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Sodium pantoprazole-loaded enteric microparticles prepared by spray drying: Effect of the scale of production and process validation

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Abstract

Pantoprazole is a prodrug used in the treatment of acid related disorders and *Helicobacter pylori* infections. It is activated inside gastric parietal cells binding irreversibly to the H^+/K^+-ATPase. In this way, pantoprazole must be absorbed intact in the intestinal tract, which indicates that enteric drug delivery systems are required for its oral administration. The purpose of this study was to investigate the physical characteristics of enteric pantoprazole-loaded microparticles prepared by spray drying using a blend of Eudragit S100® and HPMC. The microparticles were produced in different spray dryers and operational conditions at laboratory and pilot scales. Microparticles produced with two fluid nozzle atomizer and air pressure of 196 kPa presented satisfactory encapsulation efficiency and gastro-resistance. Microparticles produced with the same atomizer but using 49 kPa of air pressure presented strings in the powder. The microparticles produced in mixed flow presented very high polydispersity and the ones produced with rotating disc atomizer presented drug crystals adsorbed on the particle surfaces. The microparticles produced with two fluid nozzle atomizer and 196 kPa were prepared in three consecutive days for the process validation. The powders showed reproducible diameter, polydispersity, densities, encapsulation efficiency and gastro-resistance profile.

Keywords: Pantoprazole; Spray drying; Microparticles; Scale up; Gastro-resistance

1. Introduction

A spray dryer converts a liquid feed into solid particles with specific characteristics modeled by the equipment design, the operating conditions and the process variables (Gibson, 2001). The droplet size formed by the atomizer is directly proportional to the final particle size (Gibson, 2001). In addition, the droplet size on atomization depends upon the mode of atomization, the physical properties of the feed and the feed solid concentration (Goula and Adamopoulos, 2004). The two most common atomizers used in the pharmaceutical field are the two fluid nozzle and the rotary atomizer (Gibson, 2001). Concerning the pressure nozzle, the orifice size is chosen to control the particle size. The increase in atomizer pressure produces finer particles. On the other hand, in the rotary atomizer, the speed of the wheel controls the particle size, which reduces with the increase of the speed.

The exact characteristics expected for the final product are the first step to optimize the spray drying process. Based on these characteristics, the design and the operation variables will change. The characteristics include mainly moisture content, particle size and polydispersity, bulk and tapped densities and cohesion (Birchal et al., 2005).

Spray drying has gained more importance as a method of microencapsulation. This method has already been used to prepare microparticles with polyesters, polymethacrylates, cellulose derivatives and biopolymers containing both hydrophilic and lipophilic drugs and macromolecules. The major advantages over solvent evaporation techniques are the one-step process, the easiness to control and scale up, and the possibility of being free of organic solvent (Giunchedi et al., 2001).

The major difficulties in scaling up the spray drying process include the thermal exchange and losses, variable yields and, mostly, geometries of atomizers or turbines, drying chambers

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and cyclones. Several reports in the literature are based on laboratory scale production (Benoit et al., 1996; Palmieri et al., 2002; Oster and Kissel, 2005). The effects of process variables are difficult to assess in general terms, due to the lack of information in the literature and to the specific drying nature of most materials (Goula and Adamopoulos, 2004).

Spray dried particle distribution varies depending on the nozzle geometry, the feeding rate and the operating conditions. Although these parameters are kept very similar, they are never identical and changes are observed among different equipments (Foster and Laetherman, 1995).

The encapsulation of hydrophilic acid labile drugs by spray drying has the advantage of no necessity of organic solvents. In this case, enteric polymers can be used to prepare microparticles because they are soluble in pH higher than 6 or 7 and can be dissolved in alkaline solutions (Palmieri et al., 2002). The resulting microspheres should be able to protect acid labile drugs from gastric juice.

Sodium pantoprazole is a prodrug that inhibits the proton pump and, consequently, the acid release in gastric lumen. This prodrug is used in the treatment of digestive ulcers, gastro-oesophageal reflux disease and as auxiliary in the eradication of the *Helicobacter pylori* (Cheer et al., 2003). This prodrug reacts in acid medium. When this conversion occurs in the parietal cell canalicular lumen, it is activated by conversion to a cyclic sulfonamide, which is the active form (Cheer et al., 2003; Sachs et al., 2003). The active form, the tetracyclic cationic sulfenamide, reacts with the thiol groups of cysteines 813 and 822 of the transmembranal H^+/K^+-ATPase (Shin et al., 1993; Avner, 2000). This conversion must occur inside the gastric parietals cells, so pantoprazole should be absorbed intact by the intestinal tract, needing an enteric drug delivery system to be administered. When the pantoprazole reacts with acid in the stomach lumen before absorption, the substance is degraded and no activity is observed (Cheer et al., 2003).

Pantoprazole-loaded microparticles have been prepared using a blend of Eudragit® S100 and Methocel® F4M in laboratory scale. In vivo anti-ulcer activity evaluation has demonstrated that the microparticles were able to protect rats against ulcers induced by ethanol, while the pantoprazole aqueous solution did not present activity (data not shown).

Taking all of these into account, the aim of this work was to produce enteric microparticles containing sodium pantoprazole by spray drying in both laboratory and pilot scales and to study and validate the production process in pilot scale. The microparticles have been characterized in terms of their morphology, flowability, encapsulation efficiency and ability of stabilizing pantoprazole in acid medium.

2. Materials

Sodium pantoprazole sesquihydrate has been obtained from Henrifarma (São Paulo, Brazil). Eudragit® S100 has been kindly provided by Almapal® (São Paulo, Brazil, produced by Rohm®, Germany). Methocel® F4M was provided by Colorcon® (São Paulo, Brazil, produced by Dow Chemical, USA). All other chemicals are analytical grade.

3. Methods

3.1. Preparation in laboratory scale and characterization of microparticles

For the laboratory production scale, three batches were prepared increasing total solids concentration in the solution feed. Eudragit® S100 and NaOH were added to 100 mL of water, in the following amounts: 1.2 and 0.2, 1.5 and 0.25, and 1.8 and 0.3 g, respectively. After the solubilization, Methocel® F4M was added (0.60, 0.75 and 0.90 g) and the solution was kept at 10 °C for 24 h. Sodium pantoprazole (0.30, 0.38 and 0.45 g) was added in the solution for spray drying. The formulations were named L1, L2 and L3, respectively.

The viscosity at 25 °C of the three solutions was measured using a Brooksfield Digital Viscosimeter (model DV-II), using spindle 01. The solutions were atomized into a laboratory spray drier (Model 190 Büchi®). The equipment is equipped with a two fluid pressurized nozzle with diameter $d_0 = 0.7$ mm. Experiments were carried out under the following conditions: inlet air temperature 150 ± 5 °C, outlet air temperature 98 ± 3 °C, aspirator setting: 10, suspension feed flow rate: 0.24 L/h, airflow rate: 500 N L/h. In this small-scale equipment, droplets flow cocurrently with airflow.

Shape and surface were analyzed by scanning electron microscopy (JEOL JSM5200®) after gold sputtering using accelerating voltage of 15 kV. The particle size distribution was determined by laser diffractometry Beckman Coulter® LS 13 320 (Beckman Instruments) by dry dispersion. Average particle size was expressed as the mean volume diameter ($D_{4.3}$). Polydispersity was given by a span index, which was calculated by $(D_{0.9} - D_{0.1})/D_{0.5}$, where $D_{0.9}$, $D_{0.5}$ and $D_{0.1}$ are the particle diameters determined respectively at the 90th, 50th and 10th percentile of the undersized particle distribution curve.

The specific surface areas of microparticles were determined by the BET multipoint technique (Brunauer et al., 1938). The nitrogen adsorption–desorption isotherms of previous degassed organic-solids, under vacuum at 40 °C, were determined at liquid nitrogen boiling point in a homemade volumetric apparatus, using nitrogen as probe. The pressure was measured using capilar mercury barometer and the results were compared to alumina pattern.

To determine the drug content in the microparticles, an amount equivalent to 10 mg of pantoprazole in the microparticles was weighed and dissolved in 50 mL of 0.05 M NaOH. Drug concentration was determined in each sample after filtration (0.45 μm, Millipore®) by HPLC (Perkin-Elmer series 200; UV detector, $\lambda = 290$ nm, Shelton, USA), using a Merck® Lichrosphere® column C_{18} as stationary phase. Mobile phase consisted of acetonitrile/phosphate buffer pH 7.4 (35:65 v/v). This method was validated for specificity, linearity, accuracy, precision and detection and quantitation limit according to ICH (1996).

Size 0 hard gelatin capsules without coloring agent were filled with 90 mg of microparticles, corresponding to 16 mg of drug. Dissolution tests were conducted in USP dissolution apparatus I at 50 rpm and 37 °C. In order to determine if the microparticles were able to release 100% of the drug encapsulated, the dissolution was evaluated in phosphate buffer pH 7.4 for 480 min.

To evaluate gastro-resistance, capsules containing pantoprazole were exposed to 300 mL of 0.1 M HCl. After 1 h, a NaOH (2.6 g) and KH_2PO_4 (6.12 g) aqueous solution (600 mL) was added into the medium in order to reach pH 7.4. The samples were collected in pre-determined time intervals from 0 up to 480 min. Pantoprazole concentrations were determined by UV at 295 nm (Unicam 8625 UV/VIS spectrometer). The analytical method was validated for linearity, precision, specificity and quantitation limit according to ICH (1996).

3.2. Preparation in pilot scale and characterization of microparticles

Microparticles presenting higher amount of initial solids concentration was chosen to conduct the study in pilot scale. The pilot spray drier (Model S52 APV® Anhydro) was used with three sets of atomizers. The first set used a rotating disc under the following operating conditions: co-current flow dryer; rotational velocity of atomizer 30,000 rpm; suspension flow rate 2 L/h; inlet and outlet air temperatures 170 ± 1 and 85 ± 5 °C, respectively. Two other sets of experiments were carried out using a two fluid pneumatic atomizer with external mixing. In this nozzle, the liquid to be atomized is discharged through a central hole of diameter $d_0 = 1.5$ mm, whereas the atomizing air is injected through a ring area around the liquid hole. The atomizing air pressure varied from 49 to 196 kPa to generate droplets with different sizes (Ré et al., 2004). In one set of experiments, droplets flow in co-current with the drying air (co-current flow dryer); in the other set, droplets flow in counter-current in relation to the drying air inlet (mixed flow dryer, where the feed is sprayed upwards and the particles formed inside the dryer finish their journey in a co-current mode). Fig. 1 shows diagrams of both co-current and mixed flow apparatus used. During all the processes the room temperature and humidity were controlled in 24 ± 1 °C and 54 ± 2% of relative humidity. The dried formulation was prepared by solubilizing 36 g of Eudragit® S100, 18 g of Methocel® F4M, 9 g of pantoprazole in a solution prepared with 6 g of NaOH and 2000 mL of water. Microparticles were produced in duplicate.

Humidity was assayed gravimetrically in Mettler Toledo® HB 43 Halogen kept at 105 °C until constant weight. Microparticles were characterized by SEM, particle size distribution, specific surface area, porosity, dissolution profiles in phosphate buffer and gastro-resistance as described above for laboratory scale production. The gastro-resistant profiles were compared by f_1/f_2 method.

Rheological characteristics of the powders were also determined. Bulk and tapped densities of the spray-dried microparticles were determined using an automatic taper (AutoTap, Quantachrome® Corp.). The tapped density was measured after 1250 taps, because preliminary investigations have shown (data not shown) that the volumetric change after this number of taps was negligible. An average of three determinations was taken. From these measurements, the Carr index was determined. Note that the Carr index is defined as the difference between the tapped and the bulk density divided by the tapped density, expressed in percentage (Carr, 1965). The angle of repose was measured in Powder Characteristics Tester, Model PT-N (Hosokawa Microns®). The angle of repose is the angle between the horizontal and slope of the heap. This angle is a direct indication of the potential flowability of a powder (contact and friction between particles in motion).

3.3. Pilot scale process evaluation

The following conditions were chosen to produce microparticles: two fluid atomizer, co-current air spray contact and air pressure of 196 kPa. Three batches of 11 L were dried in three

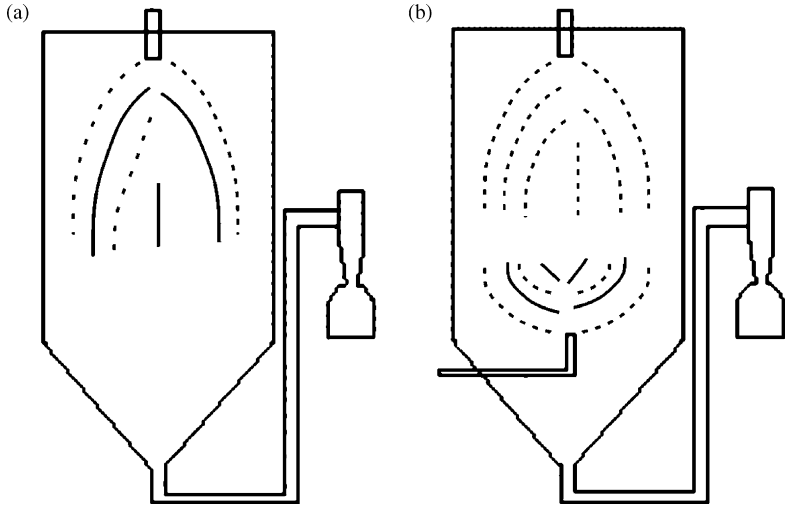

Fig. 1. Diagrams of the two types of air/spray contact in the pilot spray drier. Co-current contact used with rotating and two fluid nozzle atomizers (a) and mixed flow used with two fluid nozzle atomizer (b). Full lines indicate liquid feed and dashed lines indicate air feed.

consecutive days and the microparticles were separately analyzed. To confirm the stability of pantoprazole in the solution of the polymers (Eudragit® S100 and Methocel® F4M), samples of the solution feed were kept at room temperature in absence of light for 24 h. Samples were analyzed every 2 h by HPLC. The process yield was calculated by the obtained mass divided by the total solid raw materials in solution multiplied by 100. Microparticles were characterized by SEM, particles size distribution, humidity, surface area, flowability, drug content and gastro-resistance profiles. The true density of all samples was measured by Helium Picnometry using a Multi Pycnometer (Quanta Chrome®) at room temperature. DSC was performed in Mettler Toledo 822^e from −70 to 250 °C at 10 °C/min and N_2 flow rate of 30.0 mL/min. For the thermal analysis, Eudragit® S100 (3.6 g) and Methocel® F4M (1.8 g) were solubilized in NaOH solution (0.3 g in 100 mL) and spray dried in mini spray drier Buchi in the same conditions described above for the laboratory scale microparticles. The statistical test of ANOVA was used to compare the values obtained from each characterization.

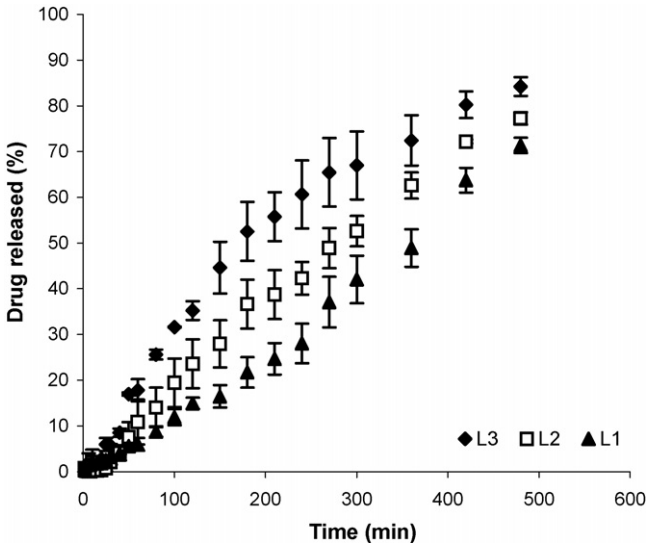

Fig. 3. Gastro-resistance profiles of the microparticles produced in laboratory scale: L1 (2.3%), L2 (2.9%) and L3 (3.4%).

4. Results

4.1. Preparation in laboratory scale and characterization of microparticles

The control of viscosity of liquid feed allows the liquid to be converted into droplets. The maximum recommended viscosity of the solutions that can be spray dried is 250 cP (Gibson, 2001). Even though all solutions presented values lower than the limit, an increasing of viscosity was observed with the increase of total solid concentration. The viscosity values of L1 (2.3%), L2 (2.9%) and L3 (3.4%) were 15.6, 28.7 and 58.5 cP, respectively.

In this way, the three solutions were able to be spray dried, and in all cases off-white powders were obtained. All three powders (L1, L2 and L3) were analyzed by SEM and the microparticles presented surface shriveling and folding (Fig. 2). This morphology is formed by uneven shrinkage forces during the drying of droplets, depending on the viscosity of the liquid feed. The tendency to shrive or fold increases with the increase of feed viscosity (Foster and Laetherman, 1995).

The particle size distribution showed differences among the three microparticles (7.50, 8.45 and 8.78 μm, corresponding to L1, L2 and L3, respectively). In general, particle size is assumed to increase with an augmentation in feed concentration, while an increase in feed solid concentration may cause a reduction of particle density presumably due to rapid crust formation, which hinders water reaching the surface, thus building up internal pressures (Goula and Adamopoulos, 2004).

The specific surface area showed similar values for the three formulations L1, L2 and L3 (70, 65 and 66 m^2/g, respectively). Although the mean diameter had increased with the increase of liquid viscosity, this variation was not observed so clearly in the surface area values, due to the precision of the measure that is 10 m^2/g.

The drug was totally released (100%) at pH 7.4 in 480 min from the three microparticle formulations. On the other hand, after the acid stage followed by release at pH 7.4 (gastro-resistance profiles), different amounts of pantoprazole were stable after 480 min. The L3 produced with the highest solid concentration solution, showed the highest protection of pantoprazole from acid medium (Fig. 3).

Considering these results, the L3 formulation was chosen to be spray dried in pilot scale due to the higher solid concentra-

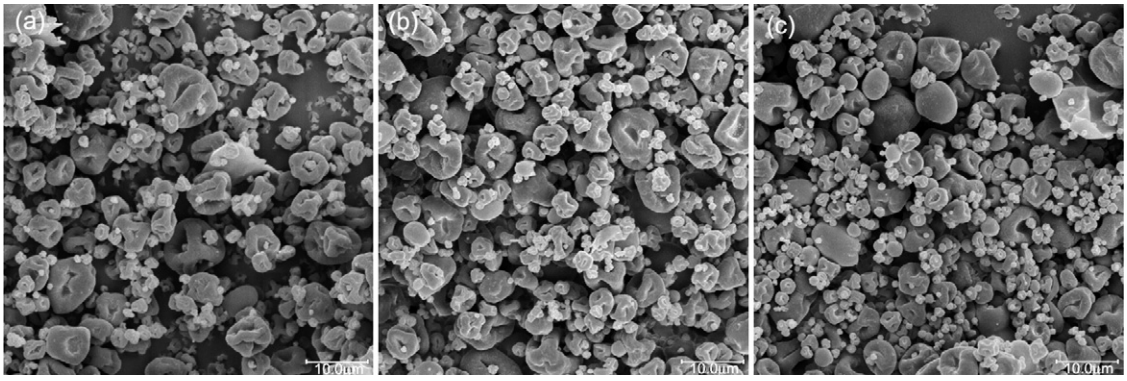

Fig. 2. SEM images of microparticles produced in laboratory scale: (a) L1 (2.3%), (b) L2 (2.9%) and (c) L3 (3.4%).

tion in the liquid feed (3.4%) and the highest stabilization of pantoprazole after acid stage.

4.2. Preparation in pilot scale and characterization of microparticles

Four different sets of atomizer, air pressure and air spray contact were tested: (i) rotating disc atomizer (RO), (ii) two fluid nozzle atomizer using air pressure of 49 kPa (N1), (iii) 196 kPa (N2) and (iv) two fluid nozzle atomizer and 196 kPa of air pressure in mixed flow (MF). Table 1 summarizes the characteristics of all four powders.

The RO-microparticles presented mean size of 38.7 μm, polydispersity (span) of 2.4 and surface area of 70 m^2/g. SEM image showed spherical and irregular particles (Fig. 4a), as well as in few particles blowholes could be observed. Furthermore, drug crystals, identified by the presence of sulfur (EDS), were visualized on the particle surface suggesting an incomplete encapsulation of pantoprazole.

The microparticles produced using two fluid nozzle atomizer (N1-microparticles and N2-microparticles) presented smaller average particle size and higher surface area than RO-microparticles (Table 1). N1-microparticles presented mean diameter of 25.7 μm, span of 2.3 and surface area of 93 m^2/g, whereas N2-microparticles presented average size of 30.8 μm, span of 3.0 and surface area of 96 m^2/g. When analyzed by SEM, N1-microparticles were formed by microparticles and strings or threads like cotton candy (Fig. 4b). Similar results have been obtained by Clarke et al. (1998) preparing microparticles by spray drying, which presented a mixture of concave microparticles and fibrous powder. The authors attributed the formation of the filaments to an insufficient force to enable the liquid filament to be broken into droplets. The formation of these filaments is influenced by the air pressure, geometry of the atomizer and the flow rate (Benoit et al., 1996). In addition, N2-microparticles presented mainly spherical particles with smooth surface and few cases of blowholes and shriveling (Fig. 4c). The reduced particle size of N2-microparticles (30.8 μm compared to 38.7 μm of RO-microparticles) led to an increase of the specific surface area of the N2-microparticles.

On the other hand, MF-microparticles prepared using the air pressure in mixed flow presented average diameter of 137.1 μm, span of 4.2 and surface area of 57 m^2/g, indicating a very high polydispersity compared to the other three powders and a reduced surface area. These results are in accordance with the photomicrography (Fig. 4d) in which very different sizes of microparticles have been observed, including particles presenting less than 10 μm and over 90 μm of diameter in great quantity. The increase in the average particle size between laboratory (8 μm) and pilot scales (30 μm) has been also described by Foster and Laetherman (1995) showing approximately a two-fold to a three-fold increase in particle size.

Bulk and tapped densities (Table 1) were similar for RO-microparticles and N1-microparticles. These formulations presented different densities when compared to N2-microparticles or MF-microparticles. The higher density of RO-microparticles can be attributed to the presence of crystals on the parti-

Table 1
Characteristics of the powders produced in pilot scale in different sets of atomizers and air pressure

Atomizer	Air pressure (kPa)	Particle size (μm)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr index	Humidity (%)	Surface area (m^2/g)	Drug content (%)
Rotating disc	–(RO)	$D_{4,3}$ 38.7, span 2.4, S.D. 0.52	0.115 ± 0.002	0.221 ± 0.005	48	4.00 ± 0.24	70.58	13.14 ± 0.23
Two fluid nozzle and co-current flow	49 (N1)	$D_{4,3}$ 25.7, span 2.3, S.D. 0.13	0.122 ± 0.002	0.255 ± 0.006	48	4.02 ± 0.27	93.13	11.49 ± 0.81
	196 (N2)	$D_{4,3}$ 30.8, span 3.0, S.D. 1.68	0.064 ± 0.002	0.125 ± 0.003	48	3.37 ± 0.12	95.83	12.81 ± 0.05
Two fluid nozzle and mixed flow	196 (MF)	$D_{4,3}$ 137.1, span 4.2, S.D. 23.1	0.060 ± 0.000	0.098 ± 0.001	39	2.84 ± 0.09	57.04	12.48 ± 0.28

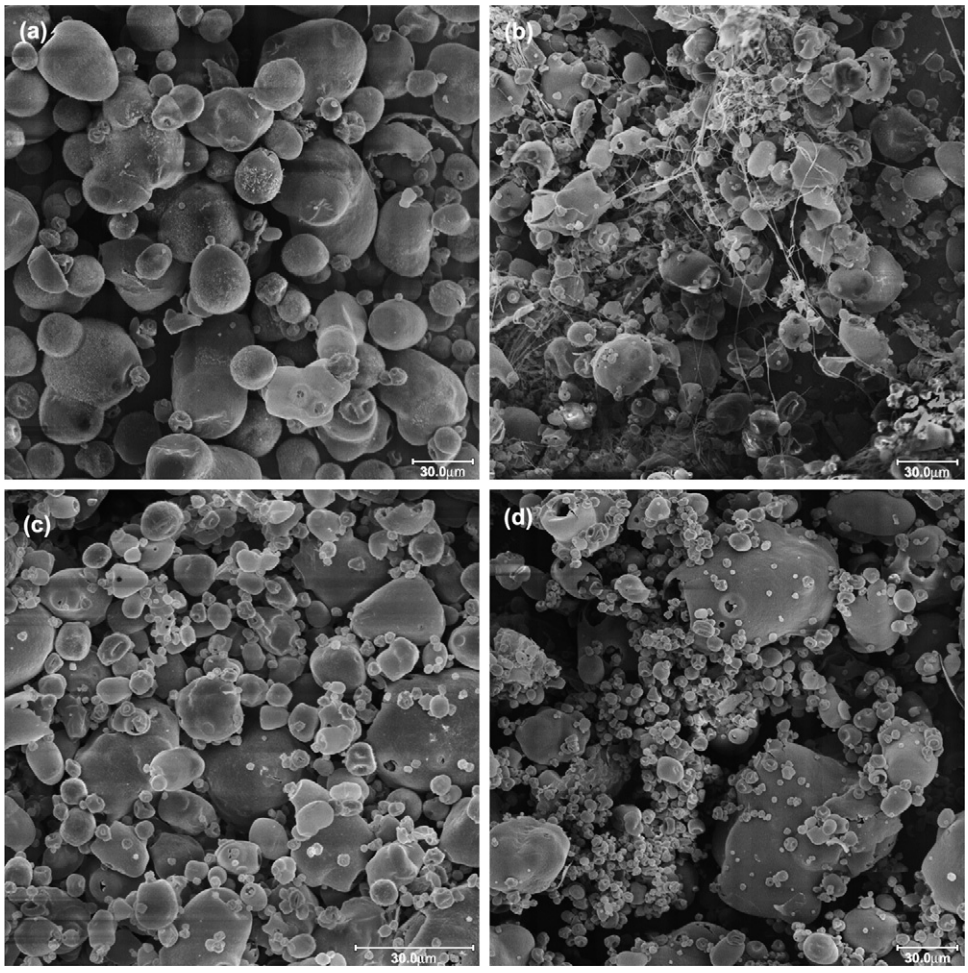

Fig. 4. Photomicrographies of the powders produced in pilot scale: (a) rotating disc atomizer (RO-microparticles), (b) two fluid nozzle atomizer and air pressure of 49 kPa (N1-microparticles), (c) two fluid nozzle atomizer and air pressure of 196 kPa (N2-microparticles) and (d) two fluid nozzle atomizer in mixed flow (MF-microparticles).

cle surface or to the large microparticles shell, since hollow microparticles were obtained (Fig. 4a). N1-microparticles presented higher bulk density (0.122 g/cm^3) than N2-microparticles (0.064 g/cm^3) or MF-microparticles (0.060 g/cm^3) probably due to the presence of the threads. The bulk densities of N2-microparticles and MF-microparticles are in accordance with previous reports for casein and NaCMC microparticles produced by spray drying containing teophylline (Foster and Laetherman, 1995; Wan et al., 1992). Tapped densities were higher for RO-microparticles (0.221 g/cm^3) and for N1-microparticles (0.255 g/cm^3) than for N2-microparticles (0.125 g/cm^3) and MF-microparticles (0.098 g/cm^3). Carr indexes (Table 1) indicated that all powders presented very poor flow (Carr, 1965).

All microparticles (RO, N1, N2 and MF) presented humidity below 4% showing the effectiveness of the drying process. The drug contents were 11.49 ± 0.81% (N1-microparticles), 12.48 ± 0.28% (MF-microparticles), 12.81 ± 0.05% (N2-microparticles) and 13.14 ± 0.23% (RO-microparticles), corresponding to the encapsulation efficiencies of 88.1%, 95.7%, 98.2% and 100.1%, respectively. However, for RO-microparticles the encapsulation was not complete according to the SEM analysis that showed unencapsulated crystals (Fig. 4a). In the case of N1-microparticles, the low value of encapsulation efficiency was probably due to the lost of drug and the formation of strings during the drying process.

Concerning the drug release in phosphate buffer at pH 7.4, all powders presented a complete release (100%) after 480 min. On the other hand, in the gastro-resistance evaluation (Fig. 5), the formulations presented different profiles. Comparing these profiles using f_1/f_2 method, N2-microparticles and MF-microparticles were similar. Both stabilized 94% of the initial pantoprazole content and presented dissolution efficiency of 64.9% and 63.2%, respectively. N1-microparticles presented faster release attributed to the presence of strings (dissolution efficiency of 72.9%) and RO-microparticles presented 90% of pantoprazole stabilization and dissolution efficiency of 60.5%.

Taking into account the characteristics of microparticles concerning the encapsulation efficiency, the average particle size, the morphology and the gastro-resistance, the N2-microparticles, produced with two fluid nozzle atomizer and air pressure of 196 kPa, were chosen in order to validate the process.

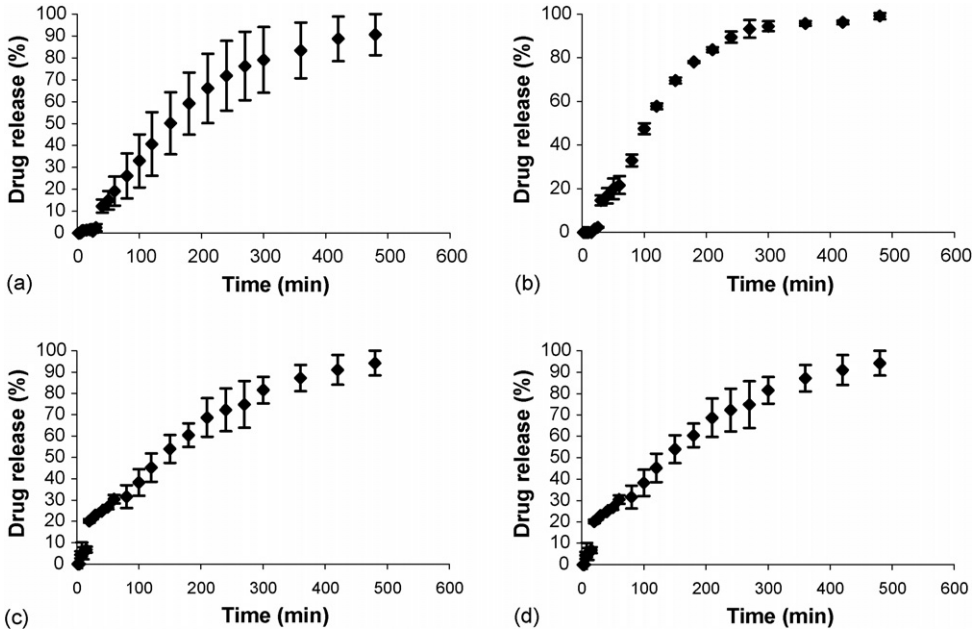

Fig. 5. Gastro-resistance profiles of microparticles produced in different sets of atomizers/pressure: (a) rotating disc atomizer (RO-microparticles), (b) two fluid nozzle atomizer and air pressure of 49 kPa (N1-microparticles), (c) two fluid nozzle atomizer and air pressure of 196 kPa (N2-microparticles) and (d) two fluid nozzle atomizer in mixed flow (MF-microparticles).

4.3. Pilot scale process evaluation

In order to evaluate pantoprazole stability during the preparation of microparticles, a stability study was conducted. The stability of pantoprazole dissolved in the solution of the polymers was evaluated before spray drying at room temperature and in the absence of light for 24 h. Every 2 h a sample was collected and no decrease in the pantoprazole concentration was observed by HPLC.

Three different batches of 11 L were spray dried in three consecutive days keeping constant room temperature and humidity (24 °C and 54%, respectively). The yields were 61.4%, 63.7% and 56.3% in the three consecutive days, respectively. The three powders were analyzed by SEM (Fig. 6) and no difference in the shape of microparticles has been detected among the batches.

Microparticles presented real density of 1.37, 1.36 and 1.38 g/cm^3 (Table 2) from batches 1, 2, and 3, respectively. Bulk density values were 0.061, 0.064 and 0.073 g/cm^3 and tapped density values were 0.108, 0.110 and 0.148 g/cm^3, corresponding to the three batches. Real, bulk and tapped densities were not significantly different among batches ($p = 0.39$, $p = 0.06$ and $p = 0.07$, respectively). The angles of repose were similar among samples ($p = 0.48$) and confirmed the poor flow of the powders (over 40°) (Carr, 1965). The encapsulation efficiencies were 98.9%, 99.5% and 100.6% for the three batches, respectively. The powders presented specific surface areas around 100 m^2/g. The particle size distributions of the three powders were very close showing reproducibility in the mean size (22 μm).

DSC analysis of unloaded microparticles (produced without the drug) showed one endothermic peak at 87 °C (Fig. 7). No event was observed for Methocel® F4M at the temperatures investigated. DSC analysis of sodium pantoprazole sesquihydrate showed an endothermic peak at 156 °C, and an exothermic peak at 198 °C (degradation) (Fig. 7). According to the literature, pantoprazole melting and dehydration are parallel processes in the case of sesquihydrate form (Zupancic et al., 2005).

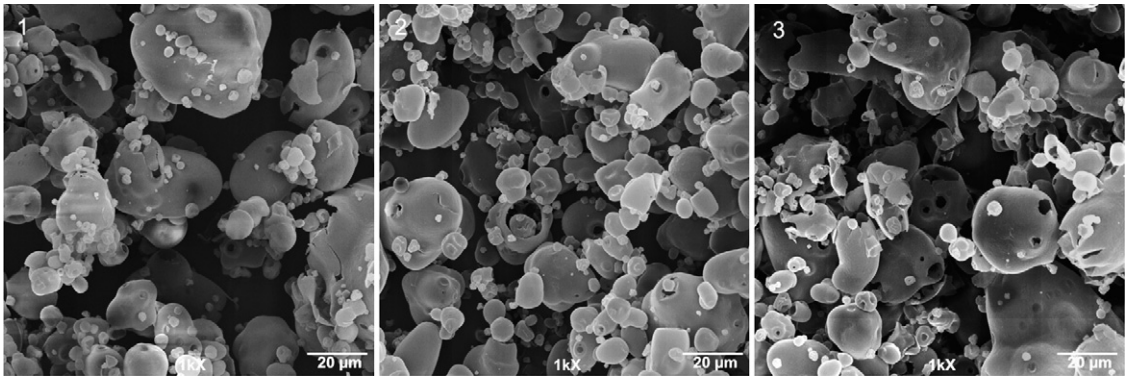

Fig. 6. SEM images of the microparticles produced in pilot scale in three different days showing the similarity among the batches.

Table 2
Characteristics of the three batches of microparticles prepared in pilot scale

Batch	Particle size (μm)	Real density (g/cm^3)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr index	Angle of repose (°)	Humidity (%)	Surface area (m^2/g)	Drug content (%)
1	$D_{4,3}$ 21.73, span 2.14, S.D. 1.49	1.37 ± 0.02	0.061 ± 0.003	0.108 ± 0.016	44	43.2 ± 2.3	2.11 ± 0.03	93.35	12.90 ± 0.08
2	$D_{4,3}$ 22.36, span 2.00, S.D. 1.42	1.36 ± 0.02	0.064 ± 0.002	0.110 ± 0.000	42	40.9 ± 2.1	2.26 ± 0.16	100.53	12.97 ± 0.97
3	$D_{4,3}$ 22.86, span 2.11, S.D. 1.82	1.38 ± 0.02	0.073 ± 0.003	0.148 ± 0.005	51	42.2 ± 2.1	3.6 ± 0.14	96.78	13.13 ± 0.43

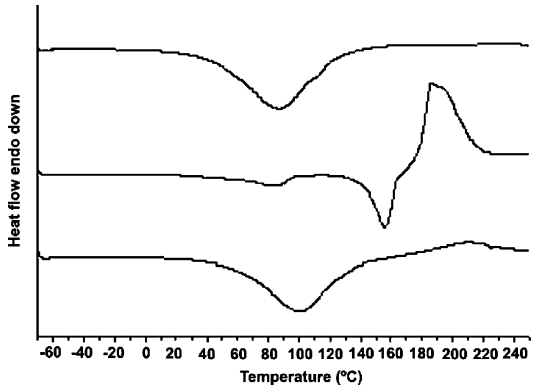

Fig. 7. Thermograms of (up to down): microparticles prepared without drug (spray dried Methocel® F4M and Eudragit® S100), sodium pantoprazole sesquihydrate and batch 2 of pantoprazole-loaded microparticles.

The exothermic event is the degradation of the drug. In the pantoprazole-loaded microparticle thermogram, one endothermic event appears at 100 °C, which corresponds to the melting of the polymer blend. The results suggest that pantoprazole-loaded microparticles are composed by a homogeneous phase, in which the drug is molecularly dispersed in the blend. According to the literature, the disappearance of any event of the drug indicates its encapsulation (Ford and Timmins, 1999).

The three batches presented complete release of pantoprazole after 480 min in phosphate buffer at pH 7.4. Furthermore, the powders presented very similar gastro-resistance profiles (Fig. 8) and the same total amount of pantoprazole stabilized in acid medium (91.4%, 90.2% and 92.3% for batches 1, 2 and 3, respectively). Dissolution efficiencies were 58.7 ± 2.5% for batch 1, 55.7 ± 2.1% for batch 2 and 60.2 ± 1.1% for batch 3. Statistical analyses showed no significant differences among the batches ($p = 0.40$).

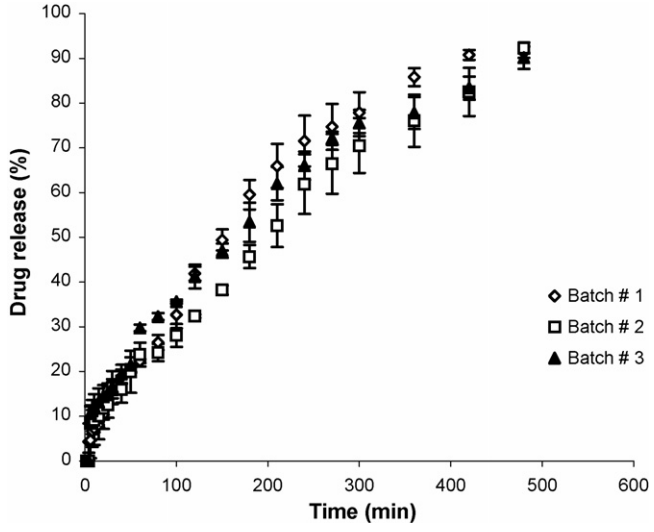

Fig. 8. Gastro-resistance profiles of the three batches of pantoprazole-loaded microparticles prepared to verify the process reproducibility.

5. Conclusions

Pantoprazole-loaded microparticles were successfully prepared by spray drying in both laboratory and pilot scales. In laboratory scale, the viscosity of the solutions fed into the spray dryer affected the particle size and the drug release. The microparticles produced with higher solid concentration were chosen to be spray dried in pilot scale because this formulation presented the highest stabilization of pantoprazole in the gastro-resistance study.

At pilot scale, among the four sets of microparticles prepared varying the atomization and the air pressure, in three of them free microparticles were obtained. The microparticles prepared with rotating disc atomizer or two fluid atomizer and mixed flow (RO-microparticles and MF-microparticles) presented either crystals on the particle surface or very high polydispersity, respectively. Using two fluid nozzle and air pressure of 49 kPa (N1-microparticles) the product obtained was not adequate because it presented strings in the powder. Using the same atomizer but air pressure of 196 kPa (N2-microparticles) the microparticles presented high encapsulation efficiency and the highest stabilization of formulation in acid medium. N2-microparticles were chosen for the pilot scale evaluation.

The three batches of pantoprazole-loaded microparticles prepared to validate the process showed reproducible diameter, polydispersity, densities, encapsulation efficiency and gastro-resistance profile.

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