Received 8 Sep 2009; Accepted 4 Dec 2009; Available online 24 Sep 2010.

Revista Brasileira de Farmacognosia
Brazilian Journal of Pharmacognosy
20(5): 803-811, Out./Nov. 2010

Article

Achyrocline satureioides (Lam.) DC., Asteraceae: development of granules from spray dried powder

Gustavo F. Petrovick, Pedro R. Petrovick, Valquiria L. Bassani*

Programa de Pós-graduação em Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Av. Ipiranga, 2752, 90610-000 Porto Alegre-RS, Brasil.

RESUMO: *Achyrocline satureioides* (Lam.) DC., Asteraceae, é uma planta amplamente utilizada na medicina popular no sul do Brasil, Uruguai, Argentina e Paraguai. As características tecnológicas do extrato seco por aspersão de *Achyrocline satureioides*, produzido em escala semi-industrial, assim como a viabilidade da produção de granulados são relatadas no presente trabalho. O extrato seco por aspersão foi caracterizado como um pó fino, composto por pequenas partículas esféricas com superfície rugosa e porosa. O fator de Hausner, índice de Carr e o índice de densificação das partículas foram, respectivamente, 1,23, 18,9% e 27,2 mL, caracterizando-o como um pó com fluxo pobre e de baixa densidade. A preparação dos granulados a partir deste extrato seco por aspersão, através do método de desagregação por via seca, originou grânulos com forma irregular, superfície rugosa, mas com melhor fluxo e melhores características de compactabilidade. Estes grânulos apresentaram fator de Hausner, índice de Carr e índice de densificação de 1,09, 8,16% e 12,33 mL, respectivamente. A análise por de CLAE dos polifenóis principais quercetina, luteolina e 3-*O*-metilquercetina revelou que o processo de granulação não altera o perfil quantitativo e qualitativo dos constituintes inicialmente presentes no extrato seco. A avaliação da estabilidade física do extrato seco por aspersão e do granulado, em condições de unidade relativa de 65 e 99%, mostrou uma expressiva redução na absorção de umidade dos grânulos quando comparados com o extrato seco.

Unitermos: *Achyrocline satureioides,* fitomedicamentos, granulação por via seca, secagem por aspersão.

ABSTRACT: *Achyrocline satureioides* (Lam.) DC., Asteraceae, is a herbal specie widely used in folk medicine in the south of Brazil, Uruguay, Argentina and Paraguay. The technological characteristics of an *Achyrocline satureioides* spray dried extract powder, produced in semi-industrial scale, as well as the feasibility of the granules are reported in the present work. The spray dried powder was characterized as a fine powder consisting of small spherical particles with rough and porous surface. The Hausner´s factor, Carr's index, and densification index of the spray dried powder were, respectively, 1,23, 18,9%, and 27,2 mL, characterizing it as a poor flow and low density powder. The preparation of granules from this spray dried powder, through dry disaggregation method, yielded irregularly shaped granules, with a rough surface, but with better flow and compactability characteristics. These granules presented a Hausner´s factor, a Carr's index, and a densification index of, respectively, 1,09, 8,16%, and 12,33 mL. The LC assay of the main polyphenols, quercetin, luteolin, and 3-*O*-methylquercetin revealed that the granulation process did not changed the quantitative and qualitative profile of these constituents originally present in the spray dried powder. The comparative evaluation of the physical stability of both the spray dried powder and the granules, under relative humidity conditions of 65% and 99%, showed an expressive reduction in the humidity sorption on the granules as compared to the spray dried powders.

Keywords: *Achyrocline satureioides,* herbal medicines, dry granulation, spray drying.

INTRODUCTION

Achyrocline satureioides (Lam.) DC., Asteraceae, vegetal specie known as marcela or macela, have a wide range of therapeutic uses in the south of Brazil, Uruguay, Argentina and Paraguay as anti-inflammatory, antispasmodic, digestive, sedative, carminative, among others (Simões et al., 1998). Although the popular use has been traditionally done by oral intake of inflorescences infusions, for industrial application the development of

**E-mail: valquiria@pq.cnpq.br, Tel. +55 51 3308 3602.*

ISSN 0102-695X
DOI: 10.1590/S0102-695X2010005000020

spray dried powders have been studied (Senna et al., 1997; Teixeira, 1996) in order to overcome the main limitation of liquid extracts, its low stability. The *Achyrocline satureioides* spray dried powders have presented good stability against heat and light (Holzschuh et al., 2007). However, the poor properties of flow and compactability of the powders, mainly due to the small particle size, low density, wide range of granulometric distribution, and high hygroscopy have led to important limitations in the development of derivative solid pharmaceutical dosage forms.

In an attempt to overcome such limitations, the present work was designed to investigate the technological feasibility of granules from the spray dried powder. For this, the spray dried powder was produced on a semi-industrial scale and characterized regarding its properties of flow and compactability, comparing these properties with those presented by the corresponding granules. The main polyphenols, quercetin, luteolin, and 3-*O*-methylquercetin were used as reference in the chemical control of the process.

MATERIAL AND METHODS

Preparation of the spray dried powder (SDP)

The SDP of the *A. satureioides* (Lam.) DC., Asteraceae, was prepared by maceration of inflorescences into a 40% ethanol/water solution in the proportion of plant:solvent of 5.2% (w/v). The corresponding extractive solution containing 1.03±0.01% (w/v) of dry residue was employed to prepare the SDP. The SDP was prepared according to the method previously described by Bassani and cols. (PI 103468-5, Bassani et al., 2001) and have in its composition colloidal silicon dioxide and polysorbate 80 in a 1:1 ratio in the final product. Briefly, the spray drying process was carried out on a semi-industrial scale in a *Minor Production Spray Dryer Plant* equipment (NIRO), using the following conditions: feed flow, 160 mL/min; inlet air temperature, 175 ºC; outlet air temperature, 100 ºC, and rotational atomizer speed, 11.000 rpm.

Dry granulation of SDP

Blending of the powders

Two blends of powder (F_1 or F_2) were prepared through the mixture of SDP with excipients in a cubic-like mixer, at 36 rpm, attached to a multiuse motor (Erweka AR 400). The composition of these formulations is presented in the Table 1. For F_2 preparation, the SDP and the filler material (microcrystalline cellulose) were mixed in a cubical mixer, for 15 min, with posterior addition of the lubricant (magnesium stearate) and the flow regulator (colloidal silicon dioxide), then continuing the operation for 5 more min. The F_1 formulation was obtained by mixture the SDP and the lubricant for a period of 5 min. Mixtures of 325 g each formulation were prepared.

Preparation of the slugs

Slugs of 0.7 g were obtained through direct compression of F_1 or F_2 formulations in a single punch compression machine (Korsch EK0), equipped with a feeder and simple, circular, faceted punch of 15 mm in diameter. The compression machine was regulated by lowering the lower punch by 6 mm and by penetrating the upper punch by 4 mm. The compression of the formulation was carried out through manual operation of the machine.

Preparation of the granules (SDG)

The granulation of the slugs was performed by means of a mechanical granulator (Erweka TGIIS), in order to obtain granules of a particle size of less than 2.0 mm. Then, the granules were submitted to an oscillating granulator (Erweka FGS), equipped with 1.0 mm sieve to standardize the diameter. The granules in the range of 250 to 1000 μm of diameter were selected through the use of sieving with 0.250 and 1.0 mm mesh.

Table 1. Compositions of the formulations to obtain *A. satureioides* granules.

Compound	F_1	F_2
A. satureioides spray dried powder	99.00	69.23
PH101 microcrystalline cellulose	-	27.57
Colloidal silicon dioxide	-	2.20
Magnesium stearate	1.00	1.00

Analysis of particle size distribution

This analysis was performed by measuring the Feret's diameter of at least 500 particles by optical microscopy, with a calibrated reference scale. The magnification employed were, respectively, 3.2x for SDP and 10x for SDG.

Bulk and tapped density, hausner's factor, carr's index, and densification index

The bulk and tapped densities were determined using 10.0 g of each material in a 25 mL graduated cylinder (compacting volumeter J. Engelsmann). The values obtained from these parameters were used to calculate the Hausner's factor (Hausner, 1967), the Carr's index (Carr, 1965), and the densification index (Guyot, 1995).

Angle of repouse (Parthirana & Gupta, 1976)

The angle of repouse was determined using a device consisting of a mobile cylinder, adjusted to

the fixed base and attached to a motor which, when activated, separates the cylinder from the base by lifting it. The measure was taken directly on the register of the powder cone shadows projected onto the plane, and the angle of repouse (α) was obtained by calculation of its tangent. Thirty milliliters of each sample were used for the analysis. The results were expressed by the average of three determinations.

Determination of granule friability (Prista, 2003)

Nearly 40 mL of granules, measured in a 100 mL graduated cylinder, were selected using a sieving with mesh opening of 0.250 mm. A sample of the fraction retained in the sieve, corresponding to 30 mL, was weighed and transferred, carefully, to the 100 mL graduated cylinder. After having been closed and attached to the friabilometer, the mixture was submitted to spinning for 15 min, at 20 rpm. Then, the sample was once again submitted to the initial procedure in view to remove the fine particles. The friability was calculated based on the percentage of fine particles released.

Scanning electron microscopy (SEM)

SEM photomicrographies of SDP and SDG particles were obtained using a scanning electron microscope (Jeol JSM 6060). The samples were set up over stubs of aluminum using bi-adhesive tape made of carbon and metallized with gold coating, using the Jeol Jee 4B metallizer (JVG-IN).

Liquid chromatography (LC) analysis

The three main phenolic constituents, quercetin, luteolin, and 3-*O*-methylquercetin were determined in SDP and SDG following the method reported by De Souza et al. (2002). For each sample, 500 mg (SPD or SDG) were extracted using 50.0 mL of ethyl acetate for 2 h under mechanical agitation. The liquid dispersion obtained was filtered and the solvent evaporated. The residue was dissolved with methanol and transferred to the volumetric flask of 25.0 mL. The volume was completed with solvent. An aliquot of 2.0 mL of this solution was diluted to 20.0 mL with a mixture of methanol:water solution (53:47, v/v), thus constituting the sample solution. Injections of 20 µL of this solution, in triplicate, were performed. A mixture of methanol and aqueous solution of 1% phosphoric acid (w/v) in the proportion of 53:47 (v/v) was the elluent, in an isocratic system, previously filtered through polyvinylidene fluoride membrane and degassed in an ultra-sound bath. Chromatographic conditions included: elluent flow of 0.6 mL/min and detection at 362 nm. The sensibility was 1.0 AUFS. Each sample SDP or SDG was analyzed in triplicate.

RESULTS AND DISCUSSION

Preparation and evaluation of spray dried powders

The parameters for preparation the spray dried powder in a semi-industrial scale (*Minor production spray dryer plant*, NIRO) were selected based on the conditions reported by Da Silva (2003), using the same equipment. The volume of the extractive solution, submitted to spray drying, was 63.0 L, which contained 7.95% (w/w) of dry residue (plant constituents plus the excipients). The drying process resulted in, approximately, 5.0 kg of SDP, characterizing a processing yield of 88%.

The SDP appeared as a fine yellow powder with characteristic odor and tendency to form agglomerates. The loss on drying of the SDP was 5.27%±0.01. If we consider this result as corresponding to the residual humidity, this value is within the limits accepted for powders with non-hermetic packaging (max 6% to 7%) (List & Schmidt, 1989), yet above the maximum limit of 4% set for dry extracts (Farmacopéia Brasileira, 1988). The particle size distribution of SDP (Figure 1) reveals that, approximately, 50% of the particles present diameters below 13 µm, while, approximately, 90% below 23 µm, characterizing the SDP as a very fine powder (Farmacopéia Brasileira, 1988). This characteristic of fine powder can be related, partially at least, to the use of colloidal silicon dioxide as drying excipient, and/or to the low concentration of soluble solids in the feed solution (List & Schmidt, 1989; Masters, 1976).

The low mean size of the SDP particles (13.09 µm±3.23) is characteristic of spray dried powders obtained from *Achyrocline satureioides* (Lam.) DC., Asteraceae, extractive solution in similar operational conditions using colloidal silicon dioxide as excipient (Lemos Senna, 1993; Da Silva, 2003). The standard deviation observed, higher than 2.0, represents a wide range of particle size distribution (Wells, 1988), which can be observed in the SDP analysis in Figure 1.

Table 2 presents the results of the characterization of the compactability and the flow of SDP, which characterize SDP as a powder with potential problems of compactability and non-spontaneous flow due to its stable packing. Even the difficulty in determining the angle of repouse, characterized by high relative standard deviation, corroborates this tendency. The SDP photomicrographies (Figure 2) reveal that the particles present spheroidal form with porous and rough surface, but of small dimension.

The LC profile of the major polyphenols, quercetin, luteolin, and 3-*O*-methylquercetin, from SDP is showed in the Figure 3, while the corresponding concentration is presented in the Table 3.

In summary, the results demonstrate that the spray drying of an *A. satureioides* extractive solution in semi-industrial scale resulted in a powder with excellent production yielding. However, the particles presented

small size, porous, and rough surface, characteristics which can be related to the poor flow and compactability.

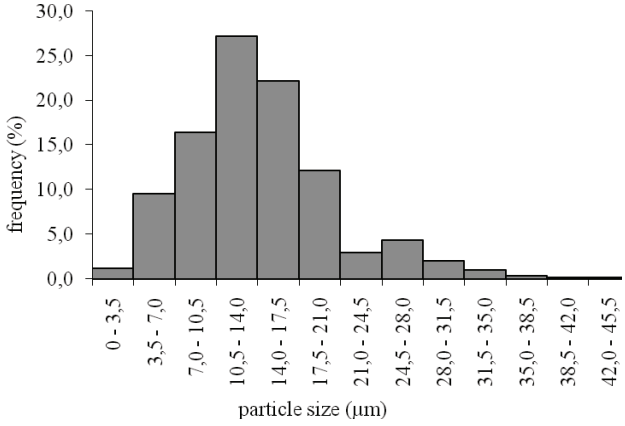

Figure 1. Particle size distribution of the *A. satureioides* spray dried powder.

Preparation of SDP granules (SDG)

Preparation and characterization of the slugs

The granules were prepared by compaction followed of disaggregation. For compaction, the choice of the excipients was based on the results reported by De Souza et al. (2005) (F_1) and Couto (2000) (F_2), who defined the use of microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide as appropriate excipients for other herbal derivatives granules (*Phyllanthus niruri*).

It is well know that the slugs for granulation should present a thickness in the range of 3 to 4 mm in view to facilitate the disaggregation process (Prista, 2003). In this manner, in our tests the average weight was adjusted so that the slugs would present a thickness within this range and hardness higher than 50 N. This value of hardness, higher than that usually set for tablets (Farmacopéia Brasileira, 1988), of 30 N, is due to the requirement that compact must be able to resist breakage, without the loss of large quantities of fine powders in the granulation process. With this, we were able to obtain slugs with average weight of 0.7 g.

During compaction of the F_1 or F_2 to obtain the slug, an atypical phenomenon was observed, which deserves mention. When high penetration of the upper punch in the matrix was applied, the compact change its color, appearing completely darkened. We also observed that when the penetration of the upper punch was adjusted to lower deepness, no darkness in the slugs was observed. The first hypothesis formulated to explain this phenomenon was the degrading of the flavonoids, and/or a possible influence of compression excipients (Schreier & Miller, 1985). To elucidate these hypothesis, slugs with and without color changing were produced using the F2 formulation. The analysis of the these slugs, by LC, was then performed and significant differences in the concentration of the major flavonoids between the F2 Slug (without color changing) and the corresponding darkened slugs were found (Table 3). Additionally, in order to check the influence of the excipients added to the slugs obtention in the darkness phenomena, slugs only with SDP in absence of any excipient with (SD dark slug) and without the presence of darkness (SD slug) were also prepared and analyzed. As first observed also in this case, when high penetration of the upper punch in the matrix was applied, the compact appeared completely darkened. The results of the LC evaluation of the major polyphenol concentrations

Table 2. Compactability and flow characteristics of the *A. satureioides* powder and granules.

Parameter	Experimental data $\overline{X}$ ±s (RSD%)	
	Powder	Granules
Bulk density (g/mL)	0.513±0.011 (2.09)	0.462±0.007 (1.48)
Tapped density (g/mL)	0.633±0.003 (0.52)	0.503±0.009 (1.77)
Hausner's Factor	1.234±0.036 (2.94)	1.089±0.014 (1.25)
Carr's Index (%)	18.93±2.36 (12.49)	8.16±1.15 (14.04)
Densification Index (mL)	27.17±2.566 (9.44)	12.333±2.517 (20.40)
Angle of repouse (º)	15.48±4.984 (32.20)	23.90±1.36 (5.71)

Table 3. Major phenolic constituents in *A. satureioides* powder, in the slugs and in the granules, determined by LC.

Phenolic constituent	Concentration (%, w/w) ±s (RSD%)					
	Powder	F2 Slugs	F2 Dark Slug	SD Slugs	SD Dark slugs	Granules
Quercetin	0.3882±0.003 (0.66)	0.3431a±0.001 (0.25)	0.3154b±0.000 (0.03)	0.3576c±0.001 (0.31)	0.3586c±0.001 (0.40)	0.3367±0.003 (0.87)
Luteolin	0.1689±0.001 (0.54)	0.1313a±0.000 (0.13)	0.1398b±0.001 (0.62)	0.1379c±0.000 (0.34)	0.1377c±0.000 (0.18)	0.1463±0.002 (1.14)
3-*O*-methylquercetin	0.8897±0.002 (0.26)	0.6963a±0.001 (0.15)	0.7582b±0.003 (0.37)	0.7258c±0.002 (0.27)	0.7209c±0.002 (0.23)	0.7577±0.003 (0.42)

RSD = Relative standard deviation; SD = Slugs without excipients, only with the *A. satureioides* spray dried powder; Averages followed by the same letter on the lines do not differ when submitted to the Student t test (α = 0.05)

(Table 3) demonstrate that the slugs containing only SDP, without color changing, presented no significant difference ($\alpha = 0.05$) among the phenolics concentration compared to that in correspondent slugs with color change; therefore, it can be inferred that the darkness of the slugs was not determined by the flavonoid degradation, neither by the presence of the excipients The concentration of phenolics in the slug takes into account only the amount of SDP, disregarding the excipients that compose the slugs.

Although this is not the main focus of the present work, we cannot fail to mention the observations made by Smith and his collaborators (Smith et al., 2000), who, upon studying the photostability of some polyphenols, among them luteolin and quercetin, confirmed that after exposing these to luminous radiation, it was possible to observe changes in their coloration due to modifications in their reflectances. The yellow coloration of the quercetin is lost quickly, while the coloration of the luteolin become blackening. The authors attribute such modifications to the probable formation of molecular aggregates with changing the λ_{max} to higher wavelengths than those presented by non-aggregated polyphenols. In the present work, it is not possible to establish a relationship between the presence of aggregates and the interaction of the excipients in the SDP. Further investigations to enlighten this phenomenon in a complex matrix as an herbal powder are running in our Laboratory.

The slugs were, therefore, prepared by adjusting the penetration of the upper punch in such way as to reach the hardness of the slug, which would not cause the color change of the material. Thus, the obtained compacts were designed, respectively, F_1 and F_2 slugs. Its technological characteristics (Table 4) differ significantly ($\alpha = 0.05$). Despite no quality specifications are available for slugs produced by dry granulation, the technological assessment allows a comparative analysis of their characteristics from the different formulations. For this reason, in this study specification for tablets was referred for comparison. The differences observed between the average weights of F_1 and F_2 slugs, although statistically significant, can be considered acceptable under the technological point of view. In any case, these can be attributed to the difference of flow and filling of the compression chamber between F_1 and F_2.

The F_1 formulation resulted in slugs with deformation characteristics which became the evaluation of its hardness and friability not possible. The characteristics of deformation of F1 slugs resulted in extremely high values of hardness. The compact did not break during the hardness test, the material when crushed, became deformed causing ruptures only in their centers. Maintaining the crushing force until the maximum limit of the hardness tester, the final value was extremely high. Thus, the value presented in Table 4 expresses the force applied at the moment that

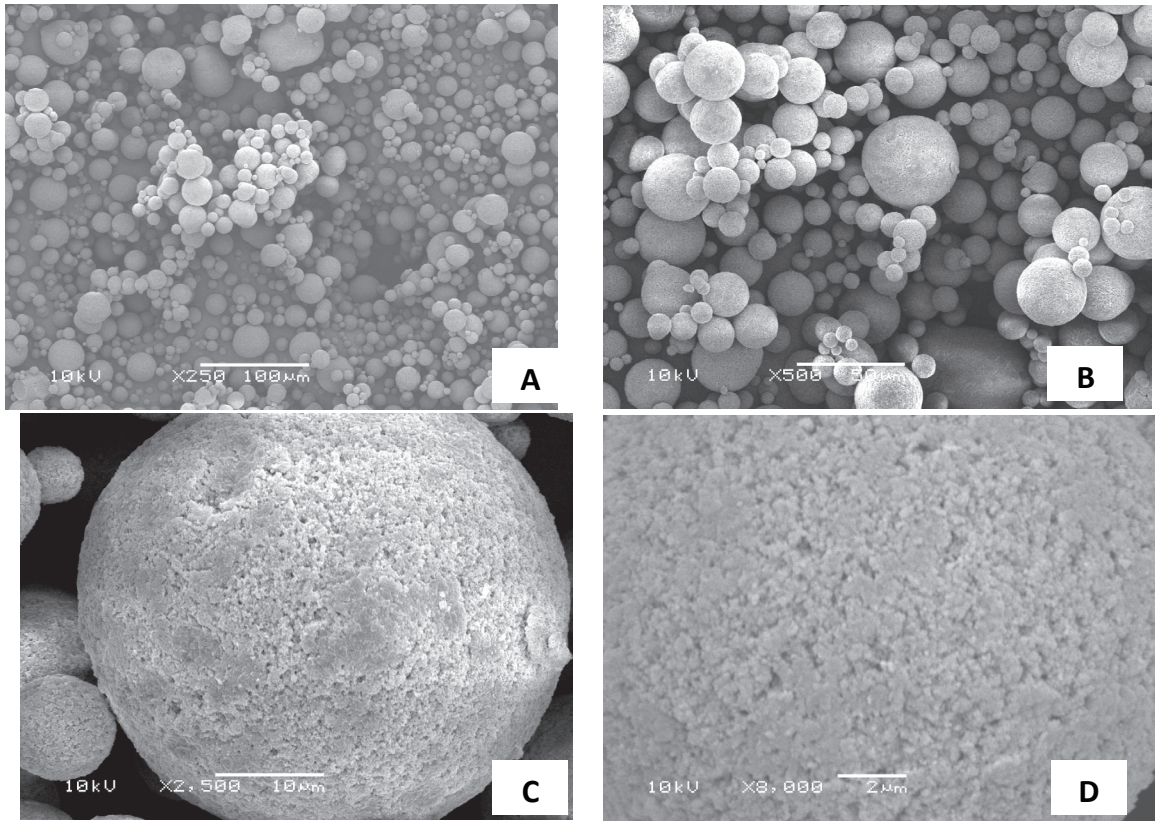

Figure 2. Photomicrographies of the *A. satureioides* spray dried powder magnified at (A) 250x, (B) 500x, (C) 2500x, and (D) 8000x.

the first fracture in the slugs appeared.

The results obtained in the assessment of friability of the F_1 slugs were also atypical. After the analysis time had lapsed, the slugs presented an increase in their weight. The test was repeated three times with similar results. A plausible explanation for such phenomenon is the hygroscopy of the SDP since this can be found in a proportion of 99% (w/w) in the slugs. The friability test of the F_2 slugs did not presented this phenomenon, and showed that the resistance to the abrasion is below the maximum limit allowed for tablets (Farmacopéia Brasileira, 1988), whose accepted value is the maximum loss of 1.5% (w/w) of its weight.

The F_1 slugs presented disintegration time of 39 min, value above the maximum limit (30 min) specified for tablets (Farmacopéia Brasileira, 1988). In contrast, the F_2 slugs is within the set limits, difference which can be related to the presence of microcrystalline cellulose in F_2 (Kibbe, 2000; Hoepfner et al., 2002; The United States Pharmacopoeia, 2008). The concentration of the major flavonoids in the F2 slugs is presented in Table 3.

Taken together, the characteristics presented by the F_2 slugs determined its selection for the next step of dry granulation.

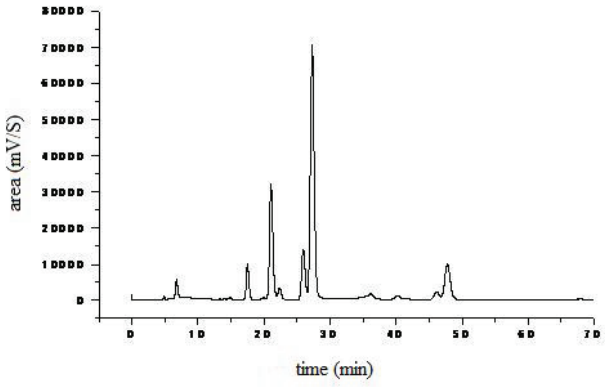

Figure 3. LC profile of the *A. satureioides* spray dried powder. (**1**) quercetin, (**2**) luteolin, and (**3**) 3-*O*-methylquercetin. Shimpac CLC-ODS (M) RP-18 Column (5 µm-250 mm x 4 mm), pre-column with Lichrosorb RP-18 (10 µm) stationary phase. Solvent methanol:aqueous solution of phosphoric acid at 0.16 mol/L (53:47, v/v). Flow of 0.6 mL/min, detection at 362 nm, sensibility of 1.0 AUFS.

Granulation and characterization of the granules

The yield of the granulation process was 60%. Despite the low F_2 slug friability, the granulation process presented a larger production of fine powders, characteristic already reported for other herbal products (De Souza et al., 2005; Couto et al., 2000).

The average size of the granules obtained from F_2 slugs (SDG) was 1.19 mm±0.31. The analysis of the particle size distribution of the SDG (Figure 4) allows observing that more than 90% of the particles presented diameters within the range of 0.7 to 1.7 mm, while approximately 58% presented diameters between 0.7 and 1.3 mm.

As regards the technological parameters, in an overview, the granules presented better compactability and flow characteristics than those of the SDP (Table 2). In addition, lower values of bulk and tapped densities were observed due to the increase in the particle size, overcoming one of the main limitations of SDP.

The Hausner's factor observed (1.089) indicates a better packing stability of the granules in comparison to those of the SDP (1.234). The value of the compressibility index (Carr's index) (8.16) shows an improvement in the flow properties of the SDG as compared to that of the SDP (18.93). Carr's index values of above 15% characterize materials presenting poor flowability and problems in the packing, which is the case of SDP and other herbal spray dried powders (Couto et al., 2000; Augsburger & Vuppala, 1997; Summers & Aulton, 2002).

The densification index, which for the SDP is higher than 20 mL, characterize it as being a material with potential limitations in packing during the compression process (Guyot et al., 1995). The granulation of SDP caused a significant improvement in this characteristic (SDG; 12.3 mL).

Regarding the angle of repouse, in a first view, the results observed for the SDG and SDP (below 30°) would characterize both as free flow materials. However, the flow of SDP occurs in blocks, differently of the SDG, which presents a regular flow.

The friability of the granules was 7.35% (w/w). When compared with the friability of the slugs from which it was originated (0.17%), can be observed an increase, most likely due to the disaggregation process. The loss of drying of the SDG was 5.72% (w/w). Bearing in mind this value as the residual humidity, this parameter can be considered to be within the defined limit for packaged powders in non-hermetic containers (List & Schmidt, 1989).

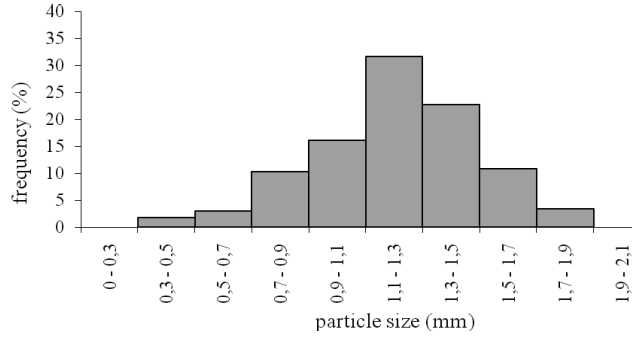

Figure 4. Particle size distribution of the granules of *A. satureioides* spray dried powder.

The photomicrographies of the granules (Figure 5) obtained through SEM, reveals granules with irregular structures and rough surfaces. Under higher magnification

Table 4. Characteristics of the *A. satureioides* powder slugs.

Parameter analyzed	Experimental data $\overline{X}$ ±s (RSD%)	
	F_1 Slugs	F_2 Slugs
Average weight (mg)	668[a]±3.88 (0.58)	660[b]±3.50 (0.53)
Hardness (N)	93.06[a]±4.61 (4.95)	99.30[b]±7.64 (7.70)
Height (mm)	3.298[a]±0.010 (0.30)	3.546[b]±0.008 (0.23)
Diameter (mm)	14.964[a]±0.035 (0.23)	15.087[b]±0.026 (0.17)
Friability (%)	-0.06	0.18
Disintegration time* (min)	39.62[a]±1.29 (3.25)	5.79[b]±0.71 (12.27)

RSD = Relative standard deviation; F_1 slugs= slugs obtained from the F_1 formulation; F_2 slugs = slugs obtained from the F_2 formulation. Averages followed by the same letter on the lines do not differ when submitted to the Student t test (α = 0.05);.* n = 6.

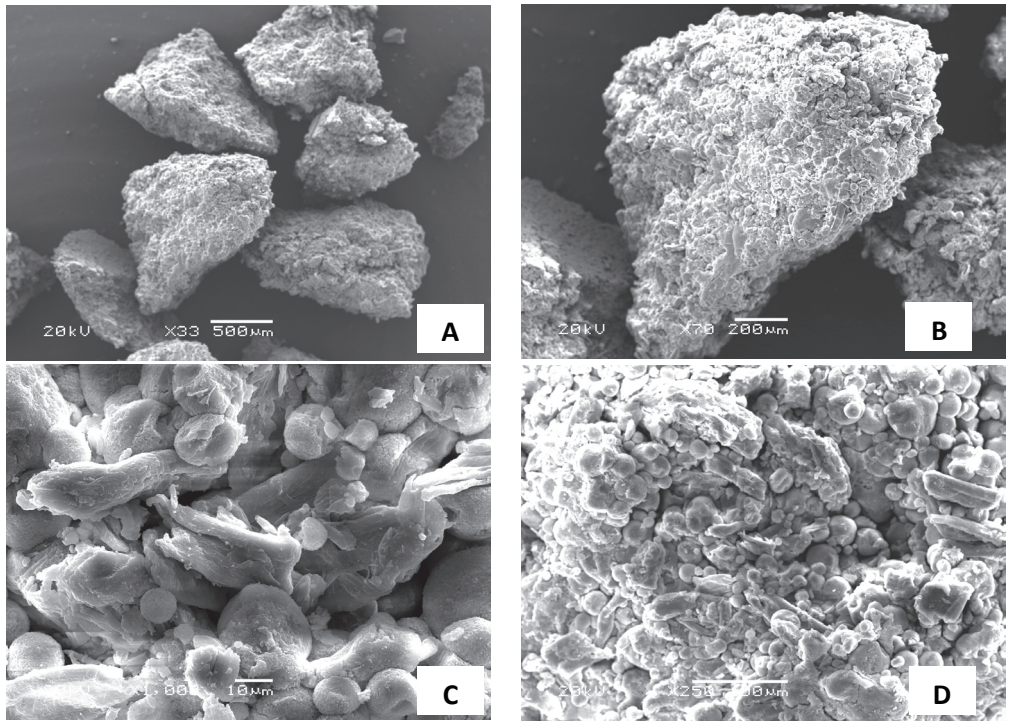

Figure 5. Photomicrographies of the granules of *A. satureioides* spray dried powder magnified at (A) 33X, (B) 70X, (C) 250X, and (D) 1000X.

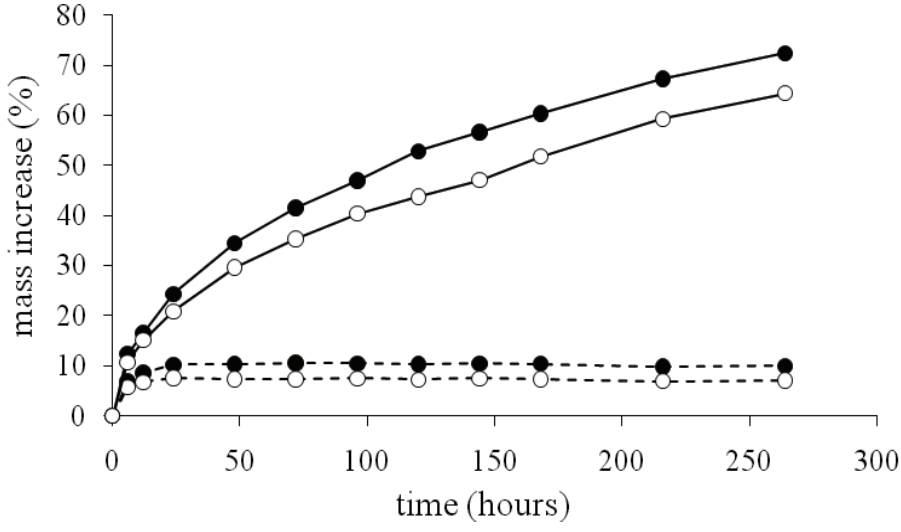

Figure 6. Isotherms of humidity absorption for *A. satureioides* spray dried powders (●) and the corresponding granules (○) in environments of controlled atmospheres with relative humidity of 65% (- - -) and 99% (—).

(Figure 5c and 5d), can be observed structures with rounded extremities, whose form remained unchanged even after the stages of compaction and disaggregation. The presence of microcrystalline cellulose fibers is also observed.

The polyphenol LC analysis of the granules reveals the presence of peaks with retention times identical to those presented in the SDP (Figure 3). However, they are in lower intensity due to the presence of excipients. The corresponding concentrations in the SDG are showed in Table 3. No additional peaks were observed in the chromatogram, denoting the absence of degradation product detectable by the employed chromatographic system.

The exposure of SDP and SDG to environments with relative humidity of 65% and 99% demonstrated that both are sensitive to the humidity (Figure 6). As can be verified, the SDP exposed to the relative humidity of 65% presented rapid increase in weight over the first 24 h, absorbing approximately 10.20% (w/w) of its weight in water and progressing in a lower proportion in the subsequent hours until reaching stability. Likewise, when submitted to the relative humidity of 99%, the initial increase was very quick, considering that in the first 24 h it absorbed 24.36% (w/w) of its weight in water. In both relative humidities, the presence of agglomerates was observed in the SDP at the end of 11 d. The SDG presented lower absorption of humidity in both environments of relative humidity of 65% and 99%, absorbing, respectively, 7.64% (w/w) and 20.84% (w/w) of its weight in water, over the first 24 h. After this period, there was a tendency for the stability of absorption of humidity in both environments of relative humidity. This lower absorption of humidity presented by SDG can be mainly related to the lesser surface area exposed to the atmosphere, without ruled out the role of the excipients within the formulation (De Souza et al., 2005; Miller, 1997; Ansel et al., 2000). As regards the sensorial characteristics, neither the SDP nor the SDG presented changes in coloration in the relative humidity environment of 65%. However, in the 99% relative humidity environment, the both powders became brown. Studies above the stability of *A. satureioides* powder and its major flavonoids against ambiental conditions were performed by Holzschuh et al. (2007) and corroborate with our results. In this study the instability of these flavonoids was evaluated, especially under stress conditions (90% relative humidity and temperature of 50 ^{o}C), but the elucidation of the degradation and oxidation products still has to be enlightened.

CONCLUSIONS

The *A. satureioides* (Lam.) DC., Asteraceae, spray dried powder was prepared in semi-industrial scale, from 40% ethanol extractive solution, with an excellent yield in the spray drying process (88%). Nevertheless, its flow and compactability characteristics were not appropriate for the preparation of derivative pharmaceutical forms, especially by direct compression. The granulation of the spray dried powder allowed the obtaining of the granule, whose technological characteristics as Hausner's factor, the Carr's index, and the densification index revealed more favorable properties.

In summary this first report on the preparation of granules from *Achyrocline satureioides* spray dried powders demonstrated, besides its feasibility, that the granules presented better technological characteristics, overcoming one of the main limitations of SDP.

Moreover, the results open several investigative perspectives in view to optimize the product and to enlighten the darkness phenomenon observed when high compression forces were employed.

ACKNOWLEDGEMENTS

We wish to thank to the Brazilian government for the funding of this research and scholarship, through the governmental agencies CNPq and CAPES.

REFERENCES

Ansel HC, Popovich NG, Allen LV 2000. *Formas farmacêuticas e sistemas de liberação de fármacos.* São Paulo: Premier.

Augsburger LL, Vuppala MK 1997. Theory of granulation. In: Parikh DM (Ed.). *The Handbook of Pharmaceutical Granulation Technology.* New York: Marcel Dekker.

Bassani VL, Teixeira HF, Ortega GG, Lemos-Senna E, Simões CMO, Sonaglio D, Petrovick PR 2001. Processo para obtenção de extratos de *Achyrocline satureioides* e produto obtido. Brazil. *INPI. BR PI 103468-5.*

Carr R 1965. Evaluation flow properties of solids. *Chem Eng Sci 72*: 163-168.

Couto AG 2000. *Desenvolvimento e avaliação tecnológica de granulado contendo produto seco nebulizado de* Phyllanthus niruri *L. (quebra-pedra)*. Porto Alegre, 188p. Master's dissertation, Graduate Studies Program in Pharmaceutical Sciences, Federal University of Rio Grande do Sul.

Couto AG, Ortega GG, Petrovick PR 2000. Granulação. *Caderno de Farmácia 16*: 13-20.

Da Silva DM 2003. *Desenvolvimento de forma farmacêutica semi-sólida contendo extrato padronizado de* Achyrocline satureioides *(Lam.) DC. Asteraceae.* Porto Alegre, 98p. Master's dissertation, Graduate Studies Program in Pharmaceutical Sciences, Federal University of Rio Grande do Sul.

De Souza KCB, Schapoval EES, Bassani VL 2002. LC determination of flavonoids: separation of quercetin, luteolin and 3-*O*-methylquercetin in *Achyrocline satureioides* preparations. *J Pharmaceut Biomed 28*: 771-777.

De Souza TP, Spaniol B, Petrovick PR 2005. Avalição de comprimidos revestidos por película contendo alta

concentração de poduto seco por aspersão de *Phyllanthus niruri*. *Acta Farm Bonaer 24*: 61-67.

Farmacopéia Brasileira 1988. 4th ed. São Paulo: Atheneu.

Guyot JC, Arnaud P, Becourt P, Cassiere JP, Chulia D, Duchêne D, Ferrand D, Gouaihardou J, Langlois C, Lequien C, Malfroid F, Pourcelot Y, Renoux R, Sergot S, Tore P 1995. Commentaires relatifs aux methods générales d'analyse des formes orales solides récemment introduites dans les pharmacopées française et européenne. STP *Pharma Pratiques 5*: 482-494.

Hausner HH 1967. Friction conditions in a mass of metal powder. *Int J Powder Metall 3*: 7-13.

Hoepfner EM, Reng A, Schmidt PC (Ed.) 2002. *Fiedler Encyclopedia of Excipients for Pharmaceutical, Cosmetics and Related Areas, 5th* ed. Aulendorf: Cantor.

Holzschuh MH, Schapoval EES, Da Silva DM, Bassani VL 2007. Thermal and photo stability of phenolic constituents of an *Achyrocline satureioides* spray-dried powder. *Pharmazie 62*: 902-906.

Kibbe AH 2000. *Handbook of Pharmaceutical Excipients*, 3rd ed., Washington: American Pharmaceutical Association.

List PH, Schmidt PC 1989. *Phytopharmaceutical Technology.* Boca Raton: CRC.

Lemos Senna EMT 1993. *Desenvolvimento de extratos secos nebulizados de* Achyrocline satureioides *(Lam.) DC. Compositae (marcela)*. Porto Alegre, 140p. Master's dissertation, Graduate Studies Program in Pharmaceutical Sciences, Federal University of Rio Grande do Sul.

Masters K 1976. *Spray drying.* New York: John Wiley.

Miller RW 1997. Roller Compaction Technology. In: Parikh DM (Ed.). *The handbook of Pharmaceutical Granulation Technology.* New York: Marcel Dekker.

Parthirana WK, Gupta BK 1976. Determination of angle of repose by shadow tracing method. *Can J Pharm Sci 11*: 30-32.

Prista LVN 2003. *Tecnologia Farmacêutica.* Lisboa: Calouste Gulbenkian.

Schreier P, Miller E 1985. Studies on flavonol degradation by peroxidase (donor: H_2O_2-oxidoreductase, EC 1.11.1.7): part 2-quercetin. *Food Chem 18*: 301-317.

Senna EL, Petrovick PR, Ortega GG, Bassani VL 1997. Preparation and characterization of spray-dried powders from *Achyrocline satureioides* (Lam.) DC. extracts. *Phytother Res 11*: 123-127.

Simões CMO, Mentz LA, Schenkel EP, Irgang BF, Stehmann JR 1998. *Plantas da medicina popular do Rio Grande do Sul.* Porto Alegre: Editora da UFRGS.

Smith GJ, Thomsen SJ, Markham KR, Andary C, Cardon D 2000. The photostabilities of naturally ocurring 5-hydroxyflavones, flavonols, their glycosides and their aluminium complexes. *J Photochem Photobiol 136*: 87-91.

Summers M, Aulton ME 2002. Granulation. In: Aulton ME. *Pharmaceutics The Science of Dosage Form Design.* 2. ed. Edinburgh: Churchill Livingstone.

Teixeira HF 1996. *Avaliação da influência de adjuvantes farmacêuticos sobre características físicas, químicas, tecnológicas e farmacológicas de extratos secos nebulizados de* Achyrocline satureioides *(Lam.) DC.-Compositae (Marcela)*. Porto Alegre, 146p. Master's dissertation, Graduate Studies Program in Pharmaceutical Sciences, Federal University of Rio Grande do Sul.

The United States Pharmacopoeia 2008. 31th ed. Rockville: United States Pharmacopeial Convention.

Wells JI 1988. *Pharmaceutical precompound: the physicochemical properties of drug substances.* London: Ellis Horwood.