DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(6), 1035-1047 (1994)

OPTIMIZATION OF GRANULATES IN A HIGH SHEAR MIXER BY MIXTURE DESIGN

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ABSTRACT

Optimization of wet granulation in a 10 litre high shear mixer was examined by mixture design. Lactose, corn starch and cellulose microcrystalline were used as eccipients of the granules. Mixing ratios of these eccipients were selected as formulation factors. In addition, the impeller speed and granulation time was employed as independent process variables. A two-phase experimental strategy was drawn up: one phase for the percentages of the three eccipients and the other phase for the determination of the influence of process variable on geometric mean diameter. The percentages were studied using a Scheffè simplex-centroid design, and the other phase was examined using a Doehlert experimental matrix.

INTRODUCTION

Granulation is a process within the production of solid dosage forms (granules, tablets, capsules) and improves the properties of the product needed for the subsequent steps.

In order to obtain certain characteristics of the final product, a number of excipients is added to the active substance.

In this work, the influence of various mixtures composed of three excipients (lactose, corn starch, microcrystalline cellulose) has been studied on the properties of the granulates.

A 10 L high-speed granulator has been used and the methodological approach developed consists in reducing the number of necessary experiences. It replaces a limited knowledge with a spatial knowledge by performing the experimental measurements on mixtures which give more information postulating also a matrix and a Scheffè mathematical model. Furthermore the influence of the process variables in the studied mixtures was considered by using a Doehlert experimental matrix.

Experimental results suggest usefulness and reliability of the mixture design for further investigation to process transfer.

MATERIALS AND METHOD

Materials

Lactose (200 mesh, DMV, The Netherlands), corn starch (Gianni, Italy), microcrystalline cellulose (Avicel pH 102) and hydroxypropylmethylcellulose (Methocel E 5 Premium, Faravelli, Italy) were used in the formulations.

Instruments

Zanchetta Roto J granulator, vibrating apparatus (Octagon 2000, Endecotts), set of sieves (80, 100, 125, 160, 200, 250, 315, 400, 500, 630, 800,1250, 2000 μm), scanning electron microscope (Philips 500) and flow rate apparatus (Pharma Test) were employed.

Granulate manufacture

A 1 kg batch of lactose, corn starch and cellulose microcrystalline, is mixed using the impeller at 150 rpm for 10 min. The powder has been granulated with hydroxypropylmethyl cellulose (2%) aqueous solution. The binder solution has been added by spraying at a flow rate of 50-70 ml/min, pressure of 4.0 bar and atomized by a pneumatic nozzle of 0.3 mm diameter. During this phase the impeller speed was set at 150 rpm. The final step of granulation has been carried out using the impeller at 300 rpm for 10 min.

170 g samples have been withdrawn and the drying of the granulated product has been carried out in a hot-air oven at 60°C for 4 hours.

Characterization of the granules

The geometric mean diameter by weight (D_{50}, μm),the geometric standard deviation and flow rate (g/sec) were measured and the methodologies were described previously (1).

Mixture formulation

The initial formulation for the mixtures is constituted by corn starch 43 %, Avicel 43%, lactose 12% and Methocel 2%.

The amount of water (H_i = initial moisture) required by the binding solution was calculated according to the equation:

$$H_i = \text{kg of water/kg of dried powder} \times 100$$

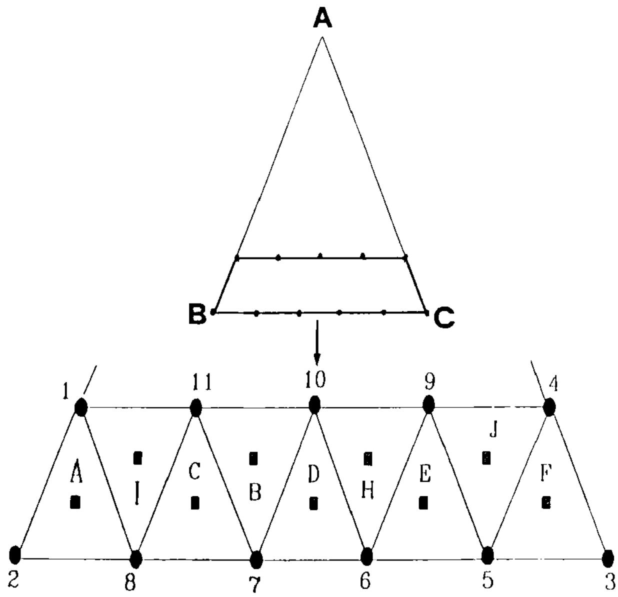

FIGURE 1

Definition of the experimental domain by truncature of the initial three-components triangle. A: lactose; B: corn starch; C: cellulose microcrystalline.

In the case of lactose, corn starch and Methocel, the selected H_i value was equal to 23% whereas for the Avicel, H_i was equal to 40%.

EXPERIMENTAL DESIGN

Preliminary trials have been carried out by employing a mixture containing mainly lactose. However, the latter one causes some drawbacks in the final granulation step, since it promotes the adhesion of the wet mass to the mixer bowl.

In order to avoid the undesired phenomenon the lactose content has been limited to 12%. As a consequence, an unsimmetric experimental domain has been obtained, which does not allow the design of Scheffè matrix (2).

Therefore the following strategy has been followed: the experimental domain has been divided into six small simplexes which enable the study of Scheffè matrixes. A series of mixtures, corresponding to different formulations, has been planned according to the simplexes reported in Figure 1. The matrix for these informative mixtures is reported in Table 1.

TABLE 1

Mixture design for three formulation factors.

Formulation	Formulation factor (%)		
	Lactose (%)	Avicel (%)	Corn starch (%)
1	12	88	0
2	0	100	0
3	0	0	100
4	12	0	88
5	0	20	80
6	0	40	60
7	0	60	40
8	0	80	20
9	12	22	66
10	12	44	44
11	12	66	22

Besides, nine more informative mixtures have been planned and they represent the overall centroid of the symplexes. These points correspond to coded values equal to [0.33, 0.33, 0.33] of the independent variables. After having granulated the mixture, their characterizations have been accomplished by taking into consideration the factors:geometric diameter, geometric standard deviation and flow rate.

The results are reported in Figures 2, 3, 4.

The data indicate minimum variations of both geometric mean diameter and geometric standard deviation, except for experiments number 1 and 2.

Therefore, the mixtures endowed with the optimal technological properties have been selected by evaluating the flow rate. It is noteworthy that no addition of excipients has been needed. The most satisfactory results have been achieved in experiments 5, 9, J.

The results led us to narrow the experimental domain by delimiting it within the points corresponding to the following informative mixtures: 9 (Z_1), 5 (Z_2), J(Z_3).

MODELLING OF THE GEOMETRIC MEAN DIAMETER BY WEIGHT

In order to verify the existence of any interaction (either sinergistic or antagonistic) among the mixtures, a matrix has been designed according to the Scheffè reduced cubic model (3). The matrix is reported in Figure 5.

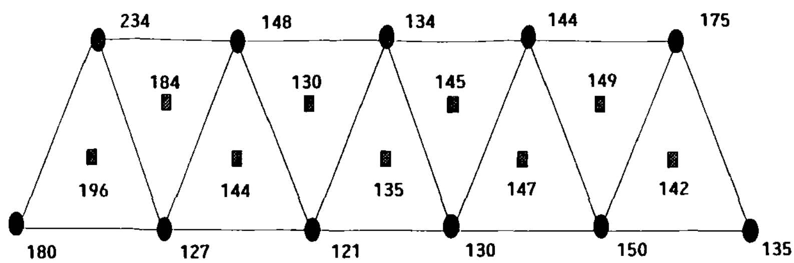

FIGURE 2
Geometric mean diameter in µm.

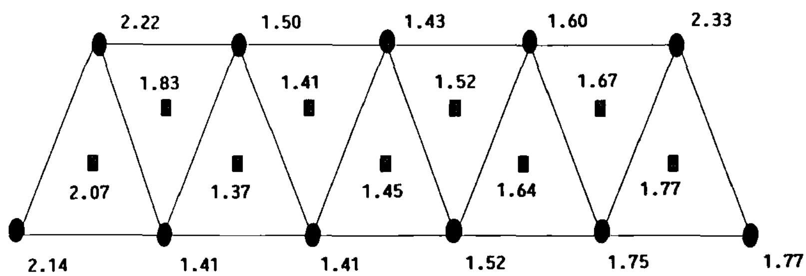

FIGURE 3
Geometric standard deviation.

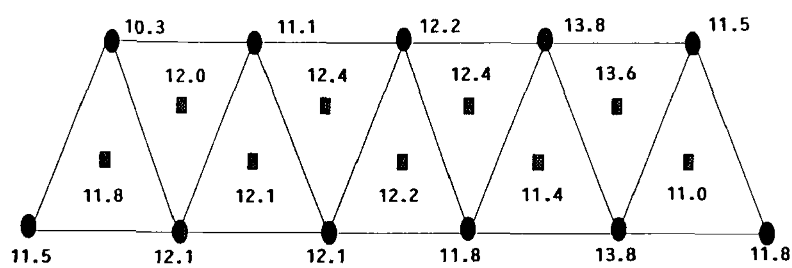

FIGURE 4
Flow rate (g/sec).

	Z_1	Z_2	Z_3
1	1.0000	0.0000	0.0000
2	0.0000	1.0000	0.0000
3	0.0000	0.0000	1.0000
4	0.5000	0.5000	0.0000
5	0.5000	0.0000	0.5000
6	0.0000	0.5000	0.5000
7	0.3333	0.3333	0.3333
8 X	0.6667	0.1667	0.1667
9 X	0.1667	0.6667	0.1667
10 X	0.1667	0.1667	0.6667

X CHECK POINTS

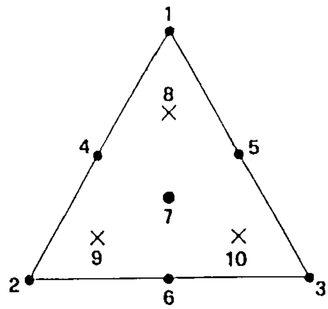

FIGURE 5
Matrix of Scheffè reduced cubic model-design.

TABLE 2
Regression equation for geometric mean diameter by weight.

Regression coefficient value of eq.1		Geometric mean diameter Experimental	predicted [a)]
$a_1(Z_1)$	143.7	144	143.72
$a_2(Z_2)$	149.9	150	149.90
$a_3(Z_3)$	148.9	149	148.90
$a_{12}(Z_1Z_2)$	19.3	152	151.63
$a_{13}(Z_1Z_3)$	1.3	147	146.63
$a_{23}(Z_2Z_3)$	-18.4	145	144.81
$a_{123}(Z_1Z_2Z_3)$	157.8	155	153.58
		149	150.30
		151	151.76
		149	149.76

a) Using Eq. 1

The corresponding model is described by the following equation :

$$Y = a_1Z_1 + a_2Z_2 + a_3Z_3 + a_{12}Z_1Z_2 + a_{13}Z_1Z_3 + a_{23}Z_2Z_3 + a_{123}Z_1Z_2Z_3 \quad \text{(eq.1)}$$

The experimental data have been analyzed by regression analysis according to the proposed model and the results are shown in Table 2.

The calculated coefficients indicate a significant positive interaction among mixtures Z_1, Z_2, Z_3 and a negative interaction between mixtures Z_1 and Z_2.

The experimental results are in good agreement with the calculated values, since discrepances are comparable to the experimental error.

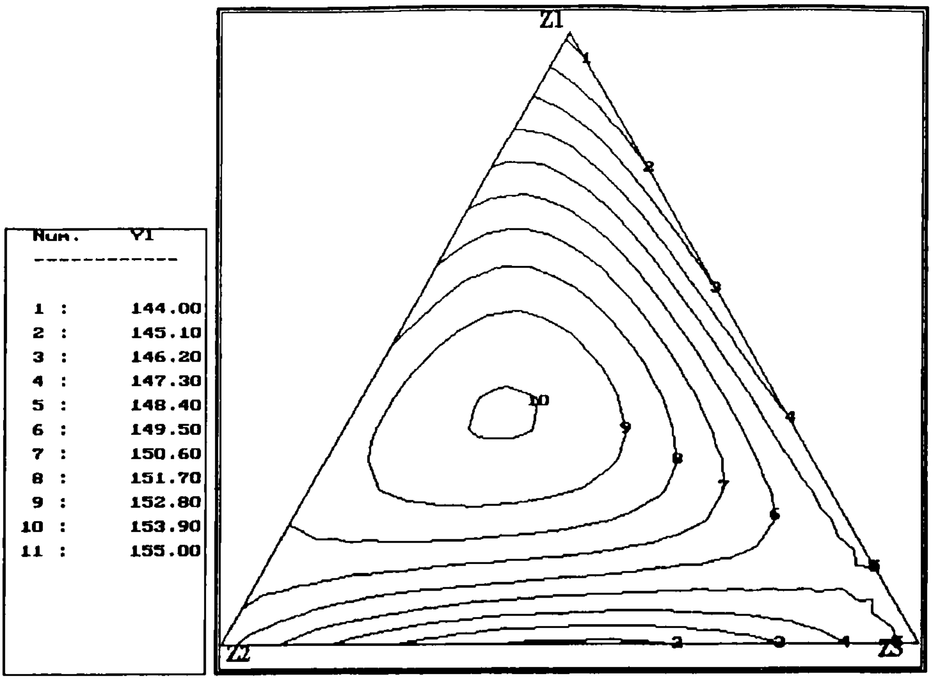

FIGURE 6
Contour plots of geometrical mean diameter.

Therefore the model is suitable for describing the studied variable in the Roto granulator.
Figure 6 illustrates the contour diagrams obtained from equation 1.

The diagrams describe the variation of geometrical mean diameter as a function of the composition of three mixtures (Z_1, Z_2, Z_3) . The function is not linear and indicates the importance of the interactions among Z_1, Z_2, Z_3, as mentioned before.

ANALISIS OF THE GRANULATE SHAPE

Since differences have been observed in the geometric mean diameter and in the geometric standard deviation, we analyzed the microstructures of the granules at the electronic microscope.
From the photographs it is possible to notice that mixtures Z_1 and Z_4 correspond to spheric granulates while mixtures Z_3 yield partially irregular granulates. (Fig 7,8,9).

The irregulal shape of the granulates is probably due to the different composition of the mixtures. In fact, mixture Z_2 contains 80% of corn starch and its particles can be incorporated irregularly in the granules (Fig 10). As a consequence, regularly spheric

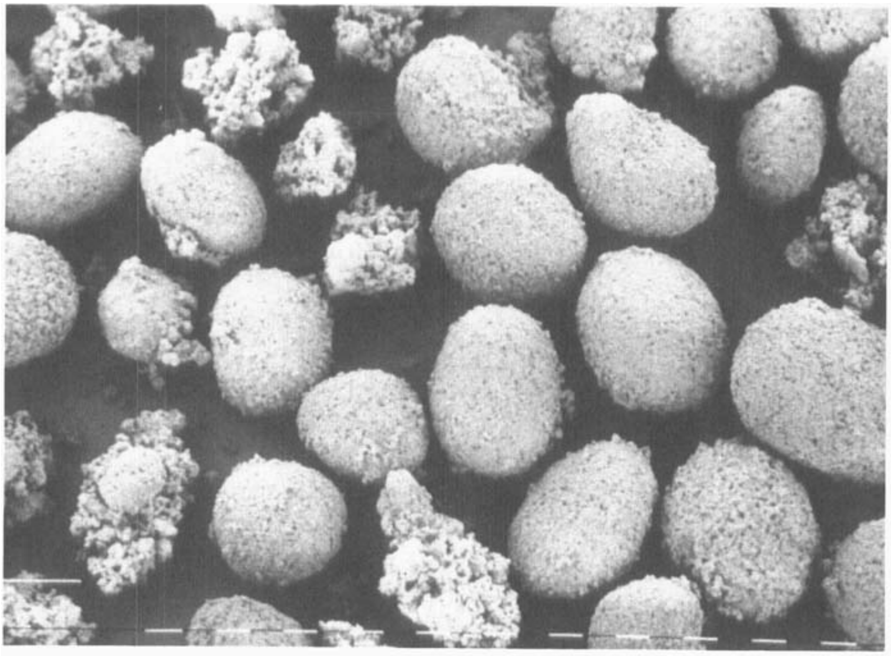

FIGURE 7
SEM photograph of a granule(mixture Z_1).

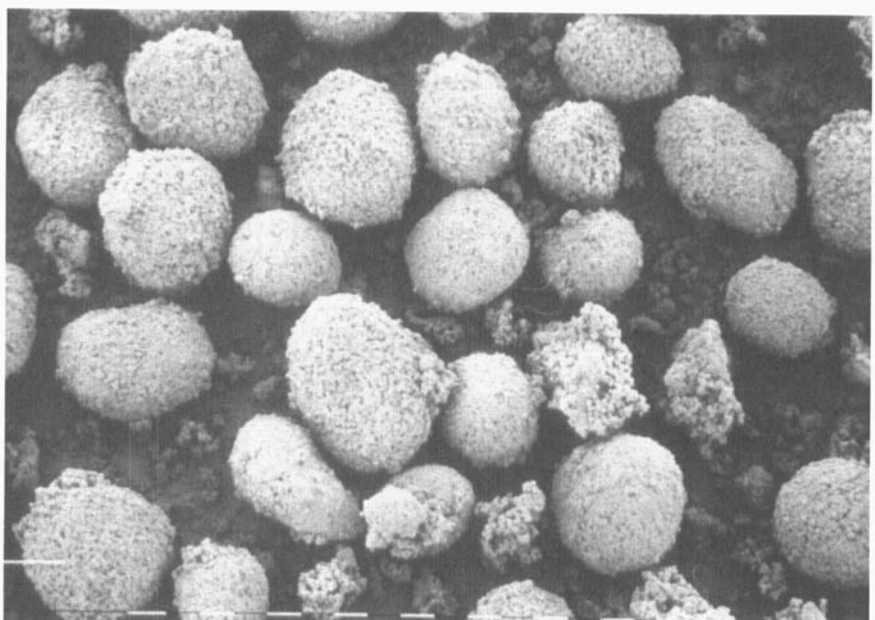

FIGURE 8
SEM photograph a granule (mixture Z_4).

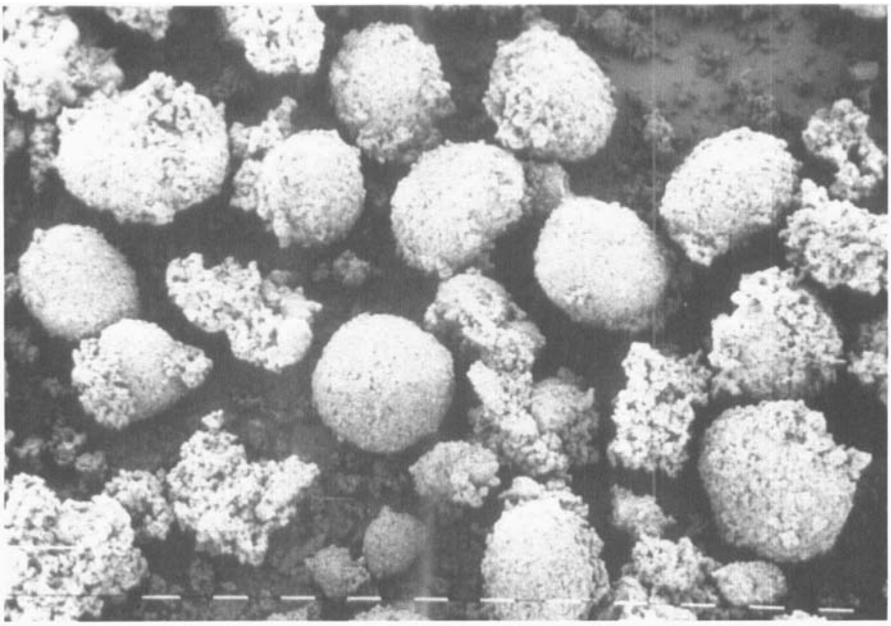

FIGURE 9
SEM photograph a granule (mixture Z_3).

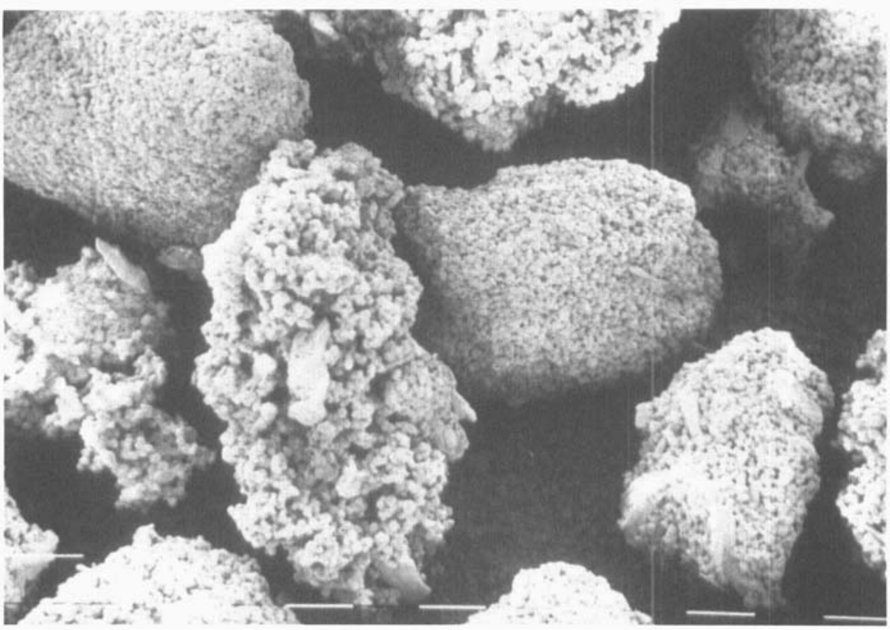

FIGURE 10
SEM photograph a granule (mixture Z_2).

TABLE 3

Levels of process variables.

Factor	Lower limit (-1)	Centre (0)	Upper limit (+1)
X_1 (impeller speed)	150 rpm	300 rpm	400 rpm
X_2(granulation time)	10 min	15 min	20 min

granulates can be obtained by employing mixtures whose compositions can be chosen within the following set of value limits: lactose 6-12%, Avicel 18-22%, corn starch 66-70%.

THE INFLUENCE OF PROCESS VARIABLES ON THE MIXTURES.

The experimental domain is reported in Table 3.

We can postulate that each experimental response Y_i can be represented, in the experimental domain concerned, by a quadratic equation of response surface:

$$Y_i(X_1,X_2) = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2$$

In order to have a forecast that is of the highest possible quality we have chosen an experimental matrix proposed by Doehlert (4). With two variables this experimental matrix consists of seven experiments organized as depicted in Fig 11.

The resulting strategy consists in combining two different types of experimental matrices: the Doehlert matrix and the mixture matrix (Scheffè reduced cubic model).

There are two equivalent strategy of representing the two experimental matrices:

a) within the space of the impeller speed (X_1) and granulation time (X_2), for each experiment given by a Doehlert experimental matrix, i.e., for a determined value of X_1 and X_2 one will establish seven formulations, in accordance with the mixtures given by the mixture experimental matrix (a total of 49 experiments) (Fig 12)

b) within the space of the mixtures (Z_1,Z_2,Z_3) for each experiment given by the mixture experimental matrix, i.e., for a granulation with a given formulation, one will vary the X_1 and X_2 process variables in accordance with the indications given by the Doehlert experimental matrix (a total of 49 experiments) (Fig 13).

From the analysis of the results, we can see that the geometrical mean diameter is influenced by the two process variables taken into consideration.

In order to show the influence of these variables, we considered the zone of experimental domain which gives a geometrical mean diameter higher than 150 µm. From Fig14 we can see that, working with high impeller speeds, the chosen zone comes out of the studied

No.	X_1	X_2
1	0	0
2	1	0
3	−1	0
4	0.5	0.866
5	−0.5	−0.866
6	0.5	−0.866
7	−0.5	0.866

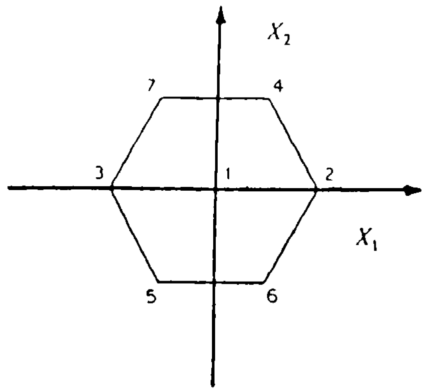

FIGURE 11
Distribution of the experimental points in the space of 2 variables for a Doehlert matrix.

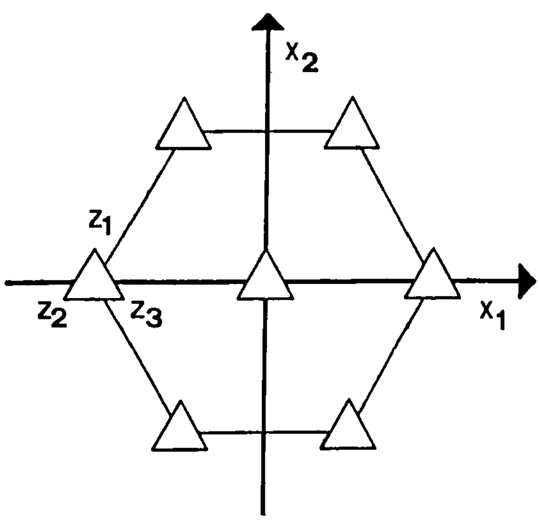

FIGURE 12
Set of the 49 experiments represented in the space of the X_1 and X_2.

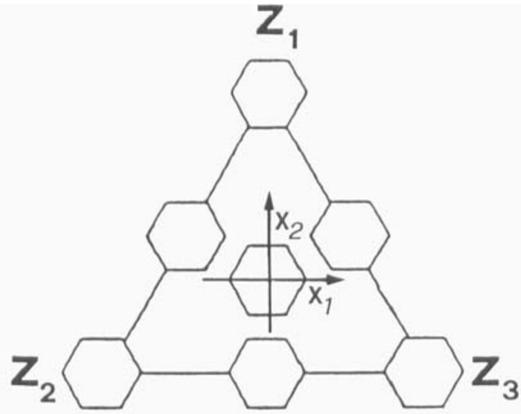

FIGURE 13
Set of the 49 experiments in the space of the Z_1,Z_2,Z_3.

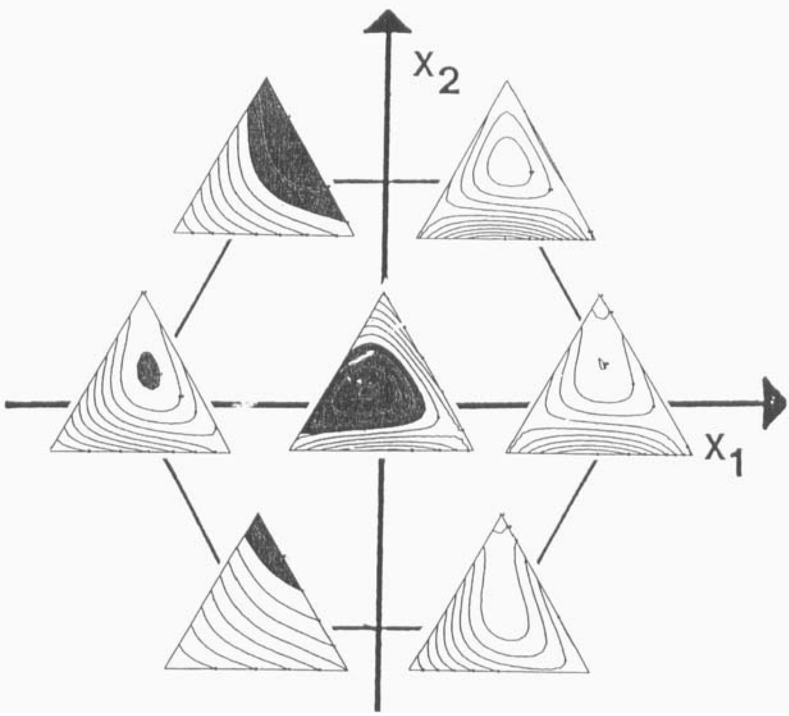

FIGURE 14
Contour plots of geometric mean diameter of the seven process variable combinations.

experimental domain, while at lower speeds the zone shifts, but still remains within the studied experimental domain.

CONCLUSIONS

The application of the experimental research methodology allowed us to select some mixtures which give better results at least concerning the considered variables. By describing with a mathematical model the granulation phenomena in a high speed granulator we obtain the contour graphs and so we can have an excellent mean to interpretate the results in order to take further decisions. Furthermore, we combined two different kinds of variables, on one side the mixtures and on the other side the process variables, obtaining a general model which comes from the product of the two models:

$$Y = (X_1,X_2,Z_1,Z_2,Z_3) = Y\ (X_1,X_2) \times Y\ (Z_1,Z_2,Z_3)$$

The design and evaluation of the process resulted in successful product development. The study lends itself to further investigation concerning the application of the proposed general model to process transfer.

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