Optimization of Tablets Containing a High Dose of Spray-Dried Plant Extract: A Technical Note

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Luiz Alberto Lira Soares,[1,2] George González Ortega,[2] Pedro Ros Petrovick,[2] and Peter Christian Schmidt[3]

[1]Departamento de Farmácia—UFRN, Av. General Cordeiro de Farias s/n, 59010-180, Natal, Rio Grande do Norte, Brazil
[2]Programa de Pós-Graduação em Ciências Farmacêuticas—UFRGS, Av. Ipiranga, 2752, 90610-000, Porto Alegre, Rio Grande do Sul, Brazil
[3]Department of Pharmaceutical Technology, University of Tübingen, Auf der Morgenstelle 8, D—72076, Tübingen, Germany

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INTRODUCTION

The development and production of tablets containing a high dose of active ingredients is a complex and extensive technological challenge. Dried plant extracts are often used as therapeutically active material in the manufacture of tablets. They are quite often very fine, poorly compressible, and very hygroscopic powders. Additionally, tablets containing a high amount of dried extract show prolonged disintegrate times; therefore, the release of the active constituents is affected.[1-3] Some alternatives have been proposed to minimize these problems. Granulation is the technique most often used to improve the technological properties of these products. However, because of the products' high hygroscopicity, extracts cannot be granulated using aqueous systems. Thus, dry granulation may be used to produce granules from dried herbal extracts.[2,3] Slugging is a simple dry granulation process in which material is compacted in a tablet press and then goes through a milling process. Previous work showed that the use of lubricants during direct compression of vegetable dried extracts increased the disintegration time.[2] On the other hand, Rocksloh et al[2] and von Eggelkraut-Gottanka et al[3] showed that tablets with a high amount of magnesium stearate incorporated into the granules had shorter disintegration times than did tablets containing the powdered mixture.

Experimental design affects the systematic and effective evaluation of differences among formulations.[4-7] Central composite design (CCD) is the second-order design most often employed to study and optimize tablet formulations.[8-11] With CCD, it is possible to create response surfaces that allow the ranking of each variable according to its significance on the responses studied. Therefore, with reduced time and experimental effort, it may be possible to predict what formulation composition will produce a desired response.[12-17]

Corresponding Author: Departamento de Farmácia—UFRN, Av. General Cordeiro de Farias s/n, 59010-180, Natal, Rio Grande do Norte, Brazil. Tel: + 55 84 32154355; Fax: +55 84 32154340. E-mail: phtech@uol.com.br

The aim of this study was to evaluate the effect of the concentration of sodium carboxymethylcellulose (CMC-Na) and colloidal silicon dioxide (CSD) on the crushing strength, disintegration time, and friability of tablets containing high doses of spray-dried extract (SDE) dry granulations, using a CCD.

MATERIALS AND METHODS

Materials

SDE

Maytenus ilicifolia aerial parts were extracted by maceration using distillated water (1:10, wt/vol). Colloidal silicon dioxide (Aerosil 200, Degussa AG, São Paulo, Brazil) was added to the miscella in a ratio of 2:8 of adjuvant to dry residue.[18] The dispersion was dried using a Production Minor spray-dryer (GEA, Copenhagen, Denmark), provided with a rotating disk. The operational conditions were rotation disk speed of 9500 rpm, inlet temperature of 149°C, outlet temperature of 99°C, and feed ratio of 140 mL/min.

Excipients

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

Methods

Slugging and Granulation[19]

The SDE from *M ilicifolia* (486.0 g) was blended in a Turbula mixer (Model T2C, Willy Bachofen, Basel, Switzerland) for 5 minutes, with 7.0 g of CSD and 7.0 g of magnesium stearate. Slugs of 0.8 g 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 instrumented 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 Messefix V. 2.3 software (Dr. R. Herzog, Tübingen, Germany).

The slugs were crushed in a dry granulator (Erweka TG IIS coupled to a 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 an Erweka AR 400 multipurpose motor; Erweka GmbH) using a 1.0-mm sieve. The granulate fraction between 250 and 1000 μm was chosen for tablet optimization.

Preparation of Tablets

Tablets were prepared from each formulation described in Table 1. The granule proportion was kept constant at 71.23% (wt/wt). The amount of CMC-Na and CSD was established according to each formulation, and MCC was in concentration sufficient to 100% (Table 1). The different formulations were blended for 10 minutes in the Turbula mixer. Then CSD was sieved through a 315-μm sieve onto the mix, and the final mixing was performed for 5 minutes.

Exactly 250.0 mg from each formulation was weighted (n = 40) and compressed at 11.0 ± 0.5 kN on a single-punch tablet machine EK 0 (Korsch AG) using a flat-faced tooling 10 mm in diameter.

Experimental Design and Calculations

The independent variable factors for the CCD were the concentrations of CSD and CMC-Na. The dependent variables (responses) were tablet crushing strength, disintegration time, and friability. To compare the effect of the factors, the values were coded (Table 1). A second-order model was established for the responses (Equation 1). Calculations were performed by last-square method using SigmaStat 1.0 (Jandel Corp, Richmond, VA). The validation of the mathematical model was performed through analysis of variance, multiple-correlation coefficients, and estimation of the lack of fit using Excel 2000 (Microsoft Corp, Redmond, WA).[10,11,14,15]

$$Y = b_0 + b_1 . X_1 + b_2 . X_2 + b_{12} . X_1 . X_2 + b_{11} . (X_1)^2 + b_{22} . (X_2)^2 \quad (1)$$

where Y was the response (crushing strength, disintegration time, or tablet friability), and b_0 ... b_{22} were the regression coefficients.

Crushing Strength

The tablet crushing strength was determined using 6 randomly selected tablets for each test formulation (Hardness tester TBH-30; Erweka GmbH).[20]

Disintegration Time

Disintegration time was measured according to the European Pharmacopoeia without disks (Disintegration tester PTZ1; Pharmatest GmbH, Hainburg, Germany). Water at 37°C was used as the test medium. For each formulation, 6 randomly selected tablets were tested.[20]

Friability

Tablet friability was measured as the percentage of weight loss of 20 tablets tumbled in a friabilator (Model PTF1;

Table 1. Central Composite Design Matrix and Tablet Composition*

Exp	CSD (Coded)	CMC-Na (Coded)	CSD (%, wt/wt)	CMC-Na (%, wt/wt)	CSD (mg)	CMC-Na (mg)	MCC (mg)
1	–1	–1	0.50	2.50	1.25	6.25	73.43
2	1	–1	1.90	2.50	4.75	6.25	69.93
3	–1	1	0.50	7.50	1.25	18.75	60.93
4	1	1	1.90	7.50	4.75	18.75	57.43
5	0	0	1.20	5.00	3.00	12.50	65.43
6	0	0	1.20	5.00	3.00	12.50	65.43
7	0	0	1.20	5.00	3.00	12.50	65.43
8	1.414	0	2.19	5.00	5.47	12.50	62.95
9	–1.414	0	0.21	5.00	0.53	12.50	67.90
10	0	1.414	1.20	8.50	3.00	21.34	56.59
11	0	–1.414	1.20	1.45	3.00	3.64	74.29

*Exp indicates the experimental run; CSD, colloidal silicon dioxide; CMC-Na, sodium carboxymethylcellulose; MCC, microcrystalline cellulose. The concentration of granulations was 71.23% (wt/wt) or 178.8 mg per tablet (equivalent to 173.09 mg of spray-dried extract or 138.47 mg of native extract).

Table 2. Experimental Data for Tablet Crushing Strength, Disintegration Time, and Friability*

Exp	Crushing Strength (N)	Disintegration Time (min)	Friability (%, wt/wt)
1	124.0 (6.8)	9.60	0.47
2	97.7 (8.4)	7.20	0.58
3	115.2 (10.0)	6.68	0.52
4	96.7 (6.0)	6.10	0.61
5	108.2 (8.8)	6.38	0.54
6	110.3 (5.3)	7.37	0.57
7	105.2 (2.3)	6.73	0.56
8	106.0 (5.1)	6.33	0.58
9	126.8 (6.2)	8.13	0.52
10	101.7 (4.6)	5.75	0.58
11	107.0 (7.8)	10.05	0.52

*Exp indicates the experiemental run. Standard deviations appear in parentheses.

Pharmatest GmbH). After 5 minutes of rotation at 25 rpm, the dust of tablets was removed and the percentage of weight loss calculated.[20]

Results and Discussion

The results for crushing strength, disintegration time, and tablet friability are shown in Table 2. The experimental data from Table 2 were used to generate second-order models for each dependent variable. A summary of the regression analysis is shown in Table 3.

The proposed mathematical models showed good multiple correlation coefficients (r^2). For both tablet crushing strength and disintegration time, the calculated multiple correlation coefficients indicated that more than 94% of the experimental variance could be explained by the proposed equations. Additionally, for tablet friability, the mathematical model described more than 99% of the experimental behavior. The calculated F-ratios of the regressions were significant when compared with the theoretical value (Table 3). Because the lack-of-fit test was not significant, the experimental variations could be attributed only to a randomized error. Thus, the fitted models provided an adequate approximation of the true values, and no violations of the model assumptions occurred.[15,16]

Crushing Strength

Concerning the tablet crushing strength, the most important effect was imputed to CSD. On the other hand, the terms related to CMC-Na and interaction between factors were of only minor importance. According to the *t* test (Table 3), the linear term of CSD was the main factor and had a negative effect revealed by a decrease in the crushing strength. It was followed by the CSD quadratic term. The contribution of the second-order term was interpreted as the presence of a curvature and represents the nature of the response surface system (maximum, minimum, or saddle system). Thus, the positive signal observed with the CSD quadratic term revealed the concave form of the curve.[16] The response surface indicated that the response was inversely proportional to the CSD concentration (Figure 1). No statistically significant effect on the tablet resistance was observed by the increase of the CMC-Na concentration. The maximal crushing strength was obtained for tablets containing a lower concentration of CSD. The observed decrease in tablet crushing strength with increasing CSD concentration can be explained by the glidant distribution, as small particles, over the whole surface of the formulation components, act as a mechanical barrier and interfere with the bond properties of the blend.[21]

Friability

The response of tablet friability was statistically affected by only linear terms (Table 3). As was observed for crushing strength, the concentration of CSD plays an important role in the decrease of the tablet's mechanical resistance.

Table 3. Summary of the Regression Results for Tablet Crushing Strength, Disintegration Time, and Friability

Variables	Crushing Strength (N)		Disintegration Time (min)		Friability (%, wt/wt)	
	Value	*t* Test	Value	*t* Test	Value	*t* test
b_0	107.9	58.42*	6.827	25.02*	0.557	46.20*
b_1	–9.278	8.20*	–0.691	4.13*	0.036	4.83*
b_2	–2.162	1.91	–1.263	7.56*	0.021	2.79*
b_{12}	1.95	1.21	0.455	1.93	–0.005	0.48
b_{11}	3.757	2.79*	0.159	0.80	–0.0046	0.52
b_{22}	–2.27	1.68	0.492	2.48*	–0.0046	0.52
r^2	0.9425	—	0.9446	—	0.9902	—
F regression	17.25Â†	—	16.88**	—	5.69**	—
F lack of fit	1.42	—	0.62	—	1.59	—

*Significant for $\alpha = .05$.

†Significant for $\alpha = .05$ ($F_{.05\ [5,5]} = 5.05$).

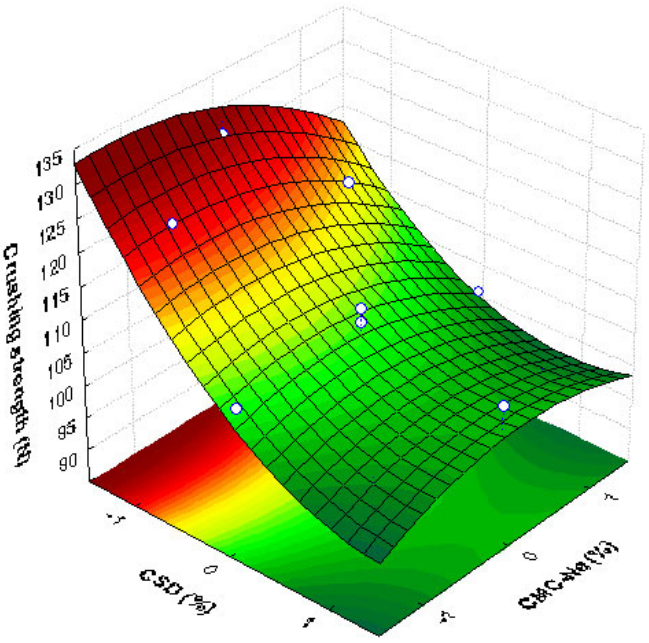

Figure 1. Effects of Aerosil and Ac-Di-Sol concentrations on the crushing strength of tablets.

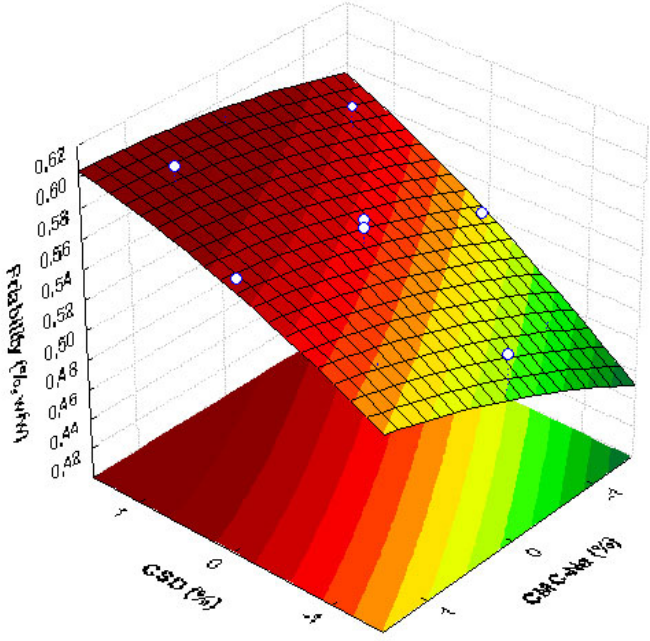

Figure 2. Effects of Aerosil and Ac-Di-Sol concentrations on the friability of tablets.

According to *t* test sequence, the CSD linear term was the main factor, followed by the CMC-Na linear term. The other terms had no significant influence. The concentrations of CSD and CMC-Na were directly proportional to the tablet friability. However, all formulations showed tablets with satisfactory friability independent of the factor levels. The response surface analysis demonstrated that lower friability was obtained when lower proportions of CMC-Na and CSD were used (Figure 2).

Disintegration Time

The addition of disintegrant to the tablet is usually necessary to achieve or improve the tablet disintegration. The prediction of disintegration time of tablet formulations by mathematical model can be difficulty because of the numerous parameters influencing such response. In fact, the type and concentration of disintegrant, the disintegration mechanisms (ie, swelling or capillary forces), and the compression force can affect the disintegration behavior in different ways.[3,22] However, in this study, this variable showed a satisfactory coefficient of determination. This can be attributed to the lower level of interaction observed between independent variables.

As expected, the tablet disintegration time was primarily affected by the amount of CMC-Na in the formulation. The CMC-Na linear term was the primary factor responsible for the decrease in the tablet disintegration time. This was followed by both the CSD linear term, which showed a similar effect on the response variable, and the CMC-Na quadratic term. The interaction between the 2 factors and the quadratic term of CSD had no influence on the tablet disintegration. The shortest disintegration time was achieved at the higher concentration of CMC-Na. However, the increase of the CSD concentration in the absence of variation in the proportion of CMC-Na resulted in a negative effect, decreasing the disintegration time (Figure 3).

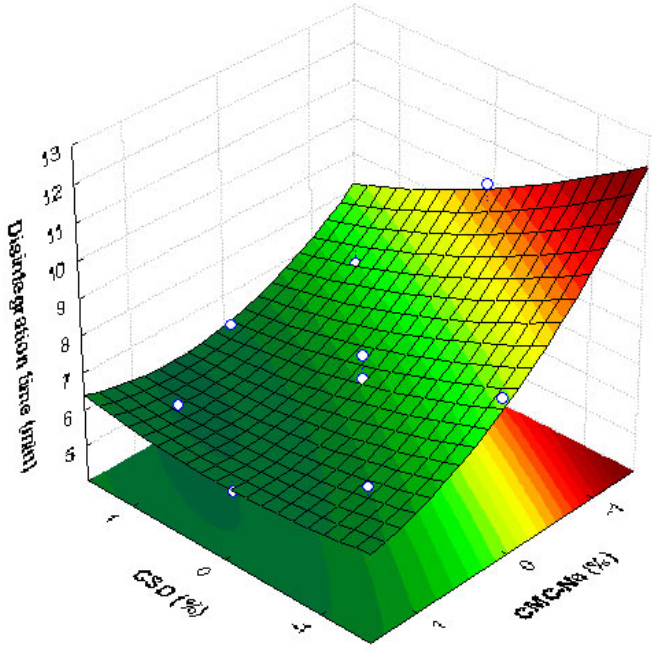

Figure 3. Effects of Aerosil and Ac-Di-Sol concentrations on the disintegration time of tablets.

CONCLUSIONS

Optimization of CSD and CMC-Na in tablet formulations containing a high dose of SDE from *M ilicifolia* was performed by central composite design (CCD) and response surface methodology (RSM). The study demonstrated that CSD affected mainly the hardness and friability, while CMC-Na modified the disintegration times. The optimum formula for minimum disintegration time and friability, and maximum crushing strength, was found to contain 1.2% (wt/wt) of CSD and 5.0% (wt/wt) of CMC-Na. At these conditions, the tablet shows a crushing strength of 107.9 N, a friability of 0.56% (wt/wt), and a maximum disintegration time of 6.8 minutes.

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