DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(7), 823-831 (1995)

EXPERIMENTAL DESIGN FOR A GRANULATION PROCESS WITH "A PRIORI" CRITERIAS

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ABSTRACT

Optimization techniques representr analytical tools available for the best solution to a particular problem.
Pharmaceutical product and process design problems were structured as constrained optimization problems and subsequently solved by the "a priori" optimality approach using an exchange algorithm.
The effect of the amount of added water plus granulation time and impeller speed on two properties of the granulates were investigated.
Experimental results obtained for the optimal formulation agreed well with the predictions.

INTRODUCTION

Generally, any scientist who faces an experimental reproducible phenomenon, feels the need to achieve an empirical model which can describe the phenomenon and its dependence on explicative variables.
Here we describe an experimental research methodology, which makes possible to organize the experimental work in a rationalway, while decreasing the number of experiments (1-4).
This approach moves from the determination of "X_i" matrixes, which consist of nearly orthogonal qualities.
The search for a suitable matrix, i. e. able to give the best information, has to take into account all the experimental requirements and constraints.
The suitability of the regression model depends on the planning of the experiments (experimental design) and on the nature (type) of the postulated empirical model.
The experimental outputs are used to determine the coefficients of the above mentioned model (2-3-5).
However the quality of the information given by the experimental design can be evaluated only using "a priori" criterias illustrated in Figure 1.

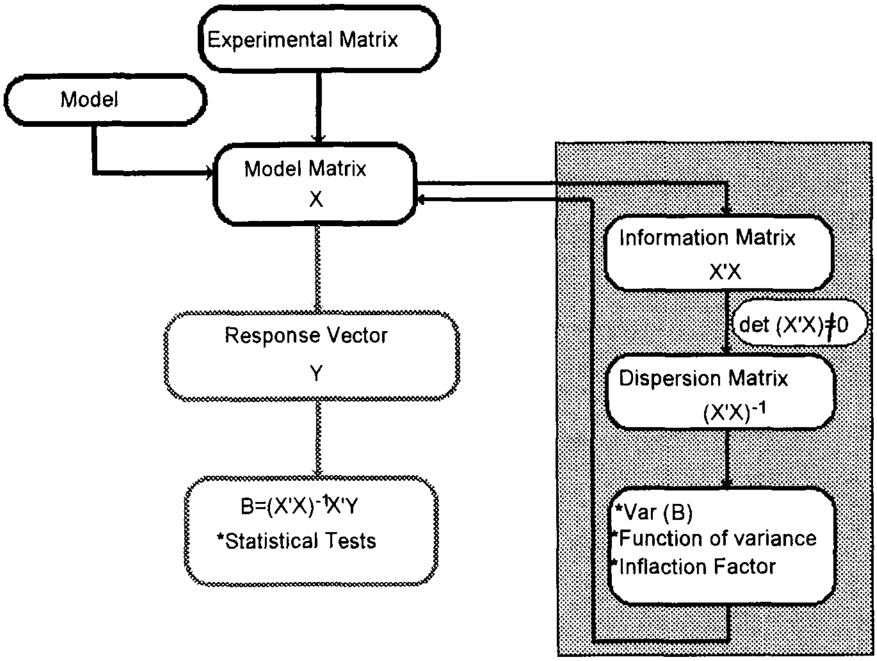

FIGURE 1

Flow diagram for the appraisal of the suitability of the experimental matrix ("a priori" method) and the evaluation of the mathematical model ("a posteriori" method).

In the present work we have studied the effects of process variables on the characteristics of a placebo granulate formulation; the "central composite design" was optimised by the "a priori" optimality approach using an exchange algorithm.

EXPERIMENTAL SECTION

MATERIALS

Lactose (200 mesh, DMV, the Netherlands), corn starch (Gianni, Italy, geometric mean diameter 15 μm) and polyvinylpyrrolidone K25 (Gaf, Italy) were used as starting materials.
The formula for a 2 kg batch was (w/w):Lactose 68.2, corn starch 29.8 and polyvinylpyrrolidone 2%.

TABLE 1
Steps of granulation and sizing processes.

ACTION	APPARATUS	FIXED PARAMETERS	VARIABLES	RESPONSES
DRY MIXING	Zanchetta Roto J	impeller speed: 150 rpm, mixing time: 10 min		
ADDITION OF THE SOLUTION	- " -	solution addition rate: 1l min, impeller speed: 150 rpm	moisture level %-(w/w)-(X_1)	
WET MASSING	- " -		impeller speed (X_2), granulation time (X_3)	
DRYING	Hoit-air oven	temperature: 60°C		
SIZING	Erweka AR 400	set of sieves (315, 500, 800, 1250, 2000 μm)		mean diameter and geometric standard deviation

METHODS

2 kg batches of formulation were prepared by mixing, wetting and wetmassing the powders in a Zanchetta Roto J granulator (Table 1).
The details regarding the granulator and the experimental procedures have already been described in our previous reports (6).
One characteristic of the granules were measured:

Particle size distribution after screening on a vibrating apparatus (Erweka AR 400) for 10 min (315, 500, 800, 1250 and 2000 μm sieves). This distribution led to the geometric mean diameter calculated from SAPRA program (7).

EXPERIMENTAL DESIGN

Three process variables were studied:
X_1 : moisture level
X_2 : impeller speed
X_3 : granulation time
The three parameters and their levels are listed in Table 2. The lower and the upper limits of each variable were selected according to the conditions already defined (6).

TABLE 2
Levels of process variables.

Parameters	Coded variables (X_i)	X_i levels -1	0	+1
moisture level % (w/w)	X_1	17.5	18.5	19.5
impeller speed (rpm)	X_2	250	375	500
granulation time (min)	X_3	3	6.5	10

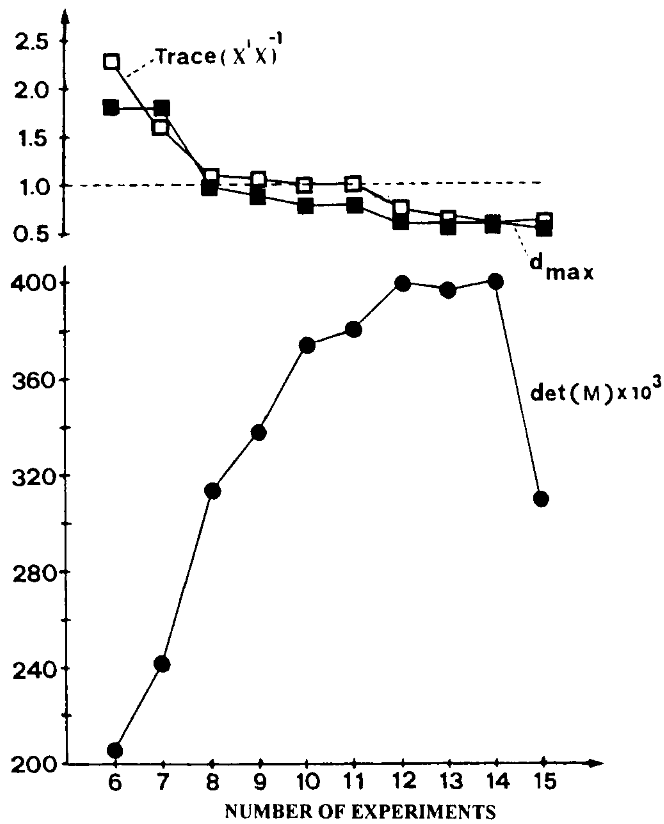

FIGURE 2

Variation of the determinant (M) - ● ,of the trace $(X'X)^{-1}$ - □ and of the function of variance (d_{max}) - ■ with the number of experiments.These values where determined by the following equations: det(M) = det(X'X)/n^p; Sum=var(b0) + var(b1) + var(b3) + var(b22) + var(b13)=(c_{00} + c_{11} + c_{33} + c_{22} + c_{13}) σ^2 =Trace$(X'X)^{-1}$ σ^2; $d_{max,n}$ = $x'_{un}(X'X)^{-1}x_{un}$; where: n = experiments from the total set of N candidate points, p = number of coefficients in the postulated model, x_{un} = vector of the coordinates of the model at point u.

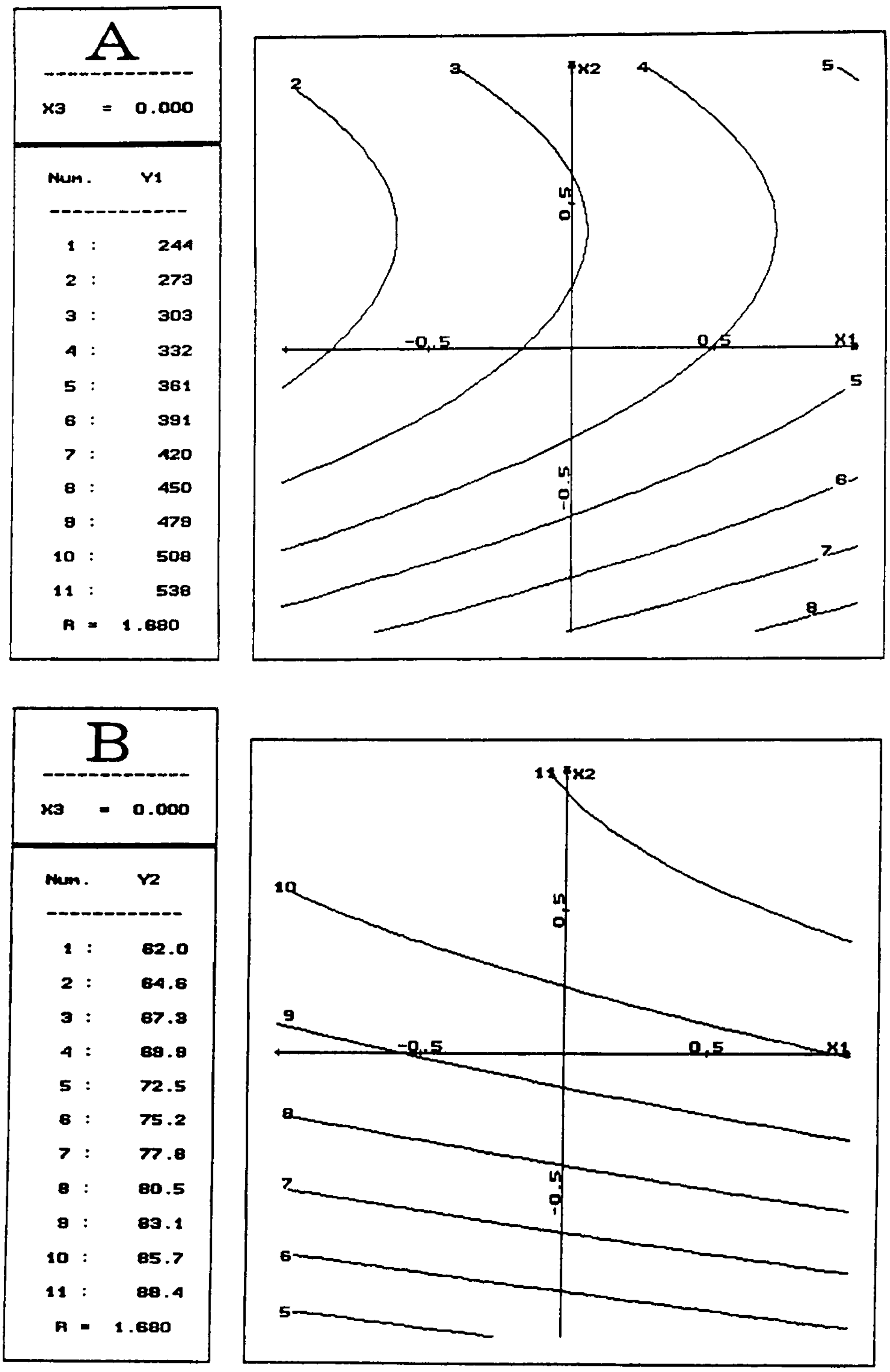

FIGURE 3

Response Surfaces for **a)** Geometric mean diameter (Y_1), and **b)** Percentage of particles smaller than 1250 μm (Y_2) , as function of moisture level (X_1) and impeller speed (X_2). X_3 (granulation time) = 6.5 min, level 0

TABLE 3
"A PRIORI" - optimal experimental design.

N^0	X_1	X_2	X_3
1	-1	-1	-1
2	+1	-1	-1
3	-1	+1	-1
4	+1	+1	-1
5	-1	-1	+1
6	+1	-1	+1
7	-1	+1	+1
8	+1	+1	+1
9	0	-1.6818	0
10	0	1.6818	0
11	0	0	-1.6818
12	0	0	1.6818

TABLE 4

Inflation factor, coefficient of variance for the coefficients of the model for the design given in Table 3.

Coefficient	Coefficient of variance	Inflation factor
β_1	0.125	1.00
β_2	0.073	1.00
β_3	0.073	1.00
β_{22}	0.118	1.00
β_{13}	0.125	1.00

The main effects of these variables were to be estimated, along with second order effect of X_2 and the effect of interaction X_1X_3. The following mathematical model was postulated:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{22} X_2^2 + \beta_{13} X_1 X_3 \qquad \text{(eq. 1)}$$

The method of exchange algorithms was chosen in order to optimize the experimental design for the following reasons:

- the considerable restraints on the number and type of experiments: not more than 15 experiments;

TABLE 5

Estimated model parameters for "a priori" - optimal experimental design.

	Y_1	Y_2
bo	314.77	84.64
b1	<u>44.62</u>	1.68
b2	<u>-47.14</u>	<u>7.64</u>
b3	8.77	1.87
b22	<u>55.33</u>	<u>-3.72</u>
b13	<u>37.12</u>	-1.41

The coefficients of the model having great influence for each response are underlined.

- the nature of the model, which is incomplete, asymmetric, and with numerous missing interactions.

These restrictions cannot be satisfied by any classical experimental design such as the composite Box matrices, Box-Behnken, Doehlert or Hoke matrices, nor hybrid matrix (8). The corresponding full "central composite design" matrix consists of 15 experiments. We used the exchange algorithm to determine whether by carrying out a subset of these experiments we could estimate the coefficients in the model with sufficient accuracy and precision. These calculations were performed using the NEMROD programme (9).

The resulting experimental design is known as a "a priori"-optimal design (1-10).

As the model contains 6 coefficients it was necessary to carry out at least 7 experiments to determine the coefficients.

We randomly selected 6 of 15 experiments and determined which of the 6 experiments had the least information. The latter are was replaced by the remaining point with the most information, the procedure being repeated until the exchange of points gave no further improvement in the precision of estimation of the coefficients.

The process was repeated for 6 up to 15 experiments and the efficiency of the "a priori" criteria was calculated. This is a measure of information for experiment and is plotted as a function of the number of experiments in Figure 2.

From the analysis of the valus of the various criterias reported in Figures 2 we decided to select the experimental design with 12 experiments reported in Table 3.

The inflation factors, relative values of the variances of the estimates of the coefficients are given in Table 4. They show that this experimental design will enable to calculate all coefficients with the same precision and to estimate the overall optimum.

Two response variables were chosen:

Y_1 = geometric mean diameter by weight, µm

Y_2 = percentage of particles smaller than 1250 µm.

TABLE 6
Optimum conditions and experimental results.

Response variable	**Optimum condition**	**Theoretical**	**experimental results**
Geometric mean diameter by weight (μm)	X_1=18% w/w X_2=468 rpm	288	275
Percentage of particles smaller than 1250 μm	X_3=6,5 min	87.5	88

The coefficients of the model could be estimated for each of the response variables. The coefficients b_i represent the estimation of the main effects βi of the factors X_i. Similarly b_{ii} represent the estimations of the second order effects β_{ii} and b_{ij} the estimations of the interactions bij between X_i and X_j.

RESULTS AND DISCUSSION

The responses Y_1 and Y_2 were analyzed by regression analysis according to the proposed model (eq. 1), and the estimated model parameters are listed in Table 5.

As Table 5 shows, the moisture level (X_1) and impeller speed (X_2), its second-order effect (X_2^2), and interaction effect (X_1X_3) between impeller speed and granulation time are the more important effects on the response Y_1. The Y_2 response is affected by the impeller speed and its second-order effect.

A number of methods is available for determining optimal conditions for manufacturing in pharmaceutical technology: these are non-direct methods requiring a mathematical model to be postulated, including response surface analysis (8-9). In our case, response surfaces were drawn over the experimental factor space using the NEMROD programme (9).

Example are given in Figure 3.

Optimum zones are obtained for different responses by analyzing the graphs of response surface and the results are listed in Table 6 .

The granulate was prepared using the theoretical optimum conditions. The experimental results are comparable with the theoretical responses, calculated from eq. 1, and with the estimates of the coefficients in Table 5.

It can be pointed out that the method of response surface analysis possesses a good predictability in the optimization of the granulation process in a small high shear mixer.

CONCLUSIONS

particularly when there are restrictions in the amount of raw material and restraints on the type of experiments are present.The method is also to be recommended when mixed models are investigated by studying various variables at multiple levels.

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