Drug Development and Industrial Pharmacy, 32:661–667, 2006

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040600637564

Taylor & Francis

In Vitro Dissolution Studies of Sodium Diclofenac Granules Coated with Eudragit L-30D-55® by Fluidized-Bed System

O. S. Silva
Chemical Engineering School, State University of Campinas, Campinas – SP, Brazil

C. R. F. Souza and W. P. Oliveira
Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto – SP, Brazil

S. C. S. Rocha
Chemical Engineering School, State University of Campinas, Campinas – SP, Brazil

ABSTRACT The objective of this work was to study the dissolution process of sodium diclofenac granules coated with a polymeric suspension of Eudragit L-30D-55® by fluidized bed. Methacrylic acid-methylmetacrylate copolymer, also known as Eudragit, has been used as a pH sensitive coating material to protect drug substances prior to delivery to the human intestines. The sodium diclofenac granules were prepared by wet granulation technology using microcrystalline cellulose (MICROCEL), sodium diclofenac, and polivinilpirrolidone K-30. The granules coating operation was carried out in a fluidized bed with top spraying by a double-fluid nozzle. The dissolutions studies of the coated granules were performed in triplicate in a dissolution test station according to USP XXIII (1995) "in vitro testing requirements" Method A (paddle method, rotation of 100 RPM and temperature fixed at 37°C). The dissolution mediums were 0.1N HCl solution and a pH 6.8 phosphate buffer solution, following the pH change dissolution procedure specified in USP for enteric-coated articles: 2 h of exposure to 750 mL of 0.1N HCl followed by testing in 1000 mL of pH 6.8 phosphate buffer, the pH being adjusted with 250 mL of 0.2 M tribasic sodium phosphate solution. The released amount of sodium diclofenac was periodically determined by UV spectrophotometry at wavelength of 276 nm, using a spectrophotometer UV-VIS HP 8453. The coated product showed gastric resistance properties confirming the feasibility of the fluidized bed for applying enteric coating in granules and pharmaceutical powders.

KEYWORDS Enteric coating, Drug release, Sodium diclofenac, Fluidized bed, Eudragit®

INTRODUCTION

Particle coating technology has been applied in various fields, including pharmaceutical, chemical, food processing, and fertilizers with several purposes such as protection of the drug from the environment and controlling the release rate of a substance or even for esthetical aspects.

The fluidized-bed coater equipped with a top spray nozzle is viable for applying coating in microgranules, according to studies conducted by Silva (2003) and Silva and Rocha (2004).

Address correspondence to S. C. S. Rocha, Chemical Engineering School, State University of Campinas, C.P. 6066, CEP 13083-970, Brazil; Tel: +55 19 3788-3929; Fax: +55 19 3788-3922; E-mail: rocha@feq.unicamp.br

Basically, the fluidized-bed coating consists of passing a preheated gas through a bed of uncoated particles with a velocity higher than the minimum fluidization velocity. The particles are intensively mixed, providing enough energy for the drying of the coating layer formed on the product surface. The coating material can be fed as a solution, dispersion, suspension or melted, in general in the form of tiny droplets by means of a spray nozzle.

Sodium diclofenac (SD) is a nonsteroidal anti-inflammatory drug (NSAID), commonly used for the long-term treatment of rheumatic disorders, such as osteoarthritis, rheumatoid arthritic, and ankylosing spondylitis (Ichikawa et al., 1997). This drug is completely absorbed following oral administration, but its elimination half-life is relatively short, 1–2 h (Skoutakis et al., 1988). It is also known that repeated oral administration of SD as well as other NSAIDs in long-term therapy cause gastrointestinal disturbances. Therefore, the NSAIDs are good candidates for the development of an oral-controlled release formulation, mainly to reduce or eliminate the irritation of the gastrointestinal mucosa (Hosny & Al-Helw, 1998).

MATERIALS AND METHODS

Materials

MICROCEL Particles

Microcrystalline cellulose particles–MICROCEL MC-500 (Blanver, Brazil), with a bulk density equal to 980 $kg.m^{-3}$, sphericity of 0.62 and size ranging from 0.21 to 0.42 mm–was the selected material used in the fluid dynamic studies and as excipient for SD granules preparation. The size range was selected by sieving. The MICROCEL sphericity was determined by image analysis of the particle using an optical microscope. The sphericity is evaluated by the ratio of the biggest inscribed circle and the smallest circumscribed circle obtained for the particles projection images acquired. The measurement procedure is made for a sample of around 100 particles. The average value is adopted as the sphericity value.

Sodium Diclofenac Granules

The sodium diclofenac granules used in the coating experiments were prepared by wet granulation (Prista et al., 1981), using microcrystalline cellulose (MICROCEL MC-500), sodium diclofenac (Natural Pharma Ltda, Brazil), and polivinilpirrolidone K-30 (Purifarma Ltda, Brazil). The granules was prepared according to the formulation presented in Table 1. MICROCEL and sodium diclofenac were premixed for complete homogeneity. PVP K-30, solubilized in the water:ethanol solution (1:2) was added to the powder mixture. The wet mass was granulated by forcing it through a sieve of mesh size 1.2 mm. The resulting granules were dried in a hot air oven (40°C for 24 h). The granules prepared were classified by sieving in two granulometric ranges: from 0.30 to 0.60 mm and from 0.60 to 0.70 mm, using a sieve shaker.

TABLE 1 Formulation Used for Granules Preparation

Material	(%) w/w
MICROCEL	60
Sodium diclofenac	20
Polivinilpirrolidone K-30	20

Coating Suspension

The coating suspension was constituted by Eudragit L-30D-55® (Röhm Degussa Hüls Group, Germany), talc, titanium dioxide, magnesium stearate, triethyl citrate, and polyethylene glycol as plasticizer, lake colorant, and distilled water, having solids weight concentration of 12%. The coating suspension was developed, aimed at obtaining a uniform and smooth coating surface. This suspension was developed during fluidized-bed coating of MICROCEL particles carried out previously (Silva & Rocha, 2004). The composition of the coating suspension and operating conditions used are listed in Tables 2 and 3, respectively.

TABLE 2 Composition of the Coating Suspension

Composition	(% w/w)
Eudragit L 30 D-55®	16.70
Polyethylene glycol (%)	0.75
Talc (%)	2.75
Magnesium stearate (%)	1.00
Titanium dioxide (%)	1.20
Colorant (%)	0.80
Triethyl citrate (%)	0.50
Water (%)	76.30

TABLE 3 **Operating Conditions Used in the Coating Experiments of Sodium Diclofenac Microgranules**

Operating conditions	Value
Inlet air temperature (°C)	70
Outlet air temperature (°C)	30–45
Inlet air flow rate (m^3/min)	0.18
Liquid flow rate (g/min)	11.40
Size range of particles (mm)	0.30–0.60 and 0.60–0.70
Atomization pressure (kPa)	206.8

Experimental Apparatus

Figure 1 shows a schematic diagram of the experimental setup used in this study. The fluidization column was constructed in plexiglass having 0.14 m of inner diameter and 0.6 m of height. The lower end of the column is fixed by a 0.2-m-high *plenum* chamber (10). The air distributor is a stainless steel perforated plate with a free area of 5%. Before entering the bed, the fluidizing air flow rate is measured by an orifice plate and preheated by an electrical heater. The elutriated particles are collected at the column outlet by a cyclone. The nozzle atomizer (12) was supplied by a compressed air line (7) and the coating suspension was conveyed by a Masterflex® peristaltic pump (16).

Methods

Before the coating experiments, the fluid dynamic tests were conducted aiming to establish appropriate fluidization conditions, which were based on the observation of bed dynamics related to the operational gas velocity. The superficial velocity of the air in the bed is calculated by Eq. 1:

$$U = \frac{Q}{\rho_g \cdot A_t} \tag{1}$$

where Q is the air mass flow rate, ρ_g is gas density, and A_t is the cross-sectional area of the bed. The air flow rate fed to the system, Q, was calculated as a function of the differential pressure on the orifice meter, using Eq. 2, based on Ower and Pankhurst (1977):

$$Q = 0.718\left[\frac{\Delta P}{273.15+T}\right]^{0.5} - \left[\frac{0.22}{P_{sta}} \cdot \frac{(\Delta P)^{1.5}}{(273.15+T)^{0.5}}\right] \tag{2}$$

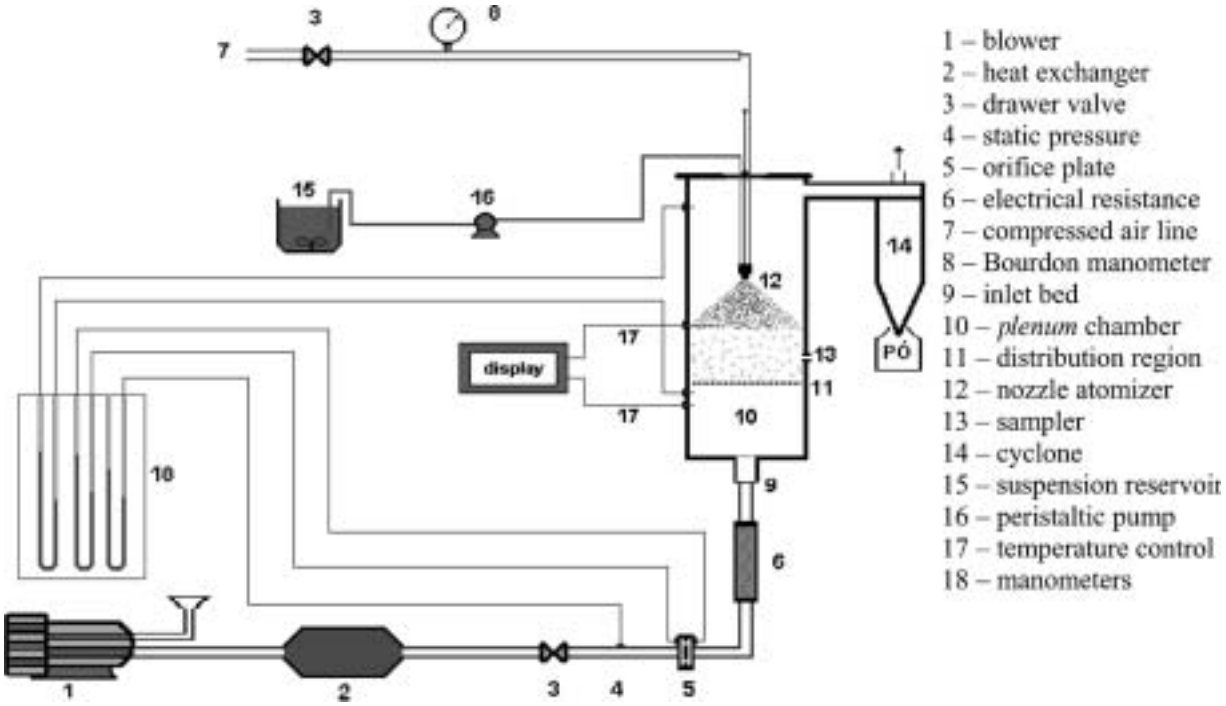

FIGURE 1 **Schematic Diagram of the Fluidized Bed.**

Equation 2 has dimensional constants included that depend on the orifice and tube dimensions. Hence, the values of air mass flow rate obtained are given in kg/min and ΔP is the differential pressure of the orifice meter (cm of water), T is gas temperature (°C), and P_{sta} is the absolute static pressure in the gas transport line (cm of water) as expressed in Ower and Pankhurst (1977).

To study the fluid-dynamics of the fluidized bed, experimental runs were carried out using particles of MICROCEL and air at room temperature. Experimental data of the bed pressure drop as a function of the air velocity were obtained for particle sizes ranging from 0.21 to 0.42 mm. These data were used for the construction of the fluidization curve, ΔP versus U. The fluidization curve permits the determination of the fluid-dynamic parameters, minimum fluidization velocity, U_{mf}, and minimum fluidization pressure drop, ΔP_{mf}, which are very important to guarantee a stable fluidization regime during the coating process. At the minimum fluidization velocity, the bed pressure drop equals the solids apparent weight. From this condition, the fluidization regime is initiated. The operating air superficial velocity, Uop, should be higher than the minimum fluidization velocity to maintain the fluidized bed. The fluidization pressure drop is also a very important parameter as the power needed to fluidize the bed is given by the product of the pair U_{op}–ΔP.

The coating experiments started with feeding the air at room temperature to the fluidized bed. This air was heated up to the desired temperature with the aid of an electric heater. When the bed reached thermal equilibrium, it was fed with 0.5 kg of MICROCEL. The air velocity was adjusted at the value previously fixed to obtain a stable fluidized bed, based on the fluid dynamics determinations. The coating suspension was transported to the bed by a peristaltic pump from a reservoir and was sprayed on the particles by a double-fluid nozzle. The suspension flow rate was controlled by the pump revolutions and by the reservoir weight. The atomizing pressure is controlled by a valve and measured by a Bourdon manometer. The experimental conditions established for the experimental runs were defined in preliminary experiments and are given in Table 3.

In Vitro Dissolution Studies

The dissolutions studies of the coated granules were performed in replicate in a dissolution test station according to USP XXIII (1995) "in vitro testing requirements" Method A (paddle method, rotation of 100 RPM and temperature fixed at 37 °C). The dissolution mediums were 0.1N HCl solution and a pH 6.8 phosphate buffer solution, following the pH change dissolution procedure specified in USP for enteric-coated articles: 2 h of exposure to 750 mL of 0.1N HCl followed by testing in 1000 mL of pH 6.8 phosphate buffer, the pH being adjusted with 250 mL of 0.2 M tribasic sodium phosphate solution. At predefined intervals (0, 60, 120, 130, 140, and 165 min), 10 mL samples were collected using a syringe as sampler. The released amount of sodium diclofenac was determined by UV spectrophotometry at wavelength of 276 nm, using a spectrophotometer UV-VIS HP 8453.

RESULTS AND DISCUSSION

Fluid-Dynamic Analysis

Figures 2 and 3 show the experimental results of the bed pressure drop as a function of the air superficial velocity, obtained by increasing the air flow rate (Fig. 2) and decreasing the air flow rate (Fig. 3). The results are indicative of high-quality bubbling fluidization. As expected for the bubble fluidized bed, at $U > U_{mf}$ the bed pressure drop remained constant. These graphs are useful for experimental determination of U_{mf} and definition of the operating superficial gas velocity. In this work, U_{mf} was determined by Richardson's classic method (Richardson, 1971), and the value of 6.6 cm/s was obtained from Fig. 3.

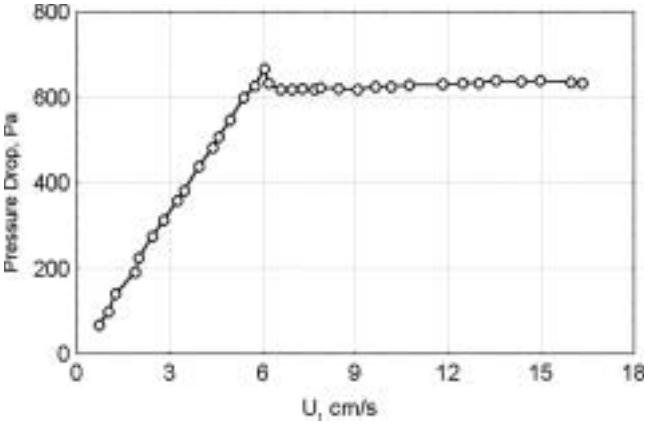

FIGURE 2 **Experimental Results of Bed Pressure Drop as a Function of the Air Flow Rate Obtained for Uncoated Particles with Increasing Flow Rate.**

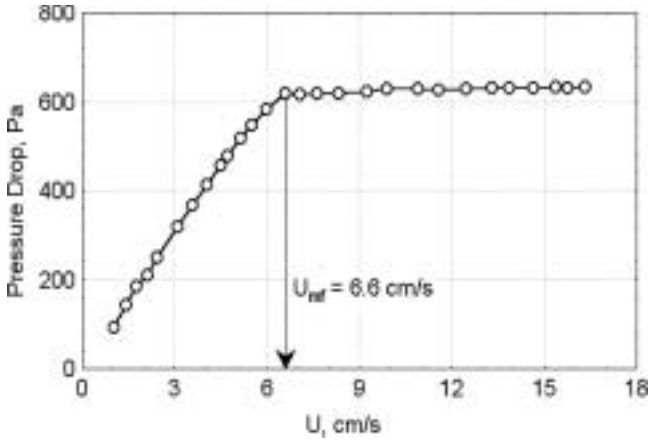

FIGURE 3 **Experimental Results of Bed Pressure Drop as a Function of the Air Flow Rate Obtained for Uncoated Particle and Decreasing Flow Rate.**

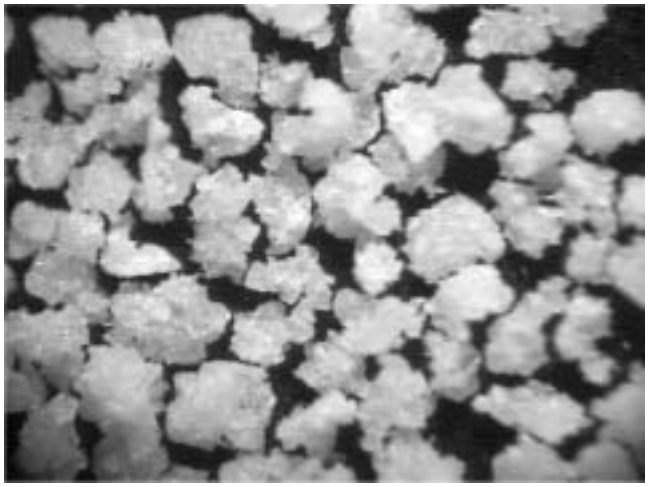

FIGURE 4 **Photomicrographs of the Uncoated Sodium Diclofenac MICROCEL Granules (40 X).**

FIGURE 5 **Photomicrographs of the Coated Sodium Diclofenac MICROCEL Granules (40 X).**

The operating velocity used in the coating runs, U_{op}, was 15 cm/s, corresponding to 2.3 times the minimum fluidization velocity, U_{mf}. An operating velocity more than two times the minimum fluidization velocity was chosen to ensure the adequate quality of the fluidization regime, with appropriate mixture of the phases inside the bed, even when the bed was wetted by the coating suspension. All range of particle sizes (from 0.21 to 0.42 mm) used in this work showed similar behavior and adequate solids movement during fluidization. The total particle load is fluidized for 5 min before starting the coating process to separate smaller particles that could adhere one to another due to high cohesion ($d_p < 0.1$ mm).

Coating of Granules Loaded with Sodium Diclofenac

Figures 4 and 5 show photomicrographs of the uncoated and coated granules of sodium diclofenac (40X magnified), respectively. It can be verified that the particles were individually coated and agglomerates were not formed, thus obtaining the desired coated product.

In Vitro Dissolution Studies

The dissolution tests were carried out in replicate, following the procedure presented in the section "In Vitro Dissolution Studies". Two distinct series of assays were performed:

Dissolution 1 – Samples of uncoated granules in size range of 0.30–0.60 mm plus samples of coated granules corresponding to coating times of 25, 50, and 75 min were used.

Dissolution 2 – Samples of uncoated granules in size range of 0.60–0.70 mm plus samples of coated granules corresponding to coating times of 25 and 50 min were used.

The dissolution results were expressed as percentage released over time. Figures 6 and 7 show the experimental data obtained for the two series of experiments carried out, respectively. From the graphs presented it can be observed that the uncoated granules released higher quantities of sodium diclofenac in the acid stage comparatively with the coated granules. Moreover, the percentages of sodium diclofenac released from the coated granules have a tendency to reduce with the increment

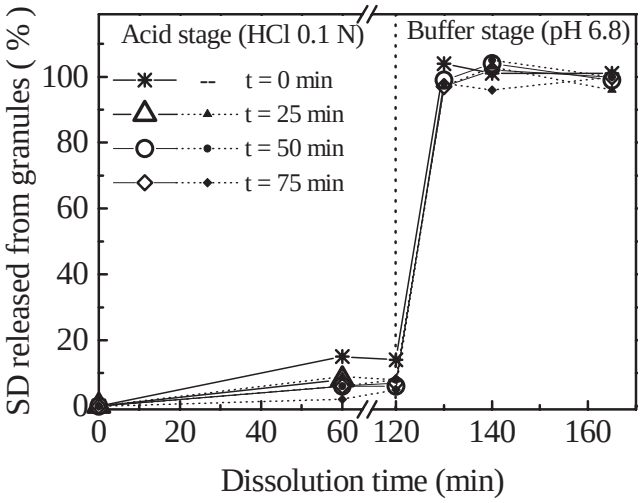

FIGURE 6 **In Vitro Dissolution Profiles of Uncoated and Coated Sodium Diclofenac Granules as a Function of Dissolution Time in Gastric and Enteric Fluid (Size Range of 0.30–0.60 mm).**

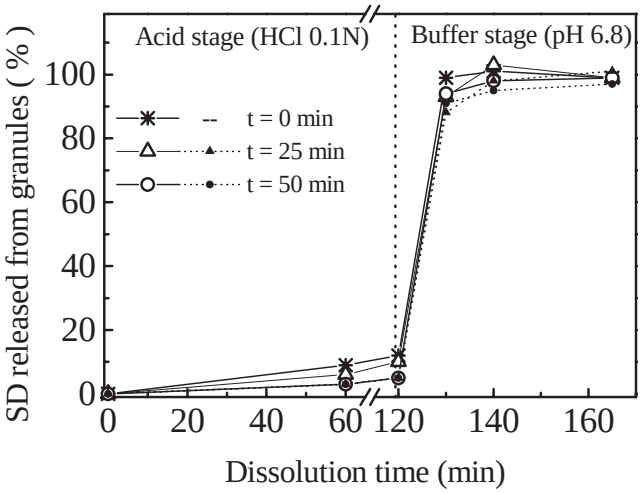

FIGURE 7 **In Vitro Dissolution Profiles of Uncoated and Coated Sodium Diclofenac Granules as a Function of Dissolution Time in Gastric and Enteric Fluid (Size Range of 0.60–0.70 mm).**

in the coating level (longer processing time), evidencing a protective effect of the coating layer formed. The release rate of the sodium diclofenac was higher for the small coated granules, effect attributed to the higher contact area and lower coating mass increase, 5% against 8% observed by the bigger ones.

Visual observations carried out during the dissolution tests showed that the uncoated granules fragmented and sank, remaining in the bottom of the dissolution vessel. The granules corresponding to 25 min of coating application became tumid and lost partially the coloration in the acid stage, undertaking a structure deformation, nevertheless, without fragmentation. These behaviors indicate that 25 min of coating application was not enough to form a strength and uniform coating layer able to support the stirring of the dissolution test. The samples of the coated granules with higher coating layers, corresponding to the end of the coating application (75 min for dissolution 1 and 50 min for dissolution 2), remained intact in acid during the dissolution in the acid stage, without changing the color and structure. As soon as the pH of the dissolution environment was changed (buffer stage), the granules disintegrated completely. The color of the dissolution medium acquires the color of the coating layer, and the sodium diclofenac was released. Only small portions of the microcrystalline cellulose can be seen in the bottom of the dissolution cubes.

The results here reported are indicative of the feasibility of the fluidized-bed system to apply enteric and/or delayed release coatings in granules and pharmaceutical powders. The success of operation is dependent on several parameters, like the coating material used, the operating conditions of the fluidized bed, and the thickness of the coating layer (mass increase), which is a function of the processing time. The results also emphasize the importance of the in vitro dissolution studies in the stages of process developments, showing the effectiveness of the fluidized bed for applying enteric coating in sodium diclofenac granules using a composition based on Eudragit L-30D-55®.

CONCLUSIONS

This paper summarizes the preparation and in vitro dissolution studies of sodium diclofenac granules coated with Eudragit L-30D-55® by fluidized-bed system. High-quality bubbling fluidization was observed for the MICROCEL particles as well as the sodium diclofenac granules for all size ranges analyzed. The dissolution results confirmed the effectiveness of the fluidized bed for applying enteric coating in sodium diclofenac granules using a composition based on Eudragit L-30D-55®.

ACKNOWLEDGEMENT

The authors express their gratitude to Foundation for Research Support of the São Paulo State (FAPESP)

for a fellowship for the first and second authors and for the financial aid.

REFERENCES

Hosny, E. A., & Al-Helw, A. A.-R. M. (1998) Effect of coating os aluminum carboxymethylcellulose beads on the release and bioavailability of diclofenac sodium. *Pharm. Acta Helv.*, *72*, 255–261.

Ichikawa, H., Fukumori, Y., & Adeyeye, C. M. (1997) Design of prolonged-release microcapsules containing diclofenac sodium for oral suspensions and their preparation by the Würster process. *Int. J. Pharm.*, *156*, 39–48.

Ower, E., & Pankhurst, R. C. (1997) *The Measurement of Air Flow*, 5th Ed. Pergamon Press.

Prista, L. N., Alves, A. C., & Morgado, R. (1981) *Pharmaceutical Technology*, 5th Ed. vol. I.: Portugal, Calouste Gulbenkian Foundation.

Richardson, J. F. (1971) *Incipient Fluidization and Particulate Systems. Fluidization*. Davidson J. F. and Harrison, D., Eds. London: Academic Press.

Silva, O. S., & Rocha, S. C. S. (2004) The influence of the moisture content of microcrystalline cellulose on the coating process in a fluidized bed. *Braz. J. Chem. Eng.*, *21 (2)*, 325–333.

Silva, O. S. (2003) Coating and drying process development of microgranules in fluidized bed. Ph.D Thesis, State University of Campinas, Chemical Engineering School, 130 p. Campinas, SP, Brazil (*in Portuguese*).

Skoutakis, V. A., Carter, C. A., Mickle, T. R., Smith, V. H., Arkin, C. R., Alissandratos, J., & Petty, D. E. (1988) Review of diclofenac and evaluation of its place in therapy as a non-steroidal anti-inflammatory agent. *Drug Intell. Clin. Pharm.*, *22*, 850–859.

United States Pharmacopeia (USP) XXIII (1995). Rockville, MD.