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Compression behavior of formulations from *Phyllanthus niruri* spray dried extract

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The aim of this study was to evaluate the compression behavior of *Phyllanthus niruri* spray dried extract as well as the influence of excipients on the properties of tablets containing a high dose (70% by weight) of this product. The effect of excipients was studied by a 2^2 factorial design. The factors investigated were the type of disintegrant (croscarmellose sodium and sodium starch glycolate) and the type of filler/binder (microcrystalline cellulose and dibasic dicalcium phosphate). The tablets were produced on a single punch tablet press using a constant compression force of 5000 N. The tablets formulated with microcrystalline cellulose presented a plastic behavior while the tablets containing dibasic dicalcium phosphate disclosed a fragmentary behavior. The disintegration time was significantly influenced by both factors, however, the tensile strength was only affected by the filler/binder. Additional experiments considering the influence of the compression force (2500 N and 5000 N) and the proportion of croscarmellose sodium (1.5%, 3.0% and 6.0%) on the mechanical properties of the tablets were performed by a 2×3 factorial design. Both factors significantly affected the tensile strength, friability and disintegration time of the tablets.

1. Introduction

Pharmacological studies with *Phyllanthus niruri* demonstrated the efficacy of aqueous extracts against kidney disorders and viral hepatitis (Calixto et al. 1998). Spray dried extract (SDE) from this plant was developed to produce stable, easier to handle and dose, intermediary technological products (Soares 1997). However, spray dried extracts generally show deficient rheological properties, poor compressibility and high moisture sensibility that impede their direct compression, thus requiring the addition of pharmaceutical excipients to overcome those problems (Renoux et al. 1996; De Souza et al. 2001; Palma et al. 2002). The excipients affect various technological parameters such as compressibility, flowability and content uniformity. Therefore, by varying the type and quantity of the excipient, it is possible to correct and optimize these characteristics (Pifferi et al. 1999). Hence, the aim of this work was to evaluate the compression behavior of *P. niruri* spray dried extract and the influence of different excipients on that process.

2. Investigations, results and discussion

The choice criteria regarding the excipients were the adequacy to direct compression (Hoepfner et al. 2002). Among the different excipients employed in the pharmaceutical industry, microcrystalline cellulose and dibasic dicalcium phosphate were selected as filler/binder due to their distinct compression behavior, while croscarmellose sodium and sodium starch glycolate were chosen as superdisintegrants by the same reason (Wade and Weller 1994). The compression parameters of the SDE and formulations are displayed in Table 1. The results suggest a main mechan-

Table 1: Real density and compression proprieties of *P. niruri* spray dried extract (SDE) and tablet formulations

Formulations	Real density (g/cm^3) X ± s	Py (MPa) X ± s	PI (%) X ± s
SDE	1.72 ± 0.006	111.60 ± 3.527	64.47 ± 1.460
F1 (CS + MC)	1.63 ± 0.011	106.09 ± 3.553	61.95 ± 1.860
FA (SSG + MC)	1.64 ± 0.009	117.21 ± 2.087	62.90 ± 2.830
FB (CS + DDP)	1.81 ± 0.010	225.59 ± 2.916	70.47 ± 0.760
FAB (SSG + DDP)	1.82 ± 0.001	223.90 ± 2.916	71.17 ± 0.420

SDE = spray dried extract; CS = croscarmellose sodium; SSG = sodium starch glycolate; MC = microcrystalline cellulose; DDP = dibasic dicalcium phosphate; Py = mean yield pressure; PI = plasticity

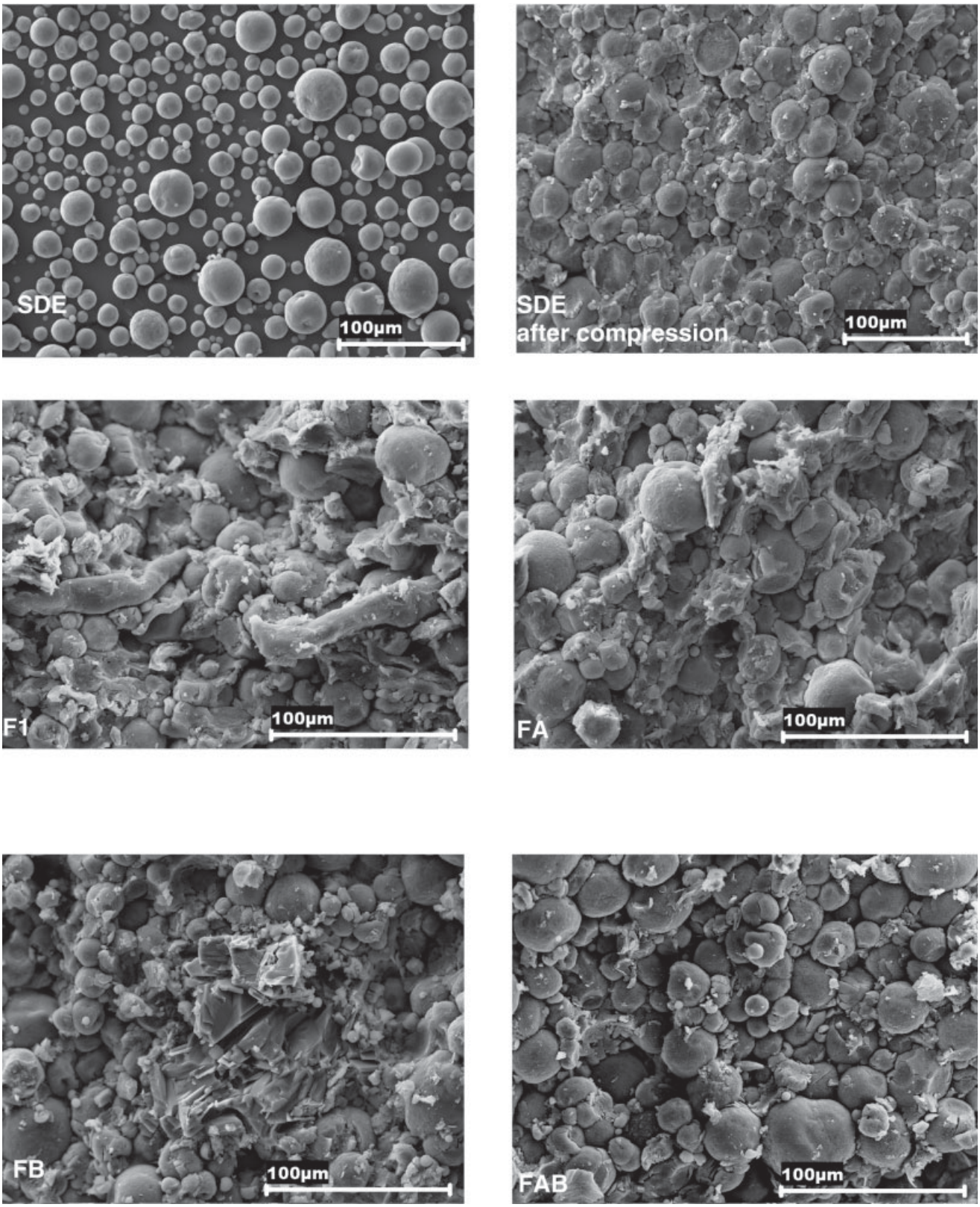

Fig. 1: Microphotographs of *Phyllanthus niruri* spray dried extract and formulations

ism of plastic deformation (Py = 111 MPa) to *Phyllanthus niruri* SDE, which is in accordance with the compression behavior of *Maytenus ilicifolia* SDE, characterized by Soares (2002) as a plastic material showing a Py of 158 MPa. The formulations F1 and FA had a compression behavior similar to *P. niruri* SDE, plastic deformation, while formulations FB and FAB showed a predominant fragmentative behavior with Py higher than 200 MPa. It is known that microcrystalline cellulose (Avicel) undergoes a plastic deformation showing a mean yield pressure (Py) around 54 MPa and dibasic dicalcium phosphate (Emcompress) is characterized as a brittle material with Py about 250 MPa (Landín et al. 1994; Doelker 1995). In spite of the high concentration of SDE (70%), it could be

still expected that excipients would be able to change the compression behavior of formulations, however addition of microcrystalline cellulose did not modify the original behavior of the SDE. On the other hand, dibasic dicalcium phosphate increased significantly the Py of formulations. Schmidt and Leitritz (1997) studying the compressional behavior of binary mixture containing microcrystalline cellulose and dibasic dicalcium phosphate at different proportions concluded that low amounts (<10%) of the latter were sufficient to modify the characteristics of the final formulation.

All products show a plasticity (PI) within the range of 60% to 70%, significantly correlated ($p < 0.05$) to the real density of the products ($r^2 = 0.9792$). These results suggest a considerable elastic recuperation of the *P. niruri* SDE and formulations (Yliruusi et al. 1997). It was observed that formulations containing microcrystalline cellulose undergo a higher elastic recovery than the dibasic dicalcium phosphate one, this can be justified by the fibrous structure of microcrystalline cellulose that protects the spherical particles of SDE, acting as a cushioning agent.

The microphotographs of the *P. niruri* SDE and the tablets are displayed on Fig. 1. It can be verified that after compression some SDE particles maintained their original spherical shape. Indeed, a part of the particles was deformed, what was necessary to bond formation, others remained intact. The same phenomena were verified in the formulations containing the excipients. This fact agrees with the high elastic recovery of the formulations and indicates a participation of SDE in the bound formation during compactation.

The mechanical characteristics of the tablets are presented in Table 2. All formulations had adequate technological properties with friability values lower than 0.6% and a disintegration time below 11 min.

The most important effect on tensile strength (Table 3) was promoted by the filler/binder. The change from microcrystalline cellulose to dibasic dicalcium phosphate decreased the tensile strength of the tablets. This fact could be explained by their different deformation behavior during compression. The brittle properties of dibasic dicalcium phosphate seems to form weaker bonds between the particles of the formulation and consequently to reduce the tablet hardness (Summers et al. 1977). These results are in accordance with Schmidt and Leitritz (1997) who observed that the presence of dibasic dicalcium phosphate in the formulations tend to decrease the tensile strength of the tablets. De Souza et al. (2000) observed that lactose, also a brittle material, reduced the tensile strength of compacts from *Maytenus ilicifolia* SDE. Otherwise, microcrystalline cellulose is referred as a typical plastic material and increases the hardness of the tablets (Ragnarson 1996).

Both factors affected significantly the disintegration time, though no interaction between them could be observed. Although all tablets showed adequate disintegration time, the data indicated that croscarmellose sodium was able to produce tablets with faster disintegration (Table 2).

From the 2^2 factorial design study, the microcrystalline cellulose as filler/binder and the croscarmellose sodium as disintegrant were selected to study the influence of the compression force and proportion of disintegrants on the mechanical characteristics of the tablets. The results are presented in Table 4, the descriptions of formulations are shown in Table 5. All the tablets showed adequate mechanical characteristics.

The ANOVA results suggested that compression force was the only factor which influenced the tensile strength and friability of the tablets.

The adjusted equation for tensile strength ($TS = -0.0183 + 0.000395 \times [Force]$) was statistically acceptable to explain the phenomenon ($p < 0.05$) ($r^2 = 0.8631$). In this case it was observed that the tensile strength of the tablets assumed a linear function of the compression force. The friability of the tablets showed similar behavior, the adjusted equation was represented as a linear function of the compression force. The friability equation ($Friability = 0.290 - 0.0000315 \times [Force]$) was significant ($p < 0.05$) and the experimental variance could be explained for 92.26% of the model ($r^2 = 0.9226$).

The ANOVA results for disintegration time (DT) of the tablets indicated that both factors significantly influenced this parameter (Fig. 2). From the adjusted equation ($DT = 8.26 - 2.69 \times [CS] + 0.0012 \times [Force] - 0.000075 \times [CS] \times [Force] + 0.29037 \times [CS^2]$) it was possible to conclude that the linear term of force and of croscarmellose sodium (CS) concentration as well as the quadratic term of CS proportion were important to explain the disintegration time behavior of the tablets. This model showed to be statistically adequate ($p < 0.013$) and the experimental variance could be explained for 99.99% of the mathematical model ($r^2 = 0.9999$).

Fig. 2 shows that the compression force exhibited a linear influence on the disintegration time, however the proportions of croscarmellose sodium had no linear influence on this parameter. The data showed a tendency to an optimal concentration of Ac-Di-Sol, around 5%.

In conclusion, this study demonstrated that the compression behavior of *Phyllanthus niruri* spray dried extract was significantly influenced by the type of excipients

Table 2: Mechanical characteristics of tablets

Formulation	TS (MPa) X ± s	DT (min) X ± s	Friability (%)
F1	1.53 ± 0.07	8.23 ± 0.12	0.13
FA	1.64 ± 0.10	10.35 ± 0.12	0.15
FB	0.81 ± 0.04	6.17 ± 0.04	0.52
FAB	0.86 ± 0.88	8.13 ± 0.11	0.54

TS = tensile strength; DT = disintegration time

Table 3: Main effect (E) and interaction (I) of factors on tensile strength (TS) and disintegration time (DT) of the tablets

Effects	Value	
	TS	DT
E_A (type of disintegrant)	+0.08	+2.04*
E_B (type of filler/binder)	−0.75*	−2.14*
I_{AB}	−0.03	−0.08

* $p < 0.05$

Table 4: Characteristics of tablets from 2 × 3 factorial design

Formulation*	TS (MPa) X ± s	DT (min) X ± s	Friability (%)
f1	2.12 ± 0.07	6.77 ± 0.03	0.12
f2	1.57 ± 0.03	8.23 ± 0.12	0.13
f3	2.28 ± 0.09	10.86 ± 0.34	0.10
f4	0.90 ± 0.07	4.67 ± 0.74	0.22
f5	0.86 ± 0.06	5.47 ± 0.60	0.20
f6	0.95 ± 0.06	7.89 ± 0.50	0.19

TS = tensile strength; DT = disintegration time

Table 5: Composition of the formulations

Composition	Formulations (mg)									
	2^2 factorial design				2×3 factorial design					
	F1	FA	FB	FAB	f1	f2	f3	f4	f5	f6
SDE	210	210	210	210	210	210	210	210	210	210
CS	9	–	9	–	18	9	4,5	18	9	4,5
SSG	–	9	–	9	–	–	–	–	–	–
MC	78	78	–	–	–	–	–	–	–	–
DDP	–	–	78	78	69	78	82,5	69	78	82,5
MS	3	3	3	3	3	3	3	3	3	3
CF	5000 N				5000 N			2500 N		

SDE = spray dried extract; CS = croscarmellose sodium; SSG = sodium starch glycolate; MC = microcrystalline cellulose; DDP = dibasic dicalcium phosphate; MS = magnesium stearate; CF = compressional force

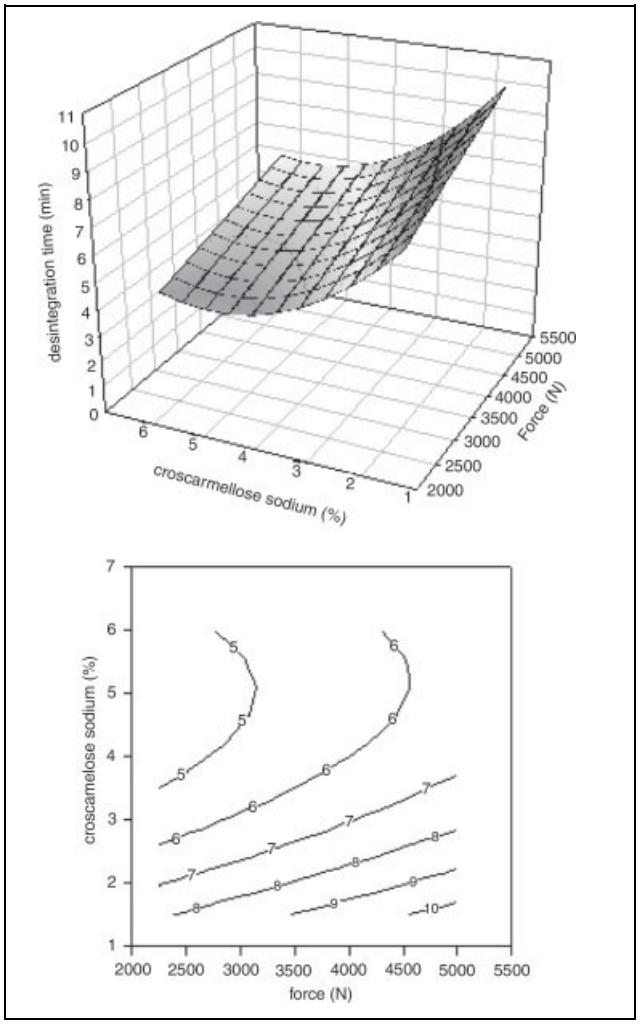

Fig. 2: Surface response of tablets disintegration time

used, although all formulations showed adequate technological characteristics. The formulations containing dibasic dicalcium phosphate produced tablets with lower strength than those produced with microscrystalline cellulose at the same compression force, and this can be explained by the fragmentation behavior of dibasic dicalcium phosphate. The compression force and proportion of disintegrant were other important parameters to the mechanical characteristics of the tablets. The tensile strength and the friability of the tablets were directly influenced by the compression force while the disintegration time was dependent either on compression force or on the proportion of disintegrant.

3. Experimental

3.1. Material

The spray dried extract (SDE) of *Phyllanthus niruri* containing 12.33 mg/g of gallic acid was prepared following the method described by Soares (1997) using a Niro Atomizer Production Minor equipment. Microcrystalline cellulose (Avicel® PH 101 – FMC), dibasic dicalcium phosphate (Emcompress® – Edward Mendell), sodium starch glycolate (Primojel® – Avebe), croscarmellose sodium (Ac-Di-Sol® – FMC) and magnesium stearate (purchased from C. Barcia S.A.) were used as received.

3.2. Experimental design

A 2^2 factorial design was employed to evaluate the effect of the excipients on the compression of the SDE (Table 6), and a 2×3 factorial design to investigate the influence of compression force and disintegrant concentration on the technological characteristics of the tablets (Table 7).

3.3. Tablet preparation

The formulations (Table 5) were prepared blending the *P. niruri* SDE, disintegrant and filler/binder in a Turbula mixer (T2C – Willy A. Bachhofen), for 15 min at 60 rpm. The magnesium stearate was added into the mixture and blended for additional 5 min.
The powders were compressed in an instrumented single punch tablet machine (J. Bonals BMT) equipped with flat-faced 9 mm punches (Martínez-Pacheco et al. 1985) by individual direct compression of 300 mg for each formulation using different compression force of 5000 N and 2500 N.

3.4. Tablet characterization

3.4.1. Compression properties

The mean yield pressure (Py) was estimated from force displacement curves following Heckel's model (Hubert-Droz et al. 1982). The plasticity (PI) was calculated from force time curves according to Yliruusi et al. (1997). The compression force was measured at the upper punch. Each

Table 6: Factors and levels for the 2^2 factorial design

Factor	Level
(A) disintegrant	(−) croscarmellose sodium (+) sodium starch glycolate
(B) filler/binder	(−) microcrystalline cellulose (+) dibasic dicalcium phosphate

Table 7: Factors and levels for the 2×3 factorial design

Formulation	Compression force (coded)	CS (coded)	Compression force (N)	CS (%, w/w)
1	+1	+1	5000	6.0
2	+1	0	5000	3.0
3	+1	−1	5000	1.5
4	−1	+1	2500	6.0
5	−1	0	2500	3.0
6	−1	+1	2500	1.5

CS = croscarmellose sodium

formulation was subjected to five force displacement cycles with a maximum force of 5000 N. The true density, required to estimate Py, was determined by a helium pycnometer (Quantachrome MPY-2).

3.4.2. Tensile strength (Fell and Newton 1970; Summers et al. 1977)

The tensile strength was calculated by determination of the crushing strength of ten tablets, measured with a Erweka TB-2A apparatus. The tablet diameter and thickness were measured by a digital micrometer (Mytutoyo).

3.4.3. Scanning electron microscopy

The inner surface of the broken tablets from the crushing strength test was examined by scanning electron microscopy (Leica S440).

3.4.4. Disintegration time

The disintegration time was determined according to the USP 25 (2002) (DT-1 Turu Grau). Water at 37 °C was used as test medium in accordance with USP 25 specifications.

3.4.5. Friability

The friability of twenty tablets was examined with a Pharma Test PTF-E apparatus following USP 25 specifications.

3.5. Statistical analysis

The effects of the factors studied on tensile strength, friability and disintegration time of the tablets were investigated by stepwise multiple regression analysis (Cochran and Cox 1969) as performed by the Statistical Package for Social Sciences (SPSS – version 11.0). The curves of response surface were obtained from adjusted equations and the graphics were plotted by SigmaPlot® version 8.0.

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