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COMMUNICATION

Response Surface Analysis Applied to the Preparation of Tablets Containing a High Concentration of Vegetable Spray-Dried Extract

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ABSTRACT

This work relates to the formulation of tablets containing a high proportion of spray-dried extracts (SDEs) from Passiflora edulis leaves. The tablets were prepared by direct compression. Colloidal silicon dioxide was selected as a glidant and moisture adsorbent, cross-linked carboxymethycellulose was used as the disintegrant, microcrystalline cellulose was the filler/binder, and tricalcium phosphate as a spray-drying adjuvant. The colloidal silicon dioxide and cross-linked carboxymethycellulose quantities and their influences on the tablet hardness and disintegration time were studied by a central composite design. The model equations were fitted to the experimental data and then validated. It could be concluded that the colloidal silicon dioxide proportion increased the hardness, and the cross-linked carboxymethycellulose proportion determined a linear decrease of the disintegration time. The optimal values chosen were 2.0% Aerosil® 200 and 2.5% Ac-Di-Sol®. The tablets showed a hardness of 85.02 N and a disintegration time of 7.35 min.

Key Words: Passiflora edulis; *Response surface analysis; Spray-dried extract; Tablets.*

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INTRODUCTION

The formulation and preparation of tablets containing a high percentage of active substances represent a very complex and effort-consuming task. This is the case of phytopharmaceuticals. The fulfilling of tablet hardness and disintegration time requirements demand the complete management and knowledge of the formulation factors affecting the quality of such pharmaceutical dosage forms. For tablets containing large dry extract quantities, the problem becomes more acute. Spray-dried extracts (SDEs) consist of very fine, poorly compressible, and very hygroscopic powder that frequently show a segregation tendency. Notwithstanding the technological factors involved in this question, few works about the formulation of tablets and related solid preparations containing large amounts of vegetable dry extracts are found (1–3). Currently, the response surface methodology (RSM) seems to be one of the most helpful statistical tools to explore and optimize this kind of problem (4–7). In addition, RSM allows the influence of each variable to be ranked according to its effect on the whole response.

The aim of this work was the improvement, applying factorial design and RSM approaches, of pharmacotechnical characteristics regarding the preparation of tablets with suitable hardness and disintegration time containing a large dose of SDE from *Passiflora edulis* leaves.

MATERIAL AND METHODS

Materials

Colloidal silicon dioxide (Aerosil® 200, Degussa, Germany) was used as the glidant and moisture adsorbent; cross-linked carboxymethycellulose (Ac-Di-Sol®, FMC, USA) as was the disintegrant, and microcrystalline cellulose (Avicel PH-101, FMC) was the filler/binder. All the excipients were used as received.

Spray-Dried Extracts

Passiflora edulis leaves extractive solutions were prepared by turboextraction (Ultra-Turrax T4, Janke, Germany) using 100 g of plant material and 1 L 40% (v/v) hydroethanolic solution. After filtration, the extractive solution was concentrated under vacuum to half of the original weight. Tricalcium phosphate (10 g; Riedel, Germany) was added to the concentrated extract as a spray-drying carrier, and the suspension was dried using a mini spray-dryer (Büchi MSD 190), provided with a 0.7-mm pneumatic nuzzle, in tangential flow at a feed speed of 3 ml/min. The inlet temperature was 150°C–152°C; the outlet temperature was 90°C, and the exhaustion was fixed at level 5.

Basic Tablet Formulation

For the basic tablet formulation, the following were used: spray-dried extract, 400 mg (equivalent to 9.2 mg of flavonoids); Aerosil 200, 6.25 to 12.5 mg; Ac-Di-Sol, 3.125 to 15.625 mg; Avicel PH-101, quantity sufficient for 650 mg. The constituents were mixed for 15 min at 20 rpm (cubic mixer, KM5 Erweka, Germany). The direct compression of each test sample was carried out separately using an eccentric tablet machine (Korsch EK0, Germany) fitted with 10 mm diameter flat punches. The tablet weight, the upper punch displacement, and other experimental conditions were kept constant. Each set of samples was assayed for hardness and disintegration time within 24 hr after tablet production.

Hardness and Disintegration Assay

The tablet hardness, expressed as the radial crushing resistance, was determined using 10 tablets for each test sample (Tester PTZ-1, Schleuniger, Germany). The tablet disintegration test was performed in accordance with the procedure and apparatus outlined in USP 23, using baskets without disks.

Statistical Experimental Design

The factors selected in this study were quantity of Aerosil 200 **Ae** and quantity of Ac-Di-Sol **Ac**. The response criteria were the hardness **H** and disintegration time **DT**. To define the experimental field, the first step was the preliminary evaluation of the factor levels using a typical 2^2 factorial design without replication. Afterward, the experimental design was transformed into a central composite design. The central composite design matrix and the tablet unit composition are shown in Table 1.

Statistical Analysis

The central composite design data were adjusted to a polynomial second-order equation by the least-square method (Sigma-Stat®, v. 1.0; Jandel Scientific, USA). The respective response surfaces were modeled from a 2^3 factorial design by addition to the 2^2 factorial matrix of five central points and four star points (Excel® 97, Mi-

Table 1

Central Composite Design Matrix, Tablet Composition, and Results for Hardness (H) and Disintegration Time (DT) Experiments

Experiment	Ac-Di-Sol (Coded)	Aerosil 200 (Coded)	Ac-Di-Sol (mg%)	Aerosil 200 (mg%)	Ac-Di-Sol (mg)	Aerosil 200 (mg)	Avicel PH-101 (mg)	Hardness (N)	*DT* (min)
1	−1	−1	0.5	1.0	3.125	6.250	215.625	80.22	12.92
2	+1	−1	2.5	1.0	15.625	6.250	203.125	70.71	5.92
3	−1	+1	0.5	2.0	3.125	12.500	209.375	83.26	9.83
4	+1	+1	2.5	2.0	15.625	12.500	196.875	88.46	6.75
5	0	0	1.5	1.5	9.375	9.375	206.250	72.86	9.02
6	0	0	1.5	1.5	9.375	9.375	206.250	70.12	9.83
7	0	0	1.5	1.5	9.375	9.375	206.250	71.88	8.25
8	0	0	1.5	1.5	9.375	9.375	206.250	65.90	8.62
9	0	0	1.5	1.5	9.375	9.375	206.250	65.70	9.54
10	+1.414	0	2.91	1.5	18.188	9.375	197.438	67.27	7.17
11	−1.414	0	0.09	1.5	0.563	9.375	215.063	85.12	13.33
12	0	+1.414	1.5	2.21	9.375	13.794	201.831	111.50	8.17
13	0	−1.414	1.5	0.79	9.375	4.956	210.669	68.74	12.17

crosoft, USA). From this model, a quadratic equation was fitted presenting the general equation:

$$Y = a + b\mathbf{x} + c\mathbf{y} + d\mathbf{xy} + e\mathbf{x}^2 + f\mathbf{y}^2$$

where *a*, *b*, *c*, *d*, *e*, *f*, denote the regression coefficients.

The central composite design model was validated statistically by analysis of variance (ANOVA), calculation and evaluation of the multiple-correlation coefficients, and estimation of the lack of fit (8).

RESULTS AND DISCUSSION

The results for hardness and disintegration time obtained from the central composite design are shown in Table 1.

The regression analysis allowed fitting Eq. 1 for the tablet hardness factor **H**.

$$\mathrm{H} = 106.70 - 28.41\mathbf{Ac} - 31.51\mathbf{Ae} + 7.35\mathbf{AcAe} + 4.563\mathbf{Ac^2} + 11.77\mathbf{Ae^2} \quad (1)$$

where **Ac** = Ac-Di-Sol factor, **Ae** = Aerosil factor, and **AcAe** = factor interaction.

The results from the ANOVA, multiple correlation analysis, lack-of-fit test, and *t* test related to Eq. 1 are given in Tables 2 and 3. The multiple regression coefficient calculated for Eq. 1 indicated that about 91% of the experimental variance can be explained ($R^2 = 0.9069$). Because the pure error was not significant [$F_{(P\ 0.95;\ FG\ 3.4)} = 6.59 > 3.77$], the experimental variation could be as-

Table 2

Statistical Evaluation and Validation Tests Applied to Equation 1 (Tablet Hardness)

Error Source	Sum of Squares	Freedom Degrees	Mean Squares	$F_{calculated}$
Regression	1796.65	5	359.33	13.65[a]
Residual	184.30	7	26.33	—
Total	1980.95	12	—	—
R^2	0.9069	—	—	—
Lack of fit	136.11	3	45.37	3.77 (n.s.)
Pure error	48.19	4	12.05	—

n.s. = not significant for $\alpha = .05$.

[a] Significant for $\alpha = .05$.

Table 3

Results of the t*-test for Equation 1 Coefficients*

Term	Coefficient	Standard Error	$t_{calculated}$
1	106.70	14.05	7.59[a]
Ac (lineal)	−28.41	9.988	2.84[a]
Ae (lineal)	−31.51	10.87	2.90[a]
AcAe (interaction)	7.351	5.131	1.43[a]
$\boldsymbol{Ac}^2$ (quadratic)	4.563	2.034	2.24[a]
$\boldsymbol{Ae}^2$ (quadratic)	11.77	2.427	4.85[a]

[a] Significant for $p = .95$.

cribed to a randomized error that was not related to the experimental model. Thus, the regression model expressed by Eq. 1 appears to be satisfactory to describe the tablet hardness behavior.

Considering the ANOVA results and the *t*-test data, all the lineal and quadratic coefficients should be considered statistically different from zero ($F_{calc.}$ 133.65 $>$ $F_{0.95;\ 5.7}$ 3.97) and consequently had a significant effect on the estimated response. The arrangement of the coefficients accordingly to the *t*-test values allowed assignment of a main positive effect (hardness increase) to the Aerosil quadratic term, followed by the Aerosil lineal term. The Ac-Di-Sol lineal term, as well as the Ac-Di-Sol quadratic term, and the interaction between the Aerosil and Ac-Di-Sol factors had only minor importance. The response surface and the corresponding contour-plot graphs showed that the hardness maximal value was almost independent of the Ac-Di-Sol concentration used when the Aerosil concentration was near 2.0% of the total tablet weight. Notwithstanding, when Ac-Di-Sol concentrations were lower than 1.0% but greater than 2.0%, maximal hardness values could also be observed if the Aerosil concentration remained slightly lower than 2.0% (Figs. 1 and 2).

To the disintegration time parameter **DT** was fitted Eq. 2:

$$\begin{aligned} DT = {} & 21.2601 - 6.4661\mathbf{Ac} - 6.2577\mathbf{Ae} \\ & + 1.9593\mathbf{AcAe} + 0.3915\mathbf{Ac}^2 \\ & + 0.6325\mathbf{Ae}^2 \end{aligned} \qquad (2)$$

where **Ac** = Ac-Di-Sol factor, **Ae** = Aerosil factor, and **AcAe** = factor interaction.

The results from the ANOVA, multiple correlation analysis, lack-of-fit test, and *t* test related to Equation. 1 are given in Tables 4 and 5.

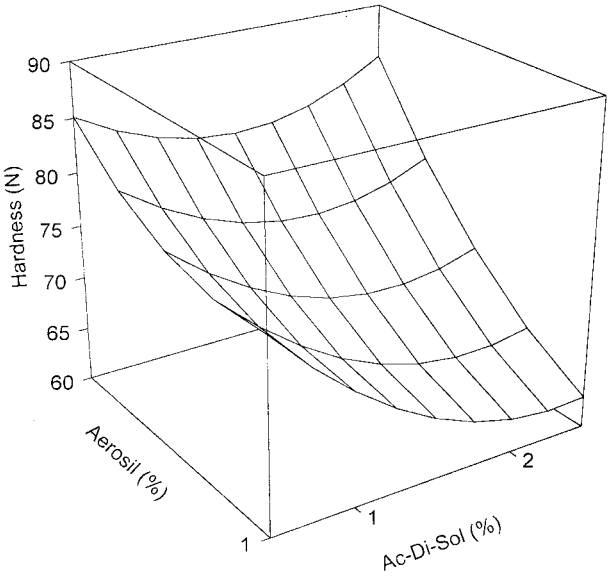

Figure 1. Response surface calculated to the tablet hardness according to Eq. 1.

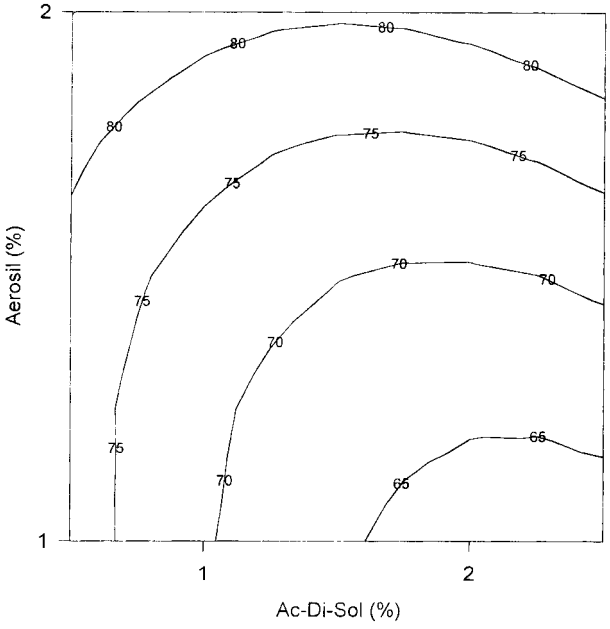

Figure 2. Contour-plot graphic calculated to the tablet hardness according to Eq. 1.

Table 4

Statistical Evaluation and Validation Tests Applied to Equation 2 (Tablet Disintegration Time)

Error Source	Sum of Squares	Freedom Degrees	Mean Squares	$F_{calculated}$
Regression	59.3155	5	11.8631	19.61[a]
Residual	4.2346	7	0.6049	—
Total	63.5511	12	—	—
R^2	0.9333	—	—	—
Lack of fit	3.0910	3	1.0303	3.67(NS)
Pure error	1.1436	4	0.2859	

n.s. = not significant for $\alpha = .05$.
[a] Significant for $\alpha = .05$.

For Eq. 2, the estimated F value (19.61) was greater than 3.97 ($F_{(P\ 0.95;\ FG\ 5.7)}$), and the t-test results demonstrated that all the equation coefficients were statistically significant. The negative influence of the lineal terms related to Aerosil and Ac-Di-Sol was higher than the others. In the sequence, the Ac-Di-Sol quadratic term and the Ac-Di-Sol-Aerosil interaction factor both presented a positive influence on the tablet disintegration time. In this decrease, 93% of the experimental total variance, respective of the tablet disintegration behavior, could be explained by Eq. 2. In view of the ANOVA and lack-of-fit test results, Eq. 2 could be considered validated.

The shortest disintegration time was observed when the concentration of Ac-Di-Sol was higher than 2.45% and the Aerosil concentration was kept between 1.0% and 1.6%. The negative effect on the disintegration time was also evident using higher Aerosil concentrations when combined with lower Ac-Di-Sol concentrations (Figs. 3 and 4).

It can be observed that the maximal hardness does not correspond necessarily to a minimal disintegration time (Figs. 2 and 4). Likewise, the contour graph area around

Table 5

Results of the t *Test for Equation 2 Coefficients*

Term	Coefficient	Standard Error	$t_{calculated}$
1	21.0107	3.156	6.65[a]
Ac	−6.7414	2.243	3.01[a]
Ae	−5.7264	2.440	2.35[a]
AcAe	1.9593	1.152	1.70[a]
$\boldsymbol{Ac}^2$	0.6011	0.459	1.31[a]
$\boldsymbol{Ae}^2$	0.4554	0.645	0.70

[a] Significant for p = .95.

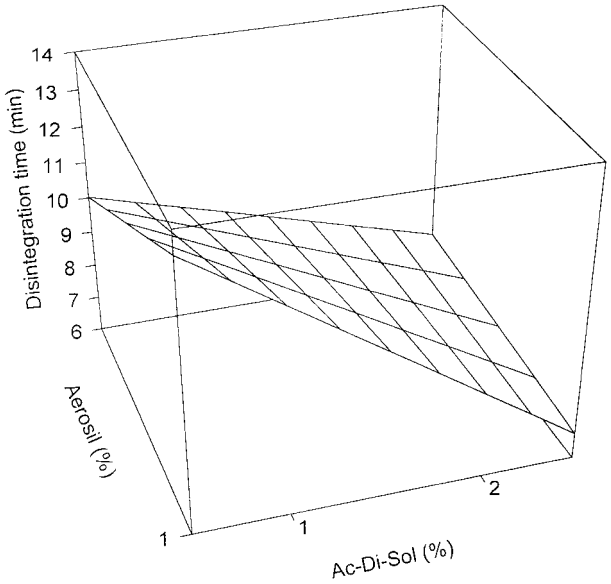

Figure 3. Response surface calculated to the tablet disintegration time according to Eq. 2.

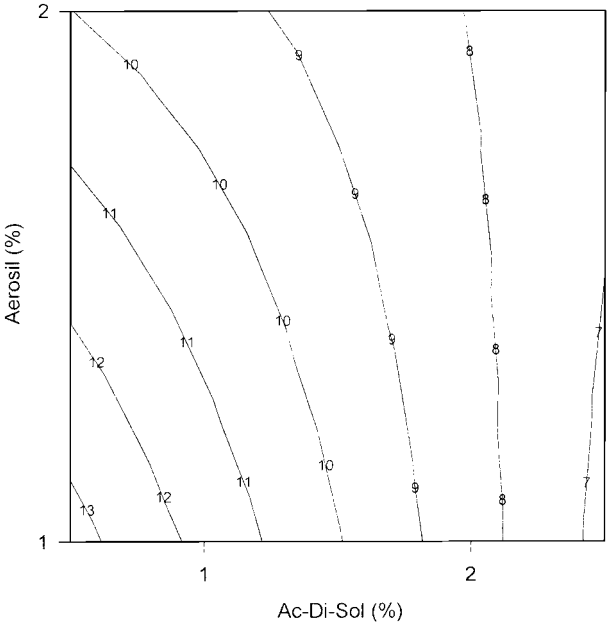

Figure 4. Contour-plot graphic calculated to the tablet disintegration time according to Eq. 2.

Table 6

Optimized Tablet Unitary Composition and the Respective Experimental Hardness and Disintegration Time Values

Spray-dried extract	400 mg (equiv. to 9.19 mg of flavonoids)
Aerosil 200	12.5 mg
Ac-Di-Sol	15.63 mg
Avicel PH-101	196.87 mg
Total weight	625 mg
Hardness	85.02 N
Disintegration time	7.35 min

the minimal disintegration time restricts the localization of the optimal point for Aerosil and Ac-Di-Sol concentrations. Considering the overlapping zones of both contour graphs, it was possible to establish a disintegration time around 7 min. For this value, the higher tablet hardness values correspond to an Aerosil concentration lower than 2.0% and 2.5%, respectively. The optimized basic tablet formulation and the measured hardness and disintegration time are given in Table 6.

CONCLUSIONS

The Aerosil 200 proportion affected the hardness in a positive way, increasing the values. The Ac-Di-Sol proportion determined a linear decrease of the disintegration time and affected the tablet hardness in accordance with the Aerosil proportion used. The optimal values chosen were 2.0% Aerosil 200 and 2.5% Ac-Di-Sol, which are within the ordinary concentration limits accepted for conventional tablets.

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