Programa de Pòs-Graduação em Ciências Farmacêuticas, Universidade Federal do Rio Grande do Sul, Porto Alegre – RS, Brazil

Influence of adjuvants on the dissolution profile of tablets containing high doses of spray-dried extract of *Maytenus ilicifolia*

T. P. DE SOUZA, V. L. BASSANI, G. GONZÁLEZ ORTEGA, T. C. T. DALLA COSTA and P. R. PETROVICK

Dedicated to Prof. em. Dr. Dr. h.c. Karl Ernst Schulte on the occasion of his 90th birthday

A 2^3 factorial design was used in order to evaluate the influence of some adjuvants on the dissolution profile of tablets containing high doses of *Maytenus ilicifolia* spray-dried extract. Tablets were prepared on a single punch tablet press using 15 mm flat punches by individual direct compression of 650 mg from each formulation containing 375 mg of the spray-dried extract. The factors investigated were disintegrant (croscarmellose sodium or sodium starch glycolate), lubricant (colloidal silicon dioxide or magnesium stearate) and filler/binder (microcrystalline cellulose or lactose). The dissolution profiles were analyzed to determine the dissolution kinetics, the dissolution half-lives ($t_{50\%}$), the similarity factor (f_2) and the dissolution efficiency (DE %), which was selected as the response criteria to evaluate the factorial design. The results revealed that in spite of the high content of spray-dried powder in the tablets, the dissolution profiles of the extract did depend on the adjuvant used. The filler/binder had the most important effect on the dissolution efficiency of the tablets.

1. Introduction

Maytenus ilicifolia is a medicinal plant commonly found in Southern Brazil and popularly known as "espinheira-santa". It is used in the Brazilian folk medicine due to its antiulcerogenic effects. Pharmacological studies carried out with spray-dried extract of *M. ilicifolia* confirmed these therapeutic properties [1, 2].

Spray-drying is a technique widely used in the preparation of phytopharmaceuticals. Spray-dried extract can be used either as a dosage form or as an intermediate product for the manufacturing of several pharmaceutical dosage forms such as capsules and tablets [3]. However, these powders show poor rheological properties and need the addition of adjuvants to improve their technological behavior [3–5].

Formulation adjuvants have shown to influence the mechanical properties of a tablet as well as the disintegration time and the drug dissolution rate [6]. In order to achieve a reproducible bioavailability behavior of the product, drug stability and physical tablet properties must be maintained within narrow limits which require a thorough study of the physicochemical properties of drug and tablet [6]. There are few reports in the literature about phytotherapic tablets dissolution behavior [7, 8]. Therefore, it is very important to establish the dissolution profile of spray-dried extracts and to determine the influence of adjuvants on this parameter.

The aim of this study was to investigate the influence of filler/binders (lactose or microcrystalline cellulose), lubricants (magnesium stearate or colloidal silicon dioxide) and disintegrants (croscarmellose sodium or sodium starch glycolate) on the dissolution profile of tablets containing high doses of *Maytenus ilicifolia* spray-dried extract.

2. Investigations, results and discussion

Fig. 1 shows the average dissolution profiles of the tablets. As can be seen, the dissolution profiles of the extract showed different behavior, depending on the adjuvant used. All formulations released more than 85% of the extract content in the first 25 min. However, after 5 min formulations 1, A, B and AB, all containing lactose, released more than 30% of the extract while formulations C, AC, BC and ABC, all containing microcrystalline cellulose, released no more than 19%.

While the release from formulations containing lactose (Fig. 1A) occurs fast, the dissolution from cellulose formulations (Fig. 1B) shows a gradual and slower behavior. In order to explain this situation, the characteristics of the filler/binder, major adjuvant used in the formulations, must influence the release of the extract constituents. Lactose is soluble in water and therefore does not interfere with the water uptake needed for the extract dissolution. On the other hand, cellulose is insoluble in water and has great water uptake capacity, decreasing the availability of the medium to dissolve the extract. These properties of cellulose explain the gradual release of the extract from such tablets [9]. Another reason for the different behaviors observed could be the filler/binder relationship to the extract particles inside the tablets. While lactose allows an immediate contact of the dissolution medium with the extract, increasing its dissolution, cellulose permeates the compact mass, decreasing the extract contact with the dissolution medium and, consequently, impairing its release [4, 10].

Fig. 2 and Table 1 show the distinct behavior of the two groups of formulations: one with lactose, which resulted in a first-order kinetic release and other with cellulose, resulting in a zero-order kinetic release. The kinetics of the formulations confirms that gradual and slower dissolution profile of tablets with cellulose.

The ANOVA test of dissolution half-life ($t_{50\%}$) shows statistically significant differences among the formulations ($\propto = 0.05$). The Student-Newman-Keuls test revealed that the lactose group is statistically different from the cellulose group. Within the lactose group, formulation 1 is equivalent to formulations A and B and formulation AB is statistically different from all three. In the cellulose group, formulations C and BC are considered equivalent, as well as formulations AC and ABC but these two groups are statistically distinct. This test confirms the influence of adjuvants on the release kinetics of the extract.

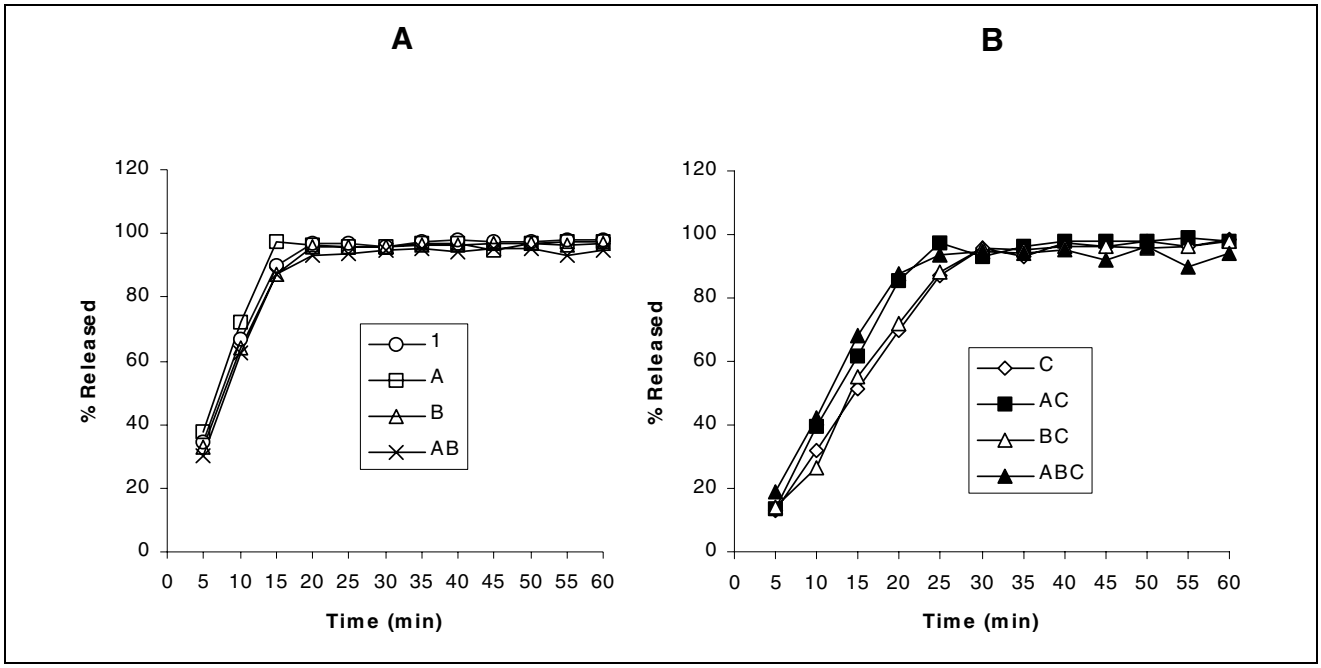

Fig. 1: Dissolution profiles of tablets containing high doses of *Maytenus ilicifolia* spray-dried extract. Panel A: lactose group; panel B: cellulose group

The dissolution efficiencies (DE %) of the eight formulations tested are listed in Table 2. Formulations containing cellulose, independent of the other adjuvants used presented the slower release. The ANOVA demonstrated a statistically significant difference among the formulations ($\propto = 0.05$). The Student-Newman-Keuls test revealed that the lactose group differs significantly from the cellulose group. There are three groups of equivalent formulations: 1 and A, B and AB, BC and C, that are statistically different among themselves and from the other formulations.

Table 2 presents the results of the evaluation of the factorial design. The ANOVA analysis showed that the effect A (disintegrant), the effect C (filler/binder) and the interaction AC (disintegrant /filler binder) are statistically significant ($\propto = 0.05$).

The most important effect for the dissolution efficiency was the presence of the filler/binder in the formulation. Between the two levels of this factor, the change from lactose to cellulose decreased the DE %. As mentioned before, this effect may be explained by the solubility of the filler/binder: while cellulose is insoluble in aqueous medium, lactose is soluble. This property is capable of improving the DE % of tablets with high doses of vegetable extract [11]. Although the major component of the tablets is the vegetable extract, the characteristics of the chosen filler/binder determined the tablet DE %.

The presence of disintegrant in the formulations also markedly influences DE %, although to a smaller degree. The type of disintegrant used in this work is known as superdisintegrant, but its efficiency depends on the method of manufacture and/or physico-chemical characteristics of the tablet formulation [12]. The analysis of the influence of this factor (Table 3) demonstrates that the presence of croscarmellose sodium increased the DE %.

Fig. 3 represents the statistically significant interaction AC. When the filler/binder is lactose, the influence of the type of disintegrant on DE % is almost negligible. On the other hand, when cellulose is used the DE % is highly

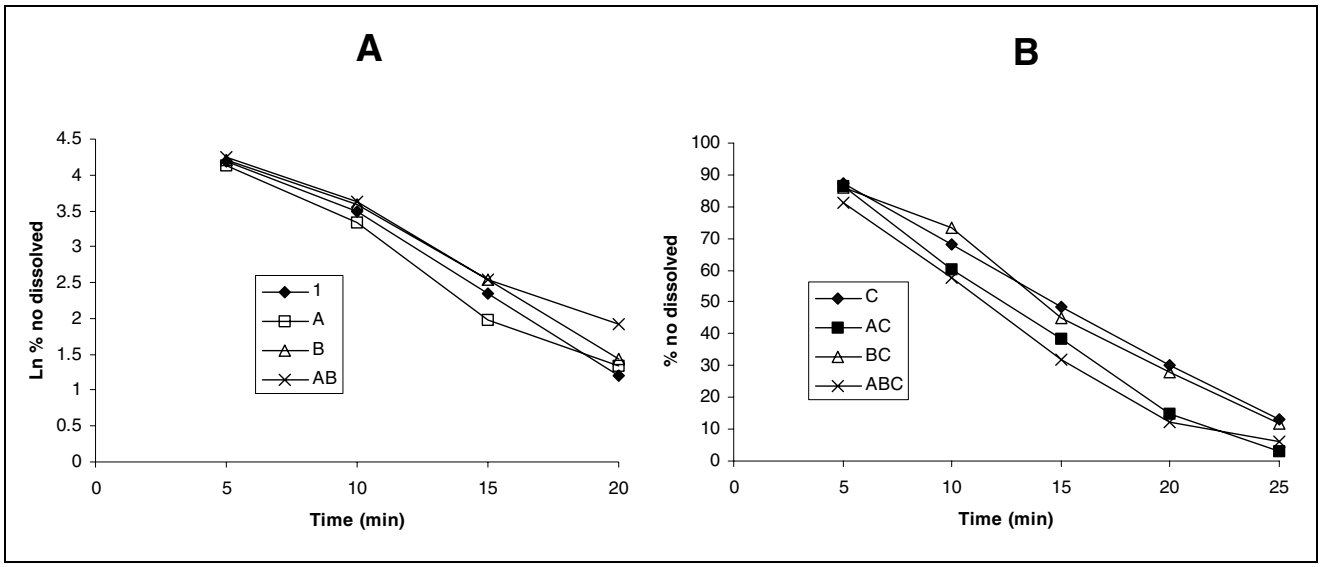

Fig. 2: Profile of the percentage of amount not dissolved *vs* time for the eight formulations. Panel A: lactose group; panel B: cellulose group

Table 1: Dissolution kinetic parameters of the formulations

Formulation	Release kinetics	Rate constant (k)	Half-life ($t_{50\%}$)	DE (%) $\bar{x} \pm s$
1 (E/GSS/MST/LAC)	first-order	0.1723	7.8	63.76 ± 2.09
A (E/CCS/MST/LAC)	first-order	0.1733	7.4	65.43 ± 2.63
B (E/GAS/CSD/LAC)	first-order	0.1595	8.4	62.22 ± 1.45
AB (E/CCS/CSD/LAC)	first-order	0.1411	9.8	61.09 ± 2.32
C (E/GSS/MST/CMC)	zero-order	3.3857	13.8	40.59 ± 2.61
AC (E/CCS/MST/CMC)	zero-order	4.1257	11.4	48.40 ± 2.53
BC (E/GSS/CSD/ CMC)	zero-order	3.4293	13.4	40.92 ± 1.02
ABC (E/CCS/CSD/CMC)	zero-order	4.0051	11.2	50.87 ± 2.54

E – extract; GSS – starch sodium glycolate; CCS – croscarmellose sodium; MST – magnesium sterarate; CSD – colloidal silicon dioxide; LAC – lactose; CMC – microcrystalline cellulose

Table 2: Main effect (E), interaction (I) and crossover analysis of factors and interactions on the dissolution efficiency of the tablets

Main effects (E)	Value	MS	Variance ratio
E_A (disintegrant)	4.5875	42.09	667.97**
E_B (lubricant)	−0.7725	1.19	18.94
E_C (filler/binder)	−17.9175	642.07	10189.62**
Interactions (I)			
I_{AB}	−0.1775	0.06	NS
I_{AC}	+4.2975	36.94	586.18**
I_{BC}	+2.1875	9.57	151.88*
I_{ABC}	+1.2525	3.14	49.79
Error (AB) = 0.06			

F tabulated: * $\propto_{0.1} = 39.86$; ** $\propto_{0.05} = 161.4$

Table 3: Similarity factor (f_2) between formulations

Lactose group Reference – Formulation A		Cellulose group Reference – Formulation ABC	
Formulation 1	72.9	Formulation AC	67.6
Formulation B	62.8	Formulation BC	45.9
Formulation AB	58.9	Formulation C	44.9

affected by the type of disintegrant used. Better results were obtained with croscarmellose sodium as disintegrant.

The similarity factor (f_2) is a measure of the similarity of the dissolution profiles between two products. Two dissolution profiles are considered identical when f_2 ranges from 50 to 100 [13, 14]. When the similarity factor was used to compare the formulation with better DE % from the lactose group (A) with the formulation with better DE % from the cellulose group (ABC), f_2 was smaller than 50 showing that the dissolution behaviors of this two groups are not similar. These two formulations were used as references to compare the dissolution profiles among the lactose and cellulose groups. Table 4 presents these results.

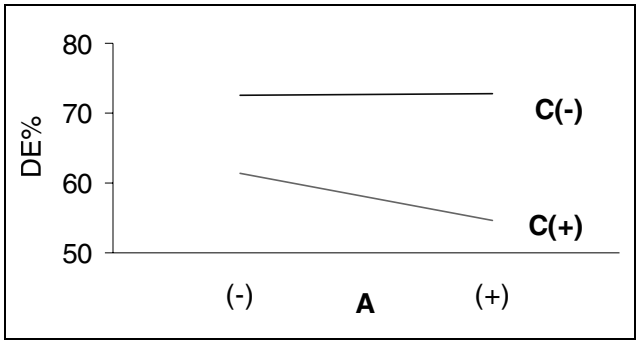

Fig. 3: Interaction AC between lubricant and filler/binder

Table 4: Factors and levels for the 2^3 factorial design

Factor	Level
(A) disintegrant	(+) croscarmellose sodium
	(−) sodium starch glycolate
(B) lubricant	(+) colloidal silicon dioxide
	(−) magnesium estearate
(C) filler/binder	(+) microcrystalline cellulose
	(−) lactose

Table 5: Composition of the formulations containing spray-dried extract of *Maytenus ilicifolia*

Composition	Formulations (%)							
	1	A	B	C	AB	AC	BC	ABC
E	57.69	57.69	57.69	57.69	57.69	57.69	57.69	57.69
GSS	3.00	–	3.00	3.00	–	–	3.00	–
CCS	–	3.00	–	–	3.00	3.00	–	3.00
MST	1.00	1.00	–	1.00	–	1.00	–	–
CSD	–	–	2.00	–	2.00	–	2.00	2.00
LAC	38.31	38.31	38.31	–	38.31	–	–	–
CMC	–	–	–	37.31	–	37.31	37.31	37.31

E – spray-dried extract; GSS – starch sodium glycolate; CCS – croscarmellose sodium; MST – magnesium sterarate; CSD – colloidal silicon dioxide; LAC – lactose; CMC – microcrystalline cellulose

All formulations within the lactose group, independent of their compositions, were similar showing f_2 bigger than 50 (Table 5). In the cellulose group only formulation AC was similar to the reference formulation ABC. This fact suggests that the type of disintegrant and lubricant did not influence the dissolution of tablets prepared with lactose, but caused differences within the cellulose group.

The result of the similarity factor disagrees with the results of the ED % in two cases. While the ED % showed a significant difference between formulations A and AB and between formulations A and B, the similarity factor for these comparisons were 58,9 and 62,8, respectively, showing similarity between these dissolution profiles. A similarity factor equal or bigger than 50 assumes a difference no bigger than 10% between the dissolution profiles of the test and the reference at any sampling time point. Reducing this difference to 5%, the similarity factor should be equal or bigger than 65 [14]. Applying these criteria both tests, ED % and f_2, would give analogous results. Although the statistical analysis of ED % showed

significant differences among these formulations for $\alpha = 0.05$, these divergence may not be biologically important because it implies that the difference between the dissolution profiles has to be smaller than 5%, which can be considered as a too narrow dissolution specification for plant extracts.

In conclusion, it can be stated that the dissolution profile of the tablets containing high doses of spray-dried extract of *Maytenus ilicifolia* depends on the adjuvants used in the formulations. The filler/binder was the adjuvant with the strongest effect on the dissolution profile. When the filler/binder used was lactose the extract showed first-order release kinetics while when cellulose was used, a zero-order profile was observed, independent of the other adjuvants added to the formulations. The filler/binder also caused differences in all the other parameters studied (half-life, dissolution efficiency and similarity factor). The dissolution efficiency was greatly affected by the adjuvants, with filler/binder and disintegrant type being the most important factors. Lactose and croscarmellose sodium were the adjuvants that resulted in better dissolution efficiency of the tablets.

All methods used to analyze the dissolution profiles of the tablets showed that the extract dissolved in a different way depending on whether the formulation contained lactose or cellulose. Although the tablets consisted of high amounts of the spray-dried extract, the determinant for the dissolution behavior was the type of adjuvants used in the formulation.

3. Experimental

3.1. Materials

Spray-dried extract of *Maytenus ilicifolia* containing 133.6 mg/g of polyphenols, calculated based on pyrogallol standard, was prepared following previously described methods [15].

Adjuvants: microcrystalline cellulose (Microcel®-MC 101), sodium starch glycolate (Explosol®) and croscarmellose sodium (Explocel®) were obtained from Blanver (São Paulo, Brazil), colloidal silicon dioxide (Aerosil® 200) was obtained from Degussa (Frankfurt, Germany), lactose and magnesium stearate were granted from State Pharmaceutical Laboratory (FEPPS/Brazil). All adjuvants were used as received.

3.2. Experimental design

The formulations were prepared according to a 2^3 factorial design, evaluating the qualitative factors and levels shown in Table 4.

3.3. Tablets preparation

Eight different tablet formulations containing spray-dried extract of *Maytenus ilicifolia* (375 mg) and adjuvants were prepared (Table 5). The extract and the adjuvants were mixed in a cubic blender at 20 rpm for 30 min.

The powders were compressed in a single punch tablet press (Korch EK0), using 15 mm flat punches, by individual direct compression of 650 mg from each formulation. All tablets were produced with similar hardness (from 46 to 56 N).

3.4. Dissolution studies

Dissolution tests were performed according to the USP 23 using the paddle apparatus with 900 ml of water at 37 ± 1 °C as dissolution medium. A dissolution apparatus (Pharma Test PTW SIII) was coupled to a 10-way peristaltic pump and a multiple flow cell spectrophotometer (Hewlett-Packard 8452A), controlled by a multibath dissolution testing system (Hewlett-Packard). The paddle speed was set at 100 rpm. Sink conditions were maintained throughout the experiments. The assay was carried out with six tablets from each formulation. The dissolution profile of the extract from each formulation was obtained through recording the absorbance at 270 nm, every 5 min, during a 60 min period.

The parameters determined from the dissolution profiles were dissolution efficiency (DE %), dissolution kinetics and similarity factor (f_2).

In order to determine the dissolution efficiency, the areas under the dissolution curves were calculated by trapezoidal rule from 0 to 25 min [16].

The extract dissolution profiles from each formulation was analyzed assuming zero or first order kinetics, by linear regression of the data. The dissolution rate constant was calculated from the slope of the % no-dissolved *vs* time, for the zero order kinetics (K_0), or from the slop of the ln % no-dissolved *vs* time, for the first order kinetics (K_d) [17, 18].

The dissolution half-lifes ($t_{50\%}$) were determined by means of the following equations:

$$t_{50\%} = \frac{100}{2 \times K_0} \quad (1)$$

$$t_{50\%} = \frac{0{,}693}{K_d} \quad (2)$$

The similarity of the average dissolution profiles obtained was determined using the similarity factor (f_2). For these calculations, the formulation that showed better dissolution efficiency was used as reference (R), and the others considered as test (T), in comparison to it. The similarity factor was determined by the following equation [17, 13]:

$$f_2 = 50 \cdot \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{i=1}^{n} (R - T)^2 \right]^{-0{,}5} \cdot 100 \right\} \quad (3)$$

Where n is the number of sampling time points; R is the percentage of the reference dissolved and T is the percentage of the test dissolved up to each time point. The number of sampling time points was limited to one time point after the time at which any of the two formulations compared reached 85% of dissolution.

For the analysis of the factorial design, the dissolution efficiency (DE %) was selected as response criteria.

3.5. Statistical analysis

The parameters obtained from the dissolution profiles were evaluated statistically by analysis of variance and Student-Newman-Keuls test. The analysis of the effect for the different factors and interactions in the factorial design was performed by Yate's method. The residue variation was estimated by Daniel's method [19].

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Pedro Ros Petrovick
Programa de Pós-Graduação em Ciências Farmacêuticas
Universidade Federal do Rio Grande do Sul
Av. Ipiranga, 2752
90610-000 Porto Alegre – RS
Brazil
prpetrov@farmacia.ufrgs.br