AAPS PharmSciTech, Vol. 9, No. 2, June 2008 (© 2008)
DOI: 10.1208/s12249-008-9095-z

Research Article

Rapid Development and Optimization of Tablet Manufacturing Using Statistical Tools

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Received 7 December 2007; accepted 24 March 2008; published online 6 May 2008

Abstract. The purpose of this paper was to develop a statistical methodology to optimize tablet manufacturing considering drug chemical and physical properties applying a crossed experimental design. The assessed model drug was dried ferrous sulphate and the variables were the hardness and the relative proportions of three excipients, binder, filler and disintegrant. Granule properties were modeled as a function of excipient proportions and tablet parameters were defined by the excipient proportion and hardness. The desirability function was applied to achieve optimal values for excipient proportions and hardness. In conclusion, crossed experimental design using hardness as the only process variable is an efficient strategy to quickly determine the optimal design process for tablet manufacturing. This method can be applied for any tablet manufacturing method.

KEY WORDS: crossed experimental design; ferrous sulfate; multivariate techniques; statistical strategy; tablet manufacturing.

INTRODUCTION

In pharmaceutical industries, manufacturers of generic tablets are usually focused on the optimization of the excipient mixture composition to obtain a product that meet established standards (1,2). Pharmaceutical literature, already abounds with statistical methods considering mixture design to optimize excipient proportions. Several tablet compositions of extended and fast release have been established with this methodology (3–7). However tablet properties do not only depend on the excipient percentage in the solid dosage. Some compression and granulation process variables such as: compaction force, compression velocity, tableting temperature, impeller speed and blending time can also have influences (8).

In order to solve the optimal tablet manufacturing in an integral way, two main strategies have been used; multivariate and crossed experimental designs (8,9). Multivariate design is a combination of classical experimental designs with multivariate techniques such as principal component analysis or partial least square (10). Crossed experimental design describes every response variable as a function of the manufacturing process parameters and ingredient percentages. For instance, multivariate designs have been used to optimize two-step process, granulation-tableting, and the excipient types and their proportions in tablet formulation (11). However crossed experimental design has not been widely employed.

The application of multivariate and crossed experimental designs is experimentally tedious but allows for finding the optimal operational conditions and ingredient percentages for any given system. In general, experimental design strategies to develop pharmaceutical solid forms are complex, expensive and time-consuming because of the large number of factors that influence on the drug behavior (12). This highlights, the need to combine technological and statistical knowledge to reduce traditional methods for establishing optimal tablets.

According to the criterion of the authors, the most important variables to consider are hardness and the types and proportion of excipients regardless of the tablet manufacture process (direct compression or wet granulation).

Wet granulation variables such as: operational factors were not considered in this design because dependent variables such as: wet mass density and viscosity, particle size distribution, flowability or tableting parameters at the end of this granulation are more important (13). Based on this criterion; the reduction of experimental variables, specifically granulation variables, is possible and as a consequence the total experimental work to develop a new tablet.

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The purpose of this paper was to develop a statistical methodology for tablet manufacturing using ferrous sulfate as a model drug. This methodology was based on a crossed experimental design considering the hardness as the only process variable and the proportion of main ingredients of the formulation as mixture variables.

MATERIALS AND METHODS

Materials

The following active pharmaceutical ingredient and excipients were used: dried ferrous sulphate (Merck, Germany), polyvinylpyrrolidone (PVP) Kollidon K25 (Basf, Germany), Microcrystalline cellulose (MCC) (Blanver, Brazil), sodium starch glycolate (Explotab) (Gustav Parmentier, Germany), magnesium stearate (Otto Barlocher GmbH, Germany). All other chemicals and solvents were of analytical reagent grade.

Methods

Preparation of ferrous sulphate tablets

The composition of the fast release ferrous sulphate tablets and the range for three excipients under study are listed in Table I. The drug and MCC were weighed and mixed. The PVP dissolved in Ethanol was added to make a wet mass in a lab mixer. The end point of the granulation process was determined using the wet mass density as criterion. Then the wet mass was granulated through a 14 mesh sieve. Granules were dried at 40 °C in an oven for 8 h, and sieved through a 16 mesh sieve, after that they were blended with a constant percentage of magnesium stearate and Explotab. Each 320 mg tablet containing 65 mg elemental iron was compressed using 5/16 in. diameter normal concave punches at three hardness values, 5.5, 6.5 and 7.5 kgF/Monsanto (Table II). Tablets were produced in an instrumented eight-punch press (Ronchi, Italy). The upper punch force was registered in an analyzing recorder (Yokogawa model 3655E).

Methods for characterization of granules

The granule mean particle size and the size distribution were measured by applying a shaking sieve with a set of sieves of the following apertures; 800, 500, 250, 125, 63, 45 μm.

The flow rate was determined according to the fixed-funnel method (14). The stainless steel funnel end with a wall angle of 45° and 2.3 cm outlet orifice diameter was placed 10 cm above a flat base. The funnel was filled with 100 g of granules to measure the time of granule mass flow through the funnel and calculate the flow rate by the mathematical Eq. 1 (each reported value is the average of three determinations):

$$F_r = \frac{m}{0.785 \cdot d_o^2 \cdot t} \quad (1)$$

Where:

F_r is the flow rate expressed as gram per square centimeter per second, m is the granules mass (gram), d_o is the outlet orifice diameter of the funnel (centimeter) and t is the time required (second) for the granules mass to flow through the metal funnel (14).

For the determination of bulk and tap densities, 60 g of the sample was poured in a 100 mL tared graduated cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density (D_b) according to the mass/volume ratio. For tap density (D_t) the cylinder was tapped 1,000 times using a tap density analyzer (Erweka SVM1, Germany).

The percent compressibility (C) was measured and calculated from Eq. 2 (15):

$$C = \frac{D_t - D_b}{D_t} \times 100 \quad (2)$$

Methods for characterization of tablets

The percentages of friability were calculated as the percentage of weight loss of 20 tablets after 100 rotations in an Erweka Abrasion Tester (Model 1AP, Germany). Tablet height was measured with an Ultra-Micrometer Fowler (USA) sensitive 0-1 in. The hardness was quantified by using a tablet hardness tester of Monsanto type (Toshiba, India). The disintegration time (second) was determined by mean of a disintegrator Erweka ZT 120 (Germany) apparatus. Deionized water at 37±1 °C was used as the immersion medium. All measurements were made in triplicate.

Chemical characterization of the tablets including dissolution of ferrous sulphate was measured according to the USP

Table I. Variables in the Mixture Design

Formulation components	Levels	
	Low (%)	High (%)
X_1 = percent of MCC in tablet	23.6	29.6
X_2 = percent of PVP in tablet	3.0	5.0
X_3 = percent of Explotab in tablet	2.0	6.0
Magnesium stearate	Constant	

The amount of dried ferrous sulphate was fixed at 203 mg. The tablet weight was 320 mg.

Table II. D-optimal Mixture Design for Granules Properties and Crossed Experimental Design for Tablet Properties

Sample	Cellulose (%)	PVP (%)	Explotab (%)	Hardness (kgF/Monsanto)
1	25.60	3.00	6.00	5.5
2	27.60	5.00	2.00	5.5
3	28.60	4.00	2.00	5.5
4	25.10	4.50	5.00	5.5
5	23.60	5.00	6.00	5.5
6	26.27	3.67	4.67	5.5
7	29.60	3.00	2.00	5.5
8	25.60	3.00	6.00	5.5
9	25.60	5.00	4.00	5.5
10	24.60	4.00	6.00	5.5
11	26.93	4.33	3.33	5.5
12	27.60	3.00	4.00	5.5
13	27.60	5.00	2.00	5.5
14	29.60	3.00	2.00	5.5
15	23.60	5.00	6.00	5.5

Note: this experimental matrix was repeated two more times at hardness values, 6.5 and 7.5 KgF/Monsanto respectively to generate the crossed experimental design.

Table III. Physical–Mechanical Parameters of the Granules

Experiments	Mean particle sizes (μm)	Flow rate (g/cm^2 s)	Tap density (g/cm^3)	Bulk density (g/cm^3)	Carr's Index (%)
1	178.3	15.35	0.91	0.68	25.6
2	240.3	15.35	0.80	0.63	21.1
3	203.6	14.25	0.87	0.65	25.5
4	235.9	17.18	0.92	0.69	24.7
5	230.3	13.52	0.88	0.71	19.0
6	193.0	14.25	0.95	0.74	21.8
7	187.1	15.35	0.96	0.69	28.1
8	211.7	14.25	1.02	0.75	25.9
9	230.0	16.45	0.86	0.71	17.4
10	219.5	14.25	0.86	0.68	20.9
11	220.0	16.45	0.89	0.68	23.6
12	200.7	14.25	1.00	0.72	28.0
13	208.9	14.25	0.86	0.65	24.4
14	180.8	13.15	0.90	0.66	26.7
15	241.7	15.35	0.89	0.68	23.6

The number of the experiments and excipients proportions are defined in Table II.

27th ed. The dissolution test was carried out by the Paddle method, at a paddle speed of 50 rpm, in 900 mL HCl 0.1 N at 37±0.5 °C, and a dissolution time of 45 min. The dissolution tester employed was the Erweka DT 600 (Germany). The iron concentration of each sample (n=6) was determined employing atomic absorption spectrophotometry at a wavelength of 248.3 nm (UNICAM 929 AA Spectrometer). The dissolution profile was made taking 5 mL samples at 10, 20, 30 and 45 min while the same volume of fresh dissolution medium was returned to the vessels.

Statistical analysis

The definition and data processing of experimental designs for granules and tablet properties were made in Design Expert version 6.0.1 software. D-optimal mixture design for three components (MCC, PVP, Explotab percentages) was used for modeling the granule parameters, the number of experimental points (15) were enough to adjust special cubic models (Eq. 3):

$$\left(\begin{array}{l} Y = b_1 \cdot X_1 + b_2 \cdot X_2 + b_3 \cdot X_3 + b_{12} \cdot X_1 \cdot X_2 + b_{13} \cdot X_1 \cdot X_3 \\ \quad + b_{23} \cdot X_2 \cdot X_3 + b_{123} \cdot X_1 \cdot X_2 \cdot X_3 \end{array}\right) \tag{3}$$

A crossed experimental design was employed for tablet properties modeling. The mixture variables were the same for granulation step and the process variable was hardness at three levels (5.5, 6.5, 7.5 kgF/Monsanto). This second design is able to fit mathematical models, special cubic for the excipient proportions and quadratic for the hardness. The best fitting mathematical model was selected based on the comparison of the predicted residual sum of square (PRESS). This statistical parameter indicates how well the models fit the data, and the chosen model PRESS should be small relative to the other models under consideration (5). The goodness and lack of fit tests were also used to demonstrate the model statistical adjusts. Desirability function was the numeric method to optimize mixture and process variables in tablet manufacturing.

The SIMCA P version 11.0 software and Statgraphics Plus 5.0 were used to carry out the principal component analysis (PCA) and the cluster analysis for granule variables. The aim for the application of the PCA and the cluster analysis was to detect similitude or difference among the 15 granules included in D-optimal mixture design.

RESULTS AND DISCUSSION

The present statistical strategy includes the following stages. Firstly, it is necessary to define the excipients and elaboration method in accordance with chemical and physical properties of the drug and its function in the human body. Secondly, the excipients with the greatest impact on granule and tablet properties should be selected for optimizing excipient proportions in the formulation, together with the definition of hardness range. Then, mixture variables and hardness are combined using a crossed experimental design (Table II). However, in spite of the few variables required for this strategy, costs could still be appreciable. A multivariate methodology can be used to reduce the experimental cost. Especially in granulation–compression

Table IV. Best Models for Granules Variables and Some Statistical Parameters

Variable	Model	Press	p value (lack of fit test)	p value (goodness of fit)
Mean particle sizes (MPS) (μm)	$MPS = 3.39428 \cdot X_1 + 23.80752 \cdot X_2 + 6.42855 \cdot X_3$	2658.02	0.9746	0.0003
Flow rate (FR) (g/cm^2 s)	$FR = 0.37716 \cdot X_1 + 0.80143 \cdot X_2 + 0.41376 \cdot X_3$	25.03	0.5210	0.5107
Tap density (TD) (g/cm^3)	$TD = 0.030783 \cdot X_1 - 0.018556 \cdot X_2 + 0.039996 \cdot X_3$	0.03	0.8595	0.0030
Bulk density (BD) (g/cm^3)	$BD = 0.020073 \cdot X_1 + 6.60516 \cdot 10^{-3} \cdot X_2 + 0.031770 \cdot X_3$	0.01	0.7445	0.0256
Carr's Index (CI) (%)	$CI = 1.05604 \cdot X_1 - 1.58916 \cdot X_2 + 0.53874 \cdot X_3$	82.06	0.4945	0.0037

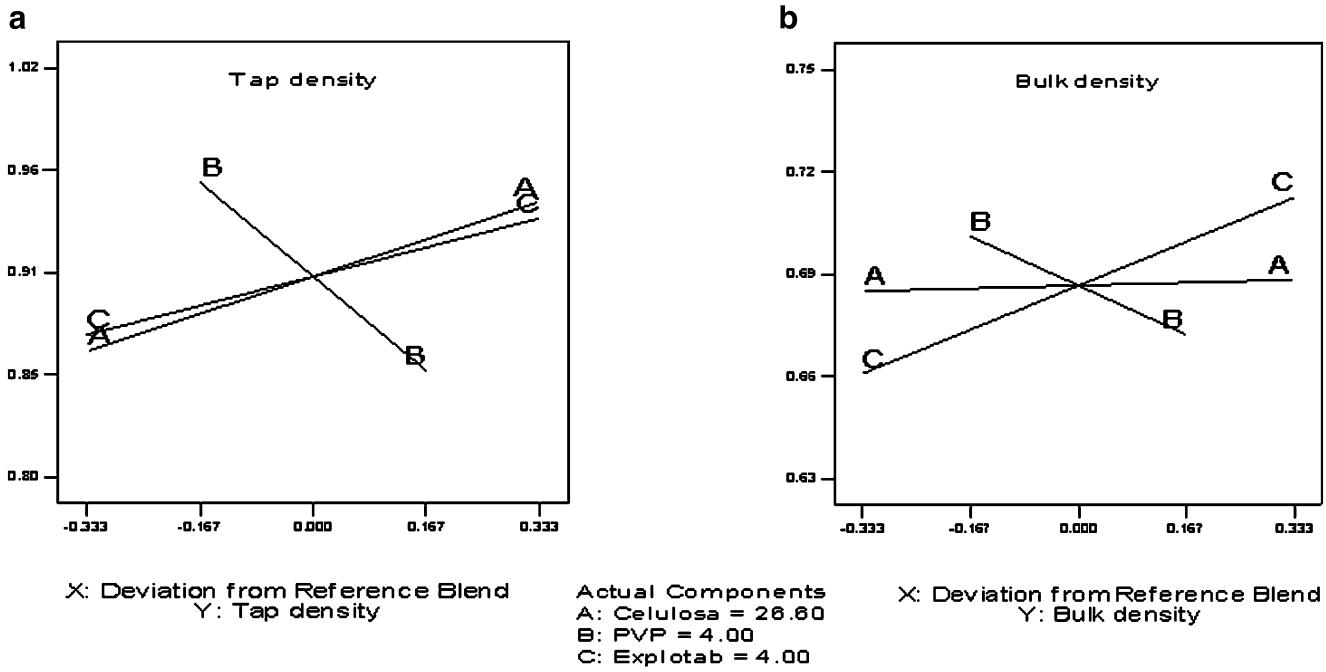

Fig. 1. Cox trace graphs for **a** tap density (g/cm^3) and **b** bulk density (g/cm^3) of granules

processes, the compression of all mixtures at different hardness values for subsequent chemical and mechanical tablet assessments would be limited due to cost restraints.

Finally, granule and tablet properties are described as mathematical functions of excipient proportions and hardness. Then, the best hardness and excipient proportions can be obtained using the numeric multiple optimization procedure known as the desirability function.

This methodology could be useful for any tablet manufacturing method. In the direct compression method, it is further recommended because the granulation variables do not exist. However, the present methodology was applied for the wet granulation method where the granulation step variables were omitted because of the scale-up of granulation processes is a difficult task and the trial and error methods have been suggested (16).

Specifically, the principal difficulty with wet granulation in high-shear mixers is to decide "when to stop": hence, the importance of controlling the end point. It has been also demonstrated that the operational parameters in high-shear mixers do not have a significant influence on the granulation effectiveness. Thus, the manufacturers can lose time and money meticulously studying granulation variables on lab scale such as: mixing time, fill level, liquid spray rate, *etc.* (16).

Characterization of granules

A D-Optimal mixture design was carried to determine the granule behavior as a function of selected excipient proportions. The results of granule variables (Table III) allowed adjusting the best numeric model for each variable

Table V. Granule Size Compositions of the Mixtures Included in D-optimal Mixture Design

Run	>800 μm	800–500 μm	500–250 μm	250–125 μm	125–63 μm	63–45 μm	45 μm–collector
1	3.48	1.96	10.40	57.92	13.56	9.56	3.92
2	8.52	4.96	29.92	46.12	7.76	3.88	0.24
3	4.60	3.40	18.12	52.08	12.84	7.00	2.16
4	11.56	10.96	20.44	40.16	10.44	5.44	1.84
5	8.00	6.84	23.72	45.64	8.88	5.40	2.84
6	5.24	3.36	14.36	52.48	16.60	6.04	2.08
7	3.40	2.76	12.76	53.56	17.64	8.04	2.32
8	6.36	7.40	17.16	42.64	16.44	7.12	3.08
9	7.64	5.60	25.60	45.80	9.56	5.08	1.40
10	6.40	5.00	22.64	47.68	9.92	6.32	2.92
11	9.32	5.76	23.32	44.12	9.28	6.84	1.72
12	4.40	6.00	16.00	44.92	13.68	8.52	7.44
13	7.48	4.08	19.64	51.24	11.24	3.80	0.32
14	2.58	1.53	10.47	59.43	16.24	9.07	0.68
15	9.80	9.68	24.52	39.68	10.48	4.80	0.88

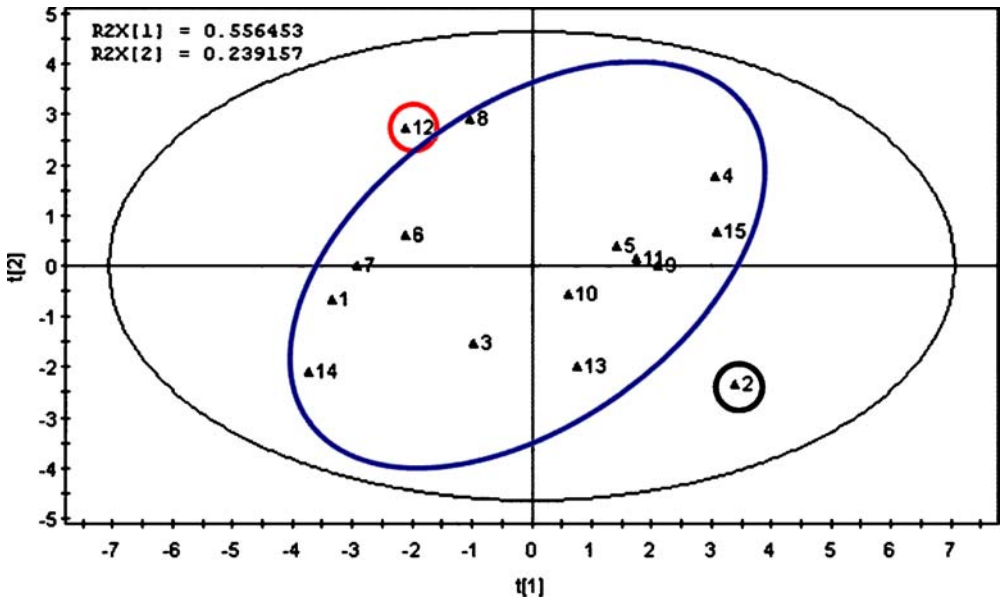

Fig. 2. Principal component analysis for granule properties without Carr's Index inclusion (Score plot). Cluster analysis by Nearest Neighbor method and Squared Euclidean metric distance

(Table IV). The flow rate was independent of the excipient percentage because the goodness of fit and lack of fit tests were not significant for a linear model ($p>0.05$), the best adjusted model, suggesting that the values for flow rate in the experimental region are oscillating around a central value.

The mean particle size showed a significant linear dependence with excipient proportions (Table IV). The positive influence of PVP percentage was expected because its function is binding the excipients and favoring the mechanical resistance of the formed particles in the granulation process.

Tap and bulk densities also confirmed a linear dependence with excipients proportions. It is important to emphasize that the influences of ingredient percentages are similar for both variables, although the sign of the coefficients for PVP are different (Table IV). The equations listed in Table IV are Scheffé models that can conduce to false interpretations of components influence, especially in mixture problem with constrains. For solving this problem, Cox models are prefer (17). Figure 1a and b illustrate Cox models for tap and bulk densities respectively. As predictable, the PVP percentage is inversely proportional to tap and bulk densities due to the particle size, and the increase in free space among particles causing an increase of the volume per mass unit.

The Carr's Index showed a behavior similar for bulk and tap densities (Table IV). The direct measurement of the granule flowability (flow rate) is not in concordance with the indirect measurement (Carr's Index). Many studies suggest that flow properties are manner test performance dependent

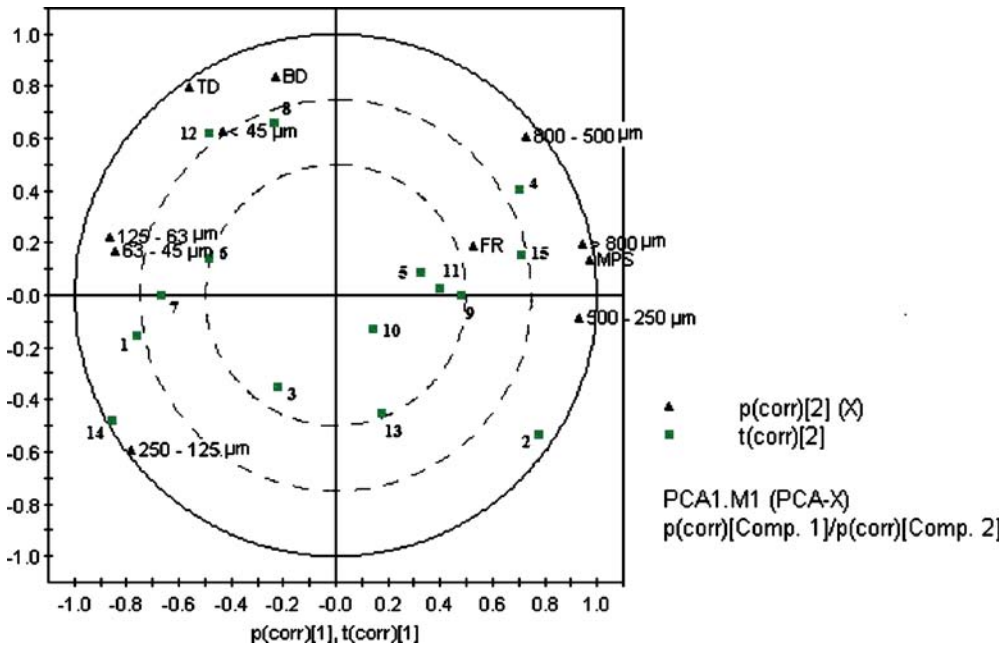

Fig. 3. Biplot graph (scores and loading) for granules properties not including Carr's Index

(18,19). Results can also vary with the prior measurement sample manipulation (20). Therefore, a direct method to evaluate the fluidity is recommended. In the present study, the Carr's Index was eliminated in subsequent analysis.

The granule size composition is very useful to reproduce the granulation process on large-scale (Table V). In this study the experimentation cost was not significant and all formulations were compressed at three hardness values, under the crossed experimental design definition.

The practical alternative of this methodology for more complicated and expensive tablet manufacturing problems is the PCA to reduce the variable number through the formulation scores in principal components (PC) and to combine them with the hardness employing a central composite design, Box–Behnken design, or a three level factorial design.

In this work the PCA was used to determine the differences and similarities among granules and the influencing variables. The PCA was applied from the Tables III and V without including the Carr's Index.

In Fig. 2 are represented the 15 granules of the D-Optimal design in a score plot. This figure allows visualizing with fewer dimensions the data included in Tables III and V facilitating the detection of similarities among granules. In summary, three clusters were detected.

The Biplot graphic (Fig. 3) allowed detecting the variables, which cause the differences among granules. The granules corresponding to experiment 12 had high percentages of small particle fractions whereas in experiment 2 a contrary effect for granules was observed. The rest of the granules had similar properties (Fig. 3).

According to the loading proximity of granule descriptor variables, tap and bulk densities increase in proportion to the small particle fraction percentage. This relationship is explained by the reduction in void space among particles and as a consequence the volume decreases. In addition flow rate, mean particle size and large size fractions are positively correlated because particle size increase generally produces high flow rates (Fig. 3).

Characterization of tablets

The 15 granules were compressed at three hardness values: 5.5, 6.5, and 7.5 kgF/Monsanto (Table VI). The models, which describe the behavior of four tablet parameters: height (Eq. 4), friability (Eq. 5), disintegration (Eq. 6) and press force (Eq. 7) are:

$$\begin{aligned}\text{Height} = {} & 0.052579 \cdot X_1 - 2.62130 \cdot X_2 - 3.52454 \cdot X_3 \\ & + 0.11666 \cdot X_1 \cdot X_2 + 0.15255 \cdot X_1 \cdot X_3 \\ & - 3.46884.10^{-3} \cdot X_1 \cdot \text{Hardness} + 1.08370 \cdot X_2 \\ & \cdot X_3 - 0.42157 \cdot X_1 \cdot X_2 \cdot X_3 \end{aligned} \quad (4)$$

$$\begin{aligned}\text{Friability} = {} & 0.45958 \cdot X_1 + 14.98142 \cdot X_2 + 11.41912 \cdot X_3 \\ & - 0.60478 \cdot X_1 \cdot X_2 - 0.48654 \cdot X_1 \cdot X_3 - 0.065843 X_1 \cdot \\ & \text{Hardness} - 3.74444 \cdot X_2 \cdot X_3 - 2.21416 \cdot X_2 \cdot \text{Hardness} \\ & - 1.62392 \cdot X_3 \cdot \text{Hardness} + 0.13925 \cdot X_1 \cdot X_2 \cdot X_3 \\ & + 0.089203 \cdot X_1 \cdot X_2 \cdot \text{Hardness} + 0.069262 \cdot X_1 \\ & \cdot X_3 \cdot \text{Hardness} + 0.54043 \cdot X_2 \cdot X_3 \cdot \\ & \text{Hardness} - 0.020029 \cdot X_1 \cdot X_2 \cdot X_3 \cdot \text{Hardness} \end{aligned} \quad (5)$$

Table VI. Results of Crossed Experimental Design (Tablet Properties)

Run	Height (mm)	Friability (%)	Disintegration (min)	Press force (kN)
1	4.412	0.14	22.00	2.96
2	4.438	0.23	40.00	1.61
3	4.582	0.25	38.00	1.49
4	4.558	0.51	55.00	2.83
5	4.233	0.28	45.00	3.63
6	4.249	0.33	54.00	4.23
7	4.420	0.42	48.00	1.94
8	4.248	0.57	29.00	3.18
9	4.296	0.45	42.00	2.96
10	4.234	0.40	37.00	3.55
11	4.248	0.48	55.00	2.19
12	4.424	0.32	65.00	3.71
13	4.511	0.60	56.00	1.44
14	4.576	0.45	35.00	2.50
15	4.778	0.23	62.00	2.33
16	4.311	0.14	27.00	3.77
17	4.384	0.17	40.00	2.79
18	4.686	0.30	44.00	2.56
19	4.235	0.25	76.00	5.62
20	4.120	0.24	42.00	4.55
21	4.243	0.32	50.00	4.39
22	4.216	0.25	77.00	4.98
23	4.186	0.30	45.00	5.10
24	4.173	0.20	48.00	3.69
25	4.187	0.26	51.00	3.95
26	4.315	0.22	70.00	3.41
27	4.412	0.26	65.00	4.64
28	4.454	0.49	60.00	2.59
29	4.523	0.29	65.00	3.49
30	4.841	0.21	61.00	3.20
31	4.210	0.15	50.00	5.76
32	4.200	0.13	75.00	4.01
33	4.100	0.20	60.00	4.83
34	4.140	0.24	62.00	6.74
35	4.200	0.18	49.00	5.27
36	4.250	0.25	52.00	5.12
37	4.130	0.14	109.00	5.47
38	4.090	0.27	69.00	6.36
39	4.130	0.16	68.00	5.04
40	4.080	0.16	57.00	4.83
41	4.130	0.09	70.00	4.88
42	4.360	0.11	80.00	5.70
43	4.340	0.14	76.00	3.18
44	4.400	0.18	111.00	5.22
45	4.730	0.34	68.00	4.46

$$\begin{aligned}\text{Disintegration} = {} & 2.69837 \cdot X_1 + 147.76500 \cdot X_2 \\ & - 69.34025 \cdot X_3 - 5.96929 \cdot X_1 \cdot X_2 \\ & + 2.11103 \cdot X_1 \cdot X_3 \\ & + 0.48545 \cdot X_1 \cdot \text{Hardness} \end{aligned} \quad (6)$$

$$\begin{aligned}\text{Press force} = {} & -0.090549 \cdot X_1 + 6.30955 \cdot X_2 - 4.27100 \\ & \cdot X_3 - 0.25871 \cdot X_1 \cdot X_2 + 0.16978 \cdot X_1 \cdot X_3 \\ & + 0.048190 \cdot X_1 \cdot \text{Hardness} - 0.015823 \cdot X_3 \\ & \cdot \text{Hardness} \end{aligned} \quad (7)$$

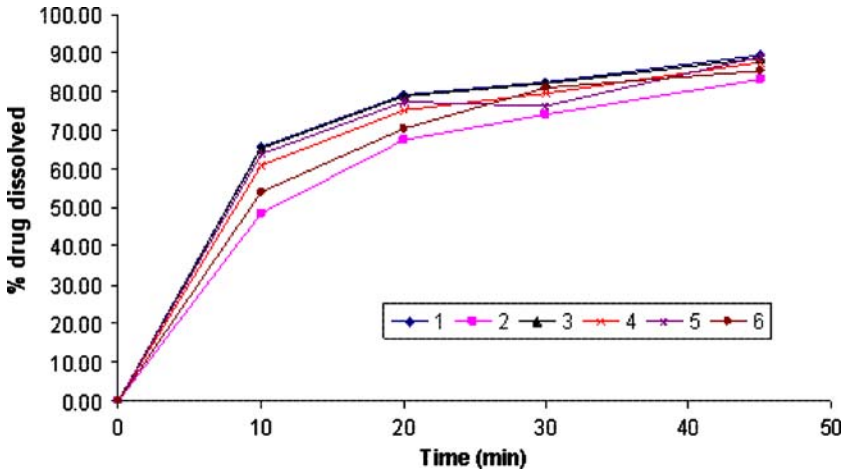

Fig. 4. Dissolution profile for tablets elaborated according to run 1 belongs to crossed experimental design. 1, 2,….,6 dissolution vessels

In order to determine if tablet properties are affected by hardness in equal magnitude for all mixtures, elimination of a mixture variable of the models is suggested. If the transformed model considers hardness as an isolate variable, the hypothesis is accepted (21). The Height (Eq. 8), Friability (Eq. 9) and Press force (Eq. 10) showed this behavior:

$$\text{Height} = 4.88325 + 0.027479 \cdot X_2 - 0.017814 \cdot X_3 - 0.090567 \cdot \text{Hardness} \quad (8)$$

$$\text{Friability} = 0.90718 + 3.62143 \cdot 10^{-3} \cdot X_2 - 3.88078 \cdot 10^{-3} \cdot X_3 - 0.097333 \cdot \text{Hardness} \quad (9)$$

$$\text{Press Force} = -3.37068 - 0.42804 \cdot X_2 + 0.28090 \cdot X_3 + 1.21065 \cdot \text{Hardness} \quad (10)$$

Negative values for hardness in height and friability and positive in press force were expected according to the relation among the variables. Nevertheless, the disintegration showed a complex relation among the mixture variables and hardness.

Tablet optimization

Since height and friability showed acceptable values, the only criterion to optimize the tablet manufacturing was the minimum disintegration time using desirability function with an importance value of 5. In more complex solid pharmaceutical systems like extended release tablets, more response variables should be included, principally drug release at different times. Even in some fast release solid systems in which granule flow properties show a significant relationship with the excipient percentage should be considered them in the desirability function.

The proportions that guarantee the minimum disintegration time were: MCC (25.47%), PVP (3.13%) and Explotab (6.00%) and a hardness value of 5.5 kgF/Monsanto. Hence, the experimental conditions are very close to experiment number 1 of the crossed experimental design (Table II).

In sample 1 the minimum disintegration time corresponded with the minimum values of binder proportion and hardness and the maximum vale of the disintegrant within each respective range studied. Finally it is important to verify the chemical quality and *in vitro* dissolution of the tablets. The dissolution profile of experiment 1 is illustrated in Fig. 4. The percentage of the released drug was greatest than the required (80%) (22). The rest of chemical parameters satisfied the USP XXVII requirements. In this way the ferrous sulphate tablet was optimized rapidly and more cost-effectively.

CONCLUSIONS

Crossed experimental design using hardness as the only process variable is an efficient strategy to quickly determine the optimal design process for tablet manufacturing. This method can be applied for any tablet manufacturing method.

ACKNOWLEDGMENTS

Authors would like to thank the financial support granted by Quimefa Group and Merck for supplying dried ferrous sulphate. Authors kindly thank Mrs. Relma Tavares de Oliveira for the inspiration and Yohana and Brenda Morón for their kind contributions. Authors are also grateful to Mena Cayetana Ramos from "Salvador Allende" hospital for the carefully reviewing of the paper.

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