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Research Article

Compressional Behavior of a Mixture of Granules Containing High Load of *Phyllanthus niruri* Spray-Dried Extract and Granules of Adjuvants: Comparison between Eccentric and Rotary Tablet Machines

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Abstract. The purpose of this paper was to evaluate the compressional behavior of granules containing high load of a *Phyllanthus niruri* spray-dried extract in eccentric (ETM) and rotary (RTM) tablet presses. Tablets were constituted by spray-dried extract granules (SDEG, 92%), excipient granules (EXCG, 7.92%), and magnesium stearate (0.08%). SDEG was obtained by dry granulation and EXCG, composed of microcrystalline cellulose (62.9%) and sodium starch glycolate (37.1%), by wet granulation. Particle size distribution was fixed between 0.250 and 0.850 mm. Tablets did not evidence any mechanical failures, such as lamination or capping, or anomalous weight variation in either tablet machine types. Upper and lower tablet surface photomicrographs from ETM and RTM tablets showed differences in porosity and texture. Different RTM speeds suggested the visco-plastic behavior of the formulation, since, by slowing down rotation speeds, the tensile strength of the tablets increased significantly, but the porosity and disintegration time were not affected. Tablets produced in RTM showed lower friability and porosity than ETM tablets, which did not reflect on higher tensile strength. The EXCG distribution at upper and lower surfaces from ETM and RTM tablets was quantified by image analysis and evaluated through statistical methods. Spray-dried extract release was not influenced by the type of equipment or operational conditions to which the compacts were submitted. Construction and operation differences between both tablet presses influenced the final product, since tablets with similar tensile strength, made by distinct tablet machines, exhibited different quality parameters.

KEY WORDS: eccentric tablet machine; image analysis; *Phyllanthus niruri*; rotary tablet machine; spray-dried extract.

INTRODUCTION

Phyllanthus niruri L is a medicinal plant that has its popular use worldwide associated to the treatment of urolithiasis (1). The technological development of *P. niruri* spray-dried extract and solid dosage forms have been widely studied in our research group that found non-favorable condition for direct compression (2), leading to the idealization of granules that were produced by dry (3) and wet (4) granulation for further compression. However, it was only in the course of this study that tablets were produced in a rotary tablet machine (RTM).

During the development of tablets, it is indispensable to know the role the mixture to compress plays during the compression cycle in eccentric and rotary tablet machines, models available for these studies.

Construction and operational differences between tablet machines can vary the characteristics of the final product, even though they come from the same tablet formulation (5). While eccentric tablet machines work slower, usually with one compression station and application of compression force in one direction (uniaxial), rotary tablet machines work at higher speed and the compression force is produced by lower and upper punches, while both are moving and penetrating inside the die. Besides, rotary tablet machines present what is called dwell time, an event during the compression phase when no vertical movement of the punches is verified and the distance between punch faces is minimal and constant (6,7).

Since pharmaceutical products present time-dependent deformation (plastic and elastic), the presence of dwell time can influence the mechanical properties of the formed tablet (8,9) leading to a tablet with different characteristics from those derived from eccentric tablet machines.

The purpose of this study was to investigate the compressional behavior of a tablet mixture containing two types of granules in eccentric and rotary tablet machines, regarding technological and surface properties of the tablets by applying a technological test and image analysis.

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MATERIALS AND METHODS

Materials

Granules containing high load of *Phyllanthus niruri* spray-dried extract (SDEG) were obtained by dry granulation (10,11). Particle size distribution was fixed between 0.250 and 0.850 mm. Excipient granules (EXCG), composed of microcrystalline cellulose (Microcel MC 101, Blanver/Brazil) (62.9%) and sodium starch glycolate (Explosol, Blanver/Brazil) (37.1%), were obtained by wet granulation (3). The granules produced were sieved and separated using 0.850, 0.710, 0.600, 0.500, 0.355, 250, and 125 mm sieves for further reconstitution in the same particle size distribution as SDEG.

Preparation of the Tablet Mixture

The tablet mixture was composed of 92% of SDEG, 7.92% of ECXG, and 0.08% of magnesium stearate (3). At this ECXG proportion, the tablets produced had, theoretically, 3% of starch glycolate in their constitution. Both granules were blended in a cubic mixer (Erweka KM5/Germany) for 20 min and for additional 5 min after adding magnesium stearate.

Characterization of the Tablet Mixture (TM)

Bulk and Tapped Densities, Hausner's Ratio, and Carr's Index (12,13)

The equivalent of 10.0 g of the tablet mixture (n=3) was placed into a 25-mL cylinder and the initial volume was measured for bulk density determination. Using a mechanical tapping device (J. Engelsman/Germany), the tapped density was determined. Hausner's ratio and Carr's index were calculated from the values obtained.

Density

The density of each component of the tablet mixture (SDEG and EXCG) was measured using an air comparison pycnometer (Accupyc 1330, Micromeritics/USA). The calculated real density (ρ_{calc}) of the tablet mixture was determined by Eq. (1).

$$\rho_{calc} = \sum \rho_i \cdot c_i \quad (1)$$

where ρ_i is the real density of each component of the formulation and c_i the proportion of each component in the final tablet mixture.

The resulting blend was compressed into tablets, as described below.

Preparation of Tablets in Eccentric Tablet Machine (ETM)

Tablets were produced in a single punch tablet press EK0 (Korsch/Germany) using flat-faced punches (12 mm) in three different compressional forces: 40, 60, 80 N, nominated as EM40, EM60, and EM80, respectively. This compressional force range was based on previous force×hardness behavior studies (3,4). In each case, a batch of 100 tablets of 500 mg was prepared.

Preparation of Tablets in Rotary Tablet Machine (RTM)

A ten-station rotary tablet machine 10/PSC (LAWES 2000/Brazil), also using flat-faced punches (12 mm), was used to produced tablets in three different velocities: 15, 22.5, and 30 rpm. These velocities were chosen according to instruction provided by the manufacturer, based on the lowest, intermediate, and highest velocities in which the machine works. In each case, a batch of 100 tablets of approximately 500 mg was prepared and named RM15, RM22, and RM30.

Characterization of Tablets from ETM and RTM

Dimensional Evaluations

Weight (Mettler-Toledo International/USA), diameter, and thickness from 20 tablets of each batch were measured with a digital micrometer (Mytutoyo 0–25 mm/1″/Japan) 24 h after compression; hence, apparent density could be calculated.

Tensile Strength (14)

The crushing strength (hardness tester Schleuniger/Germany) and tensile strength (TS, MPa) were also determined (Eq. 2):

$$TS = \frac{2 \times F}{\pi \times D \times h} \quad (2)$$

where F is the crushing strength (N), D is the diameter of the tablet (mm), and h the thickness of the tablet (mm).

Radial Elastic Recovery (15)

Radial elastic recovery (ER%) of 20 tablets of each batch was calculated after Eq. (3).

$$ER\% = \frac{D_{24} - D_0}{D_0} \times 100 \quad (3)$$

where D_{24} is the diameter of the tablet 24 h after compression and D_0 the matrix diameter.

Volume Recovery (16)

Volume recovery (V_r, Eq. 4) was determined for tablets produced in ETM only. In the compression phase, the distance between both punches' heads (Δp) was measured using a digital micrometer. Also, compression chamber volume at compression moment (V_{cp}, Eq. 5), matrix radius (r_m, 6 mm), and tablet volume after 24 h (V_t) were determined.

$$V_r = \frac{V_t - V_{cp}}{V_t} \times 100 \quad (4)$$

$$V_{cp} = \pi \times r_m^2 \times \Delta p \quad (5)$$

Table I. Technological Characterization of SDEG, TM, and EXCG

Experiment	Experimental data mean±SD (DPR%)		
	SDEG	TM	EXCG
Real density (g/cm^3)	1.634±0.0007 (0.04)	1.627	1.560
Bulk density (g/ml)	0.6853±0.01 (1.16)	0.6076±0.01 (2.63)	0.1841±0.004 (2.17)
Tapped density (g/ml)	0.6963±0.01 (1.00)	0.6468±0.01 (2.94)	0.2009±0.01 (3.48)
Bulk volume (ml/g)	1.4592	1.6458	5.4318
Tapped volume (ml/g)	1.4362	1.5461	4.9776
Carr's index (%)	2.04±0.04 (1.96)	6.06±0.18 (3.03)	8.29±1,32 (15.97)
Hausner's ratio	1.02±0.01 (0.88)	1.06±0.02 (1.98)	1.09±0.02 (1,.7)
Repose angle (°)	21.82±0.87 (3.99)	22.55±0.57 (2.53)	27.14±1.00 (3.68)

SDEG spray-dried extract granule, *TM* tablet mixture, *EXCG* excipient granule

Porosity (17)

Porosity (ε) was calculated after apparent density (ρ_{ap}, derived from tablet weight and volume) and real density (ρ_{calc}), as shown by Eq. (6).

$$\varepsilon = \left(1 - \frac{\rho_{ap}}{\rho_{calc}}\right) \times 100 \quad (6)$$

Scanning Electron Microscopy

Scanning electron microscopy (SSX-550, Shimadzu/USA) was applied in order to visualize the structure of the upper and lower surfaces of the tablets.

Friability (18)

Friability (friabilator apparatus Roche, J. Engelsmann/Germany) was determined for 20 tablets as the percentage of weight loss after 5-min tumbling, following USP 30 specifications.

Disintegration Time (18)

Disintegration time (disintegration tester coupled to a JEL-70 motor, J. Engelsman/Germany) was determined in water at 37±1°C and the result expressed as the average of six determinations.

Dissolution Profile (18)

Release of spray-dried extract (SDE) from tablets was determined in a paddle dissolution tester (PTW SIII Pharma Test/Germany) following method II, at 100 rpm, as described in USP 30 and water at 37±1°C as dissolution medium. Concentration of SDE was performed by direct spectrophotometry at 275 nm (Hewlett-Packard 8452A/USA) every 5 min during 40 min, total time of the experiment.

Surface Image Analysis (19)

Excipient granules (EXCG) distribution at the upper and lower surfaces of the EM40, EM60, EM80, RM15, RM22, and RM30 tablets was evaluated by imaging analysis. The tablets were allocated in a cubic box with controlled and constant luminosity (bright lamp, 15 W, Empalux) in order to maintain and prevent the influence of brightness over the pictures taken. Pictures were taken from both surfaces of 20 tablets of each type using a digital camera (Sony Cyber-shot DSC-W50) which was placed 23 cm from the tablets' surface, distance kept constant during all the experiment. The initial digital treatment, contrast enhancement, and transformation to black and white images was made using Photoshop CS3 (Adobe/USA), having the same treatment for each image. The obtained files were handled with a free image analysis software (20) (ImageJ 1.37v, National Institute of Health/USA) when they were cut in identical circles of 113.04 mm^2 area in order to delimit the space for evaluation. The characteristics obtained for each surface were the number of particles of EXCG, the total area occupied by this granule,

Table II. Technological Characterization of Tablets Produced in Eccentric Tablet Machine (Mean±SD)

Tablet code	Crushing strength (N)	Tensile strength (MPa)	Mean weight (mg) (DPR%)
EM40	40.9±3.54	0.62±0.04	501.07^b±3.91 (0.78)
EM60	63.0±1.83	0.98±0.09	506.32^a±6.54 (1.29)
EM80	81.0±2.74	1.32±0.04	496.49^c±4.00 (0.80)
			501.3±0.004

Mean values in a column followed by the same letter did not differ significantly (Tukey test, α=0.05).
SDEG spray-dried extract granule, *TM* tablet mixture, *EXCG* excipient granule

Table III. Dimensional Parameters of Tablets Produced in Eccentric Tablet Machine (Mean±SD)

Tablet code	ρ_{ap} (g/cm^3)	ε (%)	ER (%)	R_v (%)
EM40	$1.27^c \pm 0.01$	$22.13^a \pm 0.65$	$1.27^a \pm 0.03$	$65.81^c \pm 0.09$
EM60	$1.31^b \pm 0.02$	$19.30^b \pm 1.04$	$1.14^b \pm 0.03$	$67.97^b \pm 0.07$
EM80	$1.34^a \pm 0.01$	$17.53^c \pm 0.73$	$1.03^c \pm 0.05$	$69.62^a \pm 0.08$

Mean values in a column followed by the same letter did not differ significantly (Tukey test, $\alpha=0.05$)
ρ_{ap} apparent density, ε porosity, *ER* radial elastic recovery, R_v volume recovery

and the percentage this area represents over the surface. The value of the average area of the particles was calculated dividing the value of the total area occupied by these granules by the number of particles.

Statistical Analysis

The linear regression analysis, the one-way analysis of variance (ANOVA) followed by Tukey multi-comparison test, *F* test, and Student's *t* test were employed at a confidence level of $P<0.05$ in order to investigate differences among the studied groups of samples, and the softwares Microsoft Excel® and Statgraphics Plus 5.0 were used.

RESULTS AND DISCUSSION

Tablet Mixture Characterization

The results for technological characterization of the spray-dried extract granule (SDEG), tablet mixture (TM), and excipient granule (EXCG) are shown in Table I. One may observe that TM has intermediate technological behavior in comparison to both origin granules, indicating that, in spite of EXCG being the smallest portion of TM, it influences these characteristics in the final mixture. TM shows good packing and flowability, showed by Hausner's ratio value lower than 1.25 (13), Carr's index lower than 12 (12), and repose angle lower than 25° (12).

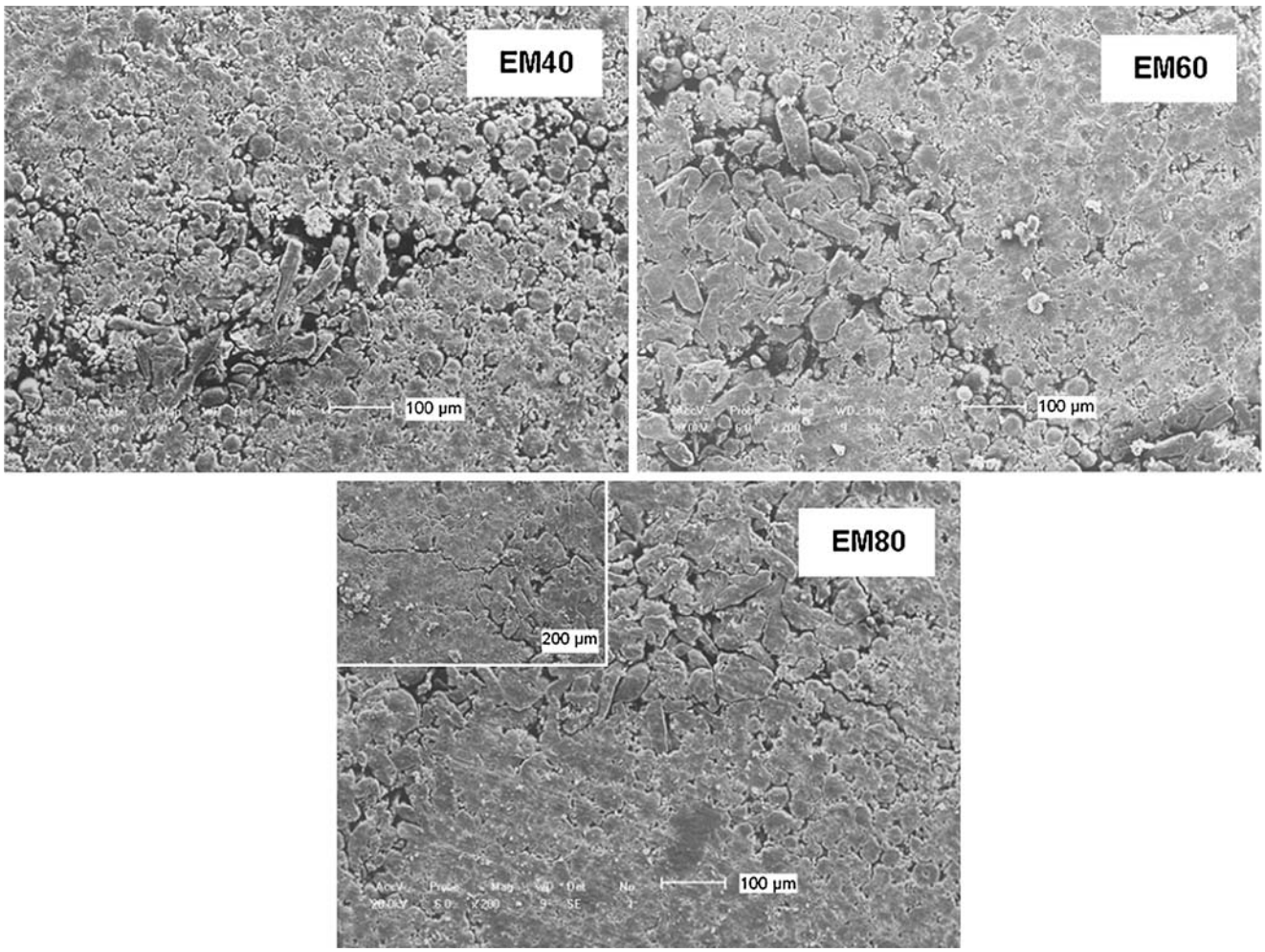

Fig. 1. Microphotography of upper tablet surfaces obtained in eccentric tablet machine

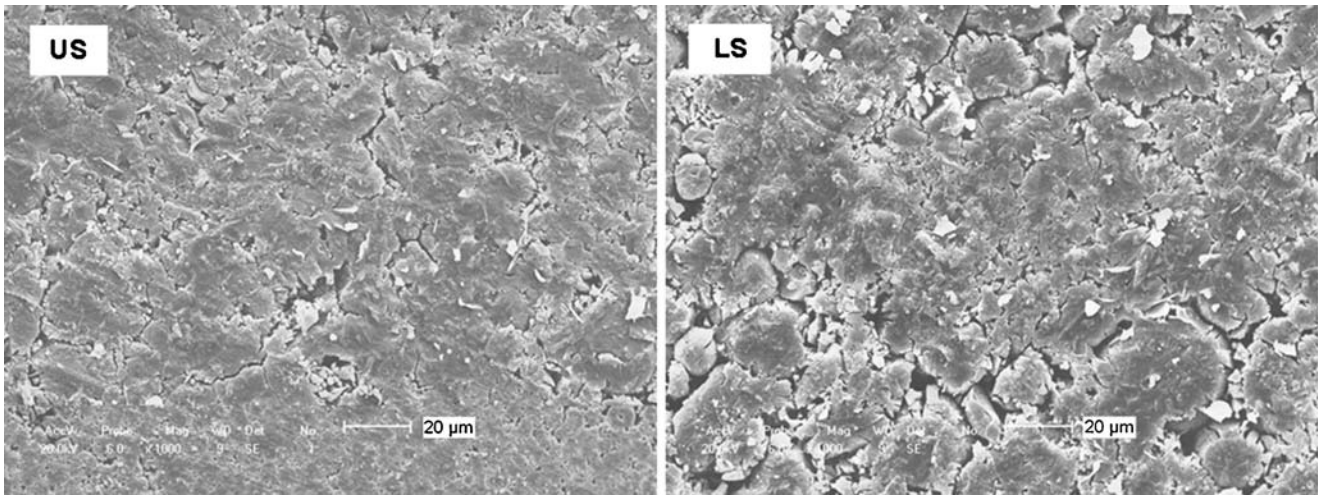

Fig. 2. Microphotographs of upper (*US*) and lower (*LS*) surfaces of EM80 tablet (×1,000)

Tablets Produced in ETM

Three types of tablets, distinguished by their crushing and tensile strength (Table II), were produced in an eccentric tablet machine. None of it evidenced lamination or capping. Table II also shows their mean weight, which was satisfactory, since it has accomplished pharmacopeial specifications (18) (maximum variation of 5%). Low relative standard deviation (RSD%) values pointed out good feeding conditions allowed by the feed system of the ETM and also by the flowability of the tablet mixture, previously presented in Table I.

Recovery volume (R_v), Table III, was calculated in order to quantify the elastic behavior of tablets, which is related to the volume the tablet shows at the point of maximum compression force and after 24 h. Denser tablets showed higher R_v (statistically different, α=0.05), indicating a tendency of higher elastic recovery with densification increase. On the other hand, radial elastic recovery (ER) was lower for denser tablets. The discrepancy between ER and R_v values can be explained by the way compression pressure is applied, in an axial direction. So, the main elastic recovery is observed in the height of the tablets after compression and 24 h after it.

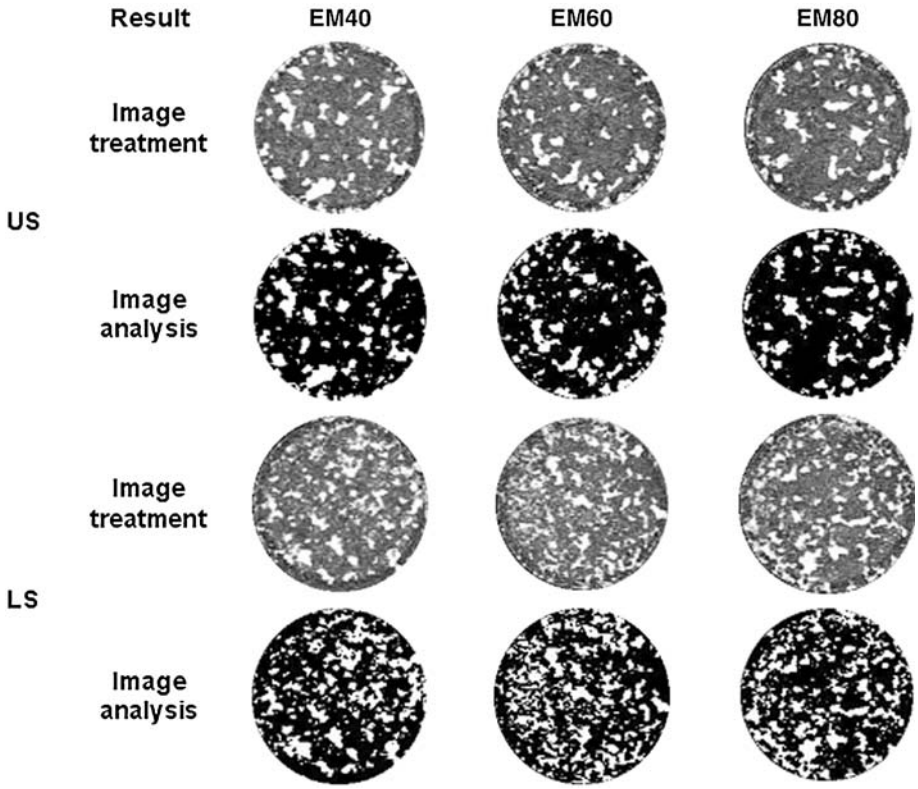

Fig. 3. Examples of images of EM40, EM60, and EM80 deriving from treatment and analysis (the *white spots* correspond to EXCG granules)

Table IV. Evaluation of the Presence of EXCG after Image Analysis in Upper and Lower Surfaces of Eccentric Machine Tablets (Mean±SD)

Surface	Data	EM40	EM60	EM80
Upper	Number of EXCG particles	65b±12.23	73a±10.75	73a±11.38
	Total area occupied (mm^2)	26.27a±4.78	22.47ab±2.12	24.65b±2.15
	Average area (mm^2)	0.41a±0.08	0.31b±0.03	0.34b±0.06
	Representative fraction (%)	23.24a±4.23	19.88b±1.88	21.81ab±1.90
Lower	Number of EXCG particles[a]	167±18.60	171±17.53	180±22.63
	Total area occupied[b] (mm^2)	37.08±4.30	36.36±3.71	37.00±1.88
	Average area[c] (mm^2)	0.23±0.04	0.21±0.03	0.21±0.04
	Representative fraction[b] (%)	32.80±3.80	32.17±3.28	32.73±1.66

Particles are referred to EXCG (excipient granules). Mean values in a line followed by the same letter did not differ significantly (Tukey test, $\alpha=0.05$)

[a] One-way ANOVA: $F_{calc}=2.27<F_{0.05(19.57)}=3.16$

[b] One-way ANOVA: $F_{calc}=0.26<F_{0.05(19.57)}=3.16$

[c] One-way ANOVA: $F_{calc}=0.98<F_{0.05(19.57)}=3.16$

Porosity (ε) presented expected behavior, since harder and denser tablets showed lower and statistically different porosity, as well as their density.

Scanning electron microscopy (Fig. 1) showed that the increase in compression force, and tablet hardness as a consequence, modified the structure of the tablets' surface, in that less smooth surfaces were presented by the hardest tablets. These results corroborate those presented by the calculated porosity and are more visible in sample EM40 and EM80. It is also shown that the most porous points at the surface are those where EXCG are placed and where both EXCG and SDEG granules are connected. In this region, the preservation of the morphology of primary particles, like SDE and microcrystalline cellulose, is also presented. One may notice that only in sample EM80 does the junction between granules present cracks, indicating that a harmful effect over bonding can be observed with the increase in the compression force.

It was possible to observe structural differences between upper (US) and lower (LS) surfaces of the tablets, mainly because of the uniaxial compression presented by eccentric tablet machine. The photomicrographs in Fig. 2 exemplify this situation for tablet EM80, where the upper surface (US) exhibits narrower particles of SDE, primary particles of the granules.

Analyses via images were able to show a disparity of distribution of both granules between US and LS, as can be seen in Fig. 3, an example of digital treated images of EM tablets. The possible reason for a significant presence of minor particles at the LS is the segregation of these particles. Once the tablet mixture is composed of a granulometric distribution range of 0.250 to 0.850 mm, the event of segregation by percolation could have occurred. This phenomenon is characterized by the tendency that minor particles have over bigger particles to set at the bottom of a granule bed, which is triggered especially by some disturbance/vibration during tableting procedure (21,22).

The data obtained for each surface after image processing using software were the number of particles of EXCG, the average size of the particles, the total area occupied by this granule, and the percentage this area represents over the surface (Table IV).

The greater number and minor average area of EXCG particles in the LS can be easily observed and confirmed by their quantification during image analysis.

Once the area evaluated was the same for the different tablets, the values obtained could be directly compared. The representative fraction occupied by the EXCG granules ranged around 3.5 percentual points and 0.7 percentual points when evaluating the US and LS, respectively, considered statistically equal between the evaluated lower surfaces. But, when comparing both surfaces in each type of tablet, this difference is greater and considered statistically different ($|t_{calc}|=10.99>t_{0.05(4)}=2.78$; P value $=0.0004<\alpha=0.05$).

Table V. Friability and Disintegration Time of Tablets Produced in ETM (Mean±SD)

Tablet code	Friability	Disintegration time (min)
EM40	0.83	14.51[b]±1.08
EM60	0.37	16.49[a]±0.52
EM80	0.31	16.56[a]±1.14
		15.85±1.16

Mean values in a column followed by the same letter did not differ significantly (Tukey test, $\alpha=0.05$)

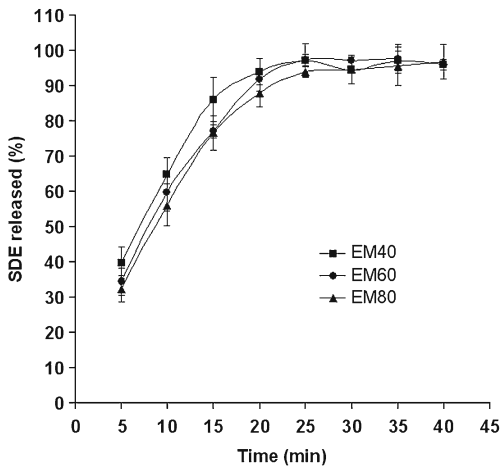

Fig. 4. *Phyllanthus niruri* SDE release by tablets produced in eccentric tablet machine

Table VI. Technological Characterization of Tablets Produced in Rotary Tablet Machine (Mean±SD)

Tablet code	Crushing strength (N)	Tensile strength (MPa)	Mean weight[a] (mg) (DPR%)
RM15	69.14a±6.14	1.16a±0.11	485.82±3.11 (0.64)
RM22	67.57ab±3.25	1.11ab±0.05	487.22±6.07 (1.24)
RM30	62.14b±4.18	1.02b±0.06	486.33±5.03 (1.03)
Mean	66.28±3.67	1.10±0.07	486.4±0.76

Mean values in a column followed by the same letter did not differ significantly (Tukey test, $\alpha=0.05$)
[a] One-way ANOVA: $F_{calc}=0.42<F_{0.05(19.57)}=3.16$

The total area occupied by EXCG particles are very similar considering the same surface, but at the lower surface, the values are smaller, independent of the tablet hardness. This consideration sustains the hypothesis that percolation might be the mechanism involved in the segregation of the particles, like previously discussed.

Friability (Table V) presented lower values for harder tablets and acceptable standards, lower than the maximum compendial limit (1.5%) (18). Starch glycolate, the super-disintegrant in EXCG formulation, has the capacity of high water uptake promoting fast tablet disintegration (23). Since the most porous points at the surface are related to EXCG, porosity may have positively influenced disintegration time, once it was lower for the most porous tablet (EM40) and statistically different from the others, too.

SDE release (Fig. 4), evaluated by the dissolution assay of the tablets, was almost 85% within the first 15 min, especially for EM40. Maximum SDE release was reached around 25 min for the three samples, being (mean±SD) 96.98± 2.72%; 98.77±4.10%, and 96.77%±4.83 for EM40, EM60, and EM80, respectively, considered statistically equal (one-way ANOVA—$F_{calc}=0.84<F_{0.05(5,15)}=3.68$). In general terms, it can be stated that different tensile strengths, porosities, and densities had no influence over SDE release in tablets produced at ETM.

Tablets Produced in RTM

Rotary tablet machine was set to produce tablets of similar weight (500 mg) and intermediate tensile strength (60 N) to those produced in eccentric tablet machine. Three different velocity productions were used. It was observed that the increase in production speed led to an increase in ejected tablets' temperature. In this study, this identification was made by sense of touch, in an empirical way. The occurrence of this phenomenon is due to the friction between the granules and between the tablet and compression tooling during ejection, which is higher with the increase in velocity production (24). The presence of lubricant in the formulation delays temperature increase, but does not avoid it (25). Also, the densification of the granules (plastic, elastic, and fragmentative deformation) itself is responsible for heat liberation during compression (26).

RM tablets showed uniformity of weight and low RSD % values (Table VI), pointing out that the change in production velocity did not influence tablet weight. Some factors that can affect tablet weight during die filling, like centrifugal force and machine vibration, can be altered by changes in rotation velocity (27). However, the filling mechanism presented by rotary tablet machines does not permit the influence of these factors over tablet weight (28). Since low RSD% values were found for ETM tablets as well, it is possible to state that tablet mixture flowability was decisive for weight maintenance. Capping was not evidenced, indicating that air was not trapped inside the die, even at the highest velocity (29).

The increase in production velocity led to tablets with lower tensile strength (Table VI), especially when compared values at 15 and 30 rpm. Association by linear regression between tensile strength and production speed is verified, where the increase of velocity provokes tensile strength decrease in an order of 0.973 MPa/rpm. The decrease in speed production causes the increase of the dwell time, situation that favors time-dependent deformation (plastic and elastic) leading to harder tablets (9,30,31). The tablet mixtures studied in this work showed plastic and brittle deformation mechanism, verified by the application of the Heckel model, with Py value of 229.01 MPa (32), a condition that explains the circumstance presented by the relation between speed production and tensile strength.

Table VII. Dimensional Parameters of Tablets Produced in Rotary Tablet Machine (Mean±SD)

Tablet code	ER (%)	ε^a (%) $\bar{x} \pm s$	$\rho_{ap}{}^b$ (g/cm^3) $\bar{x} \pm s$
RM15	0.85b±0.08	17.40±0.73	1.34±0.01
RM22	1.14a±0.04	17.62±1.04	1.34±0.02
RM30	0.80b±0.07	17.51±0.59	1.34±0.01
	0.93±0.18		

Mean values in a column followed by the same letter did not differ significantly (Tukey test, $\alpha=0.05$)
ER radial elastic recovery, ε porosity, ρ_{ap} apparent density
[a] One-way ANOVA: $F_{calc}=0.79<F_{0.05(19.57)}=3.16$
[b] One-way ANOVA: $F_{calc}=0.50<F_{0.05(19.57)}=3.16$

Even though tensile strength showed dependency upon different production velocities, porosity (Table VII) did not show the same tendency, since it was statistically the same in 15, 22.5, and 30 rpm and different tensile strength values. This situation is probably influenced by the presence of dwell time during compaction (33).

Radial elastic recovery (Table VII) was statistically the same for RM15 and RM30. Tablets RM22 showed superior expansion, indicating that speed production has not influenced ER values. Elastic recovery is a complex process and difficult to predict, since it relies upon disposition and arrangement particles have inside the tablet, and a particular state of each formed tablet and formulation (15).

EM80 tablet had similar dimensional characteristics to tablets RM15, RM22, and RM30. This similarity is reflected on near porosity values. Nevertheless, crushing and tensile

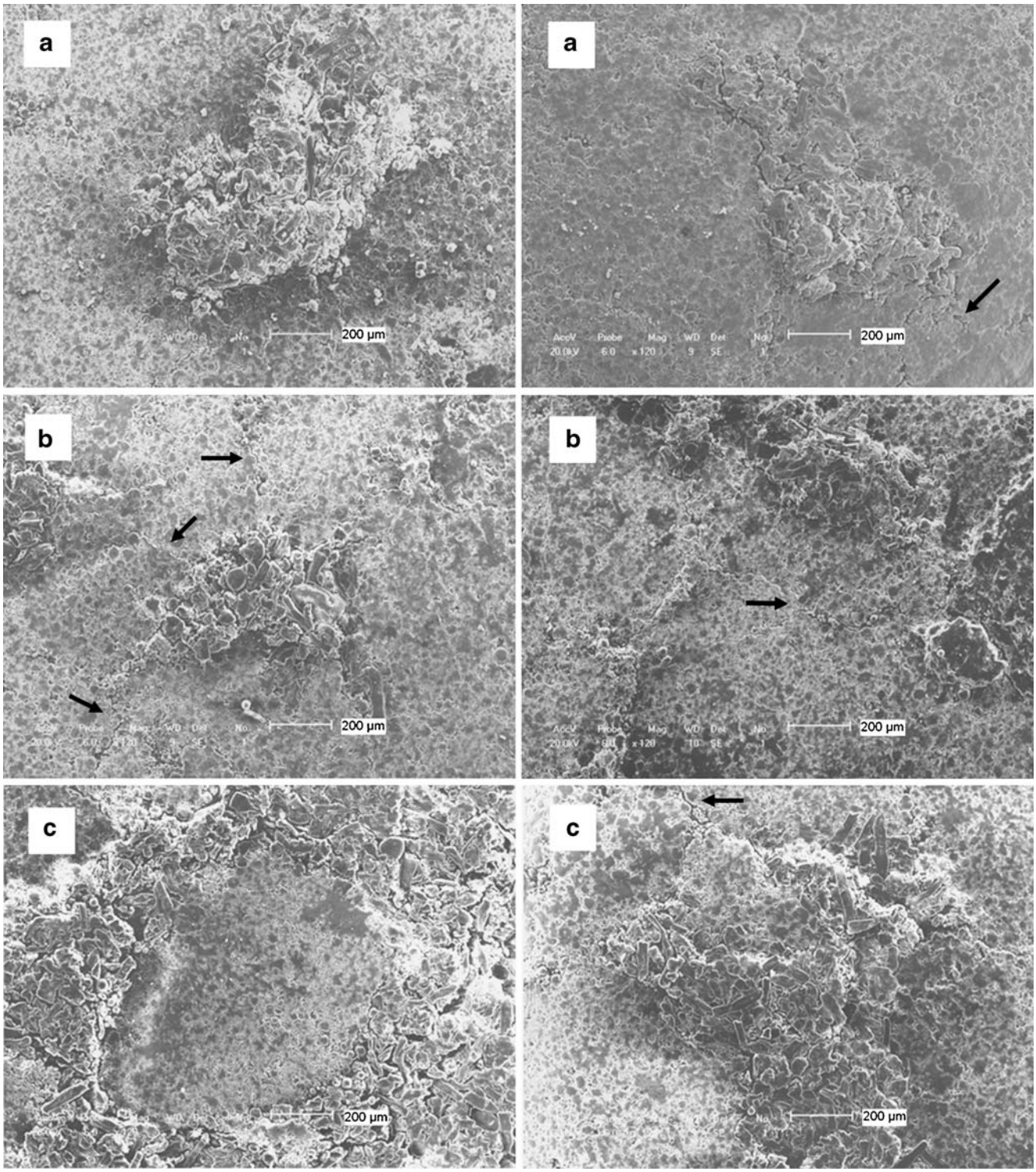

Fig. 5. Microphotographs from upper and lower surfaces from RM15 **a**, RM22 **b**, and RM30 **c** (*arrows* indicate rupture points)

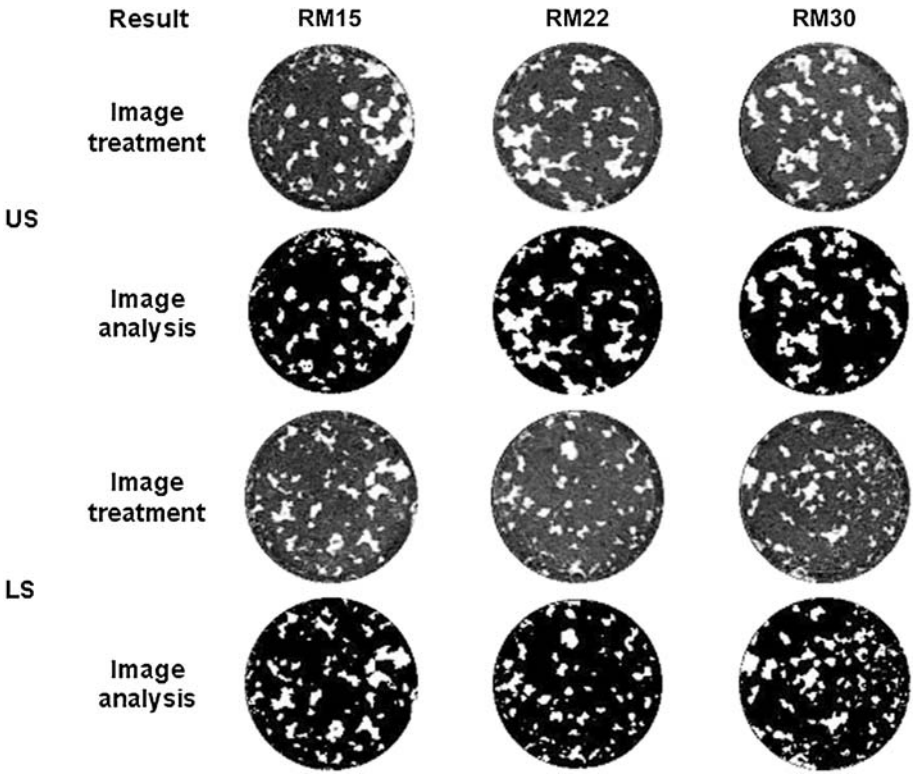

Fig. 6. Examples of images of RM15, RM22, and RM30 deriving from treatment and analysis (the *white spots* correspond to EXCG granules)

strength for EM80 tablets are superior for RM tablets, indicating influence of machine construction.

By analyzing the photomicrographs (Fig. 5) of the tablets produced in RTM, it was hardly possible to make distinctions between both upper and lower surfaces. The junction between vicinal granules is possibly related to the cracks indicated in Fig. 5, where the presence of SDE spherical particles is not visible.

As discussed before, the tablet mixture studied in this study presents time-dependent deformation, since dwell time influences the tensile strength of the tablets. EXCG present higher intrinsic plastic deformation (3) than SDEG (10), mostly related to the excipients on the formulation. Besides, EXCG is a product of wet granulation and SDEG of dry granulation, and, in general terms, dry granulation products lose their plastic deformation capacity during this technological process (34). This explains the situation showed in Fig. 5, upper surface of RM80, where a SDEG, surrounded by EXCG, appears to be placed under the surface estimated by the excipient granules. This situation can also be observed in the other photomicrographs and is an evidence of time-dependent deformation of the tablet mixture, especially allied to the EXCG. Because of it, RM tablets showed more rough surfaces, in comparison to the surfaces presented by tablets produced in the ETM.

In terms of distribution of EXCG through both surfaces, image analysis was able to show that upper surface presents higher frequency of excipient granules than lower surfaces. This situation is qualitatively demonstrated in Fig. 6.

Evaluation of parameters (Table VIII) at the upper surface was able to show that, statistically, the average area occupied by EXCG particles was the same independent on

Table VIII. Evaluation of the Presence of EXCG after Image Analysis in Upper and Lower Surfaces of Rotary Machine Tablets (Mean±SD)

Surface	Data	RM15	RM22	RM30
Upper	Number of EXCG particles	77a±15.17	57b±22.53	48b±6.77
	Total area occupied (mm^2)	24.14a±4.92	18.65b±3.53	20.07b±2.52
	Average area[a] (mm^2)	0.35±0.19	0.37±0.13	0.43±0.08
	Representative fraction (%)	21.36a±4.36	16.44b±3.11	17.75b±2.23
Lower	Number of EXCG particles	88b±14.87	101b±26.98	118a±11.69
	Total area occupied (mm^2)	21.01a±3.70	16.49b±1.84	19.48a±2.02
	Average area (mm^2)	0.24a±0.06	0.18b±0.06	0.17b±0.03
	Representative fraction (%)	18.58a±3.28	14.59b±1.63	17.23a±1.79

Particles are referred to EXCG (excipient granules). Mean values in a line followed by the same letter did not differ significantly (Tukey test, $\alpha=0.05$)

[a] One-way ANOVA: $F_{calc}=1.62<F_{0.05(19.57)}=3.16$

Table IX. Friability and Disintegration Time of Tablets Produced in Rotary Tablet Machine (Mean±SD)

Tablet code	Friability (%)	Disintegration time[a] (min)
RM15	0.87	14.27±0.93
RM22	0.57	14.48±1.00
RM30	0.09	14.03±0.58
Mean±SD		14.26±0.22

[a] One-way ANOVA: $F_{calc}=0.35<F_{0.05(4.12)}=6.93$

the production velocity. However, for 15 rpm, the other parameters are not statistically the same, as shown by applying Tukey's test after ANOVA. The same situation was not visualized at the lower surface, where average area and the total area occupied by the excipient granules were the same in RM22 and RM30 tablets, while the number and the representative fraction were dissimilar in these samples.

Therefore, a situation in which it is not possible to predict the behavior of granule distribution through the entire tablet in different velocity productions arises.

The pattern visualized in the surfaces of the tablet produced in both eccentric and rotary tablet machines (Tables IV and VIII) was independent of the tablet hardness or production velocity, respectively. For RTM tablets, the differences between both surfaces are not easily perceptive as for ETM. In this manner, by comparing the values of the four different characteristics evaluated, one can observe that there are differences in tablets produced in distinct tablet machine types.

The association of a higher number of EXCG particles with a smaller average area was found in the lower surface rather than the upper surface of both EM and RM tablets. So, it can be assumed that, irrespective of the tablet machine used, this tablet mixture has a tendency to suffer segregation by percolation mechanism occasioned by the granulometric range. In a rotary tablet machine was verified a tendency of increased concentration of pellets at the upper surface while the velocity of production was raised (19). The authors attested that the presence of powder excipient was important for this condition, in a way that bigger particles are noticed at upper, while smaller particles are presented at the lower surface.

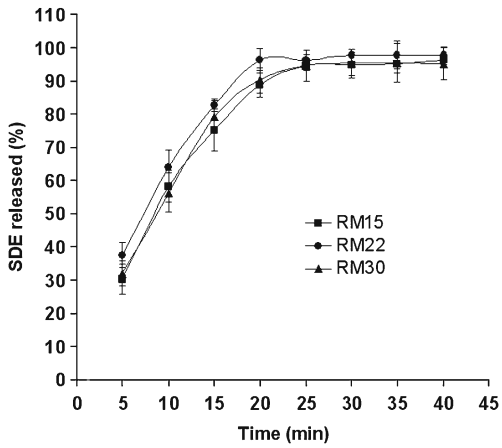

Fig. 7. *Phyllanthus niruri* SDE release by tablets produced in rotary tablet machine

Friability (Table IX) showed weight loss values less than 1%, fulfilling compendial requirements (18). It was expected that tablets produced at lower velocities with higher dwell time would present less friability (35). Instead, tablets RM15 had the most fragile surface. The situation can be explained by the circumstance that, at high speed production, maximum compression force is reached quickly. In this situation, less time is available for granules to bind inside the formed tablet, leading to minor tensile strength values. On the other hand, it favors effective bindings at the surface of the tablets, resulting in low weight loss (36). However, this phenomenon did not influence porosity (Table VII) and disintegration time (Table IX), not showing statistical differences at the speed production assayed.

Comparing tablets produced in the eccentric tablet machine and rotary tablet machine, considering the conditions assayed in this study, it can be stated that neither crushing strength nor production speed influenced disintegration time, but the porosity tablets did.

The assessments of *in vitro* dissolution of RM tablets (Fig. 7) showed maximum SDE release around 25 min, being (mean±SD) 96.73±4.06%; 95.51±2.22%, and 97.82±3.50% for RM15, RM22, and RM30, respectively. The analysis of variance showed no significant difference between the groups (one-way ANOVA—$F_{calc}=1.14<F_{0.05(5,15)}=3.68$).

Based on the dissolution assay from tablets produced in ETM and RTM, release profiles were not affected in terms of machine or production conditions employed, but were influenced by the spray-dried extract, as previously verified by other authors (3,37).

CONCLUSIONS

Construction and operation differences between both tablet presses influenced the final product, since tablets with similar tensile strength, made by distinct tablet machines, exhibited different quality parameters (apparent density, porosity, friability, surface characteristics). Dwell time showed influence over tensile strength and surface pattern, pointing out time-dependence densification mechanism of the tablet mixture. The surface evaluation through image analysis was able to confirm that production conditions lead to dissimilar distribution of tablet mixture components, but in a way that disintegration time and dissolution profile were not affected by differences between eccentric and rotary tablet machine construction.

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