Eudragit E as Excipient for Production of Granules and Tablets From Phyllanthus niruri L Spray-Dried Extract

Submitted: October 29, 2006; Accepted: November 27, 2006; Published: April 27, 2007

Tatiane Pereira de Souza,[1,3] Ramón Martínez-Pacheco,[2] José Luiz Gómez-Amoza,[2] and Pedro Ros Petrovick[3]

[1]Departamento de Farmácia, UFRN, Av Gal Cordeiro de Farias s/n, 59010-180, Natal, Rio Grande do Norte, Brazil
[2]Departamento de Tecnología Farmacéutica, USC, Facultad de Farmacia, Campus Sur, 15782, Santiago de Compostela, La Coruña, Spain
[3]Programa de Pós Graduação em Ciências Farmacêuticas, UFRGS, Av Ipiranga, 2752, 90610-000, Porto Alegre, Rio Grande do Sul, Brazil

ABSTRACT

The aim of this study was to investigate the feasibility of using Eudragit E as a granulating agent for a spray-dried extract from *Phyllanthus niruri* to obtain tablets containing a high dose of this product. The granules were developed by wet granulation and contained 2.5%, 5.0%, and 10.0% Eudragit E in the final product concentration. The tablets were produced on a single-punch tablet press by direct compression of granules using 0.5% magnesium stearate as a lubricant. The tablets were elaborated following a 2 × 3 factorial design, where Eudragit E concentration and compression force were the independent variables, and tensile strength and the extract release of the tablets were the dependent variables. All granules showed better technological properties than the spray-dried extract, including less moisture sorption. The characteristics of the granules were directly dependent on the proportion of Eudragit E in the formulation. In general, all tablets showed high mechanical resistance with less than 1% friability, less moisture sorption, and a slower extract release profile. The Eudragit E concentration and compression force of the tablets significantly influenced both dependent variables studied. In conclusion, Eudragit E was efficient as a granulating agent for the spray-dried extract, but additional studies are needed to further optimize the formulations in order to achieve less water sorption and improve the release of the extract from the tablets.

KEYWORDS: Phyllanthus niruri, spray-dried extract, wet granulation, Eudragit E100, phytopharmaceuticals.

INTRODUCTION

Phyllanthus niruri L is a medicinal plant widely distributed and used in folk medicine to treat kidney stone ailments and viral hepatitis. Pharmacological experiments confirm its therapeutic efficacy and safety.[1] Spray-dried extracts (SDEs) from medicinal plants are often used as active components in solid dosage forms because of their better stability.[2] However, these products generally present deficient rheological properties, inadequate compressibility, and high sensitivity to atmospheric moisture, resulting in difficult direct compression.[3-5]

The flowing behavior of pharmaceutical powders determines important properties of solid dosage forms. SDEs often have a small particle size and consequently poor flow, which may result in variation in weight and poor content uniformity within tablets. Particle size can be enlarged by granulation in order to increase the flow rate. This process is indicated to improve the rheological and pharmaceutical characteristics of these products,[6,7] but in this case the difficulty is to select the adequate binder agent and the appropriate granulate conditions, considering that the SDE is soluble in water and the major active substances have unknown stability.

Eudragit E is a methacrylic ester copolymer broadly used in a variety of pharmaceutical applications as a binder and as a film coating to disguise taste and odor and to protect the drug from external influences such as light, air, and moisture.[8] Therefore, the use of Eudragit E as a granulation excipient for an SDE may improve the compressional properties as well as the moisture resistance of the resulting product.[9]

The purpose of this study was to investigate the feasibility of using Eudragit E as a granulating agent for *P niruri* SDE to obtain tablets containing high doses of this product.

MATERIALS AND METHODS

Materials

SDE

The SDE of *P niruri* with a standardized concentration of gallic acid (12.33 mg/g) was prepared from an aqueous extract of *P niruri* aerial parts according to the method previously described.[10] The aqueous extract was dried using a Production Minor Spray Dryer (GEA, Copenhagen, Denmark) using Aerosil (300 mg/g) as a dryer adjuvant.

Corresponding Author: Tatiane Pereira de Souza, Departamento de Farmácia, UFRN, Av Gal Cordeiro de Farias s/n, 59010-180, Natal, Rio Grande do Norte, Brazil. Tel: +55 84 32154345; Fax: +55 84 32154340; E-mail: tpsouza@ufrnet.br

Excipients

The excipients Eudragit E 100 (Rohm Pharma, Darmstadt, Germany), Aerosil 200 (Degussa AG, Frankfurt, Germany), and magnesium stearate (C Barcia SA, Madrid, Spain) were used as received.

Preparation of Granules

The SDE was weighed and granulated with Eudragit E in acetone solution in a 12.5 wt/vol percentage. This mixture was thoroughly manually blended until an adequate consistency for granulation was achieved and was then 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. The dried granules were screened and stored. Three formulations of granules were prepared, containing 2.5%, 5%, and 10% of Eudragit E in the final concentration (Table 1).

Characterization of SDE and Granules

Apparent Densities (Bulk and Tapped Density) and Carr's Index

The bulk and tapped densities were measured in a 100-mL graduated cylinder mounted on a mechanical tapping device (J. Engelsmann AG, Ludwigshafen, Rhein, Germany). A 20-g sample was introduced into the cylinder and the initial volume was recorded. Then it was tapped ~1250 times until a constant volume was reached, and the final volume was recorded.[11] The bulk density was calculated as the ratio between the sample weight (g) and the initial volume (cm^3) and the tapped density as the ratio between the sample weight (g) and the final volume (cm^3). The compressibility of the powder was calculated using Carr's index (CI).[12]

Particle Size Analysis

The particle size analysis of the SDE was determined by an optic microscope (model 1669, Getner, Ambala, India) using Feret's diameter to measure the particles.[13] The granule sizes were determined in an automatic sieve shaker (Orto Alresa HZ50, Madrid, Spain) using 1000-, 850-, 710-, 600-, 500-, 355-, and 250-μm sieves. The particles' mean diameter (Ø) was determined by the graphic method, plotting the cumulative distribution curve and determining the diameter equivalent to 50% of the particles.[13]

Table 1. Composition of Granules Formulation*

Formulation Code	SDE (g)	Eudragit E (g)	Acetone (mL)
ED 2.5%	97.5	2.5	20
ED 5.0%	95.0	5.0	40
ED 10.0%	90.0	10.0	80

*SDE indicates spray-dried extract; ED, granules.

Scanning Electron Microscopy

The granule morphology was examined by scanning electron microscopy (S440, Leica Microscopy and Scientific Instruments Group, Heerbrugg, Switzerland).

Analysis of Gallic Acid in SDE and Granules

The gallic acid assay was realized through high-performance liquid chromatography following the methodology described by De Souza et al.[14] The analysis was performed in a Shimadzu liquid chromatography machine (LC-10 AD) equipped with an automated gradient controller (FCV-10 AL) and a Shimadzu UV/VIS detector (SPD-10 A) (Shimadzu Scientific Instruments Inc, Columbia, MD). The analytical column was a RP-18 LiChrospher 250 × 4 mm internal diameter, 5-μm particle diameter (Merck, Darmstadt, Germany) protected with a precolumn of the same material. The chromatographic method of separation was performed using a gradient method: phosphoric acid 1% (wt/wt) as solvent A and acetonitrile:phosphoric acid 1% (wt/wt) (50:50 vol/vol) as solvent B, at a flow rate of 0.6 $mL.min^{-1}$. The gradient program was as follows: 22%-24% B (7 minutes), 24%-40% B (10 minutes), 40%-100% B (8 minutes), and 100%-22% B (15 minutes). The injection volume for all samples was 20 μL, and the peaks were detected at 275 nm.

Preparation of Tablets

The granules, without sieving, were mixed with 0.5% magnesium stearate (Turbula T2C, Willy Bachofen, Basel, Switzerland, 60 rpm, 5 minutes). The tablets were prepared in a J Bonals BMT eccentric press equipped (Cornellà de Llobregat, Barcelona, Spain) with flat-faced 9-mm punches and a data handling system.[15] The press was set to produce 8 tablets per minute, and the loading depth was adjusted to obtain tablets with an SDE content of 250 mg.

The tablets were obtained following a 2 × 3 factorial design. The factors analyzed were compression force (1250 N and 2500 N) and the Eudragit E proportions in granules (2.5%, 5%, 10%).

Characterization of Tablets

Tensile Strength

The hardness of the 6 tablets from each formulation was measured with an Erweka TB-2A apparatus (Erweka GmbH,

Table 2. Characteristics of *Phyllanthus niruri* SDE and ED*

Characteristic	SDE X ± s	ED 2.5% X ± s	ED 5.0% X ± s	ED 10.0% X ± s
BD (g/cm^3)	0.76^a ± 0.01	0.41^c ± 0.01	0.43^c ± 0.01	0.51^b ± 0.01
TD (g/cm^3)	0.96^a ± 0.01	0.48^c ± 0.01	0.49^c ± 0.01	0.58^b ± 0.01
RD (g/cm^3)	1.72^a ± 0.01	1.54^b ± 0.01	1.57^b ± 0.01	1.57^b ± 0.00
CI	20.22^a ± 1.73	14.94^b ± 2.12	12.17^b ± 0.81	11.75^b ± 1.29
Ø (μm)	10.55	785	825	850
Gallic acid content (mg/g)	12.33 ± 0.04	11.91 ± 0.05	11.99 ± 0.03	11.57 ± 0.05

*SDE indicates spray-dried extract; ED, granules; BD, bulk density; TD, tapped density; RD, real density; CI, Carr's index; Ø, particle mean diameter. Mean values in a line followed by the same letter did not differ significantly (Tukey test; $P < .01$).

Hainburg, Germany). The tensile strength for each tablet formulation was calculated using Equation 1[16,17]:

$$TS = \frac{2 \times P}{\pi \times D \times t} \quad (1)$$

where TS is the tensile strength (N·cm^{-2}), P is the hardness of the tablet (N), D is the tablet diameter (cm), and t is the tablet thickness (cm). The tablet diameter and thickness were measured with a digital micrometer (Mytutoyo Co, Tokyo, Japan).

Total Porosity

The tablet total porosity was calculated from the granules' true density and tablet volume.[18] The true density was measured with a Quantachrome MPY-2 helium pycnometer (Odelzhausen, Germany).

Friability

The friability was determined with a Pharmatest PTF-E apparatus (Hainburg, Germany) following the US Pharmacopeia (USP) 27 specifications.[19]

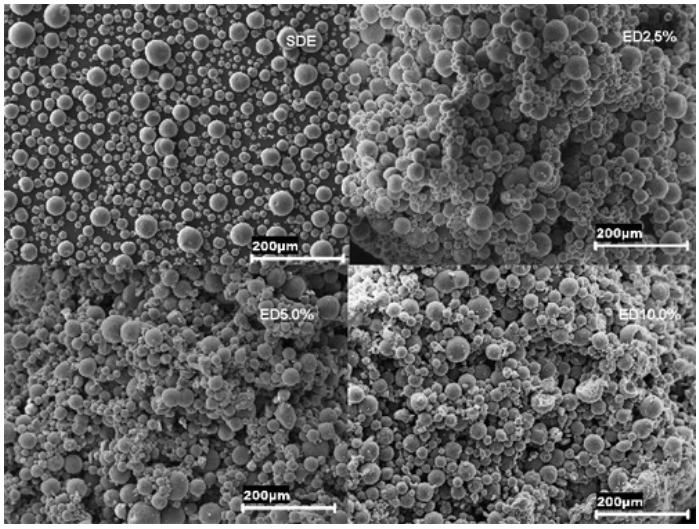

Figure 1. Electronic microphotography of SDE and ED. SDE indicates spray-dried extract; ED, granules.

Dissolution Profile

The release of the SDE from the tablets was determined in a Turu-Grau apparatus (Barcelona, Spain) in accordance with the USP 27 specifications (method II, stirring at 100 rpm). The dissolution medium was an enzyme-free artificial gastric fluid.[19] The analysis of the SDE content was performed by direct spectrophotometry at 275 nm. The release was characterized as the percentage of the SDE dissolved after 80 minutes (D_{80}).

Moisture Sorption Assay

The SDE and granules (placed in Petri dishes) and tablets (placed in open polystyrene bottles) were stored for 15 days in desiccators with a controlled environment with a temperature of 25°C and a relative humidity (RH) of 33% or 69% obtained with a saturated solution of $MgCl_2.6H_2O$ or KI, respectively.[20] The moisture sorption was determined by gravimetric analysis. The samples were weighed within the first 24 and 48 hours and then every 72 hours for 15 days. The tensile strength, the friability, and the dissolution profile of the tablets were studied to assess the influence of moisture on the mechanical properties of the tablets. This assay was performed with only the tablets containing granules with Eudragit E 10%.

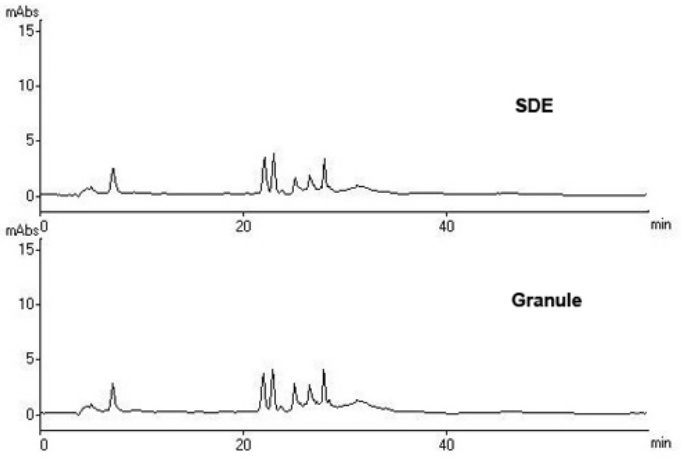

Figure 2. Chromatographic profile of SDE and granules. SDE indicates spray-dried extract.

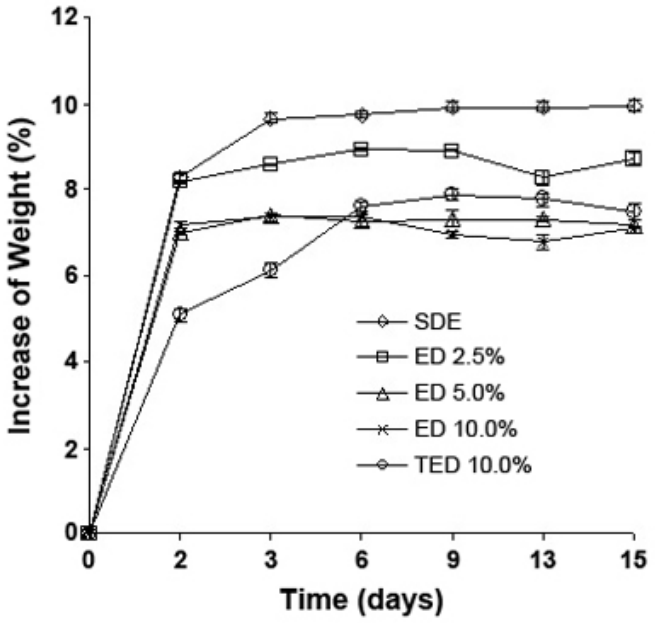

Figure 3. *Phyllanthus niruri* SDE, ED, and TED when stored at 25°C temperature and at 69% relative humidity. SDE indicates spray-dried extract; ED, granules; TED, tablet.

Statistical Analysis

The effects of the compression force and the proportion of Eudragit E on the tensile strength and the release of SDE (D_{80}) from the tablets were investigated by a 2-way analysis of variance (ANOVA), following a Tukey test to identify differences among the groups.[21] The calculations were performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 11.0).

Results and Discussion

Properties of SDE and Granules

The SDE used in this work, in accordance with USP 27 specifications, can be classified as a very fine powder with a mean diameter of 10.5 μm (Table 2). This very small size particle size may be responsible for the SDE's deficient flow properties, which is demonstrated by the CI of 20.22%.[22]

The granules clearly showed better micrometrical properties than the SDE did. No important differences of apparent density were observed among the granules, but the CI value demonstrated that granules with a higher proportion of Eudragit E had a lower CI, which is related to better powder bed stability and flow properties of the granules.[22] Furthermore, granules with a higher proportion of Eudragit E had enlarged granular diameters, which would explain their improved flow properties.

Indeed, the process of granule formation is mainly controlled by the Eudragit E, and its proportion within the formulation could influence the granule size formation.[9] We attempted to obtain SDE granules without Eudragit E, instead using only acetone as the granulating agent, but particle agglomeration was not possible, probably because not enough solid bridges formed among the SDE particles.[23]

No significant difference was observed among the granules regarding their real density (Table 2), but their real density was significantly lower than the real density of SDE. Considering the real density of the SDE (1.72 g/cm^3) and the Eudragit E (0.81 g/cm^3), the calculated real density of granules should have been 1.69, 1.66, and 1.62 g/cm^3 for granules with proportions of 2.5%, 5.0%, and 10.0% Eudragit E, respectively, but these values are higher than the experimental results. This fact suggests that some parts of the SDE can be soluble in acetone and crystallize after drying. Many factors may interfere with the true density of granules, mainly related to the binder proportion, binder solution viscosity, and solubility of formulation components.[24]

The electronic microphotography (Figure 1) indicates that wet granulation did not change the shape of the original SDE particles. Inside the granule it was possible to observe the preservation of the spherical particles of the SDE.

The gallic acid analysis was performed to verify the content of this substance in the granule as well as the existence of an interaction between SDE and Eudragit E. The chromatographic profile of the SDE shows 3 major peaks (Figure 2): 1, with a retention time of 6.5 minutes, was identified as gallic acid and used as a control substance for the SDE.[14] Identification of the 2 other peaks was not possible, but some pharmacology studies have demonstrated that gallic acid may be one of the substances responsible for the therapeutic activity of *P niruri*.[1] The chromatographic analysis demonstrated

Table 3. Mechanical Characteristics of the Tablets*

Tablet	TS (MPa) X ± s	Friability (%)	Total Porosity (%)	D_{80} (%) X ± s
ED 2.5% (2500)	1.19 ± 0.110	0.12	23.30	49.46 ± 0.79
ED 2.5% (1250)	0.66 ± 0.068	0.43	26.93	49.17 ± 2.44
ED 5.0% (2500)	1.26 ± 0.067	0.26	24.37	46.82 ± 1.42
ED 5.0% (1250)	0.59 ± 0.065	0.61	30.87	53.49 ± 3.67
ED 10.0% (2500)	1.17 ± 0.038	0.18	27.87	51.09 ± 2.58
ED 10.0% (1250)	0.55 ± 0.038	0.82	34.00	91.25 ± 2.47

*TS indicates tensile strength; D_{80}, dissolution of the SDE after 80 minutes; ED, granules.

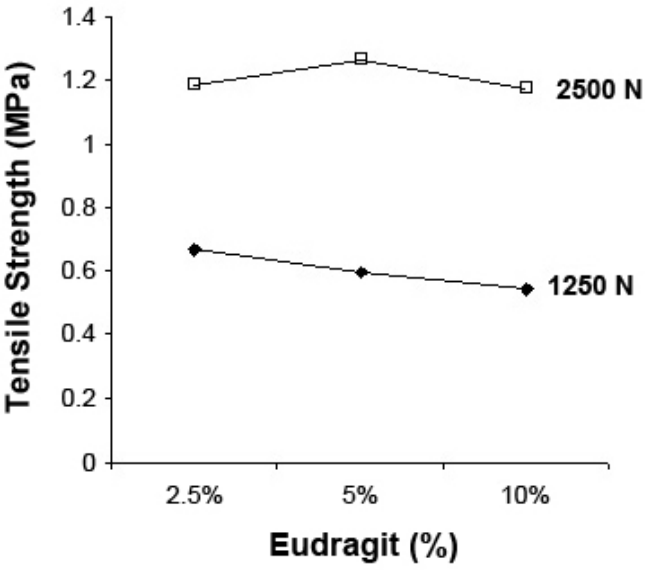

Figure 4. Interaction between force and Eudragit E concentration on tablets' tensile strength.

that neither Eudragit E nor the granulation method changed the chromatographic profile of the SDE, which confirms the absence of any significant chemical interaction among the formulation constituents. No change in the retention time of the major peaks or the appearance of degradation products was observed. The chromatographic profile of the granules is identical to the chromatographic profile of SDE (Table 2).

The moisture sorption assay demonstrated that the SDE exhibits a high sensitivity to moisture exposure (Figure 3). When stored at 25°C at an RH of 69%, the SDE showed a weight increase of almost 10% and became brownish and agglomerated. When the granules were stored at an RH of 69%, all of them had a lower weight increase than the SDE, but with different behavior. The granules with 2.5% Eudragit E had picked up the same humidity as the SDE by the second day of the experiment, but in the end, their moisture content was lower than that of SDE. On the other hand, granules containing 5% and 10% Eudragit E showed similar behavior to each other, and their moisture content was significantly ($P < .05$) lower than that of the granulate with 2.5% Eudragit E. Considering the particle agglomeration, less water sorption than for the SDE was expected, but the results demonstrated that in this case the smaller surface area of the granule was not the only important factor; the water sorption seemed to be also influenced by the proportion of Eudragit.

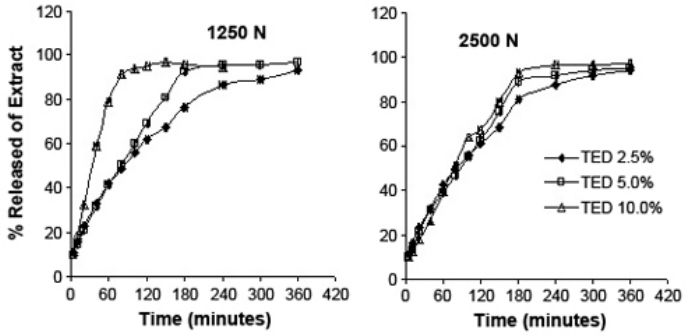

Figure 5. Dissolution profile of the tablets in accordance with the compression force. TED, tablet.

Mechanical Properties of Tablets

The mechanical characteristics of the tablets are recorded in Table 3. The total porosity shows some correlation with tensile strength, friability, and D_{80}, with correlation coefficients (r) of 0.8105, 0.9084, and 0.8122, respectively. In spite of the low values of correlation, the statistical analysis indicated a significant correlation ($P < .05$) between these parameters. Generally, tablets with high porosity tend to have low tensile strength, high friability, and consequently easier release of their content because the porous bed allows a higher uptake of water and consequently faster dissolution of the solutes.[25]

The ANOVA demonstrated that both factors studied, compression force and Eudragit proportion, significantly ($P < .05$) influenced both responses studied, tensile strength and D_{80}. However, the factor that had more influence on the tablets' tensile strength was compression force ($P = 2.01 \times 10^{-22}$). The increase of the compression force significantly enhanced the tensile strength of the tablets (Figure 4). On the other hand, higher Eudragit proportions tended to decrease the tablets' tensile strength, but the influence of Eudragit proportion ($P = 0.03$) was less significant than the influence of compression force. This fact may be related to the porosity of the tablets: higher Eudragit concentrations may create tablets with a higher porosity.

The dissolution assay of the tablets (Figure 5) showed a slow release of SDE. The formulation containing 10% Eudragit E produced with 1250 N of force had a faster dissolution and released more than 90% of the SDE within 80 minutes, while the other formulations released less than 55% of the

Table 4. Properties of the Tablets From Granules Containing 10% Eudragit on Initial Conditions and After the Exposure to Different Relative Humidity*

Relative Humidity	Tensile Strength (MPa) X ± s	Friability (%)	Dissolution Efficiency (%) X ± s
Initial	$0.77^a \pm 0.02$	0.82	$91.25^a \pm 2.48$
33%	$0.84^a \pm 0.05$	0.84	$97.20^a \pm 2.45$
69%	$0.54^b \pm 0.05$	0.99	$91.34^a \pm 4.45$

*Mean values in the same row followed by the same letter did not differ significantly (Tukey test; $P < .01$).

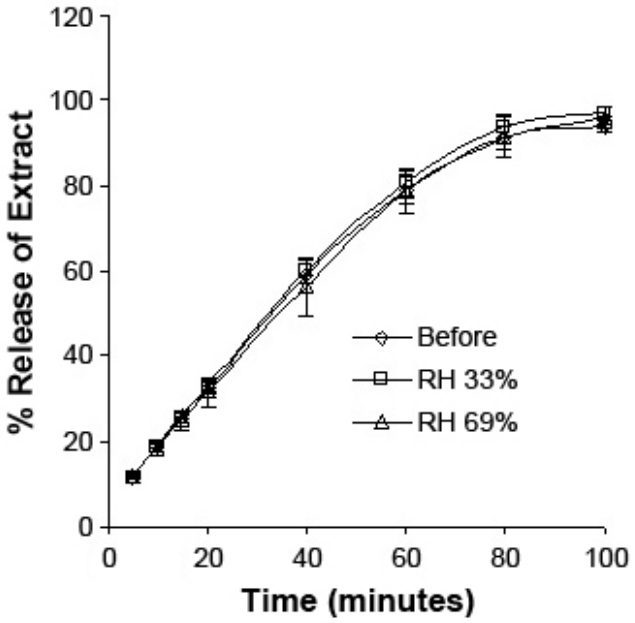

Figure 6. Release profile of spray-dried extract from the tablets containing Eudragit E before and after storage at 25°C and RH of 33% or 69%. RH indicates relative humidity.

SDE within this same time period (Table 3). However, the ANOVA demonstrated that both factors studied and their interaction significantly ($P < .01$) influenced the release time of the SDE.

The tablets subjected to the moisture stability test originated from formulations that contained granules (90% SDE and 10% Eudragit E) and 0.5% magnesium stearate and that were compressed at 1250 N. This formulation showed the best technological characteristics and the fastest SDE release. The moisture sorption assay (Figure 3) demonstrated that the tablets picked up moisture more slowly than the granules did, but at the end of the experiment the humidity content of the tablets was the same as that of the granules, so the granules' compression was not sufficient to reduce the final moisture of the tablet.

The mechanical characteristics of the tablets subjected to the moisture assay appear in Table 4. When the tablets were stored at 25°C and 33% RH, the characteristics of the tablets did not change significantly. On the other hand, when stored at 25°C and 69% RH, the tablets had a significant decrease of tensile strength, probably because of water sorption. However, the higher RH did not change the dissolution profile of the tablets (Figure 6).

Conclusions

The studies showed that the granules with Eudragit E as the granulating agent presented better flowability and lower moisture sorption behavior in comparison with the original SDE. The mechanical properties of the tablets were dependent on the Eudragit E proportion within the granules and the compression force; therefore, a higher proportion of Eudragit E with a smaller compression force resulted in better release of the SDE from the tablets. Thus, the tablets produced with granules containing 10% Eudragit E with a compression force of 1250 N were more adequate technologically.

Acknowledgments

The authors thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Conselho Nacional de Desenvolvimento Científico e Tecnológico, and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul for financial support and Prof Dr H. Derendorf of the University of Florida for comments.

References

1. Calixto JB, Santos ARS, Cechinel Filho V, Yunes RA. A review of the genus *Phyllanthus*: their chemistry, pharmacology and therapeutic potential. *Med Res Rev.* 1998;18:225–258.

2. Broadhead J, Rouan SKE, Rhodes CT. The spray-drying of pharmaceuticals. *Drug Dev Ind Pharm.* 1992;18:1169–1206.

3. Renoux R, Demazieres JA, Cardot JM, Aiache JM. Experimentally designed optimization of direct compression tablets. *Drug Dev Ind Pharm.* 1996;22:103–109.

4. Palma S, Luján C, Llabot JM, Barbosa G, Manzo RH, Allemandi DA. Design of *Peumus boldus* tablets by direct compression using a novel dry plant extract. *Int J Pharm.* 2002;233:191–198.

5. De Souza TP, Gómez-Amoza JL, Martínez-Pacheco R, Petrovock PR. Compression behavior of formulations from Phyllanthus niruri spray dried extract. *Pharmazie.* 2006;61:213–217.

6. De Souza TP, González Ortega G, Bassani VL, Petrovick PR. Avaliação da viabilidade de compressão direta de formulações contendo alto teor de produto seco nebulizado de *Maytenus ilicifolia. Acta Farm Bonaerense.* 2000;19:53–60.

7. Soares LAL, González Ortega G, Petrovick PR, Schmidt PC. Dry granulation and compression of spray-dried plant extract. *AAPS PharmSciTech.* 2005;6:E359–E366.

8. Petereit HU, Weibsbrod W. Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers. *Eur J Pharm Biopharm.* 1999;47:15–25.

9. Díaz LM, Souto C, Concheiro A, Gómez-Amoza JL, Martínez-Pacheco R. Evaluation of Eudragit E as major excipient in tablets of dry plant extracts. *STP Pharma Sci.* 1996;6:105–109.

10. Soares LAL, Bassani VL, González Ortega G, Petrovick PR. Total flavonoids determination for quality control of aqueous extractives from *Phyllanthus niruri. Acta Farm Bonaerense.* 2003;22:203–207.

11. Guyot JC, Arnaud P, Becourt P, et al. Commentaires relatifs aux méthodes générales d'analyse des formes orales solides récemment introduites dans les pharmacopées française et européenne. Rapport d'une commission SFSTP. *STP Pharma Pratiques.* 1995;5: 482–494.

12. Carr RL. Evaluation of flow properties of solids. *Chem Eng J.* 1965;72:163–168.

13. Lantz RJ. Size reduction. In: Liberman HA, Lachman J, Schwartz JB, eds. *Pharmaceutical Dosage Forms: Tablets.* New York, NY: Marcel Dekker; 1989:107–199.

14. De Souza TP, Holzschuh MH, Lionço MI, González Ortega G, Petrovick PR. Validation of a LC method for the analysis of phenolic compounds from aqueous extract of *Phyllanthus niruri* aerial parts. *J Pharm Biomed Anal.* 2002;30:351–356.

15. Martinez-Pacheco R, Gomez-Amoza JL, Vila Jato JL. Diseño de un sistema de registro de presión en máquinas de comprimir excéntrica. *Cienc Ind Farm.* 1985;4:207–211.

16. Fell JT, Newton JM. Determination of tablet strength by diametral-compression test. *J Pharm Sci.* 1970;59:688–691.

17. Summers MP, Enever RP, Carless JE. Influence of crystal form on tensile strength of compacts of pharmaceutical materials. *J Pharm Sci.* 1977;66:1172–1175.

18. Martin A, Bustamante P, Chun AH. *Physical Pharmacy.* London, UK: Lea & Febiger; 1993.

19. *USP 27, NF 22.* Rockville, MD: US Pharmacopeial Convention; 2003.

20. Nyqvist H. Saturated salt solutions for maintaining specified relative humidities. *Int J Pharm Tech Prod Tech Mfr.* 1983;4: 47–78.

21. Cochran WG, Cox GM. *Experimental Designs*. New York, NY: John Wiley & Sons; 1969.

22. Wells JI. *Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances*. London, UK: Ellis Horwood; 1988.

23. Planinsek O, Pisek R, Trojak A, Srcic S. The utilization of surface free energy parameters for the selection of a suitable binder in fluidized bed granulation. *Int J Pharm.* 2000;207:77–88.

24. Wade A, Weller PJ. *Handbook of Pharmaceutical Excipients*. London, UK: Pharmaceutical.

25. Caramella C, Ferrari F, Bounferoni MC, Rouchi M. Disintegrants in solid dosage forms. *Drug Dev Ind Pharm.* 1990;16:2561–2577.