Dry Granulation and Compression of Spray-Dried Plant Extracts

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ABSTRACT

The purpose of this research was to evaluate the influence of dry granulation parameters on granule and tablet properties of spray-dried extract (SDE) from *Maytenus ilicifolia*, which is widely used in Brazil in the treatment of gastric disorders. The compressional behavior of the SDE and granules of the SDE was characterized by Heckel plots. The tablet properties of powders, granules, and formulations containing a high extract dose were compared. The SDE was blended with 2% magnesium stearate and 1% colloidal silicon dioxide and compacted to produce granules after slugging or roll compaction. The influences of the granulation process and the roll compaction force on the technological properties of the granules were studied. The flowability and density of spray-dried particles were improved after granulation. Tablets produced by direct compression of granules showed lower crushing strength than the ones obtained from nongranulated material. The compressional analysis by Heckel plots revealed that the SDE undergoes plastic deformation with a very low tendency to rearrangement at an early stage of compression. On the other hand, the granules showed an intensive rearrangement as a consequence of fragmentation and rebounding. However, when the compaction pressure was increased, the granules showed plastic deformation. The mean yield pressure values showed that both granulation techniques and the roll compaction force were able to reduce the material's ability to undergo plastic deformation. Finally, the tablet containing a high dose of granules showed a close dependence between crushing strength and the densification degree of the granules (ie, roll compaction force).

KEYWORDS: Dry granulation, Maytenus ilicifolia, spray-dried extracts, Heckel plot, tableting.

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INTRODUCTION

Direct compression of powders requires materials exhibiting flowability and compressibility. Those parameters become more critical when the formulation contains large amounts of active substances with poor compressional properties. Spray-dried extracts (SDEs) from medicinal plants are very fine, light, and poorly compressible powders.[1] Additionally, many plant constituents are sensitive to moisture and heat. To overcome these problems, several alternatives have been suggested, such as wet granulation using nonaqueous solvents,[2] direct compression of dried extracts,[3] and the use of different excipients to improve the extract's properties or formulation for direct compression.[3,4] However, few studies have examined the use of dry granulation to enhance particle size and consequently to improve flowability and compressibility of such materials, even though dry granulation seems to be the most appropriate technique because of the hygroscopicity of the extracts.[5,6]

Dry granulation can be achieved either by slugging, using a tablet press, or by roll compaction. The desired particle size distribution can be adjusted by milling and sieving.[7] The granulation parameters can affect the mechanical (ie, compressional) properties of the granules, which subsequently can influence the tableting behavior and tablet characteristics.[8] Therefore, the evaluation of granule properties plays an important role in the prediction of tablet characteristics.[8,9]

The Heckel plot is the method most frequently used to evaluate the volume reduction of materials when pressure is applied.[10,11] It is assumed that the densification of the powder column follows a first-order kinetics. Thus, the degree of material densification is correlated to its porosity. Although the literature reveals some limitations to the Heckel's model,[12] the model has often been applied to study powder mixtures[13,14] and to evaluate the parameters of granule manufacture.[8,15,16]

This study aimed to evaluate the physical and mechanical properties of granules containing high amounts of the SDE from *Maytenus ilicifolia*, prepared by either slugging or roll compaction. For this purpose, the compressional behavior of the SDE and granules prepared by those 2 methods were evaluated using the Heckel's equation. The properties of

tablets prepared from formulations containing high doses of granules were investigated.

MATERIAL AND METHODS

SDE

M ilicifolia aerial parts were extracted by maceration using distillated water (1:10, wt/vol). Colloidal silicon dioxide (Aerosil 200, Degussa, São Paulo, Brazil) was added to the miscella in a 2:8 ratio of adjuvant to dry residue.[17] The dispersion was dried using a Production Minor spray-dryer (GEA, Copenhagen, Denmark) provided with a rotating disk. The operational conditions were 9500 rpm rotational disk speed, 149°C inlet temperature, 99°C outlet temperature, and 140 mL/min feed ratio.

Excipients

Microcrystalline cellulose (Avicel PH 101; FMC Corp, Lehmann and Voss, Hamburg, Germany), cross-linked sodium carboxymethylcellulose (Ac-Di-Sol; FMC Corp, Lehmann and Voss), colloidal silicon dioxide (Aerosil 200; Degussa AG, Frankfurt am Main, Germany), and magnesium stearate (Otto Bärlocher GmbH, Munich, Germany) were used as received.

Extract Containing Mixture (ECM)

The SDE from *M ilicifolia* (191.40 g) was blended in a Turbula mixer T2C (Willy Bachofen, Basel, Switzerland) for 5 minutes with 3.0 g of Aerosil 200 and 5.6 g of magnesium stearate. Both excipients were previously sieved through a 315-μm sieve.

Slugging

Slugs of 0.8 g from the ECM were produced at a compression force of 22.0 ± 1.0 kN using flat-faced tooling 17 mm in diameter on a single-punch tablet press EK 0 (Korsch AG, Berlin, Germany). The upper punch was equipped with 4 strain gauges (Model 3/120 LY-11; Hottinger Baldwin, Darmstadt, Germany) to measure the compression force. A Hottinger Baldwin carrier-frequency bridge was used as amplifier (Model K52 with A/D converter KWD 523D; Hottinger Baldwin). The compression data were acquired and processed using a Messefix v. 2.3 software (Dr. R. Herzog, Tübingen, Germany).

Roll Compaction

The ECM was compacted using a GMP Mini-Pactor (Gerteis Maschinen + Processengineering, Jona, Switzerland). The gap width between the press roll was set to 1 mm and the compactor roll speed to 2 rpm. Compaction forces of 5, 10, and 15 kN/cm (force per cm of roll width) were applied using a press roll (diameter 250 mm, width 25 mm) with a knurled surface.[6]

Milling

The milling conditions were kept constant for compacts. The slugs from the single-punch press or ribbons from the compactor were crushed in a dry granulator (Erweka TG IIS coupled to an Erweka AR 400 multipurpose motor; Erweka GmbH, Heusenstamm, Germany) to obtain granules with a particle size < 2.00 mm. The resulting material was passed through an oscillating granulator (Erweka FGS coupled to a Erweka AR 400 multipurpose motor; Erweka GmbH) using a 1.0-mm sieve. The granule fraction between 250 and 1000 μm was chosen.

Particle Size Analysis

The particle size distribution of 50 g of each granule was determined by sieve analysis on a sieve-shaker (Retak 3D, Retsch GmbH and Co KG, Haan, Germany) using 250-, 355-, 500-, 630-, 710-, and 900-μm sieves. The cumulative size frequency was calculated, and the mean particle sizes (x´) were estimated using an RRSB-Net.[18]

Scanning Electron Microscopy (SEM)

SEM pictures of each granule batch were taken using a Zeiss DSM 940 A (Carl Zeiss, Oberkochen, Germany) secondary electron microscope at an accelerating voltage of 5 kV. Samples were mounted on aluminum pins by double adhesive tape and sputtered with gold using a Biorad Sputter Coater (Biorad, Munich, Germany) at 10^{-2} to 10^{-3} bar and 2.5 kV for 3×60 seconds.

Bulk and Tapped Density (Hausner´s Ratio and Carr´s Compressional Index)

The density parameters were determined using 10.0 g of each material in a 25-mL graduated cylinder ($n = 3$) (tapping device: J. Engelsmann AG, Ludwigshafen am Rhein, Germany).[19] The values were used for the calculation of Hausner's ratio[20] and Carr's compressional index.[21]

Flowability

The flow properties of the sample were evaluated by the dynamic flow determination. The apparatus used according to Guyot et al[22] consisted of a 110-mm diameter stainless steel funnel, 30 mm in diameter discharge mouth and a wall angle of 40°. This system was coupled to a discharge

funnel with an outflow orifice of 10 mm in diameter and a wall angle of 40°. It also included a support for the funnels with an electronic outflow trigger and an analytical balance connected to a personal computer. Data were acquired by the MQbal software (Microquímica, Florianópolis, Brazil). The analysis was performed 3 times with 10.0 g of each sample.

Density

The density of each sample was measured using an air comparison pycnometer (Model 930; Beckmann Instruments Inc, Fullerton, CA).

Compression of the ECM and Granules

Exactly 0.200 g of the ECM and each granule batch were compressed at compression forces between 8 and 40 ± 0.5 kN on a single-punch tablet press EK0 (Korsch AG) using a round flat-faced tooling of 10-mm diameter. The crushing strengths of 6 tablets were determined 24 hours after production using a hardness tester (Model TBH30; Erweka GmbH).

Evaluation of the Granule Compressibility by Heckel Analysis[11,12]

Exactly 0.400 g of the SDE and each granule batch were compressed at 120 MPa using an eccentric tablet press EK II (Korsch AG) with a 10-mm diameter round flat-faced tooling by introducing manually preweighed material into the die. The upper punch holder was instrumented with a full Wheatstone bridge circuit of strain gauges (Model 3/120 LY-11; Hottinger Baldwin) to measure the compression force. An incremental displacement transducer (Model MT 2571; Heidenhain, Traunreut, Germany) was used to determine the upper punch displacement. The compressional data were acquired by a MGC Plus system (Hottinger Baldwin) equipped with a ML10 B voltage amplifier module (Hottinger Baldwin) to measure the compressional force and with 2 ML60 B counter modules (Hottinger Baldwin) to record the signals from the incremental displacement transducer. CATMAN v. 3.0 software (Hottinger Baldwin) was used to store and evaluate the compressional data. The system was described in detail by Dressler et al.[23]

The compressional behavior of the samples was evaluated using the Heckel equation (Equation 1):

$$ln\left(\frac{1}{1-D}\right) = K \cdot P + A \qquad (1)$$

where D was the relative density of the compact at pressure P; K was the slope; and A was the intercept of the straight line obtained by linear regression from the Heckel plot. The

relative densities D_A and D_0 were calculated from Equations 2 and 3, respectively:

$$D_A = 1-e^{-A} \qquad (2)$$

$$D_0 = 1-e^{-A_0} \qquad (3)$$

where A_0 represented the intercept of the line at $P = 0$. The difference between D_A and D_0 represented the extent of particle rearrangement (D_B). For each sample, 10 compressional cycles were performed.

The mean yield pressure (Py) was obtained as the reciprocal of the slope of the linear section in the curve.

Compression of Granules Containing Formulations

Tablet formulations according to Table 1 were mixed for 10 minutes in a Turbula Mixer T2C (Willy Bachofen, Basel, Switzerland); then, Aerosil 200 was sieved through a 315-μm sieve onto the mix. The final mixing was performed for 5 minutes.

The mixture was compressed into tablets of 0.200 g on a single-punch tablet machine EK 0 (Korsch AG) using flat-faced tooling 10 mm in diameter. Each batch was compressed at different compression force levels between 8 and 22 ± 0.5 kN.

Crushing Strength

The crushing strength of 10 tablets from each batch was determined according to the *European Pharmacopoeia Supplement* (2001)[24] using a hardness tester (Model TBH30, Erweka GmbH).

Disintegration Time

The disintegration time of the tablets was determined according to the *European Pharmacopoeia Supplement* (2001)[24]

Table 1. Tableting Formulation Containing High Dose of Granules

	Amount	
	mg/tablet	%/tablet
Granules (Magnesium stearate incorporated)	144.46* (4.00)	72.23 (2.00)
	44.54	22.27
Avicel PH 101	10.00	5.00
Ac-Di-Sol	1.00	0.50
Aerosil 200	200.00	100.00
Total weight		

* Equivalent to 138.46 mg of the spray-dried extract or 110.77 mg of native extract per tablet.

Table 2. Physical Properties of SDE, ECM, Slugged Granules, and RC Granules*

Sample	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Hausner's Ratio	Carr's Index (%)	x´ (μm)	RRSB r^2	Flow (g/s)
SDE	0.632	0.830	1.315	23.94	22.36[†]	—	[‡]
ECM	0.500	0.690	1.375	27.50	—	—	[‡]
Slug	0.659	0.706	1.071	6.59	713.00	0.9898	16.26
RC5	0.645	0.714	1.107	9.68	700.00	0.9909	15.50
RC10	0.690	0.741	1.074	6.90	701.00	0.9831	15.50
RC15	0.741	0.800	1.080	7.41	693.00	0.9734	15.87

* SDE indicates spray-dried extract; ECM, extract containing mixture; RC, roll-compacted granules at 5 (RC5), 10 (RC10), and 15 (RC15) kN/cm; RRSB indicates the correlation between granulometric distributions and the RRSB model.
[†]Determined by laser diffraction (Helos KA, Sympatec GmbH, Clausthal-Zellerfeld, Germany).
[‡]Determination not possible due to blocking of the funnel.

using a disintegration tester (Model PTZ 1, Pharmatest GmbH, Hainburg, Germany).

RESULTS AND DISCUSSION

Technological Properties of the SDE and Granules

The mode of granule preparation and the different roll compaction forces did not influence the mean particle size (x´), as shown in Table 2. The x´ values ranged from 693 to 713 μm.

The granulation process improved the technological properties of the SDE and the ECM. Concerning the granule densities, no important difference between granulation processes could be observed; however, the increase in roll compaction force produced granules with higher bulk and tapped densities. The Hausner's ratio (HR) and Carr's index (CI) are indirect and simple methods to evaluate the stability of the powder column and to estimate its flow properties. The high values of HR and CI observed for both the SDE and the ECM denote their inability to flow. The ECM's granulation by either slugging or roll compaction significantly increased the stability of the powder bed. No significant difference was observed for HR or CI among the granule batches (Table 2).

The flow behavior of the granules dynamically measured is shown in Figure 1. There were no differences between the flow properties of slugged or roll-compacted granules. Additionally, the roll compaction force did not affect the flow properties. This result is in agreement with the technological properties suggested by HR and CI evaluation. This behavior was probably due to the similarities observed for the shape and size of the granules. Because the final flow velocity of the granules was higher than 10 g/s, they could be classified as free-flowing materials according to Guyot et al.[22]

The morphology of the granules manufactured by slugging and by roll compaction was observed using an electron microscope (Figure 2). Slugged granules and roll-compacted granules at 5 kN/cm showed a coarse surface, probably because of the large amount of intact SDE particles. Roll-compacted granules at 10 and 15 kN/cm appeared to be

denser and showed a more smooth surface than the other samples, because of higher densification of the ECM owing to the roll compaction force.

Compression of the ECM and Granules

Tablets formed from granules compressed with further additives had a lower crushing strength than tablets containing nongranulated ECM (Figure 3). This reduction was similar for granules prepared by slugging and roll compaction at 5 and 10 kN/cm and more evident for granules produced by roll compaction at 15 kN/cm. The crushing strength data suggest that the increase in the compaction force (ie, densification degree) during the granulation reduces the strength of the compacted material. This reduction can be attributed to a decrease of the material's ability to undergo plastic deformation, which ability was dissipated during the granulation process. Therefore, the reworking of the granules improved their resistance to deformation upon recompression, and a higher compression force was necessary to obtain the same crushing strength compared with tablets of powder mixture (ECM). This behavior was previously observed for sodium chloride[25] and more recently demonstrated for
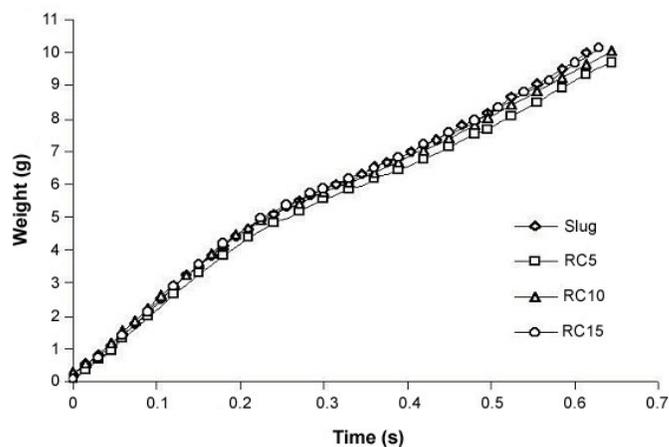
Figure 1. Flow profile of the granules. RC indicates roll-compacted granules at 5 (RC5), 10 (RC10), and 15 (RC15) kN/cm.
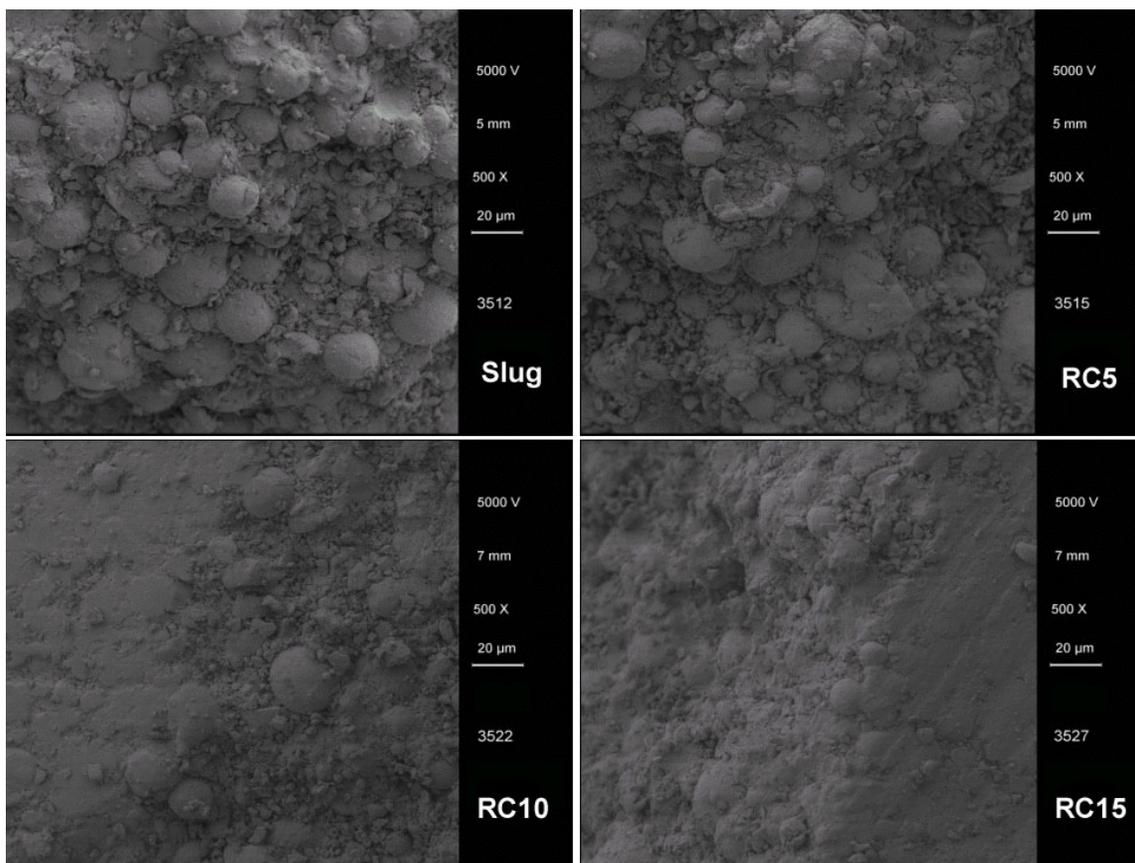
Figure 2. Scanning electron photomicrographs of different spray-dried extract–containing granules. RC indicates roll-compacted granules at 5 (RC5), 10 (RC10), and 15 (RC15) kN/cm.

several excipients and their mixtures.[8,9,14,15] In general terms, the maximum crushing strength of the tableted granules was achieved at 25 kN of compression force. Higher compression forces revealed a capping tendency during the crushing strength test (Figure 3).

Heckel Analysis

The Heckel plots for the SDE, the ECM, and granules showed no linearity at early stages of compression (Figure 4), because of particle rearrangement and the fragmentation of large aggregates under low compressional pressure.[13] When the compression force is increased, the curves became linear because of plastic deformation.

The slope of the linear part of the Heckel plot (Table 3) was correlated with the bulk and tapped densities. For Heckel parameters such as K, A, and Py, the values were very similar for both slug and roll-compacted granules.

The extent of particle rearrangement (D_B), calculated from Heckel analysis, depends on the particle surface, size, and shape and represents the particle arrangement at early compression stages.[15] D_B results from compression force action to overcome particle interactions (ie, friction and cohesion) before particle slippage and/or arrangement. The lower D_B

value shown by the SDE particles was due to the physical properties of the particles such as dominant spherical shape, small particle size (22.4 μm), and no aggregated structure. Thus, the SDE did not undergo extensive particle rearrangement. The further arrangement may be due to the
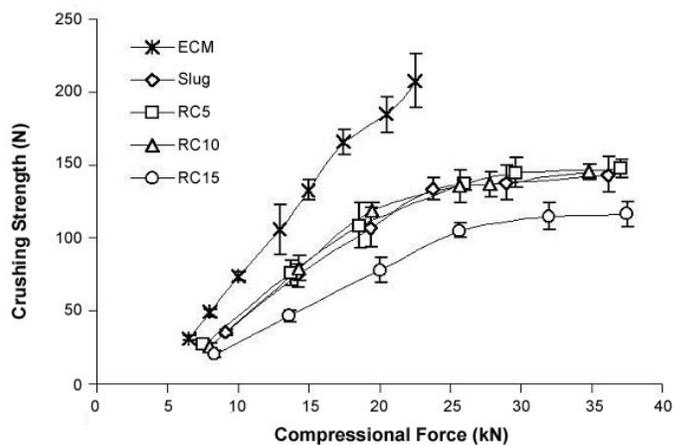
Figure 3. Crushing strength of direct-compressed granules at different compressional forces compared with the ECM. ECM indicates extract containing mixture; RC, roll-compacted granules at 5 (RC5), 10 (RC10), and 15 (RC15) kN/cm.
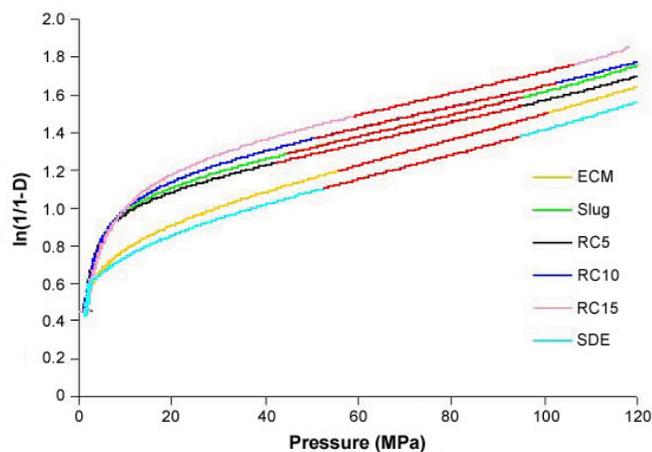
Figure 4. Heckel plots for SDE, ECM, and RC granules. Red lines show the linear portions of the compression phases. SDE indicates spray-dried extract; ECM, extract containing mixture; RC, roll-compacted granules at 5 (RC5), 10 (RC10), and 15 (RC15) kN/cm.

Figure 5. Crushing strength of final tablets. Tablets containing a high dose of slugged granules or RC granules. RC indicates roll-compacted granules at 5 (RC5), 10 (RC10), and 15 (RC15) kN/cm.

fragmentation of individual particles followed by plastic deformation. No significant increase of D_B was observed by the addition of large amounts of magnesium stearate (2.8%, wt/wt) to the SDE (ECM). In fact, the SDE and the ECM presented almost the same value of D_B. This result confirms the weak dependence of the SDE on particle slippage at an early stage of compression. However, at high pressures the presence of lubricant was effective and improved the densification of the particles.

After granulation, higher values of D_B were observed. This implies that the granules presented a more extensive particle rearrangement compared with the SDE and the ECM products. At low pressures the large granules were fractured into small ones, which facilitated the further re-arrangement. When the compression pressure was increased,

the granules showed plastic deformation. The idea that plastic deformation was the principal mechanism was also supported by the relative high Py values. Thus, this behavior revealed a reduction of the granules' ability to undergo plastic deformation. As observed by the crushing strength test, granulation of the SDE by roll compaction was satisfactory between 5 and 10 kN/cm. Thus, a roll compaction force higher than 10 kN/cm results in hard granules reaching plastic deformation. Therefore, reworking upon compression into tablets was difficult.

Properties of Tablets From Granule-Containing Formulations

Tablets containing a high dose of granulated dried extract from *M ilicifolia* were produced following the formulation described in Table 1. In Figure 5, the crushing strength of

Table 3. Heckel Parameters of the Materials Calculated From the Linear Portion of the Heckel Plot*

Sample (n = 10)	Slope K	Intercept A	Mean Yield Pressure Py (MPa)	Extend of Particle Rearrangement D_B	Density at Pressure (g/cm^3)	Coefficient of Determination r^2
SDE[†]	0.0063	0.7567	158.52	0.083	1.356	0.9999
SD	0.0002	0.0062	5.94	—	0.002	0.00001
ECM	0.0068	0.8138	146.04	0.113	1.361	0.9999
SD	0.0001	0.0035	2.20	—	0.001	0.00002
Slug	0.0057	1.0290	174.58	0.269	1.387	0.9999
SD	0.0001	0.0042	2.29	—	0.001	0.00001
RC5	0.0057	0.9955	175.14	0.259	1.388	0.9999
SD	0.0001	0.0051	1.68	—	0.001	0.00001
RC10	0.0056	1.0794	178.18	0.290	1.392	0.9999
SD	0.0000	0.0036	1.31	—	0.001	0.00002
RC15	0.0058	1.1382	173.25	0.310	1.388	0.9999
SD	0.0001	0.0053	1.79	—	0.001	0.00001

* SDE indicates spray-dried extract; ECM, extract containing mixture; RC, roll-compacted granules at 5 (RC5), 10 (RC10), and 15 (RC15) kN/cm; SD, standard deviation.

[†] An ethanolic solution of stearolic acid 1.5% was used to lubricate the machine tools.
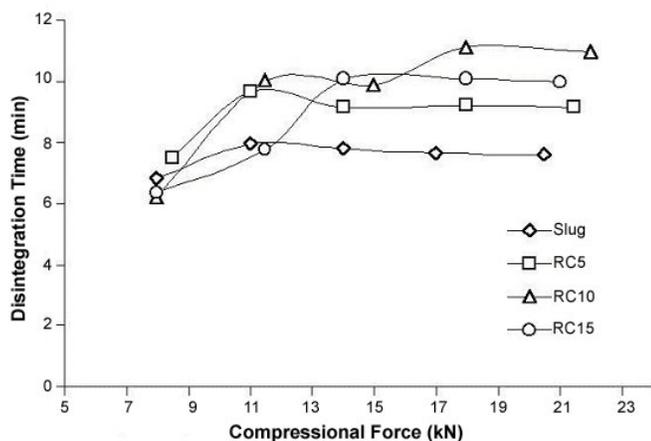
Figure 6. Disintegration time behavior of tablets containing a high dose of granules. RC indicates roll-compacted granules at 5 (RC5), 10 (RC10), and 15 (RC15) kN/cm.

the tablets is plotted against the compression force. The tablet crushing strength showed a linear dependence of compression force for granule-containing formulations. This phenomenon was independent of the granulation method or the roll compaction force. The addition of microcrystalline cellulose to the formulation seemed to enhance the plastic deformation potential of all formulations, resulting in a linear compression force/crushing strength profile without a capping tendency and leading to tablets with crushing strength values higher than those obtained by granules that were direct-compressed at the same compression force. On the other hand, a slight decrease in tablet crushing strength was observed with increasing compaction force during roll compaction. This result indicates that the increase in the granules' densification degree plays an important role in the tablets' resultant resistance.[8] Thus, if all operational conditions, such as roll compaction and compression forces, are taken into account, a similar crushing strength for the different formulations can be expected.

Concerning the disintegration times of the tablets, no important difference was observed (Figure 6). For all cases, the disintegration time increased significantly when the compression force was increased. The maximum disintegration time, achieved at 14 kN, ranged from 8 (tablets containing a high dose of slugged granules) to 11 minutes (tablets containing a high dose of roll-compacted granules).

CONCLUSION

The dry granulation of the dried extract of *M ilicifolia* improved its flowability. However, the study of compressional behavior and recompressibility showed that the degree of densification reached during the dry granulation process increased the material's resistance to further reworking. On the other hand, when plastic filler material

was added to formulations, the tableting properties of granules were increased. Besides, the differences among force-crushing strength profiles were minimized. To conclude, the evaluation of granulation properties and manufacturing technologies can help predict the characteristics of final tablets containing a high dose of those granulations.

REFERENCES

1. De Souza KCB, Petrovick PR, Bassani VL, González Ortega G. The adjuvants Aerosil 200 and Gelita-Sol-P influence on the technological characteristics of spray-dried powder from *Passiflora edulis* var. *flavicarpa. Drug Dev Ind Pharm.* 2000;26:331–336.

2. Diaz L, Souto C, Concheiro A, Gomez-Amozy LM, Martinez-Pacheco R. Evaluation of Eudragit E as excipient in tablets of dry plant extract. *STP Pharma Sci.* 1986;2:105–109.

3. De Souza TP, Bassani VL, González Ortega G, Dalla Costa TCT, Petrovick PR. Influence of adjuvants on the dissolution profile of tablets containing high dose of spray-dried extract of *Maytenus ilicifolia. Pharmazie.* 2001;56:730–733.

4. Plaizer-Vercamen JA, Bruwier C. Evaluation of excipients for direct compression of the spray-dried extract of *Harpogaphytum procumbens. STP Pharma Sci.* 1986;2:525–530.

5. Rocksloh K, Rapp FR, Abu Abed S, et al. Optimization of crushing strength and disintegration time of a high-dose plant extract tablet by neural network. *Drug Dev Ind Pharm.* 1999;25:1015–1025.

6. Von Eggelkraut-Gottanka SG, Abu Abeb S, Müller W, Schmidt PC. Roller compaction and tabletting of St. John's wort plant dry extract using gap width and force controlled roller compactor, I: granulation and tabletting of eight different extract batches. *Pharm Dev Technol.* 2002;7:433–445.

7. Miller RW. Roller compaction technology. In: Parikh DM, ed. *Handbook of Pharmaceutical Granulation Technology.* New York, NY: Marcel Dekker; 1997:99–150.

8. Freitag F, Kleinebude P. How do roll compaction/dry granulation affect the tablet behavior of inorganic materials? Comparison of four magnesium carbonates. *Eur J Pharm Sci.* 2003;19:281–289.

9. Bultmann JM. Multiple compaction of microcrystalline cellulose in a roller compactor. *Eur J Pharm Biopharm.* 2002;54:59–64.

10. Heckel RW. An analysis of powder compaction phenomena. Trans. Metal. *Sci. AIME.* 1961;221:1001–1008.

11. Heckel RW. Density-pressure relationship in powder compaction. Trans. Metal. *Sci. AIME.* 1961;221:671–675.

12. Rue PJ, Rees JE. Limitations of the Heckel relation for predicting powder compaction mechanisms. *J Pharm Pharmacol.* 1978;30:642–643.

13. Ilkka J, Paronen P. Prediction of the compression behavior of powder mixtures by the Heckel equation. *Int J Pharm.* 1993;94:181–187.

14. Mitrevej A, Faroongsarng D, Sinchaipanid N. Compression behavior of spray dried starch. *Int J Pharm.* 1996;140:61–68.

15. Kochhar SK, Rubinstein MH, Barnes D. The effects of slugging and recompression on pharmaceutical excipients. *Int J Pharm.* 1995;115:35–43.

16. Horisawa E, Danjo K, Sunada H. Influence of granulating method on physical and mechanical properties: compression behavior and compactibility of lactose and microcrystalline cellulose granules. *Drug Dev Ind Pharm.* 2000;26:583–593.

17. Petrovick PR, Carlini E. Antiulcerogenic preparation from *Maytenus ilicifolia* and obtainment process.Brazil patent PI 994 502. March 6, 1999.

18. DIN 66145DIN Deutsches Institut für Normung. Darstellung von Korn-(teilchen-)grössenverteilungen—RRSB-Netz. *DIN-Taschenbuch 133—Partikelmesstechnik: Normen.* Berlin, Germany: Beuth Verlag; 1997:191–193.

19. European Pharmacopoeia. Strasbourg, France: Council of Europe; 1997.

20. Hausner HH. Friction conditions in a mass of metal powder. *Int J Powder Mettall.* 1967;3:7–13.

21. Carr RL. Evaluating flow properties of solids. *Chem Engineer.* 1965;72:163–168.

22. 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 Européene. Rapport d'une Commision SFSTP. *STP Pharma Pratiques.* 1995;5:482–494.

23. Dressler JA, Wagner KG, Wahl MA, Schmidt PC. Comparison of incremental and inductive displacement transducers on an eccentric tablet press. *Pharm Ind.* 2001;53:886–893.

24. European Pharmacopoeia Supplement. Strasbourg, France: Council of Europe; 2001.

25. Rees JE, Rue PJ. Time-dependent deformation of some direct compression excipient. *J Pharm Pharmacol.* 1978;30:601–607.