

## Development of granules from *Phyllanthus niruri* spray-dried extract

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The aim of this study was to develop granules from *Phyllanthus niruri* spray-dried extract using dry and wet granulation and to assess techniques to enable the production of granules with improved technological characteristics and yields. Granules were characterized by granulometry, rheological parameters, compression and hygroscopic behavior. Independent of the granulation technique, technologically developed granules presented particle diameter, bulk and tapped densities and compressibility indexes suitable for a solid dosage form. The compression behavior showed plastic and fragmentary deformation for granules produced by the dry granulation technique and predominantly plastic deformation for wet granulation. Concerning the humidity sorption, the study showed that granules absorb less humidity than the spray-dried extract. However, granules with Eudragit® E 100 were the least hygroscopic.

**Uniterms:** *Phyllanthus niruri*/pharmacotechnics. Granules/production. Spray-dried extract. Wet granulation. Dry granulation.

O objetivo deste estudo foi desenvolver grânulos de extrato *Phyllanthus niruri* seco por aspersão e por granulação úmida e avaliar técnicas que possibilitem a produção de grânulos com características tecnológicas e rendimentos aperfeiçoados. Os grânulos foram caracterizados por granulometria, parâmetros reológicos, compressão e comportamento higroscópico. Independentemente da técnica de granulação, os grânulos tecnologicamente desenvolvidos apresentaram diâmetro de partículas, densidades aparente e compactada e índices de compressibilidade adequados para a formulação sólida. O comportamento de compressão mostrou deformação plástica e elástica para os grânulos produzidos por técnicas de granulação seca e, predominantemente, deformação plástica para a granulação úmida. Com relação à absorção da umidade, o estudo mostrou que os grânulos absorvem menos umidade do que o extrato seco por aspersão. Entretanto, os grânulos com Eudragit E 100 foram os menos higroscópicos.

**Unitermos:** *Phyllanthus niruri*/farmacotécnica. Grânulos/produção. Aspersão. Granulação úmida. Granulação seca.

### INTRODUCTION

Development of medications containing vegetable extracts involves technological and stability problems due to difficulties with the extracts during pharmaceutical processing. Active substances are generally present in the extracts at low concentrations and therefore a large quantity of extract is necessary to produce an active dose. (Crippa, 1978; Bonati, 1980).

Spray-dried extracts are intermediate products with improved stability and easy handling in spite of their

characteristics as a fine powder with low density and high hygroscopy. These latter properties make transformation into a solid dosage form more difficult (List, Shimdt, 1989; Souza *et al.*, 2000; Soares *et al.*, 2005; Souza *et al.*, 2006). However, granulation is a technique which is used: to improve physical properties of powders such as flowage, dispersion and bulk density; to improve dosage uniformity by avoiding particle segregation; and to improve the mechanical properties of the final solid dosage form, such as compressibility and strength of tablets (Soares *et al.*, 2005; Souza *et al.*, 2007).

The granulation of vegetable extracts, in spite of decreasing the surface area of the particles, does not provide protection for dry extracts (Onunkwo, Udeala, 1995;

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Souza *et al.*, 2007). However, the addition of pharmaceutical excipients aids the granulation process and decreases the hygroscopicity of the extract (e.g. use of colloidal silicon dioxide or acrylate resins such as Eudragit® for granule coating) (Díaz *et al.*, 1996; Soares *et al.*, 2005; Souza *et al.*, 2007).

Dry extracts generally present high water solubility; water is therefore not a good solvent for wet granulation. Organic solvents must be carefully selected in order to avoid degradation upon extraction.

Against this background, the aim of this study was to develop granules from a *Phyllanthus niruri* spray-dried extract and verify techniques used to produce granules with improved characteristics.

## MATERIAL AND METHODS

### Raw material

The *Phyllanthus niruri* spray-dried extracts (SDE) were produced on a semi-industrial scale based on the methodology described by Soares (1997). The solution extract was obtained by vegetable drug decoction of aerial parts, using water as an extractive solvent at 100 °C for 15 minutes of extraction. The spray-dried extracts were produced in a spray-dryer (Production Minor with rotary disc atomizer) using 30% colloidal silicon dioxide (Aerosil® 200) as a drying agent based on the dry residue of the extracted solution.

The pharmaceutical excipients microcrystalline cellulose – MCC (Avicel pH 101, FMC corp.), magnesium stearate – ST (gift of C. Bacia S.A), colloidal silicon dioxide (Aerosil® 200, Degussa) and Eudragit® E100 (RÖHM) were used as inert agents.

### Granule production

The formulations of the granules are described in Ta-

**TABLE I** - Composition of granule formulations

Formulations	SDE (%)	ST (%)	CSD (%)	MCC (%)	Eudragit® E100 (%)
F1	69.23	1.00	2.20	27.57	-
F2	99	1.00	-	-	-
F3	97	1.00	2.00	-	-
F4	98	1.00	1.00	-	-
F5	90	-	-	-	10

SDE = spray-dried extract, ST = magnesium stearate, CSD = colloidal silicon dioxide and MCC = microcrystalline cellulose

ble I, where F1, F2, F3 and F4 formulations were obtained by dry granulation and F5 formulation by wet granulation.

### Dry Granulation (GRN)

The SDE and excipients were blended in a V-blender at 36 rpm adjusted on a drive motor (Erweka AR 400). The F1 formulation was prepared by blending SDE with filler/binder (MCC) for 15 min with addition of lubricant (ST) and glidant (CSD) and blending for a further 5 minutes. For the F2, F3 and F4 formulations the SDE was blended with excipients for 5 minutes.

Each formulation was compacted by direct compression using an eccentric compression machine (Korsch EK-0) equipped with flat-faced 15 mm punch. Granulation was performed in a dry granulator (Erweka type TGIIS) followed by size reduction in an oscillatory granulator (Erweka type FG). Granules were screened to obtain a granulometry range of 1.0 mm to 0.25 mm. Granules below 0.25 mm were re-compacted following the same methodology as described above. The compression and screening cycles were repeated until less than 10% of final particle was obtained.

The granule yield was calculated in the first granulation cycle considering the percentage of screened granules in the total mass of the formulation.

### Characterization of compacts

Friability was determined with a Roche friability test apparatus, hardness with a Scheleuniger hardness test apparatus, and disintegration time with a Pharma Test apparatus. All assays were performed according to the Farmacopéia Brasileira IV (1988).

### Wet granulation (GRU)

Wet granules were obtained with 10% (w/w) of Eudragit® E100 as a binder. The SDE was weighed and granulated with Eudragit E in an acetone solution at 12.5 w/v percentage. This mixture was thoroughly blended, until the adequate consistency for granulation was achieved, and strained through a sieve with a nominal aperture of 1 mm. The prepared granules were dried in a circulating air oven at 25 °C for 2 hours, screened and stored.

### Characterization of granules

#### Particle size analysis

The granules sizes were determined in an automatic sieve shaker (Orto Alresa HZ50) using 850, 710, 600, 500,

355 and 250  $\mu\text{m}$  sieves. The particle mean diameter ( $\bar{D}$ ) was determined by arithmetic method using equation 1 (Lantz, 1989).

$$\bar{d}_m = \frac{\sum n\bar{x}_i}{n} \quad (\text{Equation 1})$$

Where:  $\bar{d}_m$  = mean particle diameter ( $\mu\text{m}$ );  
 $\bar{x}$  = mean class diameter ( $\mu\text{m}$ );  
 $n$  = distribution frequency.

#### Reological behavior

Bulk and tapped density, and compressibility indexes were determined on apparent density test apparatus (J. Engelsmann) following the methodology described by Guyot *et al.* (1995).

#### Analysis of gallic acid by high pressure liquid chromatography (HPLC)

The assay of gallic acid in granules was performed following the methodology described by Souza *et al.* (2002). The analysis was carried out in a Shimadzu liquid chromatograph (LC-10 AD) equipped with an automated gradient controller (FCV-10 AL) and a Shimadzu UV/VIS detector (SPD-10 A). The analytical column was a RP-18 LiChrospher 250 x 4 mm id., 5  $\mu\text{m}$  particle diameter (Merck) protected with a pre-column of the same material.

#### Compression behavior

Evaluation of SDE and granule compression behavior was performed in an instrumented single punch tablet machine (J. Bonals BMT), equipped with flat-faced 9 mm punches and data acquisition system described by Martínez-Pacheco *et al.* (1985). The tablets were prepared by individual hand-weighed powder. The volume of solid in the die was adjusted to a constant content of 250 mg of SDE for all tablets. The compression was performed by automatic display with a speed fixed at 8 tablets/min.

The compression behavior of spray-dried extract and granules was determined through the Heckel model (Equation 2), used to calculate the mean yield pressure –  $P_y$  (Equation 3) and through a force-time curve model used to calculate plasticity (P%) and elastic recovery (RE%) (Equations 4 and 5, respectively) (Hubert-Droz *et al.*, 1982). Calculations were performed using a Microsoft Excel® 97 program. The compression force was measured on the upper punch using a maximum compression force of 6000 N to SDE and for dry granules and 2500 N for wet granules.

$$\ln\left(\frac{1}{\varepsilon}\right) = k \cdot P + A \quad (\text{Equation 2})$$

Where  $\varepsilon$  = porosity of the compact at pressure  $P$ ;

$P$  = pressure applied;

$k$  and  $A$  = slope and intercept, respectively, of the straight line obtained by linear regression from the Heckel plot.

$$P_y = \frac{1}{k} \quad (\text{Equation 3})$$

Where  $P_y$  = mean yield pressure;

$k$  = slope of straight line obtained by linear regression from the Heckel plot.

$$P = \frac{E_2}{E_2 + E_3} \cdot 100 \quad (\text{Equation 4})$$

Where  $P$  = plasticity (%)

$E_2$  = energy used for production of compacts;

$E_3$  = energy lost in elastic deformation.

$$RE = 100 - P \quad (\text{Equation 5})$$

Where  $RE$  = elasticity (%);

$P$  = plasticity (%)

#### Humidity sorption

The SDE and granules were stocked for 15 days in a controlled environment of 69% relative humidity. This atmosphere was obtained with a potassium iodide (KI) saturated solution containing dry residue (Nyqvist, 1983) and a controlled temperature of 25 °C. The humidity sorption was evaluated by weight increase of products, which was performed by weighing the samples in the first 24 and 48 hours, followed by consecutive weighing at every 72 hours for a period of 15 days.

#### Statistical analysis

The results were evaluated using analysis of variance (ANOVA), Tukey and Student “t” tests, performed with the SigmaStat® for Windows (version. 1.0) statistical program.

## RESULTS AND DISCUSSION

In the dry granulations, independent of formulations (Table I), all compacts were produced with a hardness range from 50 to 70 N. The compacts were obtained by automatic filling of the die with a thickness range from 3 to 4 mm. According to Auton (2002), a compact produced in a dry granulator should present a specific thickness to facilitate the process of granulation. As the formulations presented different compositions and consequently different densities, the medium weight was adjusted for all compact ranges to achieve similar thickness and hardness.

**TABLE II** - Compacts characterization

Results	Formulation			
	F1 $\bar{x} \pm s$	F2 $\bar{x} \pm s$	F3 $\bar{x} \pm s$	F4 $\bar{x} \pm s$
Mean weight (g)	0.6413 $\pm$ 0.017	0.828 $\pm$ 0.004	0.833 $\pm$ 0.01	0.8101 $\pm$ 0.003
Diameter (mm)	15.18 $\pm$ 0.017	15.19 $\pm$ 0.070	15.22 $\pm$ 0.02	15.20 $\pm$ 0.009
Thickness (mm)	3.23 $\pm$ 0.013	3.90 $\pm$ 0.025	4.07 $\pm$ 0.03	3.93 $\pm$ 0.01
Friability (%)	9.7	42.14	69.4	50.9
Hardness (N)	57.51 $\pm$ 11.3	64.6 $\pm$ 5.0	53.6 $\pm$ 8.6	55.0 $\pm$ 7.5
Disintegration time (min)	25.80 $\pm$ 6.14	10.23 $\pm$ 0.60	12.55 $\pm$ 0.97	8:00*

\* All these compacts presented the same length of disintegration time

The results of technological characterization of compacts are described in Table II. In general with the exception of F1, all formulations presented mean weight with coefficient variation below 1.5%, which could be explained by the smooth flow of SDE which enabled a homogeneous filling in the die.

Compact hardness of different formulations did not show any statistically significant difference ( $p = 0.43$ ): however, the same compacts presented different friability values. Among the formulations studied, F1 produced compacts with higher resistance, probably due to the presence of microcrystalline cellulose binder which improved cohesion of the particles (Herting, Kleinebudde, 2007).

All compacts presented disintegration times (DT) within the maximum limit (30 min) established by Farmacopéia Brasileira (1988). F1 presented a higher TD with a value close to the pharmacopeia limit and a high variation coefficient, while other formulations had smooth and fast disintegration.

F1 yielded less in the granulation process, while other granules obtained by dry granulation showed a similar yield around 60%. Wet granulation was the technique which provided the best yield (98%), Table III. Technically, the higher the granulation yield the less operational cycles and less mechanical stress needed to produce the product.

**TABLE III** - Yield (R %) of granulation process

Formulation	F1*	F2*	F3*	F4*	F5**
R %	45.82	61.2	62.8	62.4	98

\*dry granulation, \*\*wet granulation

The high friability of the compacts may be the reason for the fine particle produced from the dry granulation process. However, the experiments showed that compacts with less friability (F1) produced higher fine particles (above 50%). Granules developed by Couto (2000), obtained

from a formulation similar to F1, showed a granulation yield similar to the one presented in the present study. The low yield of granulation could be the result of uncompressed residue materials, inherent to its own formulation, due to the presence of microcrystalline cellulose that, in the compressive force used to obtain the compact, can serve as a buffer reducing the aggregation among particles of other components of the formulation. Thus, the fibrous form of microcrystalline cellulose and its provision permeating the whole compact mass may explain the low friability of the compacts formed, since it is conducive to the mechanical strength of the compacted mass. However, reducing the aggregation among the particles within the mass, results in a higher production of fine particles during the granulation of the compact (Souza *et al.*, 2000; Souza *et al.*, 2006; Bozic *et al.*, 2008).

As regards the technological parameters (Table IV), the granules generally had better characteristics of compaction and flow than the SDE, and the granules obtained by dry granulation (GRN 1, 3 and 4) presented better packing characteristics with the lowest compressibility indexes.

Although the statistical analysis indicates values of tapped density and compressibility index of GRN 2 and a GRU which is different from the other granules, these values are very similar, due to the similar size distribution of the various granules. The average diameter of particle size and the variation of distribution of particles confirm that the formulations produced granules with similar size distributions. Granules obtained by wet granulation, which yielded a considerably larger particle size than those obtained by dry granulation, were the exception; however, this did not negatively influence the rheological characteristics of the granules obtained by this method.

The characterization tests showed that there were no major technological differences among the granules produced, making it difficult to choose which of the formulations may provide the best properties for tablet development.

**TABLE IV** - Compression parameters of the SDE and granules obtained by dry (GRN) and wet (GRU) granulation

Material	bd (g/mL) $\times \pm s$	td (g/mL) $\times \pm s$	CI $\times \pm s$	$\bar{d}_m$ ( $\mu\text{m}$ ) $\times \pm s$
SDE	0.790 <sup>a</sup> $\pm$ 0.004	0.972 <sup>a</sup> $\pm$ 0.008	18.75 <sup>a</sup> $\pm$ 0,29	10.55 <sup>c</sup> $\pm$ 1.56
GRN 1	0.608 <sup>b</sup> $\pm$ 0.008	0.655 <sup>c</sup> $\pm$ 0.019	07.08 <sup>c</sup> $\pm$ 1.78	583 <sup>b</sup> $\pm$ 0.249
GRN 2	0.600 <sup>b</sup> $\pm$ 0.010	0.700 <sup>b</sup> $\pm$ 0.007	14.35 <sup>b</sup> $\pm$ 0.62	588 <sup>b</sup> $\pm$ 0.214
GRN 3	0.595 <sup>b</sup> $\pm$ 0.005	0.646 <sup>c</sup> $\pm$ 0.001	07.92 <sup>c</sup> $\pm$ 0.78	550 <sup>b</sup> $\pm$ 0.224
GRN 4	0.589 <sup>b</sup> $\pm$ 0.008	0.639 <sup>c</sup> $\pm$ 0.004	07.67 <sup>c</sup> $\pm$ 1.55	579 <sup>b</sup> $\pm$ 0.237
GRU	0.509 <sup>c</sup> $\pm$ 0.007	0.577 <sup>d</sup> $\pm$ 0.001	11.75 <sup>d</sup> $\pm$ 1.29	806 <sup>a</sup> $\pm$ 0.249

bd = bulk density; td = tapped density; CI = compressibility indexes;  $\bar{d}_m$  = particle mean diameter. Means followed by same letter do not differ on the Tukey test ( $\alpha=0.05$ )

However, based on the yield of the granulation process, F1 was excluded since it had a yield below 50%, and therefore granule determination was performed only with granules obtained from formulations F2, F3, F4 and F5.

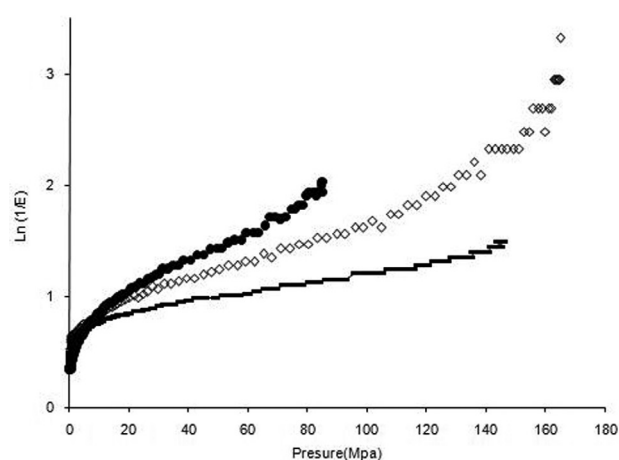
Gallic acid marker quantitative analysis (Table V) was performed to verify the homogeneity of distribution of SDE within the granules. Levels of gallic acid present in the granules were compared to those of SDE. The ANOVA showed no statistically significant difference ( $\alpha = 0.01$ ) between the levels of polyphenols in granules and the SDE, independent of the granulation technique used.

**TABLE V** - Content of gallic acid present in one gram of spray-dried extract (SDE) and granules obtained by dry (GRN) and wet (GRU) granulation

material	gallic acid (mg) $\bar{x}$ (CV%)
SDE	12.02 (1.27)
GRN 2	11.84 (0.28)
GRN 3	11.80 (0.60)
GRN 4	11.74 (0.87)
GRU	11.57 (0.45)

Compression behavior analysis was performed with the spray-dried extract, dried and wet granules. Among the dry granules, only the GRN 4 was chosen for the trial because of the technological similarity with the other granules (Table IV)

The Heckel graph (Figure 1) shows that the products had different compression behavior. In the studied system, the maximum compression for the granules obtained by wet granulation was considerably lower (2500 N), especially when compared to SDE and granules obtained by dry granulation, which allowed the application of a compression force of 6000 N. This may be explained by

**FIGURE 1** – Heckel graph,  $\diamond$  - SDE;  $\square$  - GRN4;  $\bullet$  GRU.

differences in density and porosity of the granules.

The properties of compression (Table VI) revealed a high elastic recovery for all the studied products. The mean yield pressure ( $P_y$ ) suggests that the SDE and the granules obtained by wet granulation have a predominantly plastic behavior, while the granules obtained by dry granulation have both a plastic and fragmentary behavior. Materials that are liable to plastically deform are capable of generating compacts with high mechanical strength using relatively low pressure. Furthermore, materials that deform in a fragmented manner need more pressure, therefore, during the compression process there is particle fragmentation, generating cleaner points of contact and reducing cohesion (Eriksson, Alderborn, 1995). Thus, the major advantage of materials that deform in a plastic manner upon fragmentative compression is their capability to produce compacts under low pressure, reducing load on the equipment and increasing their working lifespan.

Exposure of the SDE and the granules to a relative humidity of 69% showed that all products were sensitive to moisture (Figure 2). However, comparing SDE with the granules, the granules showed a significantly lower

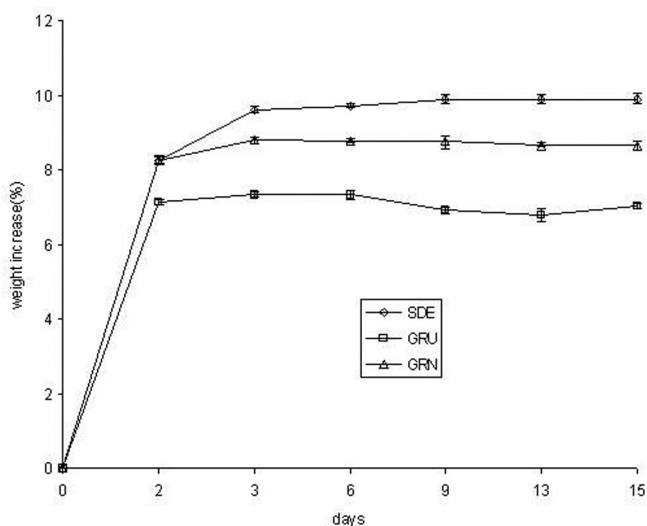
**TABLE VI** - Physical compression parameters calculated for spray-dried extract (SDE), dried granules (GRN - F4) and wet granules (GRU - F5)

samples	Py (MPa) $\bar{x}$ (CV%)	P (%) $\bar{x}$ (CV%)	E (%)
SDE	111.6 (3,16)	64.47 (2.26)	35.53
GRN4	168.5 (0,96)	60.47 (0.27)	38.53
GRU	81.08 (0,47)	64,26 (4.27)	35.74

Py = mean yield pressure, P = plasticity, E = elastic recovery

moisture sorption, which may be due to the smaller surface area of the granules and also to the presence of adjuvants in the formulation.

The presence of Eudragit E 100 in a proportion of 10% resulted in granules with significantly lower hygroscopy than the others, demonstrating the protective property of the polymer and suggesting greater stability of the granules (Petereit, Weisbrod, 1999; Souza *et al.*, 2007). These results are consistent with those described by Díaz *et al.* (1996) where, by studying the wet granulation of dry plant extracts using Eudragit® E 100 as a binder, the products were found to be considerably less hygroscopic than the dry extract.



**FIGURE 2** - Increase in the weight of products when stored in an environment with relative humidity of 69%.

## CONCLUSION

The results showed the feasibility of obtaining granule products from spray-dried extract of *Phyllanthus niruri*. Both dry and wet granulation techniques produced granules with appropriate technological characteristics and

good operational performance. The presence of Eudragit E 100 in the proportion of 10% in the granules obtained by wet granulation was efficient in producing granules with lower sensitivity to moisture. The dry granules required a higher compressive force and demonstrated plastic deformation, but with some degree of fragmentation, while the granules obtained by wet granulation presented an entirely plastic behavior.

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## REFERENCES

- AULTON, M. E. *Pharmaceutics, the science of dosage form design*. 2.ed. London: Churchill Livingstone, 2002. 675 p.
- BONATI, A. Problems relating to the preparation and use of extracts from medicinal plants. *Fitoterapia*, v.1, n.1, p.5-12, 1980.
- BOZIC, D. Z.; DREU, R.; VRECER, F. Influence of dry granulation on compactibility and capping tendency of macrolide antibiotic formulation. *Int. J. Pharm.*, v.357, n.1, p.44-54, 2008.
- COUTO, A. G. *Desenvolvimento e avaliação tecnológica de granulados contendo produto seco nebulizado de Phyllanthus niruri L. – Euphorbiaceae (quebra-pedra)*. Porto Alegre, 2000. 179p. [Dissertação de Mestrado. Faculdade de Farmácia. Universidade Federal do Rio Grande do Sul].
- CRIPPA, F. Problems of pharmaceutical technics with plant extracts. *Fitoterapia*, v.49, n.2, p.257-263, 1978.
- DÍAZ, L. M.; SOUTO, C.; CONCHEIRO, A.; GÓMEZ-AMOZA, J. L.; MARTÍNEZ-PACHECO. Evaluation of Eudragit E as major excipient in tablets of dry plant extracts. *S.T.P. Pharma Sci.*, v.6, n.1, p.105-109, 1996.
- ERIKSSON, M.; ALDERBORN, G. The effect of particle fragmentation and deformation on the interparticulate bond formation process during powder compaction. *Pharm. Res.*, v.12, n.7, p.1031-1039, 1995.
- FARMACOPÉIA Brasileira. 4.ed. São Paulo: Atheneu, 1988. p.V.1.3.1,V.1.3.2,V.1.4.1

- GUYOT, J. C.; ARNAUD, P.; BECOURT, P.; CASSIERE, J. P.; CHULIA, D.; DUCHÊNE, D.; FERRAND, D.; GOUAIHARDOU, J.; LANGLOIS, C.; LEQUIEN, C.; MALFROID, F.; POURCELOT, Y.; RENOUX, R.; SERGOT, S.; TOURE, P. Commentaires relatifs aux méthodes générales d'analyse des formes orales solides récemment introduites dans les pharmacopées française et européenne. Rapport d'une commission SFSTP. *S.T.P. Pharm. Prat.*, v.5, n.6, p.482-494, 1995.
- HERTING, M. G.; KLEINEBUDDE, P. Roll compaction/dry granulation: Effect of raw material particle size on granule and tablet properties. *Int. J. Pharm.*, v.338, n.1/2, p.110-118, 2007.
- HUBERT-DROZ, P.; MORDIER, D.; DOELKER, E. Rapid method of determination of compression behavior for preformulations studies. *Pharm. Acta Helv.*, v.57, p.136-143, 1982.
- LANTZ Jr., R. J. Size Reduction In: LIBERMAN, H.A.; LACHMAN, I.; SCHWARTZ, J.B. (Eds.). *Pharmaceutical dosage forms: tablets*. 2.ed. New York: Marcel Dekker, 1989. v.2, cap.3, p.107-199.
- LIST, P. H.; SCHIMDT, P. C. *Phytopharmaceutical technology*. Boca Raton: CRC, 1989. 552 p.
- MARTÍNEZ-PACHECO, R.; GÓMEZ-AMOZA, J. L.; VILA JATO, J. L. Diseño de un sistema de registro de presión en máquinas de comprimir excéntrica. *Cienc. Ind. Farm.*, v.4, n.2, p.207-211, 1985.
- NYQVIST, H. Saturated salt solutions for maintaining specified relative humidities. *Int. J. Pharm. Tech. Prod. Manuf.*, v.4, n.2, p.47-78, 1983.
- ONUNKWO, G. C.; UDEALA, O. K. Studies on *Rauwolfia vomitoria* root III. flow properties of *R. vomitoria* Granulations. *S.T.P. Pharm. Sci.*, v.5, n.4, p.296-301, 1995.
- PETEREIT, H. U.; WEIBSBROD, W. Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers. *Eur. J. Pharm. Biopharm.*, v.47, n.2, p.15-25, 1999.
- SOARES, L. A. L. *Padronização de extrato aquoso e desenvolvimento de produto seco por aspersão de Phyllanthus niruri L. Euphorbiaceae (Quebra-pedra)*. Porto Alegre, 1997. 169p. [Dissertação de Mestrado. Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul.].
- SOARES, L. A. L.; GEORGE GONZÁLEZ, O.; PETROVICK, P. R.; SCHMIDT, P. C. Dry granulation and compression of spray-dried plant extracts. *AAPS Pharm. Sci. Tech.*, v.6, n.3, p.E359-E366, 2005.
- SOUZA, K. C. B.; PETROVICK, P. R.; BASSANI, V. L.; GONZÁLEZ ORTEGA, G. The adjuvants aerosil 200 and Gelita-Sol-P influence on the technological characteristics of spray-dried powders from *Passiflora edulis* var. *flavicarpa*. *Drug Dev. Ind. Pharm.*, v.26, n.3, p.331-336, 2000.
- SOUZA, T. P.; GÓMEZ-AMOZA, J. L.; MARTÍNEZ-PACHECO, R.; PETROVICK, P. R. Compression behavior of formulations from *Phyllanthus niruri* spray dried extract. *Pharmazie*, v.61, n.3, p.213-217, 2006.
- SOUZA, T. P.; MARTÍNEZ-PACHECO, R.; GÓMEZ-AMOZA, J. L.; PETROVICK, P. R. Eudragit E as excipient for production of granules and tablets from *Phyllanthus niruri* L spray-dried extract. *AAPS Pharm. Sci. Tech.*, v.8, n.2, p.E1-E7, 2007.
- SOUZA, T. P.; GONZÁLEZ ORTEGA, G.; BASSANI, V. L.; PETROVICK, P. R. Avaliação da viabilidade de compressão direta de formulações contendo alto teor de produto seco nebulizado de *Maytenus ilicifolia*. *Acta. Farm. Bonaer.*, v.19, n.1, p.53-60, 2000.
- SOUZA, T. P.; HOLZSCHUH, M. H.; LIONÇO, M. I.; GONZÁLEZ ORTEGA, G.; PETROVICK, P. R. Validation of a LC method for the analysis of phenolic compounds from aqueous extract of *Phyllanthus niruri* aerial parts. *J. Pharm. Biom. Anal.*, v.30, n.2, p.351-356, 2002.

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