Drug Development and Industrial Pharmacy, 22(9&10), 997-1004 (1996)

Nonclassical Experimental Design Applied in the Optimization of a Placebo Granulate Formulation in High-Shear Mixer

D. Vojnovic, M. Moneghini, and D. Chicco

Department of Pharmaceutical Sciences, University of Trieste, 34127 Trieste, Italy

ABSTRACT

The optimization of wet granulation in a 10-liter high-shear mixer was investigated using a nonclassical experimental mixture design. Hydroxypropylmethylcellulose, lactose, cornstarch, and microcrystalline cellulose were used as excipients of the granulate, while polyvinylpyrrolidone was used as binder. Besides the minimization of the number of experiments, the strategy applied takes into account the cost of each experiment. The introduction of such a modification allowed us to select an experimental matrix giving enough information with a relatively low number of experiments and at a minimum cost.

INTRODUCTION

In studies on pharmaceutical formulations, the effects of different proportions of the excipients on the formulation properties, as well as process variables, are the most important objects of study. In the planning of such an experimental work the Scheffé mixture design can be very useful, if the experimental domain is a "simplex" one (1,2). However, in many cases limits are imposed on the excipient proportions; hence the experimental domain is not a simplex anymore and the classical experimental mixture designs have a restricted applicability. So, in such an irregular domain, it is necessary to use different strategies to plan the experimental work.

A method of statistical optimization of a mixture design was already applied by Lewis and Chariot (3) in the formulation of a modified release matrix tablet, using the *D*-optimum criterion. In a previous work we investigated the influence of the process variables, as well as the effects of the proportions of the excipients (lactose, cornstarch, and microcrystalline cellulose) on the characteristics of a granulate prepared in a 10-liter

high-shear mixer, applying the Scheffé simplex-centroid mixture design and the Doehlert design (4). In the above-mentioned works the design optimization consists in lowering the number of experiments while keeping the information given by an experimental matrix at a good quality level, yet the economical aspect of the experimentation is not taken into consideration.

The present investigation regards a four-component placebo granulate with limitations. The consequent irregular experimental domain required the use of a nonclassical experimental mixture design. Moreover, the cost of each experiment was taken into account, using the so-called ponderation function.

MATERIALS AND METHODS

Materials

Lactose (Pharmatose, 200 mesh) and cornstarch were supplied by Prodotti Gianni (Italy). Microcrystalline cellulose (MC—Avicel PH 101) and hydroxypropylmethylcellulose (HPMC—Methocel E5 Premium) were purchased from Faravelli (Milano, Italy). Polyvinylpyrrolidone (PVP—Plasdone K-25) was provided by Gaf (New York).

Granulate Manufacture

A Zanchetta Roto J granulator was used for preparation of the granulates. Batches, 0.7 kg, of lactose, cornstarch, microcrystalline cellulose, and hydroxypropylmethylcellulose were mixed using the impeller at 120 rpm for 10 min. The powder was granulated with polyvinylpyrrolidone (3%) aqueous solution. The binder solution was added by spraying at a flow rate of 50–70 ml/min, at a pressure of 4.0 bar, and atomized by a pneumatic nozzle of 0.3 mm diameter. During this phase the impeller speed was kept at 120 rpm. The final step of granulation was carried out using the impeller at 250 rpm for 8 min.

Samples weighing 150 g were taken out and the granulated product was dried in a hot-air oven at 60°C for 4 hr.

Particle Size Distribution

About 100-g samples of granulate were place on the first sieve of a nest of stainless steel sieves (63, 80, 100, 125, 160, 200, 250, 315, 400, 500, 630, 800, 1250, and 2000 μm) arranged in order of decreasing aperture size. The nest of sieves was clamped onto a sieve shaker (Octagon 200) and then subjected to vibrations for 10 min. After sieving, the amount retained on each sieve was ascertained. The particle size distribution was characterized through the determination of the geometric standard deviation, both calculated by the SAPRA program (5). The percentage in weight (w/w) of granules smaller than 1250 μm was also calculated.

Density, Porosity, and Compressibility Index

The granulate was poured into a 100-cm^3 graduated cylinder to a total volume of about 90 cm^3. To determine bulk volume (V_{10}) and tap volume (V_{2000}), the cylinder was tapped 10 and 2000 times, respectively, using a volume presser (Giuliani IG/4). Equations (1) and (2) were used to calculate the bulk density (d_{10}) and the tap density (d_{2000}), respectively:

$$\text{Bulk density} = \text{weight (g)/bulk volume } (cm^3) \quad (1)$$

$$\text{Tap density} = \text{weight (g)/tap volume } (cm^3) \quad (2)$$

True density was determined using a multivolume pycnometer (Multipycnometer, Quantachrome Corporation/Nordtest srl). At least three readings were taken for each density determination and the mean value was computed.

Porosity and compressibility index of the granulates were calculated from the density data using Eqs. (3) and (4), respectively:

$$\text{Percentage porosity} = (1 - \text{bulk density/true density}) \times 100 \quad (3)$$

$$\text{Compressibility index} = (1 - \text{bulk density/tap density}) \times 100 \quad (4)$$

Flow Rate

The flow rate of each granulate was determined by Pharma test PTG-1. Each granulate (only the fraction under 1250 μm was used) was placed in a 100-cm^3 funnel (with an orifice diameter of 6 mm) and the product was allowed to flow only under the force of gravity. The flow time was automatically estimated by the instrument itself.

EXPERIMENTAL DESIGN

Determination of Experimental Points

In previous studies on mixtures it was observed that the formulation characteristics are considerably affected by different proportions of the excipients (4,6). On the bases of such studies, the four-component formulation shown in Table 1 was set up as a model of study. According to the works just mentioned, the limits reported in the table appear to be the most adequate to obtain mixtures suitable for subsequent scaling-up studies.

All the possible compositions of a four-component mixture can be represented in a three-dimensional space by a regular tetrahedron.

The limitations indicated in Table 1 define an experimental domain which covers only a restricted part of the whole tetrahedron. This experimental domain, called "domain of interest," is not a regular simplex, but it turns out to be a polyhedron within the tetrahedron, as shown in Fig. 1.

Once the coherence of the four limitations was verified and the experimental domain was exactly depicted, we projected the experimental points using the McLean–Anderson method (1,7). The experimental points selected by this method are the following:

- The 12 vertices (corresponding to numbers 1–12)
- The 18 mid-edge points (numbers 13–30)
- The 8 centroid points of the faces (numbers 31–38)
- The barycenter of the polyhedron (number 39)

All these points are shown in Fig. 2 and in Table 2.

Ponderations

Since our aim was to project an experimental design that would give the maximum information at the minimum cost of the experimentation, we took into consideration the price of each experiment, which was calculated by summing the cost of each component present in the mixture. The costs taken into account were those reported in the catalogue of the *Prodotti Gianni,* 1994, (Milan, Italy).

The prices cannot be used exactly as they are but have to be converted into a kind of codified values, the so-called ponderations (8). In fact, it is necessary to give each one of the prices a different weight: for example, the smallest ponderations are assigned to the highest prices. The equation we used to obtain such codified values is:

$$p_i = [D - c_i)/\Sigma(D - c_i)] \times 100 \quad (5)$$

Table 1

Lower and Upper Limits of the Formulation Factors: X_1 (HPMC), X_2 (Lactose), X_3 (MC), X_4 (Cornstarch)

	Lower Limit (%)	Upper Limit (%)
HPMC (X_1)	5	10
Lactose (X_2)	40	65
MC (X_3)	0	20
Cornstarch (X_4)	22	40

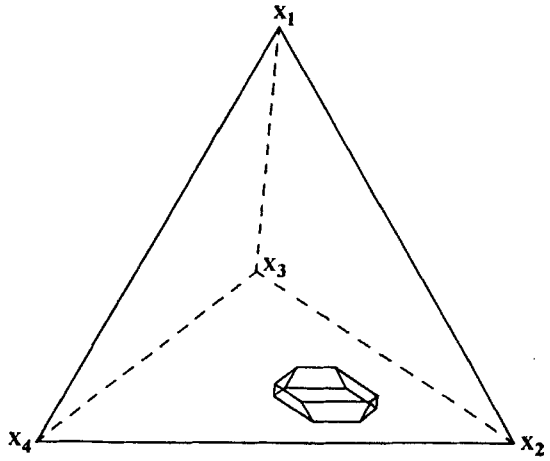

Figure 1. Experimental design for a four-component mixture with constraints. The experimental domain is represented by the three-dimensional polyhedron within the four-component tetrahedron.

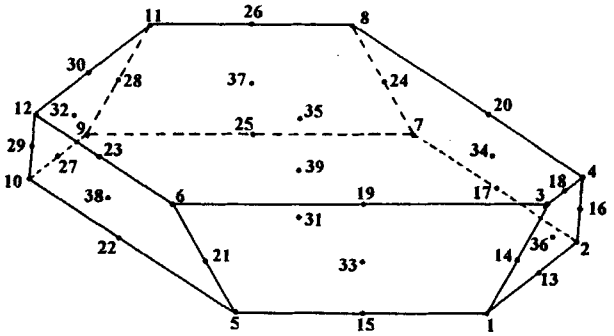

Figure 2. Selected experimental points in the "domain of interest."

Table 2

The 39 Experimental Points with the Respective Percentages of the Four Components

Exp. Points	Formulation Components (%)			
	HPMC (X_1)	Lactose (X_2)	MC (X_3)	Cornstarch (X_4)
1[a]	5.00	65.00	0.00	30.00
2[a]	5.00	65.00	8.00	22.00
3[a]	10.00	65.00	0.00	25.00
4[a]	10.00	65.00	3.00	22.00
5[a]	5.00	55.00	0.00	40.00
6[a]	10.00	50.00	0.00	40.00
7[a]	5.00	53.00	20.00	22.00
8[a]	10.00	48.00	20.00	22.00
9[a]	5.00	40.00	20.00	35.00
10[a]	5.00	40.00	15.00	40.00
11[a]	10.00	40.00	20.00	30.00
12[a]	10.00	40.00	10.00	40.00
13	5.00	65.00	4.00	26.00
14	7.50	65.00	0.00	27.50
15	5.00	60.00	0.00	35.00
16[a]	7.50	65.00	5.50	22.00
17	5.00	59.00	14.00	22.00
18	10.00	65.00	1.50	23.50
19	10.00	57.50	0.00	32.50
20	10.00	56.50	11.50	22.00
21[a]	7.50	52.50	0.00	40.00
22	5.00	47.50	7.50	40.00
23	10.00	45.00	5.00	40.00
24	7.50	50.50	20.00	22.00
25	5.00	46.50	20.00	28.50
26	10.00	44.00	20.00	26.00
27	5.00	40.00	17.50	37.50
28[a]	7.50	40.00	20.00	32.50
29[a]	7.50	40.00	12.50	40.00
30	10.00	40.00	15.00	35.00
31[a]	5.00	53.00	10.50	31.50
32	7.50	40.00	16.25	36.25
33	7.50	58.75	0.00	33.75
34	7.50	57.75	12.75	22.00
35[a]	10.00	51.33	8.83	29.83
36	7.50	65.00	2.75	24.75
37	7.50	45.25	20.00	27.25
38	7.50	46.25	6.25	40.00
39	7.50	52.17	9.67	30.67

[a]Experimental points of the chosen ponderated matrix.

where: p_i = ponderation associated to the experimental point i; c_i = price of the experiment corresponding to the experimental point i; c_{min} = price of the least expensive experiment; c_{max} = price of the most expensive experiment; $D = c_{min} + c_{max}$.

Transformation of the Mixture Variables

As we can see in Fig. 1, the experimental domain is not a regular simplex; therefore, the classical experimental matrixes are not helpful in our case. So we have to construct a matrix using an adequate strategy.

We preferred to represent the experimental points no longer as functions of q linearly dependent mixture variables (X_1, X_2, X_3, and X_4), but as functions of $q - 1$ mathematically independent variables (Z_1, Z_2, Z_3), which define a new, orthogonal coordinate system in such a way the origin is shifted to the center of the experimental domain. By a simple linear transformation it is possible to pass from one to the other coordinate system (1). The new coordinate system is shown in Fig. 3.

RESULTS AND DISCUSSION

In order to evaluate the main effects of mixture variables on some properties of the granulate, the following mathematical model was postulated on the basis of preliminary studies:

$$Y = b_0 + b_1Z_1 + b_2Z_2 + b_3Z_3 + b_4Z_1^2 + b_5Z_2^2 + b_6Z_3^2 + b_7Z_1Z_2 + b_8Z_1Z_3 + b_9Z_2Z_3 \quad (6)$$

So we have to estimate 10 coefficients. Is it really necessary to execute all the 39 experiments? And if it is not, how many experiments, and which of those 39 should be carried out to obtain enough information at a cost as low as possible? The aim is therefore to find a subset of experiments that would give, for the postulated model [Eq. (6)], a satisfactory precision of the coefficients and a good predictional quality.

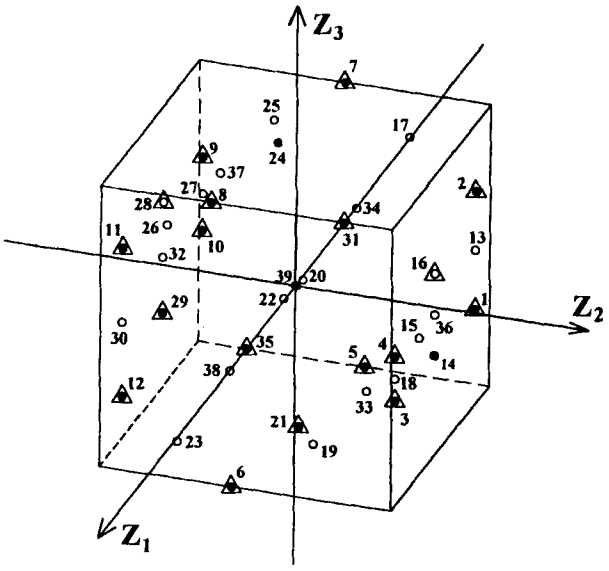

Figure 3. Experimental design projected using independent variables (Z_1, Z_2, Z_3) in four-component mixture space. Experimental points of the nonponderated matrix with 19 experiments: ●; experimental points of the ponderated matrix with 18 experiments: Δ.

As the mode contains 10 coefficients, it was necessary to carry out at least 10 experiments to determine the coefficients. The selection of the matrixes composed of 10 up to 38 experiments was carried out by a modified exchange algorithm using the NEMROD program (8).

In order to choose the most suitable one, these selected matrixes were then compared in terms of the "a priori" criteria [Det (M), Trace $(X'X)^{-1}$, and function of variance (d_{max})] as described in our previous report (9).

As mentioned before, we were interested not only in minimizing the number of experiments, but in minimizing the overall cost of the experimentation. Each experiment was ponderated using Eq. (5).

As in the case of the nonponderated matrixes, the exchange algorithm was applied to choose the optimal ponderated matrix. The comparison of the "a priori" quality criteria for the ponderated matrixes is shown in Fig. 4.

In terms of the "a priori" criteria, the most suitable ponderated matrix is the one with 18 experiments. The single experiments of this matrix are shown in Fig. 3 and Table 2.

So, the ponderation led us to a set of experiments which give good information at a minimum cost. Seven response variables were chosen:

Y_1 = geometric mean diameter by weight (μm)
Y_2 = geometric standard deviation
Y_3 = percentage of particles smaller than 1250 μm
Y_4 = porosity (%)
Y_5 = compressibility index (%)
Y_6 = flow time (sec)
Y_7 = repose angle

The estimates of the model coefficients [Eq. (5)] for each of the response variables were determined by multiple regression analysis and the results are listed in Table 3.

By use of the model coefficients reported in Table 3, response surfaces were drawn for each response. Using the desirability function (D), already successfully applied in a previous report of ours (6), it was possible to achieve the simultaneous optimization of all the response variables. In order to reach such an optimization, the following limits were fixed for each response:

$$Y_1 > 200\ \mu m,\ Y_3 > 85\%,\ Y_5 > 10\%$$

and Y_2, Y_4, Y_6, Y_7 were left without constraints. Two contour diagrams are shown in Fig. 5 as examples.

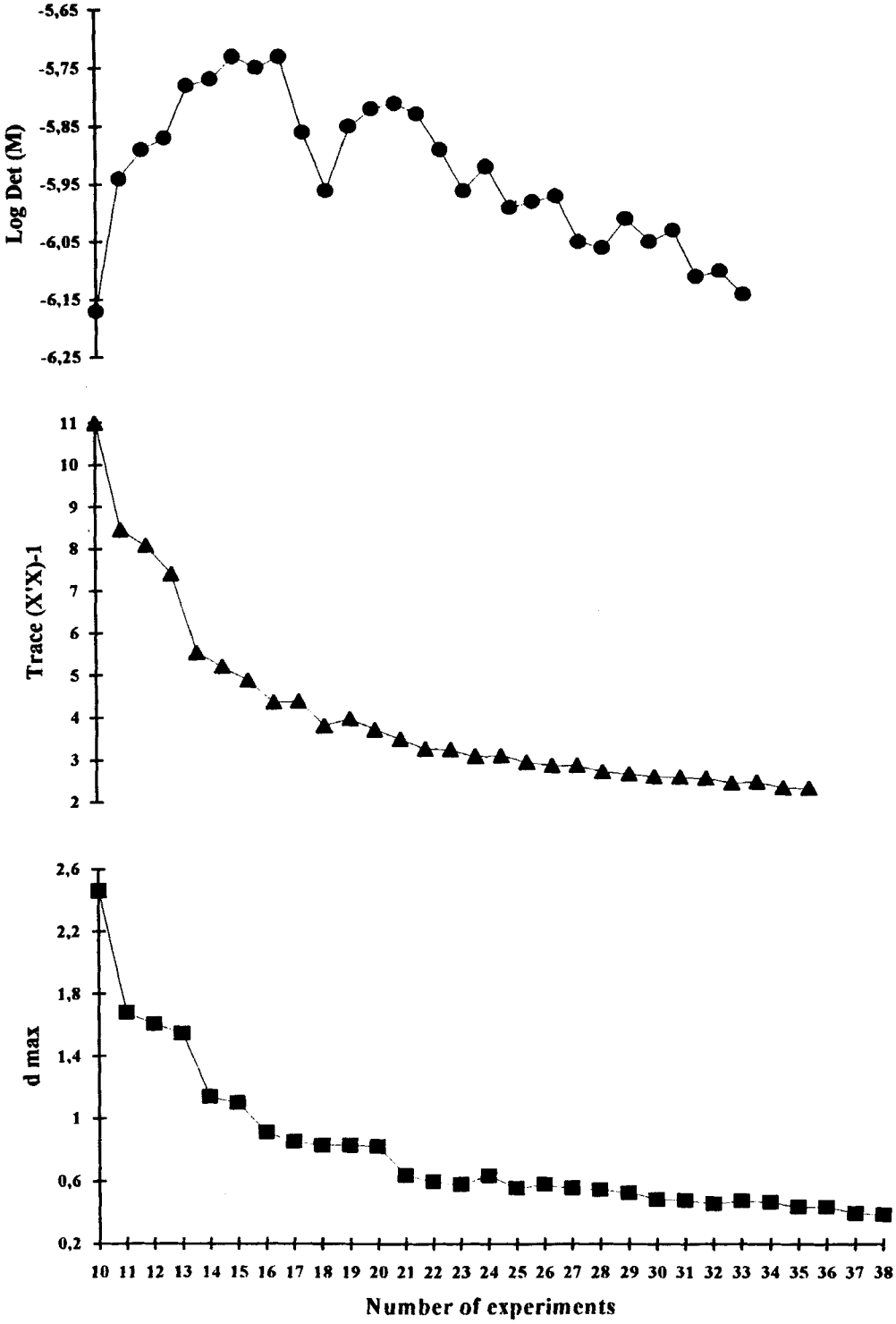

Figure 4. Comparison of the "a priori" quality criteria [Log Det (M), Trace $(X'X)^{-1}$, d_{max}] for the ponderated matrixes.

Table 3

Estimates of the Model Coefficients for Each of the Response Variables[a]

Coefficients	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7
b_0	187.47	2.03	95.07	62.26	10.19	10.03	30.70
b_1	-18.40	0.02	1.09	-0.78	0.24	0.01	-0.23
b_2	99.21	0.09	-6.64	-2.13	-1.41	0.61	0.03
b_3	1.02	-0.11	0.51	0.88	0.17	0.08	0.41
b_4	-12.26	0.06	0.06	-1.03	0.44	-0.23	-0.04
b_5	56.04	-0.05	-3.49	-0.27	1.05	-0.44	0.03
b_6	28.33	0.11	-1.09	-2.22	0.79	0.25	-0.65
b_7	-35.79	-0.02	1.77	-0.76	0.20	0.08	0.55
b_8	3.98	-0.06	1.34	-0.09	-0.24	0.11	0.38
b_9	-12.17	-0.02	3.38	-0.35	1.78	0.04	0.91

[a]The model coefficients having the greater influence on each response are underlined.

It has to be emphasized that in the analysis of such contour plots, when the transformation of dependent variables into independent ones is applied, the axes Z_1 and Z_2 represent two pure excipients: Methocel (X_1) and lactose (X_2), while the Z_3 axis represents the other two excipients: microcrystalline cellulose (X_3) and cornstarch (X_4). In the versus of increasing X_3, X_4 decreases, and vice versa.

From analysis of the Fig. 5 it can be observed that the optimal formulation that would give a granulate with the characteristics mentioned before has the following composition: Methocel 8%, lactose 50%, microcrystalline cellulose 20% and cornstarch 22%. More generally, by means of response surface, the behaviour of the responses with the variation of the mixture composition can be studied and the optimum conditions can be pointed out, depending on the technological needs.

CONCLUSIONS

The application of the mixture experimental design, in combination with the ponderation function, allowed

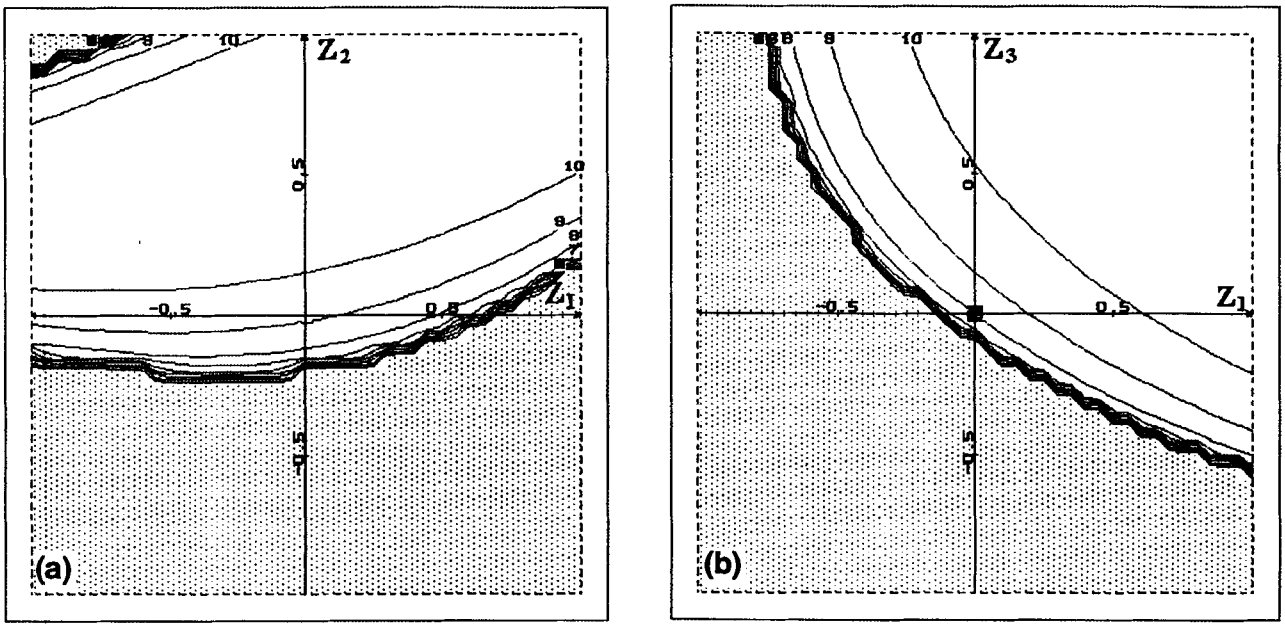

Figure 5. Contour plot of desirability function (D) for (a) $Z_1(X_1)$ and $Z_2(X_2)$; $Z_3(X_3 + X_4) = 0.982$; and for (b) $Z_1(X_1)Z_3$ and $(X_3 + X_4)$; $Z_2(X_2) = 0.982$. Response correspondence (%D): line 7, response 60, 8:70, 9:80, 10:90, 11:100.

us to select an experimental design giving good-quality information with a low number of experiments and at a minimum cost.

Such methodology made possible the study of the formulation of a placebo granulate manufactured in a high-shear mixer and to determine the dependence of the granulate characteristics on the percentage of the mixture components.

REFERENCES

1. J. A. Cornell, *Experiments with Mixtures*, Wiley, New York, 1990.
2. D. Feneuille, D. Mathieu and R. Phan-Tan-Luu, *Matrices d'expériences appliquées aux mélanges,* Laboratoire de Prospective Réactionelle et d'Analyse de l' Information, Université d'Aix-Marseille, 1983.
3. G. A. Lewis and M. Chariot, Drug Dev. Ind. Pharm., 17, 1551–1570 (1991).
4. D. Vojnovic, M. Moneghini, and F. Rubessa, Drug Dev. Ind. Pharm., 20, 1035–1047 (1994).
5. Program SAPRA (Sejalna Analiza farmacevtskih Praškov), University of Ljubljana, Department of Pharmacy, Ljubljana (Slovenia), 1990.
6. D. Vojnovic, M. Moneghini, and F. Rubessa, Drug Dev. Ind. Pharm., 19, 1479–1496 (1993).
7. R. A. McLean and V. L. Anderson, Technometrics, 8, 447–454 (1966).
8. D. Mathieu and R. Phan-Tan-Luu, NEMROD: New efficient methodology for research using optimal design, LPRAI, Université d'Aix-Marseille, 1995.
9. D. Vojnovic, M. Moneghini, and F. Rubessa, Drug Dev. Ind. Pharm., 21, 823–831 (1995).