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COMMUNICATION

Preparation and Characterization of Spray-Dried Polymeric Nanocapsules

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ABSTRACT

Recently, much interest has been generated by colloidal drug delivery systems such as nanocapsules because of the possibilities for controlled release, increased drug efficacy, and reduced toxicity after parenteral administration. Nanocapsules of poly-ε-caprolactone and Eudragit S90® were prepared. However, these systems present physicochemical instability. To dry these nanocapsule suspensions with the view of obtaining a solid form, the spray-drying process was used. Spray-dried powders of nanocapsules of poly-ε-caprolactone and Eudragit S90® were prepared by atomization in a Büchi 190 Mini-spray dryer using colloidal silicon dioxide as a technological carrier. The morphological analysis of the surface at the powders showed that nanocapsules remain intact, and no change in particle size was detected after the spray-drying process. These results suggest that this method can be an interesting alternative to dry nanocapsule suspensions.

Key Words: *Diclofenac; Nanocapsules; Spray-dried nanocapsules.*

INTRODUCTION

Nanocapsules are polymeric colloidal systems that have received considerable attention in recent years, particularly those prepared with biodegradable polymers because of their potential use as drug carriers. However, these systems present a physicochemical instability essentially due to particle sedimentation. This is an important technological problem; thus, this limitation can compromise the industrial feasibility of such systems. Suspensions of indomethacin-loaded nanocapsules are stable for 7 months (1), suspensions of diclofenac-loaded

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nanocapsules for 8 months (2), and suspensions of indomethacin-loaded nanospheres for 6 months (3). Therefore, it is necessary to improve the stability of these forms to reach a shelf life of several years (4).

Several reports in the literature show that freeze-drying is a good method of increasing the stability of nanoparticles. To improve the stability of suspensions of indomethacin-loaded nanocapsules, a freeze-dried oral dosage form was prepared (4). The main disadvantages of this method are the technological difficulty for selection of cryoprotectors and the possibility of rupture of those nanovesicles at low temperatures.

On the other hand, the spray-drying technique has been widely used for the drying of pharmaceuticals. It has been successfully employed in the preparation of microparticulate delivery systems (5,6) to improve the drug solubility (7) or the flowability of particular excipients and to dehydrate liposomes (especially when lipophilic drugs are incorporated) into the form of small particles that can be delivered to the respiratory tract and reconstituted in situ (8). The spray-drying technique exhibits advantages like low price, ease of industrial transposition, and possibility of preparation of powders with better established physicochemical characteristics than freeze-drying powders (9,10). However, at the moment, dry suspensions of nanocapsules have not been reported. This report describes the first application of this technique to dry nanocapsules suspensions with the view to obtain a solid form. Diclofenac was chosen as the model drug.

EXPERIMENTAL

Materials

Diclofenac (sodium salt) was obtained from Sigma (St. Louis, MO); poly-ε-caprolactone (PεC, MW = 40,000) was from Aldrich (Strasbourg, France); Eudragit S90® was from Röhm Pharma (Weiterstadt, Germany); phospholipid mixture (Epikuron 170®) was supplied by Lucas Meyer (Hamburg, Germany); and Poloxamer (Synperonic PE/F68®) came from ICI (Clamart, France). Caprilic/capric triglyceride (Miglyol 810®) was delivered from Hulls (Puteaux, France). Colloidal silicon dioxide (Aerosil 200®) came from Degussa (São Paulo, Brazil). All other chemicals and solvents used were pharmaceutical grade. All reagents were used as received.

Preparation of the Free Acid Form of Diclofenac

For preparation of the free acid form of diclofenac (2), an aqueous solution of sodium diclofenac was acidified to pH 4.0 with acetic acid 10%. This solution was then extracted three times with chloroform. After filtering through sodium sulfate, the solvent was removed by evaporation under reduced pressure. The diclofenac obtained was characterized by ^{1}H-NMR (nuclear magnetic resonance) (200 MHz) (Varian, Palo Alto, CA).

Preparation of Nanocapsule Suspensions

Nanocapsules of PεC and Eudragit S90 containing diclofenac were prepared as described by Fessi et al. (1). Briefly, the lipophilic solution consisted of Miglyol 810, diclofenac (free acid), Epikuron 170, the polymer (poly-ε-caprolactone or Eudragit S90), and acetone. This organic phase was added under moderate magnetic stirring to an aqueous solution containing Poloxamer as stabilizer. Acetone was eliminated by evaporation under reduced pressure, and the final concentration of the suspension was adjusted to 1 mg/ml of diclofenac.

Nanocapsules Suspension Characterization

The particle size distribution of nanoparticles was measured by laser light scattering using an N4 Coulter Nanosizer (Hialeah, FL). Zeta potential was determined in a Zetasizer®4 with a Series 7032 Multi-8 correlator (Malvern, Orsay, France). The results presented were all normalized to a value of $\zeta = -55$ mV for the standard solution (a carboxylated polystyrene latex supplied by Malvern).

Determination of Drug Content for Suspensions

Diclofenac was assayed by high-performance liquid chromatography (HPLC). The system consisted of an SPD-10A Shimadzu detector (Kyoto, Japan), LC-10AD Shimadzu pump, SIL-10A Shimadzu injector, and Nova-Pak® C18 (3.9 × 300 mm) Waters column. The mobile phase consisted of acetonitrile/water (65:35 v/v) adjusted to pH 4.0 with acetic acid 10%. The total sample volume injected was 20 μl.

Diclofenac was detected at 280 nm with a retention time of about 6.7 min. Free diclofenac (nonencapsulated) was determined in the clear supernatant after separation of the nanocapsules from aqueous medium by an ultrafiltration-centrifugation technique (Ultrafree-MC 10,000 MW, Millipore, Medford, MA). The diclofenac content of the nanocapsules was calculated from the difference between the total and free drug concentrations measured

in the nanocapsule suspension and the filtrate, respectively.

Preparation of Spray-Dried Powder

To the suspension of nanocapsules was added 55% (w/w) of Aerosil 200, and the mixture was fed into a mini-spray-dryer Büchi MSD 190 (Flawil, Switzerland) with a two-component nozzle and cocurrent flow. The inlet temperature at the drying chamber was maintained around 138°C ± 4°C. The outlet temperature was at 90°C ± 4°C. The residual water content of each spray-dried product was determined by loss of weight (11); each analysis was repeated three times.

Determination of Drug Content to Spray-Dried Powders

The spray-dried powders were dispersed in acetonitrile under magnetic stirring for 60 min at room temperature. The dispersion was filtered through a hydrophilic membrane (HVLP, 0.45 μm, Millipore), and the diclofenac was assayed by HPLC at 280 nm. The recovery of diclofenac in the spray-dried powders was estimated by correlation of theoretical and practical concentrations.

Morphological Analysis of Spray-Dried Powders

The powders were examined under scanning electron microscopy (SEM) (Phillips XL 20, Eindhoven, The Netherlands, PW6620/00) at a magnification between 1000 and 92,000. Samples were analyzed after they had been gold sputtered.

RESULTS AND DISCUSSION

The method employed allowed obtaining colloidal suspensions of diclofenac using PεC and Eudragit S90 like vesicle wall former.

Table 1 shows the mean values of the particle sizes, pH, percentage of encapsulated drug, quantity of initial load of diclofenac, and zeta potentials in the nanocapsule suspensions. All the nanocapsule suspensions showed homogeneous populations of particles with an acceptable diameter. The particle size and pH were not affected by the type of polymer used and the presence of diclofenac. The percentage of diclofenac encapsulated was always close to 100%. Similar results were obtained for D,L-lactide (PLA) nanocapsules containing diclofenac (2). The partition coefficients determined for diclofenac between the Miglyol 810 and water showed that a slight amount of drug dissolved in the aqueous phase (2), explaining the high percentage of drug encapsulation. Regarding zeta potential, the formulations had a negative charge, probably due to the chemical characteristics of polymers. The charge was more negative for the suspension prepared with Eudragit S90 than for the anocapsules prepared with poly-ε-caprolactone.

Table 2 shows the yields, weight loss, and the initial load of diclofenac in the spray-dried powders. Without adjuvant, it was not possible to spray-dry the nanocapsule suspensions due to the strong adhesion of the product onto the spray-dryer walls. This problem was avoided by addition of colloidal silicon dioxide (55% w/w), which is widely reported as a spray-drying adjuvant (6,12,13).

The spray drying yield for the powders prepared from nanocapsule suspensions was approximately 70%

Table 2

Characteristics of PεC Spray-Dried Nanocapsules (1), Eudragit S90® Spray-Dried Nanocapsules (2), and Aerosil 200® Spray-Dried (3)

Powders	Yield (%)	Weight Loss (%)	Diclofenac Recovery (%)
1	70	0.01	100
2	58	0.01	100
3	63	0.01	—

Table 1

Characteristics of PεC-NC (1) and Eudragit S90-NC (2)

Formulation	Size (nm ± SD)	pH	Initial Load of Diclofenac (% SD)	Diclofenac Encapsulated (%)	Zeta Potential (mV ± SD)
1	181.6 ± 28.0	3.95	108.5 ± 0.1	100	−31.6 ± 3.4
2	190.3 ± 62.6	4.75	104.5 ± 0.7	100	−51.7 ± 0.6

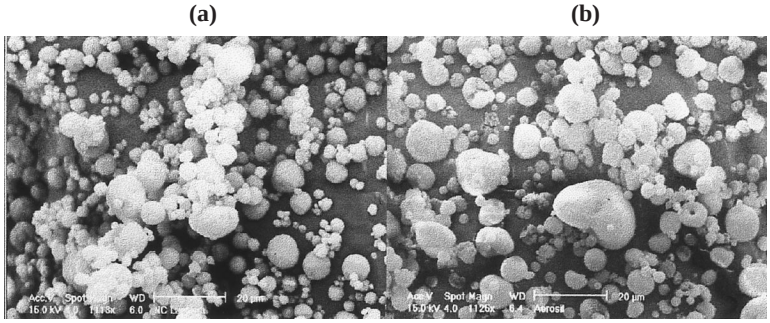

Figure 1. SEM micrographs of (a) PεC-NC spray-dried powder (×1113) and (b) Aerosil 200 spray-dried powder (×1125).

(poly-ε-caprolactone nanocapsules, PεC-NC) and 58% (Eudragit S90-NC), showing a low moisture content of 0.01% for all cases. Both PεC-NC containing diclofenac and Eudragit S90-NC containing diclofenac powders showed a percentage of diclofenac close to 100%.

The SEM analysis shows that the spray-dried powders are spherical particles, a characteristic that usually leads to a free flow (9) and represents an important characteristic for the application of spray-dried powders as an intermediary pharmaceutical product (13). However, in this case, the most interesting characteristics observed were related to the spray-dried microparticle surfaces. While the microparticles of Aerosil 200 obtained from the suspensions usually show a rugged surface with the presence of some cavities (Fig. 1), the microparticles prepared from a mixture of Aerosil 200 and PεC-NC loaded with diclofenac do not show the presence of cavities; it was clearly observed in the nanoparticles adsorbed on the surface of silicon dioxide (Figs. 2a, 2b, and 2c). There was no detectable sign of breaking of the nanocapsules. The micrographs of the surface of the spray-dried powder surface showed that nanoparticles remained intact, and no change in particle size was detected after the spray-drying process (Fig. 3). The nanocapsule size was almost the same before and after dehydration (around 200 nm).

In conclusion, this method can be an interesting alternative to dry nanocapsules suspensions and to ob-

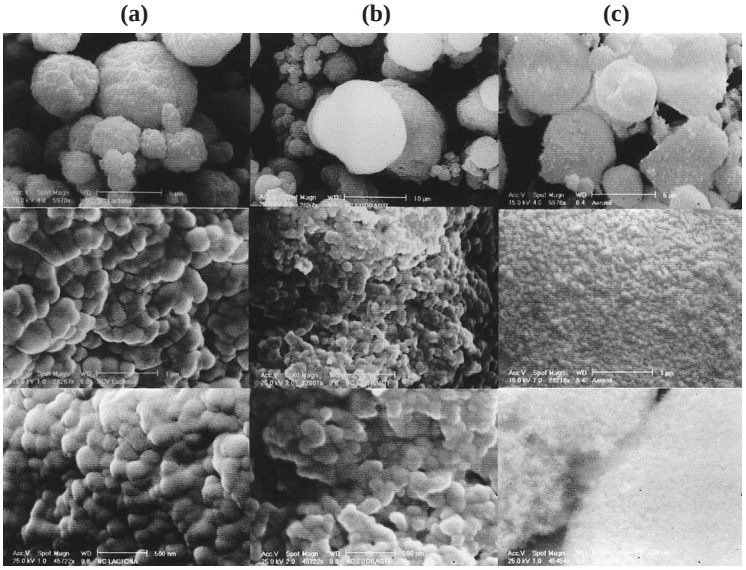

Figure 2. SEM micrographs of (a) PεC-NC spray-dried powder (×5970, ×28267, and ×45,722); (b) Eudragit S90-NC spray-dried powder (×2857, ×22,861, and ×45,722); and (c) Aerosil 200 spray-dried powder (×5978, ×28,216, and ×45,454).

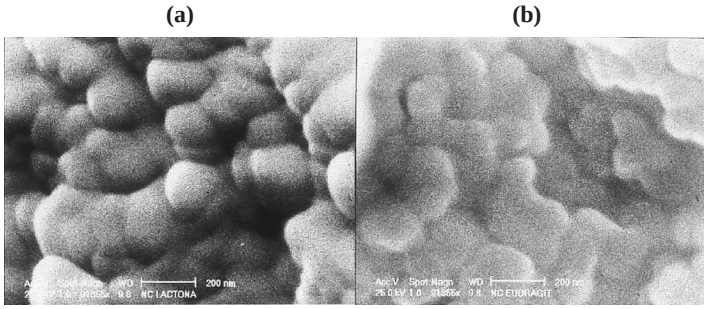

Figure 3. SEM micrographs of (a) PεC-NC spray-dried powder (×91,355) and (b) Eudragit S90-NC spray-dried powder (×91,355).

tain nanocapsules incorporated in a solid form. These results showed that the drying process does not change the nanocapsule size, and the vesicles seem to remain intact.

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REFERENCES

1. H. Fessi, F. Puisieux, and J. P. Devissaguet, Eur. Pat. 0274961 A1 (1988).
2. S. S. Guterres, H. Fessi, G. Barrat, J. P. Devissaguet, and F. Puisieux, Int. J. Pharm. 113, 57 (1995).
3. P. Calvo, J. L. Vila-Jato, and M. J. Alonso, J. Pharm. Sci., 85(5), 530 (1996).
4. S. Chasteigner, H. Fessi, G. Cave, J. P. Devissaguet, and F. Puisieux, STP Pharma Sci., 5(3), 242 (1995).
5. V. Conte, B. Conti, P. Giunchedi, and L. Maggi, Drug Dev. Ind. Pharm., 20(3), 235 (1994).
6. G. F. Palmieri, P. Wehrlé, and A. Stamm, Drug Dev. Ind. Pharm., 20(18), 2859 (1994).
7. Y. Kawashima, M. Saito, and H. Takenaka, J. Pharm. Pharmacol., 27, 1, (1975).
8. P. Goldbach, H. Brochart, and A. Stamm, Drug Dev. Ind. Pharm., 19(9), 2611 (1993).
9. J. Broadhead, S. K. E. Rouan, and C. T. Rhodes, Drug Dev. Ind. Pharm., 18(11–12), 1169 (1992).
10. H. F. Teixeira, thesis, Masters in Pharmacy, UFRGS, Porto Alegre, Brazil, 1996.
11. Farmacopéia Brasileira, 4th ed., Atheneu, São Paulo, Brazil, 1988.
12. J. L. Casadebaig, M. Jacob, G. Cassanas, D. Gaudy, G. Baylac, and A. Puech, J. Ethnopharm., 26, 211 (1989).
13. E. Senna Lemos, P. Petrovick, G. Gonzalez Ortega, and V. L. Bassani, Phytother. Res., 11, 123 (1997).