator for 24 h and then in closed vials for 15 and 30 days, which preserves their morphology (Figure 8a).

H2 formulations, dried in oven at 25°C and stored in closed container, show spherical shape and smooth surface even after 15–30 days, as observable in Figure 8b. Similar behavior is shown by all formulations (A–H pd and H2 pd) kept in open dishes within 30 days; Figure 9 shows the SEM of A pd after 15 days. As expected A1–H1 pd, whose morphology was already modified after treatment at 30°C, do not

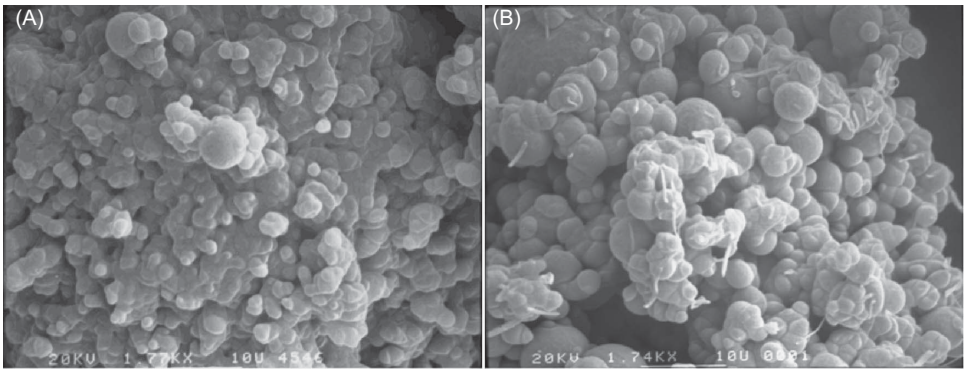

FIGURE 7. SEM of (A) A1 sg after 15 days and (B) A1 sp after 30 days. Magnification: 1,770 × (A) and 1,740 × (B).

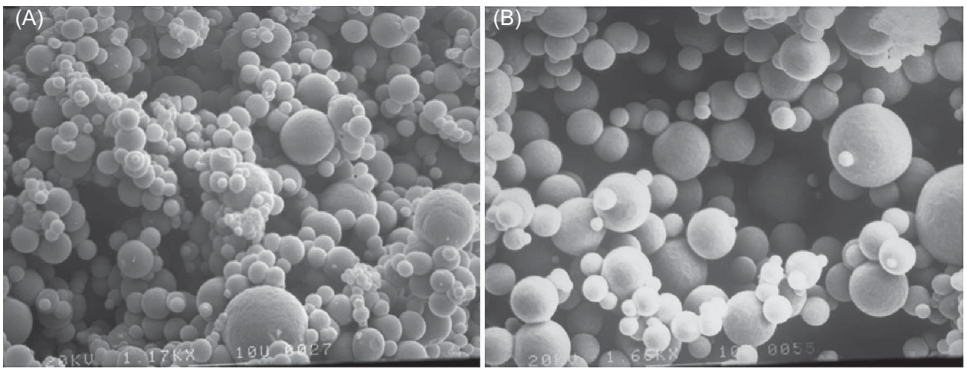

FIGURE 8. Photomicrographs of (A) C sp after 30 days and (B) of H2 sg after 30 days. Magnification: 1,170× (A) and 1,660 × (B).

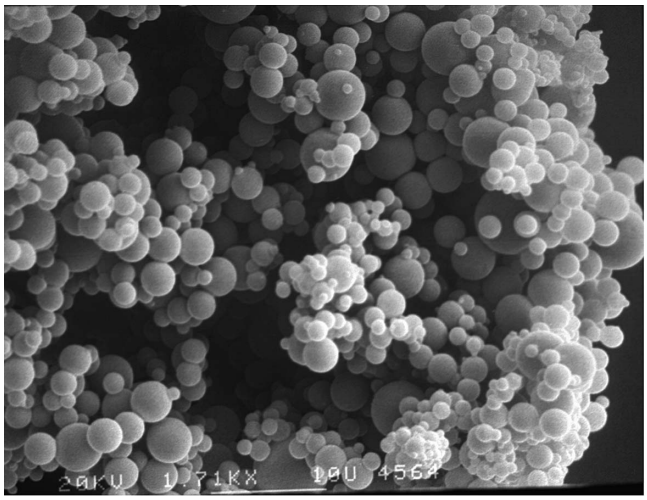

FIGURE 9. SEM of A pd after 15 days. Magnification: 1,710 ×.

show further shape changes. According to these results, the conservation in closed container, both plastic and glass, produces partial or total collapse of particles or rather their morphological alteration depends on the formulation or their drying method, indicating that not only the technological parameters but also the way of storage could influence the properties of the microspheres during the time. On the contrary, morphology or size modification is independent from the material (plastic or glass) of the storage container.

In any case, no drug crystals are present outside the microparticles.

The stored procedure in closed container causes the morphological modifications of microspheres compared with those kept in open container. It could be possible that residual traces of solvent inside the microparticles act like a plasticizer. As C and H2 shapes are unmodified even when stored in sealed containers (despite all the other formulations), this indicates that the manufacturing parameters influence the amount of organic solvent entrapped. The hypothesized effect of the residual solvent on the microsphere morphology is confirmed by the physical stability of the particles stored in open containers in which the volatile solvent can evaporate.

Differential Scanning Calorimetric Studies

The calorimetric analysis was carried out to verify the thermal behavior of ketoprofen in the microspheres after spray-drying and after storage of loaded microspheres. For this reason, the samples analyzed were as follows: (i) A and C dried in desiccator for 24 h from the production; (ii) A and C pd stored in open polystyrene dishes after 30 days; iii) A1 and C1 sp dried in oven at 30°C and kept in sealed plastic Eppendorf after the same time.

Moreover, the thermal profiles of ketoprofen, RS and RL raw materials, and blank microspheres (RS + RL) were obtained and reported in Figure 10. The drug shows an endothermic peak at 95.83°C corresponding to its melting point. RS and RL have different calorimetric profiles: both show a small endothermic peak at 60.35°C for RL and 61.44°C for RS owing to their glass transition (Tg) (Meier, 2005), but RS has a wide peak at about 30°C which appears only when the analysis starts at –40°C. This could indicate the presence of substances in the RS samples, which probably crystallize at very low temperature and then melt at 30°C. DSC profiles of blank microspheres show a wide peak with a maximum at 25°C, probably because of the Tg of RS/RL matrix and other

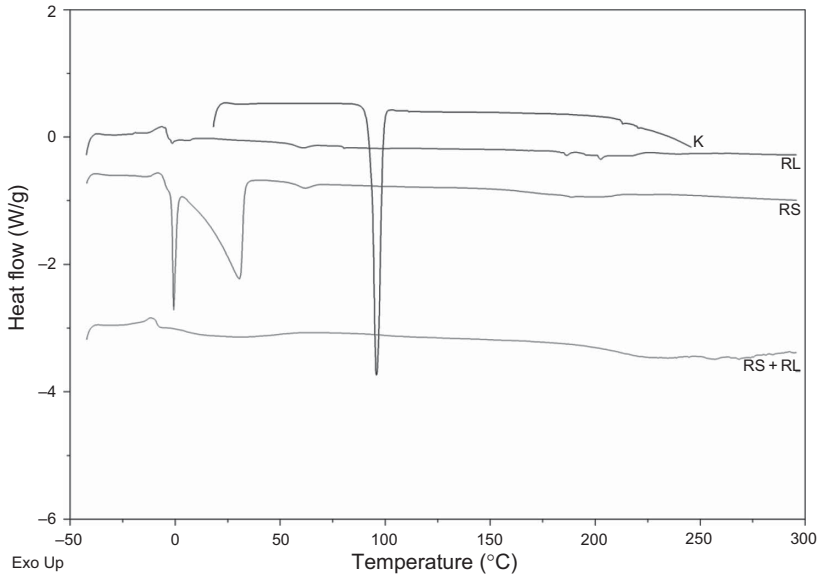

FIGURE 10. DSC profiles of ketoprofen, RS and RL raw materials, and blank microspheres (RS+RL).

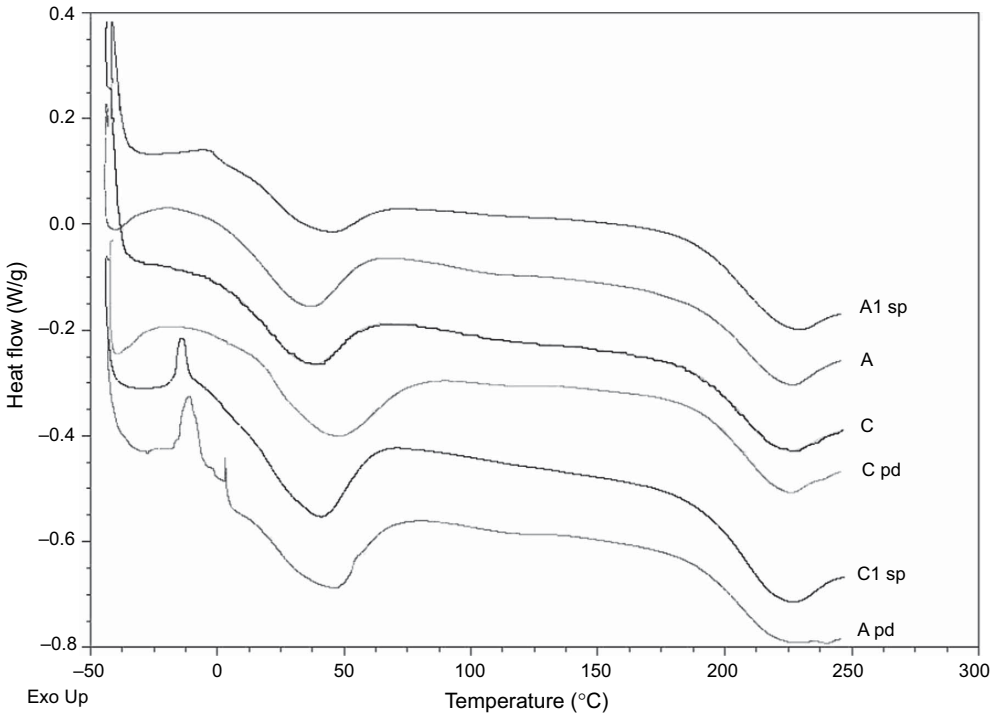

FIGURE 11. DSC profiles of A and C formulations.

endothermic peak at higher temperature (> 200°C), caused to the degradation of polymeric material.

Figure 11 shows the DSC profiles of loaded microspheres: all curves are characterized by the same wide peak of the unloaded microparticles but shifted between 35 and 50°C, depending on the formulation. These profiles explain the different behaviors of microsphere formulations when exposed to a temperature >25°C, shown during physical stability studies.

Moreover, in all thermographs the melting peak of ketoprofen is not present, neither in case of microspheres stored for 30 days; this probably means that the drug is totally amorphizated in the polymeric matrix of microspheres. In fact, Palmieri et al. (2002a) report a crystallization time of ketoprofen of 15 days.

CONCLUSION

Ketoprofen microspheres based on Eudragit® RL and RS blend can be prepared by spray-drying with good yields of production, high drug content, and encapsulation efficiency using appropriate spray-drying technological parameters. All formulations have good morphological and dimensional characteristics: spherical shape, smooth surface, and narrow size distribution.

Nevertheless, their morphology seems to be influenced by the drying and conservation methods: modifications of microspheres are observed at temperature > 25°C due to the Tg of the RS/RL matrix and after storage in sealed containers because of the residual traces of organic solvent, which are dependent on manufacturing parameters employed. When microspheres are stored in open containers, morphology does not change regardless spray-drying conditions. Thus, RS and RL 100 used as mixture and in the drug-to-polymer ratio of 1:3 are suitable to produce microspheres containing ketoprofen, by spray-drying. A large choice of manufacturing parameters can be used to obtain microparticle but specific temperature of drying and way of storage are required.

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