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SIMULTANEAUS OPTIMIZATION OF SEVERAL RESPONSE VARIABLES IN A GRANULATION PROCESS

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ABSTRACT

Wet granulation of lactose and corn starch in a 10 litre high shear mixer was examined. The optimal combination of three indipendendent variables (moisture level,impeller speed and granulation time) on four properties of the granules was investigated by simultaneaus optimization method.

The optimun zone determined in 10 litre high shear mixer was analyzed for scaling-up study.The same product was manufacted at 50 L scale and optimum theoretical results were obtained for the four response variables and are comparable with the experimental results.

INTRODUCTION

A common problem in product development involves the selection of a set of conditions, the Xs, which will result in a product with a desirable combination of properties, the Ys, response variables.

This becomes a problem in the simultaneous optimization of the Ys, each of them depends upon a set of indipendent variables,$X_1,X_2,...,X_k$. One approach to this problem has been proposed by Hartmann and Beaumont(1), Nicholson and Pullen(2) who described optimization schemes based upon the linear programming model. Harrington(3) presented an optimization scheme utilizing what he termed the desirability function. Gatza and Mc.Millan(4) gave a slight modification of Harrington function.

We will employ the form of Derringer and Suich(5) and illustrate its use in a granulation process in a high-shear mixer. .In addition, we will also plot this desirability function against two independent variables with the third one held at its optimum level. Furthermore this function will be used to propose a method for scaling-up study in a high-shear mixer.

Each of the k response variables is related to the p independent variables by the relation:

$$Y_{ij}=f_i(X_1,X_2,...,X_p)+e_{ij} \qquad i=1,2,....,k$$

$$j=1,2,....,\eta_i$$

where f_i denotes the functional relationship between Y_i and $X_1,X_2,...,X_p$. We note that this function may differ for each Y_i and that f_i represents this relationship except for an error term, e_{ij}.If we make the usual assumpton that $E(e_{ij})=0$ for each i, then we can relate the average or expected responses η_i to the p independent variables by

$$\eta_i=f_i(X_1,X_2,...,X_p) \quad i=1,2,..,k.$$

In pratice, f_i is unknown.The usual procedure is to approximate f_i by a polynomial function.We then estimate η_i by Y_i, obtained through regression techniques. The desirability function involves transformation of each estimated response variable Y_i to a desirability value d_i,where $0<d_i<1$; the value of d_i increases as the "desirability" of the corresponding response increases.The individual desirabilities are then combined using the geometric mean.

$$D=(d_1 . d_2 .. d_k)^{1/k} \qquad \text{eq.1}$$

This single value of D gives the overall assessment of the desirability of the combined response levels.Clearly the range of D will fall into the interval(0-1) and D will increase as the balance of the properties becomes more favorable.D also has the property that if any $d_i=0$ (that is ,if one of the response variables is unacceptable) then D=0 (the overall product is unacceptable). It is for these reasons that the geometric mean, rather than some other function of the d_i such as the arithmetic mean, was used.

In transforming Y_i to d_i two cases arise: one-sided and two-sided desirability transformations.

One-sided transformations

For the one-sided case,d_i increases as Y_i increases and is employed when Y_i is to be maximized.Many transformations are possible and we shall consider the transformations given by:

$$d_i = \begin{cases} 0 & Y_i \leq Y_a \\ \left[\dfrac{Y_i - Y_a}{Y_b - Y_a}\right] & Y_a < Y_i < Y_b \\ 1 & Y_i \geq Y_b \end{cases}$$

and graphed in Figure 1.

The value Y_a gives the minimum acceptable value of Y_i.The user specifies this value of Y_a, knowing that any lower value of Y_i would result in an overall unacceptable product, since $Y_i<Y_a$ would make $d_i=0$, and thus D=0, which indicates an unacceptable product.

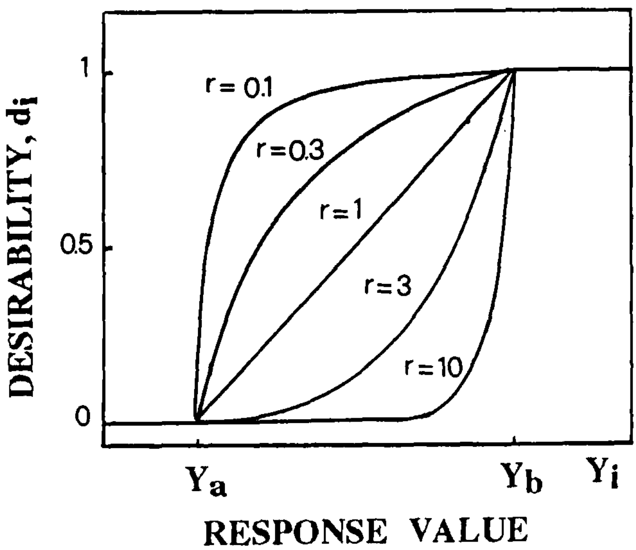

FIGURE 1

One-sided desirability functions

The value Y_b gives the highest value of Y_i. Since we are considering a one-sided transformation, there is no highest value of Y_i.However, from a practical viewpoint, one can think of Y_b as the value for Y_i such that higher values of Y_i have little additional merit.

The value of r used in the transformation would again be specified by the user.Figure 1 indicates that a large value of r would be specified if it were very desirable for the value of Y_i to increase rapidly above Y_a.In other words, even though Y_a is an acceptable value the desirability of the product would be greatly increased by having Y_i considerably greater than Y_a.

As can be seen, the desirability d_i then increases slowly as Y_i increases.Therefore, to maximize d_i and thereby D_i, Y_i must be greatly increased over Y_a.On the other hand, a small value of r would be specified if having values of Y_i considerably above Y_a were not of critical importance. A value of r=0.1, for example, would mean that any value of Y_i above Y_a was just about as desirable as any other value of Y_i above Y_a.

Two-sided trasformations

The two-sided transformation arises when the response variable Y_i has both a minimum and a maximum constraint. We shall consider the transformations given by:

$$d_i = \begin{cases} \left[\dfrac{Y_i - Y_a}{C_i - Y_a}\right]^s & Y_a \le Y_i \le C_i \\ \left[\dfrac{Y_i - Y_b}{C_i - Y_b}\right]^t & C_i < Y_i \le Y_b \\ 0 & Y_i < Y_a \quad or \quad Y_i > Y_b \end{cases}$$

In this situation Y_a is the minimum acceptable value of Y_i and Y_b is the maximum acceptable value.Values of Y_i outside these limits would make the entire product unacceptable. The value selected for c_i would be that value of Y_i which was most desirable and could be selected anywhere between Y_a and Y_b .The values of s and t in the two-side transformations play the same role as r does in the one-sided transformation.

In Figure 2 several different values of t and s are plotted.This figure also shows that large values for s and t would be selected if it were very desirable for the value of Y_i to be close c_i. In this case the desirability d_i would not get large until Y_i got close to c_i. On the other hand, if almost any value of Y_i above Y_a and below Y_b were acceptable, then small values of s and t would be chosen. Moderate values for s and t (near 1) would represent a compromise between the two extremes.One could also select a large value of s and a small value of t if it were desirable for Y_i to increase rapidly to c_i while almost any value of Y_i above c_i but below Y_b was also desirable.

The procedure outlined can be used to maximize some of the d_i (corresponding to certain Y_i) while in putting constraints on the other Y_i. similar to a linear .For

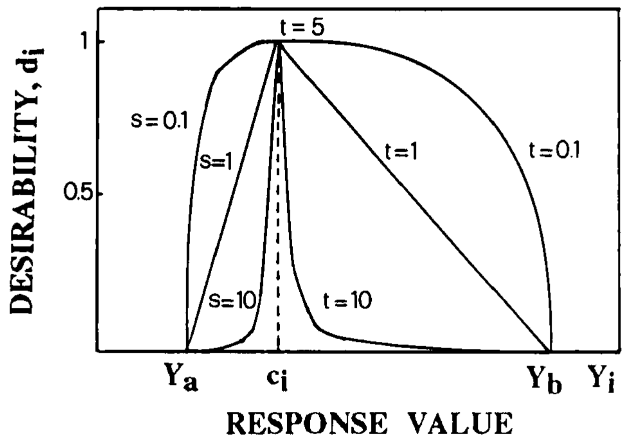

FIGURE 2

Two-sided desirability functions

those Y_i that are subject to constraints one uses extremely small values of the exponents (r,s, and t) and allows Y_a and Y_b to act as the boundary values.

Methods of optimization

We have assumed that Y_i is a continuous function of the X_h.From eq.2 and 3 we see that the d_i are a continuous function of Y_i and from eq.1 that D is a continuous function of the d_i.Therefore,it follows that D is a continuous function of the X_h. As a result, existing univariate search techniques can be used to maximize D over the independent variable domain.In essence,the desirability function condenses a multivariate optimization problem into a univariate one. An added benefit of the method is the ability to plot D as a function of one or more independent variables.

EXPERIMENTAL SECTION

Materials- Lactose(200 mesh,DMV,The Netherlands),corn starch(Gianni,Italy) and polyvinilpirrolidone K 25(Gaf,Italy) were used as starting materials.

Instrument- The Zanchetta Roto J and Roto P granulators are similar in design to many vertical high speed mixer granulators having a large impeller.

TABLE 1

Experimental design

N°	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	-1.68	0	0
10	+1.68	0	0
11	0	-1.68	0
12	0	+1.68	0
13	0	0	-1.68
14	0	0	+1.68
15	0	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	0	0	0
20	0	0	0

Granulate manufacture- A 2 kg and 10 kg batch of lactose (68.2%) and corn starch (31.8%) were granulated with an aqueous solution of povidone(2%).Impeller speed was set at 493 or 245 rpm respectively for Roto J and Roto P.The granulation time was 8 minutes.The drying of the granulated product was carried out in a hot-air oven at 60° C in 4 hours.

Physical measurements of granules- A set of sieves (315,500,800,1250 and 2000 µm) connected to a vibrating apparatus (Erweka AR 400) was used and the particle size distribution was characterized through the determination of the geometric mean diameter by weight ($D_{50\%}$,µm) and the geometric standard deviation (r_g).

The percentage in weight (w/w) of granules which are smaller than 1250 μm is also calculated.Flow rate (g/sec) was carried out by determining the time required to discharge 100 g of granules through a 0.8 cm orifice of a glass funnel.

Choise of experimental design- A three-variables, rototable, central composite design with six center points (Table 1) was employed to generate the data which were then fitted to the second degree polynom (eq.3).

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 \quad \text{(eq.3)}$$

A central composite response surface design was employed because of favorable post experience with such design (6).

RESULTS AND DISCUSSION

The optimal combination of three independent variables moisture level(X_1), impeller speed(X_2), granulation time(X_3), was sought.

The properties to be optimized and constraint levels were:

geometric mean diameter by weight,	$Y_1 > 200$ µm
percentage of particles smaller than 1250 µm	$Y_2 > 80\%$
geometric standard deviation,	Y_3-without constraint
flow rate (g/sec),	Y_4-without constraint

For Y_1 and Y_4 the one-sided transformation, given by eq.2, were used and are shown in Figs 3 and 4. As can be seen, we set Y_a=200, Y_b=300 µm and r=0.1 in the transformation given by (eq.2) for Y_1 and Ya=80%, Yb=92% and r=10 for Y_2. While Y_3 and Y_4 were used without constraint and are shown in Figure 5.

The next step was to use the coefficients given in Table 2 along with various values of X_1,X_2 and X_3 to obtain lhe Y_i.Each Y_i was then transformed into a d_i

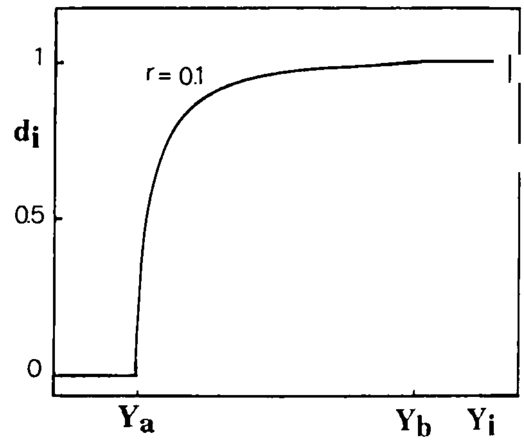

FIGURE 3

Graph of transformation used for Y_1

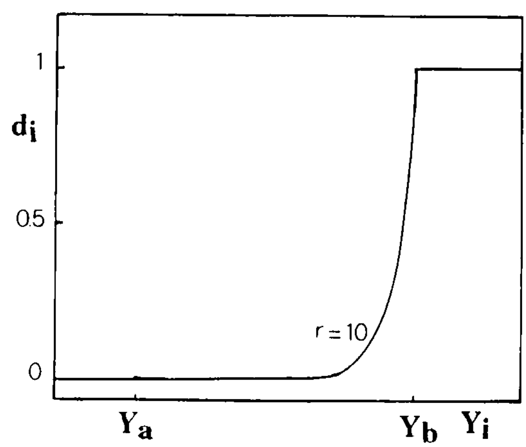

FIGURE 4

Graph of transformation used for Y_2

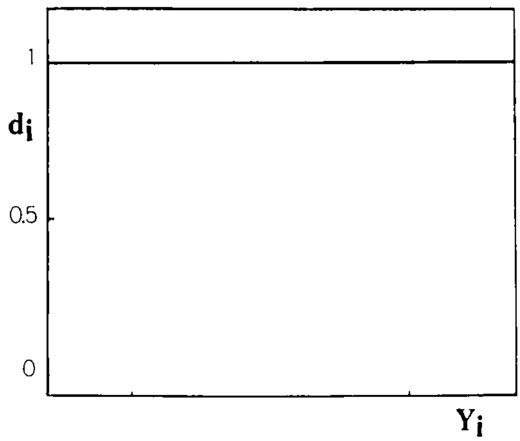

FIGURE 5

Graph of transformation used for Y_3 and Y_4

TABLE 2

Estimated model parameters

	Y_1	Y_2	Y_3	Y_4
b_0	293.48	53.09	7.83	83.45
b_1	53.72	-1.63	-0.89	0.99
b_2	-49.76	-6.08	-0.14	7.68
b_3	8.18	-0.83	-0.14	1.64
b_{11}	20.03	-1.13	-0.13	-0.50
b_{22}	59.99	4.82	0.18	-2.48
b_{33}	12.61	-0.97	0.31	-0.99
b_{12}	21.87	1.47	0.36	-2.74
b_{13}	40.87	0.45	-0.05	-1.23
b_{23}	18.37	0.70	-0.10	-0.59

TABLE 3

Optimum conditions and predicted properties

Position of the optimal point	
X_1= -1.309 (moisture level, 17.19% w/w)	
X_2= 0.943 (impeller speed, 493 rpm)	
X_3= 0.463 (granulation time, 8 min)	
predicted properties	desirability (d)
Y_1=227	d_1=0.904
Y_2=90.74	d_2=0.360
Y_3=1.67	d_3=1
Y_4=8.33	d_4=1
Maximum composite desirability, D=0.799	

using (eq.2) as illustrated in figures 3 and 4. The four d_i were combined into a single D using eq.1.Hence,for each level of X_1,X_2, and X_3, a D value was obtained.

We then searched through the levels of X_1, X_2, and X_3 to find the optimun value for D. This process was carried out with the program for computer, NEMROD (7).The algorithm employed converged in 3699 iterations.

The resulting optimum formulation is shown in Table 3. The maximum composite desirability was 0.799 and all of the constraints have clearly been met. The value of 0.799 has little phisical meaning, except that indicates the level of the X where the maximum D occurs.

Figures 6, 7 and 8 show the contour plots of D for two independent variables with the third one held at its optimum.All these plots present a very sharp surface in the maximum region, so that even a small shift from optimum of the X values would yield a significant decrease of desirability.(Figs. 9, 10, 11)

The feasibility of scaling-up to 50L high shear mixer was analyzed utilizing the following equation:

$$Vp = Vr\ P\ \Pi / 60 \quad \text{eq.4}$$

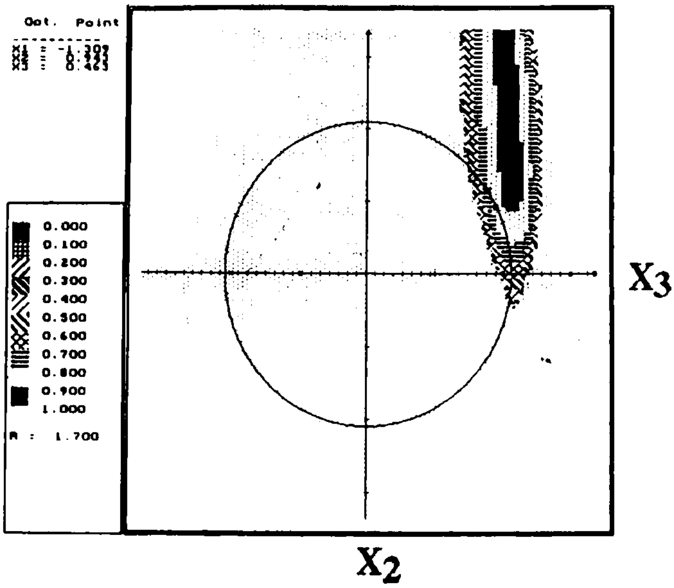

FIGURE 6

Contour plots of D for X_2 and X_3

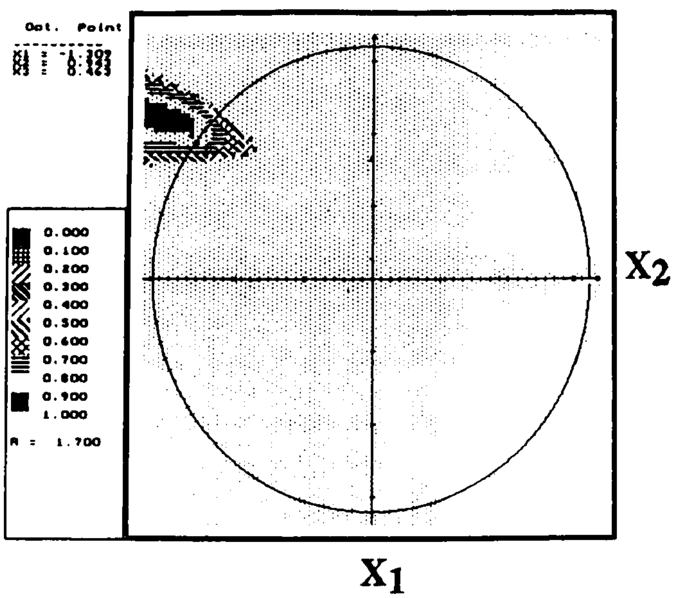

FIGURE 7

Contour plots of D for X_1 and X_2

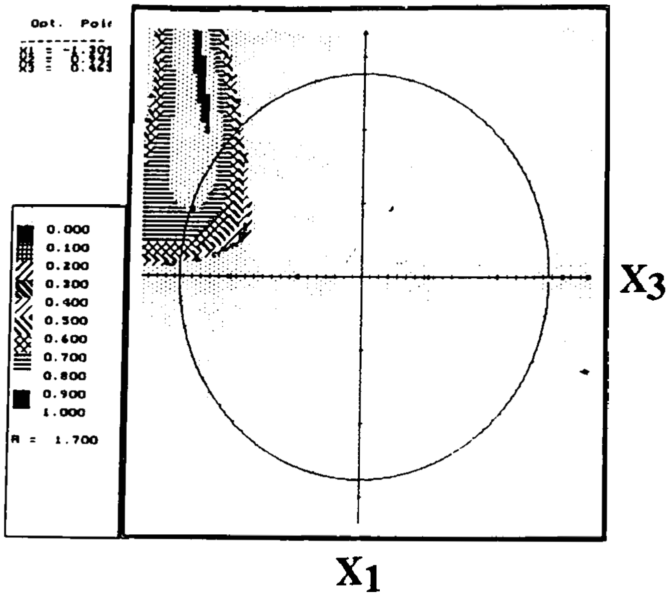

FIGURE 8

Contour plots of D for X_1 and X_3

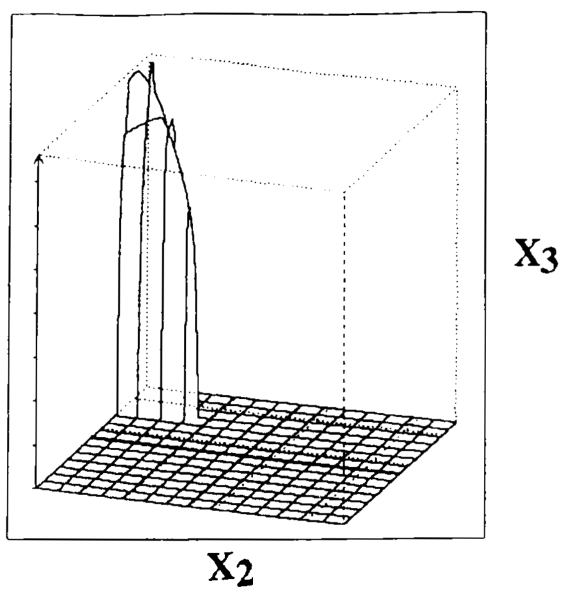

FIGURE 9

Optimun zone for X_2 and X_3; and X_1 = -1.309

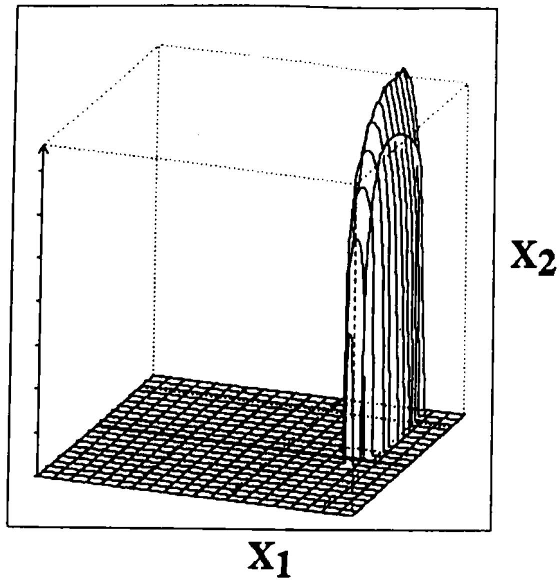

FIGURE 10

Optimun zone for X_1 and X_2; and $X_3 = 0.463$

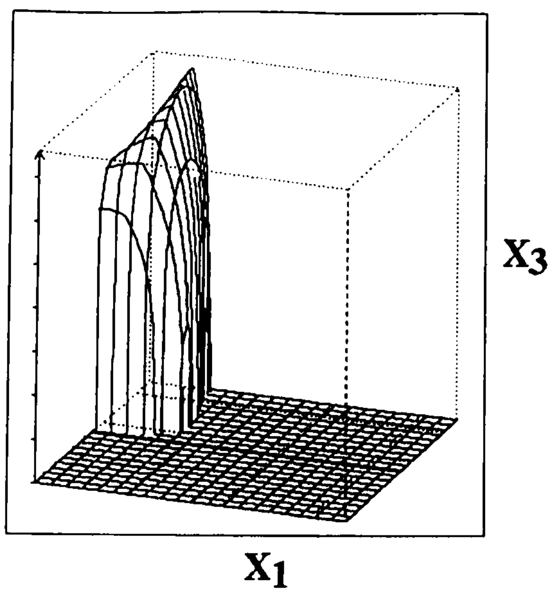

FIGURE 11

Optimun zone for X_1 and X_3; and $X_2 = 0.943$

TABLE 4

Results for "Optimal scaling - up" conditions

Responses	Experimental results 10L batch	50L batch	Theory
Geometric mean diameter by weigh(µm)	246	258	227
Geometric standard deviation	3.0	2.5	1.67
percentage of particles smaller that 1250 µm (%)	86	87	90.74
Flow rate (g/s)	7.60	10.52	8.33

where Vp = periferic rate (m/ sec)

Vr = impeller rotation speed (rpm)

P = diameter of the mixer (m)

The results for both batches of different capacity are given in Table 4 where they are compared with the theoretical responses, calculated from equation 3 and from the estimates of the coefficients in Table 2.

The optimum, determined at 10L, proved suitable for scaled up manifacture at 50L.

Data analysis shows a higher value of geometric standard deviation for 10L than 50L batch, as a consequence different flow rates have been obtained due to the different shape of the granules produced (Fig. 12). The mixers used are not

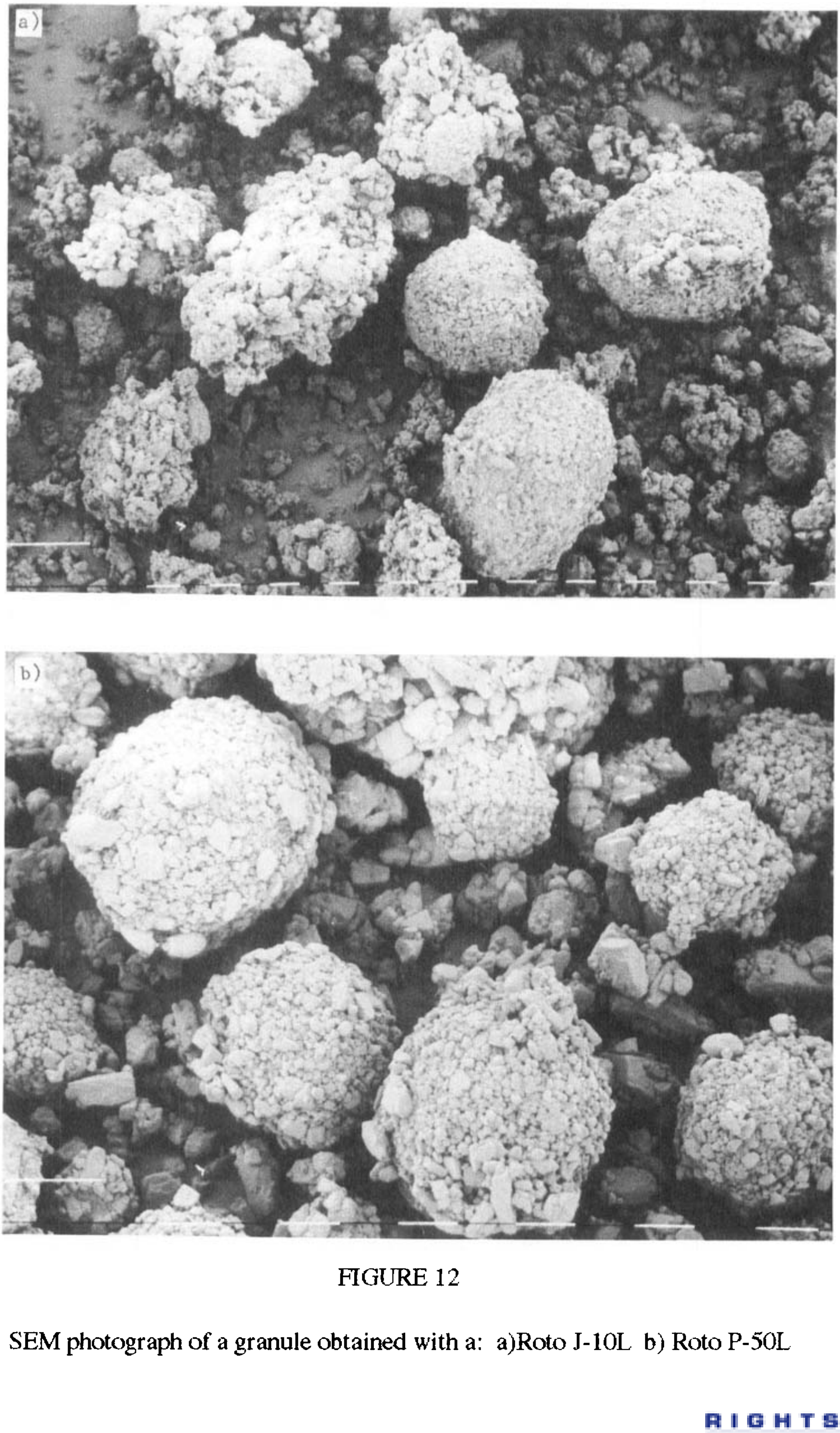

FIGURE 12

SEM photograph of a granule obtained with a: a)Roto J-10L b) Roto P-50L

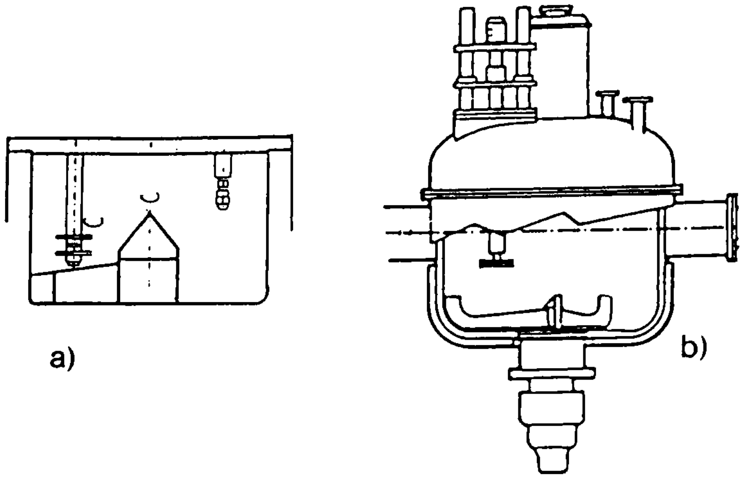

FIGURE 13

Vertical high speed mixer: a) Roto J-10L b) Roto P-50L

geometrically similar and have different internal structure causing (Fig. 13) differences between the granules.

CONCLUSIONS

Simultaneans optimization of several response variables may be used in the pharmaceutical process of granulation to plan the experimental design and to find optimal zone of the physical properties of the granulate. The method is also recommended for scaling-up study in a high shear mixer.

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