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Full Length Original Research Paper

Design, Optimization and Evaluation of Clozapine tablets by response Surface Analysis

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Abstract: The purpose of this work was, applying experimental design methodology on tablet formulation development by direct compression, to evaluate the influences of magnesium stearate and sodium croscarmelose quantities upon clozapine tablets, by a Central Composite Design. The results were fitted to non-linear regression and a second order equation was used to plot response surface graphics. The results showed that hardness and friability were influenced by magnesium stearate quantities, decreasing the mechanical resistance of tablets, and the sodium croscarmelose quantities caused a linear decreased on disintegration time and a increased on dissolution efficiency of tablets, on the studied experimental field.

Keywords: Central composite design, Direct compression, Experimental statistical design

Introduction

Direct compression is a straightforward, easiest to control, and least expensive method to produce tablets because of its advantage that possess fewer processing stages, which can increase the productivity and consequently reduce the final cost of the product [1;2]. Besides, with the elimination of heat and moisture effects, it becomes the most appropriate process for hygroscopic and thermo-sensitive drugs. However, as few drugs have the mechanical and physical properties that allow direct compression, successful tablet productions by this process is mainly dependent on the excipients that make the pharmaceutical blend [3;4]. So, the choice of excipients is extremely critical in formulating direct compression tablets.

It is well known that traditional experimentation involves a good deal of effort and time, especially when complexes processes are evaluated. Most of the experiment on tablet formulation development is still performed in an unsystematic way, by changing the levels of each variable, or factor, at a time, and keeping all the others variables constant in order to study the effects of that specific variable on the selected response. Statistical experimental design is a well-established concept for planning and execution of informative experiments. In this approach, process variables are first "screened" to determine which variable is important to the outcome, and then

follow the "optimization", when the best settings for the important variables are determined [5].

In this way, response surface methodologies have been successfully applied in drug development. The use of experimental statistical design such as Central Composite Design allows to evaluate, in an effective and systematic way, the differences among the batches and makes possible to plot surface response graphics, which allows to evaluate the influence of each variable, which can be ranked according to its effect on the whole response [5;6;7;8;9].

The aim of this work was, by using an experimental statistic design, to evaluate the influences of magnesium stearate and sodium croscarmelose quantities on the clozapine tablets hardness, friability, disintegration time and dissolution efficiency, by applying factorial design and response surface methodologies. Clozapine is a dibenzodiazepinic compound used in psychoses treatment to control schizophrenia [10].

MATERIALS AND methods

Materials

The following raw materials were used: clozapine (Medapi Farmacêutica Ltda, Brazil), sodium croscarmellose (Explocel®, Blanver, Brazil), magnesium stearate (Henrifarma Produtos Químicos e Farmacêuticos Ltda, Brazil), colloidal silicon dioxide (Aerosil® 200, Blanver, Brazil), microcrystalline cellulose (Microcel® 101, Blanver, Brazil), and spray-dried lactose (New Zealand).

Clozapine tablets preparation

Thirteen formulations were prepared using a Central Composite Design, whose experimental matrix is showed on Table 1. The proportions of magnesium stearate (STE) and sodium croscarmellose (SCC) were established empirically, according the usual concentration described on literature, ranging from 0.5 to 2.0 % to STE and 2.0 to 4.0 % to SCC. To all the formulations, colloidal silicon dioxide 0.5 % (w/w) and a mixture of microcrystalline cellulose and *spray-dried* lactose, in a proportion of 70:30 (w/w) were added.

Table 1: Central Composite Design matrix used to produce clozapine tablets.

Run	STE (coded)	SCC (coded)	STE (%)	SCC (%)
1	– 1.00	– 1.00	0.50	2.00
2	1.00	– 1.00	2.00	2.00
3	– 1.00	1.00	0.50	4.00
4	1.00	1.00	2.00	4.00
5	0.00	– 1.41	1.25	1.59
6	0.00	1.41	1.25	4.41
7	– 1.41	0.00	0.19	3.00
8	1.41	0.00	2.31	3.00
9	0.00	0.00	1.25	3.00
10	0.00	0.00	1.25	3.00
11	0.00	0.00	1.25	3.00
12	0.00	0.00	1.25	3.00
13	0.00	0.00	1.25	3.00

where : STE – magnesium stearate and SCC – sodium croscarmelose.

The powders were thoroughly mixed using an ERWEKA AR 400 mixing device (Erweka Apparatebau, Heusenstamm, Germany) at 20 rpm. The tablets were produced in a rotative tablet press (Picolla D3 – 8, Riva®), with a compressional force of 15 kN. Biconcave tablets with a diameter of 7 mm were obtained.

Hardness

The hardness of tablets (n = 10) was measured using an Erweka TBH TAG FTCQ 003 model hardness tester.

Friability

Tablet friability was calculated as the percentage weight loss of 20 tablets after 100 rotations per minute in a Roche. J. Engelsmann (Ludwigshafen, Germany) friability apparatus.

Disintegration time

The disintegration time was measured in purified water at 37 ± 1 °C and the results represent a calculated average of six determinations.

Dissolution test

Dissolution of clozapine tablets was performed according to the United States Pharmacopoeia [11] proposed method: apparatus I (basket) at 100 rpm, in 900 mL of pH 4.0 buffer acetate at 37 ± 1 °C as dissolution medium, using a *Pharma Test, PTW S III* type dissolution tester (Hamburg, Germany). Sink conditions were maintained during dissolution. Samples (n=6) were collected and then analyzed on a Hewlett–Packard 8452 A spectrophotometer (Hewlett-Packard, USA) at 290 nm for the drug content, using the *Dissolution Test Software vs. 03.01*. The dissolution efficiency of clozapine tablets, calculated by the area under curve, was obtained using the equation [1]

$$AUC = \frac{\sum_{i=1}^{i=n}(t_1 - t_{i-1})(y_{i-1} + y_i)}{2} \quad [1]$$

where t_i is the i^{th} time point, y_i is the percentage of dissolved product at time t_i.

Experimental statistical design and statistical analysis

In this study, the factors selected were amount of magnesium stearate (STE) and sodium croscarmellose (SCC). The response criteria evaluated were hardness, friability, disintegration time and dissolution efficiency of tablets. A preliminary evaluation of the factor levels was performed using a 2^2 factorial design without replication in order to define the experimental field. After that, the experimental design was transformed into a Central Composite Design, according Table 1. The data were adjusted to a polynomial second order equation by the least-square method and the respective response surfaces were modeled using the results from Composite Central Design (*StatGraphics®* Plus version 5.1, Statistical Graphics Corp., USA). The model was validated statistically by ANOVA by means of calculation and evaluation of the multiple-correlation coefficients and estimation of the lack-of-fit, using Equation [2]:

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \beta_{11}(x_1)^2 + \beta_{22}(x_2)^2 \quad [2]$$

where Y = response (hardness, friability, disintegration time, dissolution efficiency), x_1 and x_2 = equation coefficients (STE and SCC amount) and β_0.... β_{22} = regression coefficients.

Results and discussion

Hardness, friability, disintegration time and dissolution efficiency of the formulation produced according to the central composite design are shown in Table 2.

Table 2: Results for tablets Hardness (H), Friability (F), Disintegration Time (DT) and Dissolution Efficiency (DE).

Run	H	F	DT	DE
1	89.20 N	0.12 %	3.95 min	98.99 %
2	64.30 N	0.31 %	3.32 min	99.57 %
3	91.10 N	0.16 %	2.30 min	101.05 %
4	66.50 N	0.39 %	2.05 min	101,93 %
5	78.40 N	0.07 %	4.58 min	95.05 %
6	70.70 N	0.31 %	2.02 min	101.71 %
7	87.50 N	0.06 %	3.02 min	100.89 %
8	62.30 N	0.26 %	2.71 min	101.37 %
9	64.40 N	0.10 %	2.75 min	98.91 %
10	59.10 N	0.10 %	2.75 min	98.91 %
11	67.00 N	0.25 %	2.7 min	100.16 %
12	60.60 N	0.11 %	3.12 min	100.15 %
13	65.30 N	0.20 %	3.07 min	99.57 %

The results from Table 2 were used to fit an appropriated second order model from each dependent variable and the general equation was adjusted by a non-linear regression to the STE and SCC factors, allowing the determination of constant, linear, quadratic and interaction terms.

The mathematical model that describes the hardness was:

$$H = 159.831 - 43.603 \times STE - 39.414 \times SCC + 0.0984 \times STE \times SCC + 11.645 \times STE^2 + 6.407 \times SCC^2 \quad [3]$$

where H = hardness; STE = STE factor; SCC = SCC factor; STESCC = factor interaction

The results from the multiple regression coefficient calculated from equation 3 indicated that about 93 % of the experimental variance could be explained (r^2 = 0.927). Once the lack-of-fit test was not significant ($F_{(P\ 0.95;\ FG\ 3.4)}$ = 6.59 > 2.18), the experimental variation could be ascribed to a randomized error that was not related to the experimental model. Thus, the regression model expressed by equation 3 appears to be satisfactory to describe the tablet hardness behavior.

Considering the ANOVA and the *t*-test results (Table 3), with the exception of the interaction between the STE and the SCC factors, the linear and quadratic coefficients had a significant effect on the estimated response. The STE quadratic term had the higher effect on the tablet hardness, followed by the SCC quadratic term, and both showed a positive effect (hardness increase). The STE and SCC linear terms were also significant, showing a negative effect on the tablet hardness.

Table 3: Results of the *t*-test for equation 3 coefficients

Term	Coefficient	Standard Error	$t_{calculated}$
1	159.831	17.665	9.048
STE	– 43.603	10.675	4.085*
SCC	– 39.414	9.870	3.993*
Interaction	0.0984	2.677	0.0367
STE^2	11.645	2.709	4.299*
SCC^2	6.407	1.529	4.190*

* significant for a = 0.95

The response surface (Figure 1a) and the corresponding contour-plot (Figure 1b) graphs showed that tablet hardness was almost independent of the SCC concentration, but an increase in the STE concentration caused a decreased in tablet hardness. When the SCC concentration were lower than 2.5 % and higher than 3.5 %, a slight increase in tablet hardness, was observed on the experimental field.

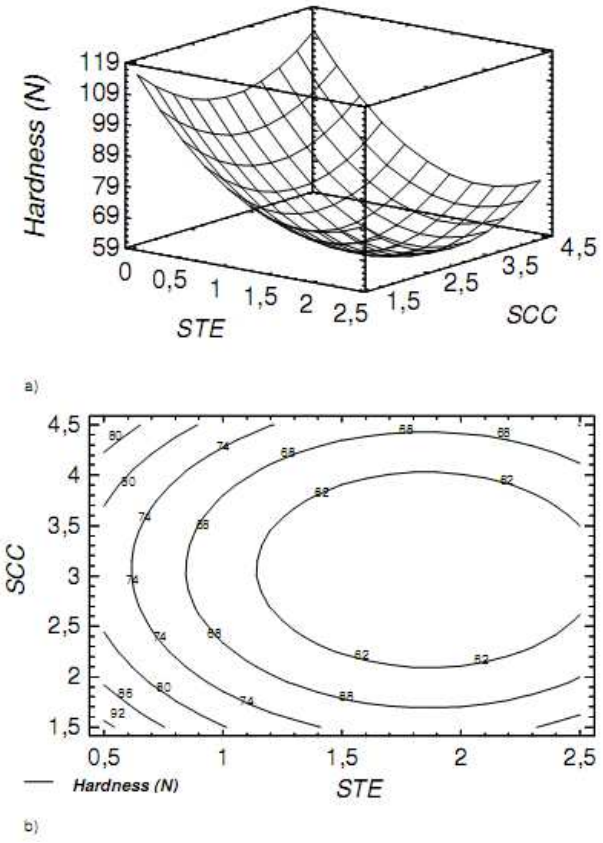

Figure 1: Response surface (a) and contour-plot graphic (b) calculated to the tablet hardness according to equation 3.

To the friability parameter F, the equation [4] was obtained:

$$F = 0.274 - 0.0185 \times STE - 0.180 \times SCC + 0.0133 \times STE \times SCC + 0.0382 \times STE^2 + 0.0368 \times SCC^2 \quad [4]$$

where F = friability; STE = STE factor; SCC = SCC factor; STESCC = factor interaction

The results from the ANOVA test were not significant (P > 0.05), so the equation 4 was not satisfactory to describe the tablet friability behavior. The lower multiple regression coefficient value (r^2 = 0.728) showed that the equation is adequate, but the mathematical model

proposed was not able to differ the obtained response (friability) and the graphic background noise. As the results from the *t*-test showed that the proposed model was not satisfactory either, (coefficients not significant – P > 0.05), the response surface and the contour-plot graphics could not be plotted.

Table 4: Results of the *t*-test for equation 4 coefficients

Term	Coefficient	Standard Error	$t_{calculated}$
1	0.274	0.321	0.854
STE	– 0.0185	0.194	0.0952
SCC	– 0.180	0.179	1.005
Interaction	0.0133	0.0486	0.275
STE^2	0.0382	0.0492	0.778
SCC^2	0.0368	0.0278	1.325

It can be observed that the hardness and friability were more susceptible to the STE concentration, and that this excipient caused a decreased in the tablet mechanical resistance. The formulations with lower STE concentration produced tablets with higher hardness and lower friability. As the lubricant particles cover the formulation components surface, they act as a mechanical barrier, interfering on the mixture binding properties and consequently producing tablets mechanically weaker [12;13].

The following mathematical model was estimated to the disintegration time, according the central composite design, resulting the equation [5]:

$$DT = 7.013 - 0.716 \times STE - 1.714 \times SCC + 0.127 \times STE \times SCC + 0.169 \times STE^2 + 0.123 \times SCC^2 \quad [5]$$

where DT = disintegration time; STE = STE factor; SCC = SCC factor; STESCC = factor interaction

The equation 5 shows that about 95 % of experimental variance could be explained by the multiple regression coefficient calculated (r^2 = 0.953). As the lack-of-fit test was not significant ($F_{(P\ 0.95;\ FG\ 3.4)}$ = 6.59 > 1.43), a possible experimental variation could be ascribed to a randomized error that was not related to the experimental model, and the regression model expressed by equation 5 seems to be satisfactory to describe the disintegration time behavior of these tablets.

According to Table 5, it was possible to assume that the mathematical model proposed to explain the tablet disintegration time behavior was adequate, and the experimental variance could be attributed to a randomized error that was not related to the experimental model.

Table 5: Results of the *t*-test for equation 5 coefficients

Term	Coefficient	Standard Error	$t_{calculated}$
1	7.120	0.937	7.599
STE	– 0.135	0.529	0.256
SCC	– 1.824	0.559	3.264*
Interaction	0.119	0.117	1.019
STE^2	– 0.178	0.139	1.239
SCC^2	0.146	0.0847	1.592

* significant for a = 0.95

The results from the *t*-test (Table 5) showed that the disintegration time was only influenced by SCC concentration, where the SCC lineal term was the main responsible for the decrease in the tablets disintegration time. All the others equations components had no statistical significance on the response. The response surface (Figure 2a) and the contour-plot graphics (Figure 2b) showed that the disintegration time decreased when higher SCC concentrations are combined with higher STE concentrations. It can be observed that the lower disintegration time was obtained when the SCC concentration was higher than 3.5 % and the STE concentration was higher than 2.0 %.

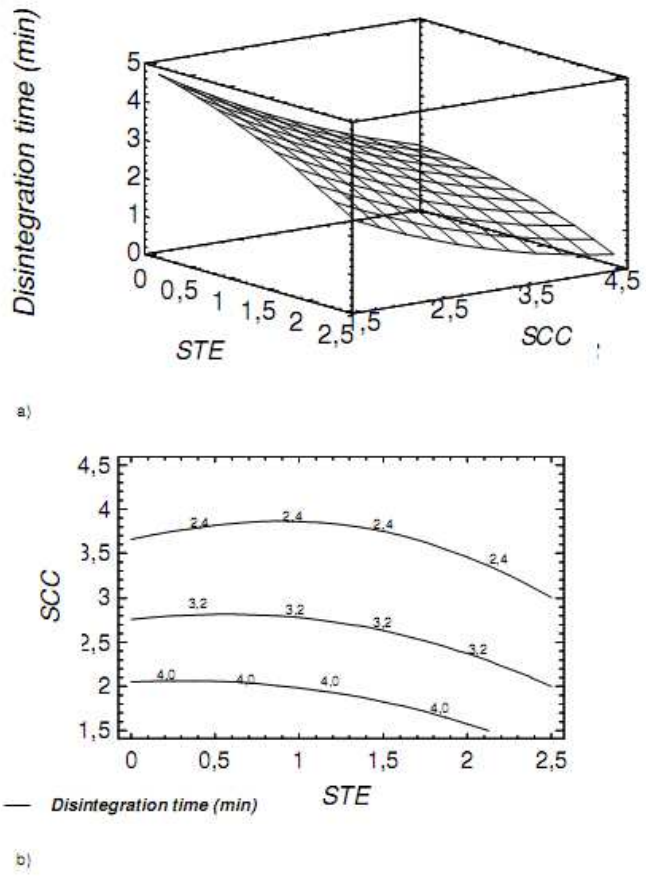

Figure 2: Response surface (a) and contour-plot graphic (b) calculated to the tablet disintegration time according to equation 5.

Tablets containing higher SCC concentrations showed lower disintegration time. The decrease in the disintegration time observed when the SCC concentration increase was also verified in early works [14;15;16], which proves the high efficiency of the disintegrant used in the production of tablets by direct compression. As the STE is a hygroscopic excipient, one expected that its presence would result in an increase in the disintegration time of tablets. However, in the studied experimental field, STE presented an unexpected effect, therefore reducing the disintegration time when its concentration was increased, demonstrating an anomalous behavior of the STE considering the disintegration time.

Equation [6] was fitted to the dissolution efficiency parameter, DE:

$$DE = 93.080 - 4.171 \times STE + 4.168 \times SCC + 0.998 \times STE \times SCC + 1.691 \times STE^2 - 0.427 \times SCC^2 \quad [6]$$

where: DE = dissolution efficiency; STE = STE factor; SCC = SCC factor; STESCC = factor interaction.

The analysis of the regression indicates that equation 6 was valid to describe the tablets dissolution efficiency (r^2 = 0.856) and the experimental variance can be attributed to the pure experimental error and does not depend on the adjustment model to the experimental data ($F_{(P\ 0.95;\ FG\ 3.4)}$ = 6.59 > 3.70). The results of the *t*-test for the equation coefficients (Table 6) demonstrate that the dissolution efficiency were influenced by the quadratic component of the STE concentration, followed by the linear component of the SCC concentration. All the others coefficients had no statistical significance on the dissolution efficiency.

Table 6: Results of the *t*-test for equation 6 coefficients

Term	Coefficient	Standard Error	$t_{calculated}$
1	93.080	3.912	23.792
STE	– 4.171	2.364	1.764
SCC	4.618	2.186	1.907*
Interaction	0.0998	0.593	0.168
STE^2	1.691	0.600	2.819*
SCC^2	– 0.427	0.339	1.260

* significant for a = 0.95

The response surface (Figure 3a) and the contour-plot graphic (Figure 3b) showed that the dissolution efficiency was mainly affected by SCC concentration, where an increase in the SCC concentration caused a faster disintegration and higher tablet dissolution efficiency. The increase in the STE concentration did not change the dissolution efficiency, however, when the STE concentration was higher than 2 %, an increase in the tablet dissolution efficiency was observed. The higher the SCC proportion, the faster the tablet disintegration and thereof the clozapine release.

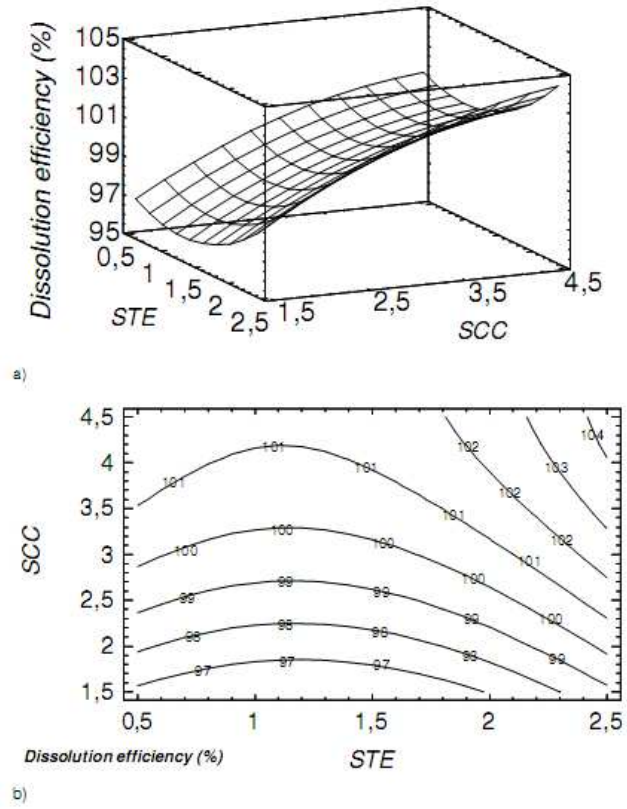

Figure 3: Response surface (a) and contour-plot graphic (b) calculated to the tablet dissolution efficiency according to equation 6.

The STE effect was best observed on the dissolution efficiency than on the disintegration time, strengthening the STE anomalous behavior upon the disintegration time. According to the surface response (Figure 3), an increase in STE concentration cause a decrease in the disintegration time, however, this increase does not reduce the dissolution efficiency values in the same extent.

Conclusions

As the development of pharmaceutical products involves effort and time, a very efficient way to enhance the value of research, to minimize the process development time and obtain information concerning the influence of the different excipients is through designed experiments. Using experimental design, such as Central Composite Design, where a given number of experiments are selected out of many possible ones, is a good way in order to obtain a statistically optimized design.

According the Central Composite Design proposed for this work, the STE concentration influenced the tablet mechanical resistance, affecting the hardness in a negative way, decreasing the obtained values, and the friability in a positive way, increasing the obtained values. The SCC proportion determined a linear decrease in the disintegration time, causing a faster clozapine release from the tablets, thereby increasing tablets dissolution efficiency. It was possible to verify a STE anomalous behavior, because the increase on its amount results in a decrease in disintegration time. However, this increase does not cause an increase on the tablet dissolution efficiency, on the experimental field.

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