DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(9), 961-972 (1992)

WET GRANULATION IN A SMALL SCALE HIGH SHEAR MIXER

D. Vojnovic, P. Selenati, F. Rubessa, M. Moneghini
Department of Pharmaceutical Sciences
University of Trieste, 34127 Trieste, Italy

and

A. Zanchetta
Zanchetta s.r.l, 55010 Lunata, Lucca, Italy

ABSTRACT

Wet granulation of lactose and corn starch in a 10 litre high shear mixer was examined. The effect of the amount of water added, granulation time and impeller speed on five properties of the granules was investigated by a response surface design.

It was shown that moisture level as a major effect on geometric mean diameter and flow rate of the granules. The impeller speed markedly influences the geometric mean diameter, geometric standard deviation, compactability index and percentage of granules smaller than 1250 μm. Finally the granulation time has an evident influence on compactability index.

Theoretical optimum conditions were obtained for the five response variables and are comparable with the experimental results.

INTRODUCTION

Wet granulation is a technological process of size enlargement used in the pharmaceutical industry to prepare powdered materials for capsules and tablets. Despite the extensive use of this technique there is a lack of systematic research concerning the relationship between process variables and granule properties on small scale high shear mixers.

A 10 litre high shear mixer was utilized for the evaluation of pregelatinized and pregelatinized-crosslinked corn starches as binding agents in presence of lactose in the wet granulation process (1). T. Schaefer et al. (2) examined the applicability of a 10 litre Baker Perkins[R] high shear mixer for melt granulation of dicalcium phosphate and lactose in presence of 15-20% w/w polyethylene glycol (PEG) 3000 and 6000. It was found that pellets of a narrow size distribution can be produced. Flanders et al. (3) prepared sustained release potassium chloride tablets using a melt granulation in the same instrument.

The purpose of the present investigation is to examine the wet granulation of lactose and starch with an aqueous solution of povidone in the Zanchetta Roto[R] J 10 litre high shear mixer. The effect of process variables on the characteristics of the granules was studied by a surface response design.

MATERIALS AND METHODS

Materials

Lactose (200 mesh, DMV,The Netherlands), corn starch (Gianni, Italy) and polyvinylpirrolidone K25 (Gaf, Italy) were used as starting materials. These products were in accordance with U.S.P. and/or the Italian Pharmacopoeia specifications.

The characteristics of the powders are listed in Table 1.

Instrument

The Zanchetta Roto J granulator is similar in design to many vertical high speed mixer granulators having a large impeller at the base of the bowl and a side mounted chopper. Both blades have variable speed controls and current monitor. It is also equipped with a cooling jacket.

Granulate manufacture

A 2 kg batch of lactose (68.2%) and corn starch (31.8%) is mixed using the impeller at 400 rpm in 10 min. The powder was granulated with 400 ml of an aqueous solution of povidone (10%). The binder solution was added by spraying

TABLE 1
Powder characteristics

Characteristics	Lactose	Starch	Povidone
geometric mean diameter by weight µm	39	15	88
geometric standard deviation	1.86	1.30	1.7
loss on drying, %	1.0	10.3	3.8
bulk density, g/cm^3	0.624	0.546	0.430
tap density, g/cm^3	0.743	0.667	0.510

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. The impeller speed was set in the interval 165-585 rpm. The final granulation time was 12.4 min and 0.1 kg samples were taken out after 0.6, 3, 6, 6.5, 10 and 12.4 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 SEM picture (Figure 1) shows the typical granule shape of the sieve fraction 315-500 µm.

A set of sieves (315, 500, 800, 1250 and 2000 µm) connected to a vibrating apparatus (Erweka AR400) 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 (ρ_g). The percentage in weight (w/w) of granules which are smaller than 1250 µm is also calculated.

Bulk density (d_{10}), tap density (d_{2000}) were determined with a volume presser (Giuliani IG/4) that dropped 10 and 2000 times, respectively.

The compactability index, $C.I. = \frac{d_{2000} - d_{10}}{d_{2000}} \times 100$ was derived.

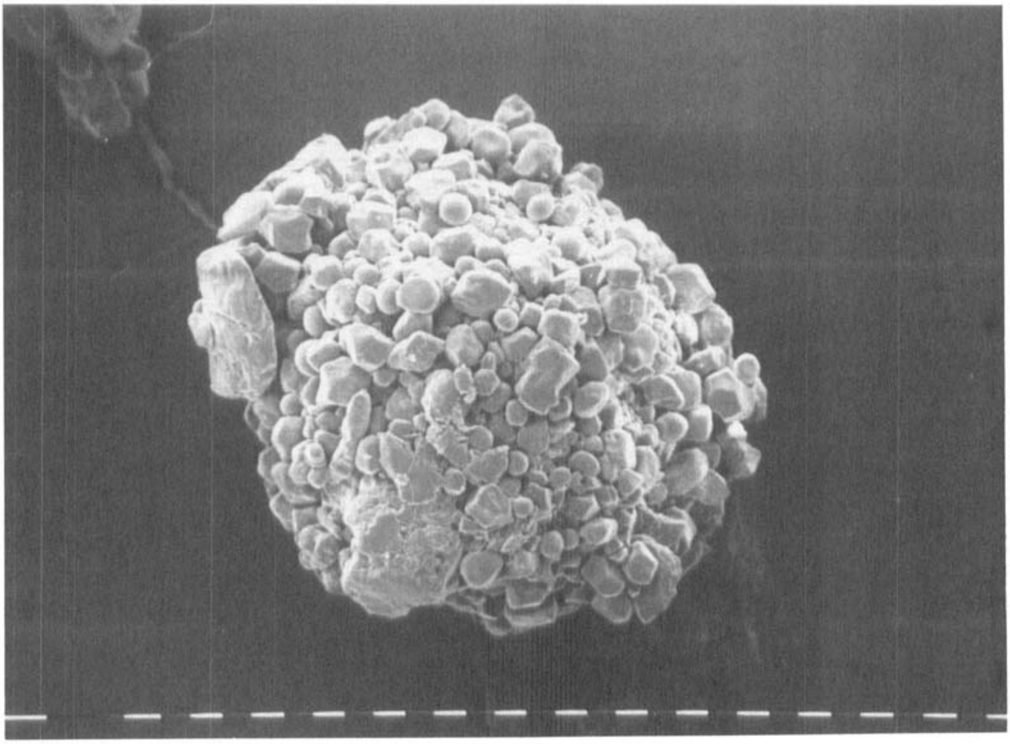

FIGURE 1

SEM photograph of a granule of the sieve fraction 315-500 μm.

Repose angle was measured by a glass funnel with a 0.8 cm stem lumen set at a distance of 7.5 cm from the plate. The tangent of the angle of repose is the ratio between the height and the radius of the powdered cone.

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.

EXPERIMENTAL DESIGN

The method of response surface analysis was chosen in order to optimise the experimental design . A response surface is an area of space defined within the upper and lower limits of the independent variables and is a function of the relationship of these variables to the measured response (dependent variable). The

TABLE 2
Matrix of "central composite 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

aim of response studies is to obtain a regressional model that provides a means of mathematically evaluating changes in the response due to changes in the independent variables. The process is optimized when the minimum or the maximum of the surface is observed (4).

Twenty granulations have been carried out and three process variables were studied:

X_1 = moisture level

X_2 = impeller speed

X_3 = granulation time

TABLE 3
Levels of process variables

Process variable	Normalized level	Experimental value
X_1, moisture level	-1.68	16.8
% w/w	-1	17.5
	0	18.5
	+1	19.5
	+1.68	20.2
X_2, impeller speed	-1.68	165
rpm	-1	250
	0	375
	+1	500
	+1.68	585
X_3, granulation time	-1.68	0.6
min	-1	3
	0	6.5
	+1	10
	+1.68	12.4

The main effects of these variables (X_1, X_2 and X_3) were to be estimated with second order effects (X_1^2, X_2^2, X_3^2) and the effects of interactions (X_{12}, X_{13} and X_{23}).

The following mathematical model was postulated:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3.$$

The experimental design selected is reported in Table 2 and represents a "central composite design" matrix (4,5).

TABLE 4
Estimated model parameters

	Y_1	Y_2	Y_3	Y_4	Y_5
b_0	293.48	53.09	14.22	7.83	83.45
b_1	<u>53.72</u>	-1.63	-0.87	<u>-0.89</u>	0.99
b_2	<u>-49.76</u>	<u>-6.08</u>	<u>-1.14</u>	-0.14	<u>7.68</u>
b_3	8.18	-0.83	<u>-1.06</u>	-0.14	1.64
b_{11}	20.03	-1.13	-0.73	-0.13	-0.50
b_{22}	<u>59.99</u>	<u>4.82</u>	<u>1.09</u>	0.18	-2.48
b_{33}	12.61	-0.97	-0.15	<u>0.31</u>	-0.99
b_{12}	21.87	1.47	0.12	<u>0.36</u>	<u>-2.74</u>
b_{13}	<u>40.87</u>	0.45	0.12	-0.05	-1.23
b_{23}	18.37	0.70	-0.25	-0.10	-0.59

The coefficients of the model having great influence for each response are underlined. The coefficients are calculated using normalized values of the process variables X_i = -1.68, -1, 0, +1, +1.68.

Experimental values for the five levels of each variables were chosen according to preliminary studies and are given in Table 3.

The physical properties of the granulates prepared are tabulated and the data analysed according to the proposed model by multiple linear regression analysis. 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 β_i of the factors X_i. Similarly b_{ii} represent β_{ii} and b_{ij} the estimation of the interactions β_{ij} between X_i and X_j.

Five response variables were chosen:

Y_1 = geometric mean diameter by weight, µm

Y_2 = geometric standard deviation

Y_3 = compactability index (C.I.)

Y_4 = flow rate (g/sec)

Y_5 = percentage of particles smaller than 1250 µm

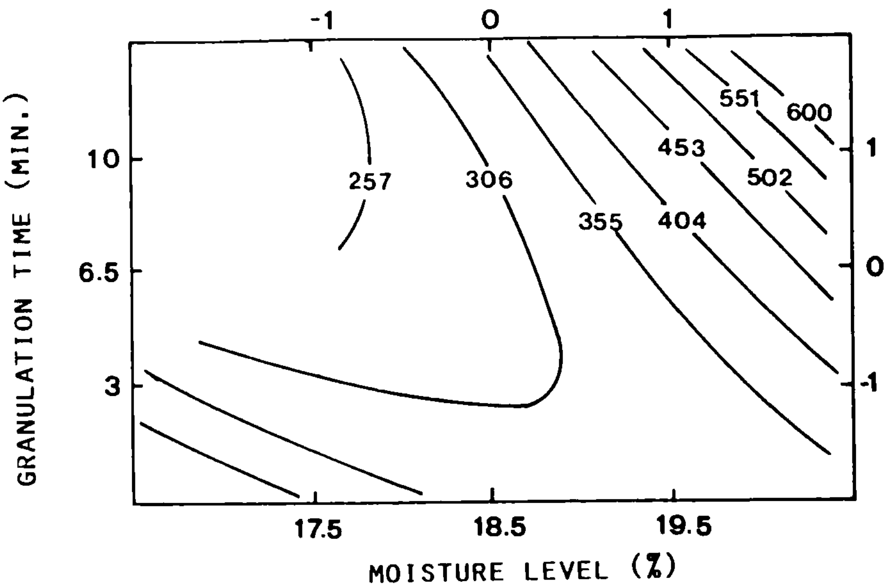

FIGURE 2
Geometric mean diameter (Y_1) as function of moisture level and granulation time. X_2 (impeller speed) = 375 rpm, level 0.

RESULTS AND DISCUSSION

The responses Y_1 to Y_5 were analysed by regression analysis according to the proposed model. The results are given in Table 4.

It can be shown that the moisture level (X_1) has a major effect on the response Y_1 and Y_4, the impeller speed (X_2) influences the responses Y_1, Y_2, Y_3 and Y_5. Furthermore the granulation time (X_3) has an evident effect on Y_3. Some second order effects and interactions are also important.

A number of methods are available for determining optimum conditions for granulation process: direct method such as simplex (6) and non-direct method including centered composite design, factorial design (8) and surface response analysis, canonical analysis (7,9). In our case response surfaces were drawn over the experimental factor space using the program NEMROD (10). Examples are given in Figures 2 to 6.

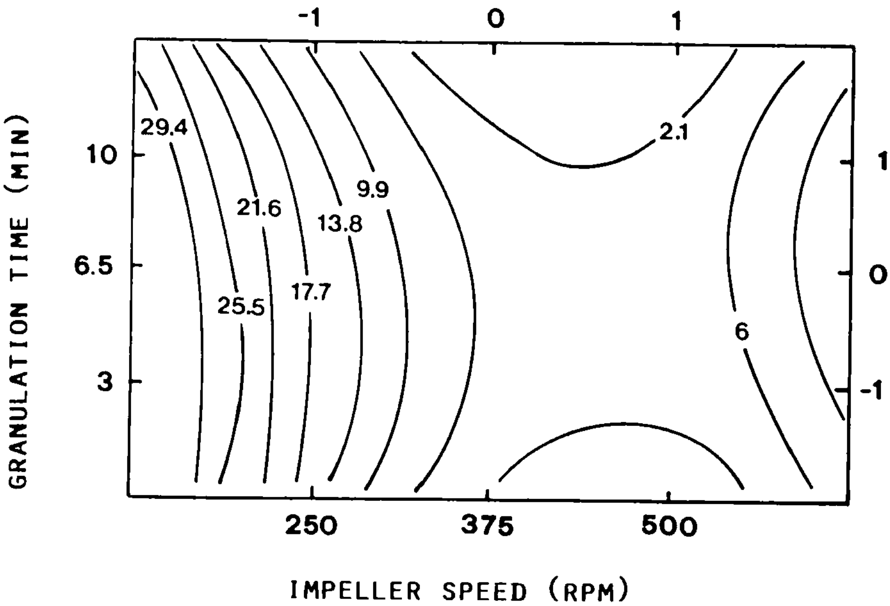

FIGURE 3
Geometric standard deviation (Y_2) as function of impeller speed and granulation time. X_1 (moisture level) = 18.5%, level 0.

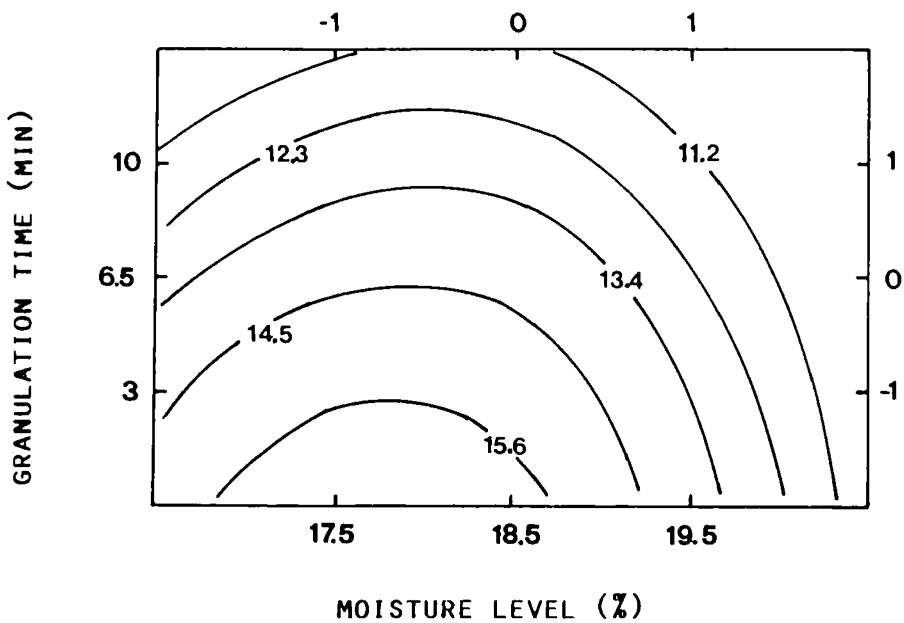

FIGURE 4
Compactability index (Y_3) as function of moisture level and granulation time. X_2(impeller speed) = 375 rpm, level 0.

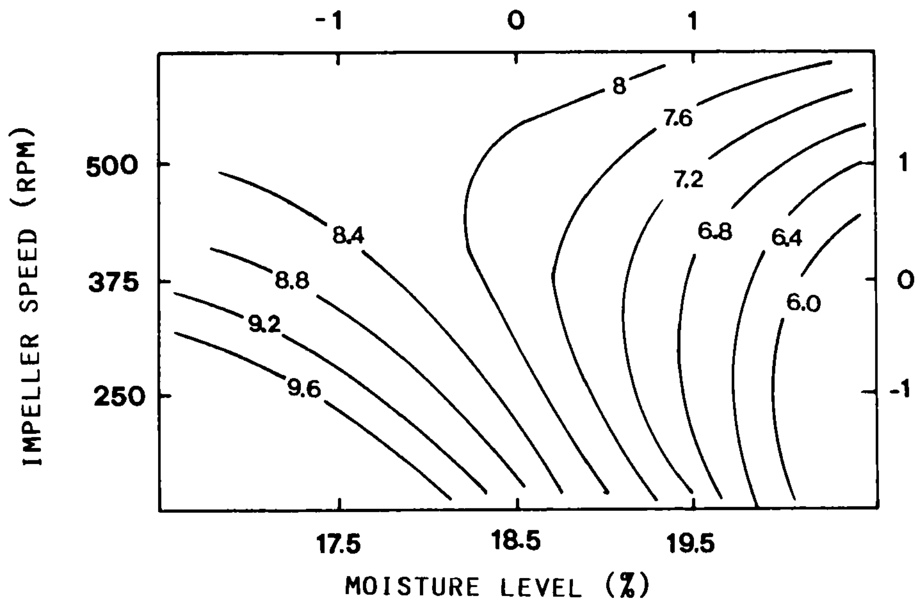

FIGURE 5
Flow rate (Y_4) as function of moisture level and impeller speed. X_3 (granulation time) = 6.5 min, level 0.

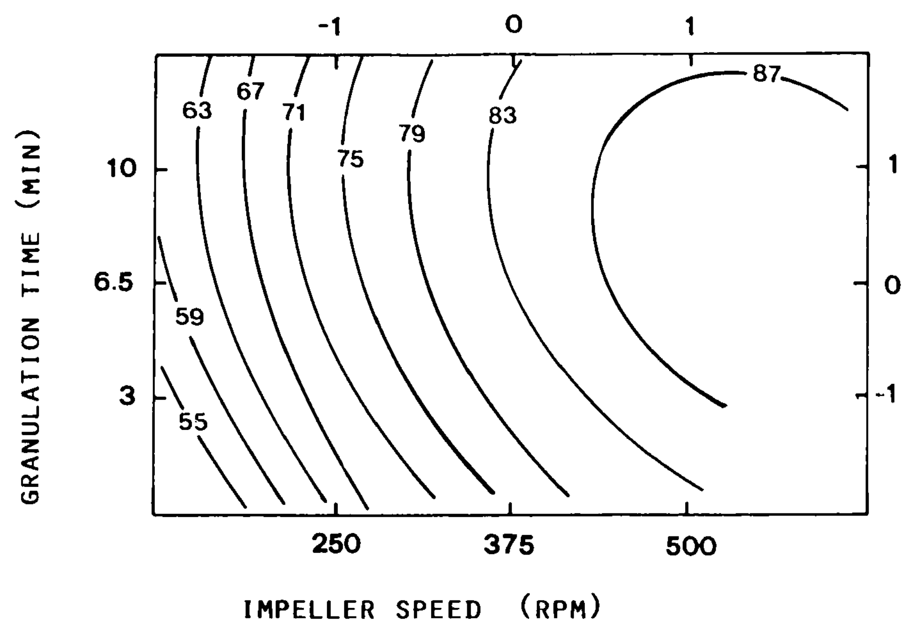

FIGURE 6
Percentage of particles smaller than 1250 µm (Y_5) as function of impeller speed and granulation time. X_1 (moisture level) =18.5% , level 0.

TABLE 5
Optimum conditions and experimental results

Response variable	optimum conditions	theoretical	experimental
		results	
geometric mean diameter by weight (μm)	$X_1 = 17.45$	230	229.5
	$X_2 = 426.5$		
	$X_3 = 8.01$		
geometric standard deviation	$X_1 = 18.4$	9.75	9.23
	$X_2 = 313.5$		
	$X_3 = 6.32$		
compactability index	$X_1 = 20.00$	10.52	10.34
	$X_2 = 407.7$		
	$X_3 = 8.44$		
flow rate (g/sec)	$X_1 = 17.92$	8.40	8.42
	$X_2 = 336.7$		
	$X_3 = 6.16$		
percentage of particles smaller than 1250 μm	$X_1 = 16.91$	95.18	92.06
	$X_2 = 588$		
	$X_3 = 8.87$		

Optimum zones are obtained for different responses by analizing the graphs and the results are listed in Table 5.

Five granulates were prepared using the theoretical optimum conditions. The experimental results are comparable with the theoretical responses, calculated from equation 1, and with the estimates of the coefficients in Table 4.

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

Centered composite design may be used in the pharmaceutical process of granulation to plan the experimental design and to find the main effects and interactions of the process variables on the physical properties of the granulate. The method is also recommended to optimize the process variable in a laboratory scale high shear mixer.

REFERENCES

1. N. Visavarungroj and J.P. Remon, Int. J. Pharm., 65, 43-48 (1990)
2. T. Schaefer, P. Holm and H.G. Kristensen, Drug Dev. Ind. Pharm., 16, 1249-1277 (1990)
3. P. Flanders, G.A. Dyer and D. Jordan, Drug Dev. Ind. Pharm, 13, 1001-1022 (1987)
4. G.E.P. Box, W.G. Hunter and J.S. Hunter , "Statistics for Experimenters", Wiley, New York, 1978; G.E.P. Box and N.R. Draper, "Empirical Model-Building and Response Surfaces", Wiley, New York ,1987.
5. D. Feneuille, D. Mathieu and R. Phan-Tan-Luu, "Methodologie de la Recherche Experimentale- Etude des surfaces de reponse", L.P.R.A.I.-Universite' d'Aix- Marseille, 1983
6. M. Chariot and J. Ser, Labo-Pharma-Probl. Tech., 31, 456-460 (1983)
7. M. Chariot, G.A. Lewis, D. Mathieu , R. Phan-Tan-Luu and H.N.E. Stevens, Drug Dev. Ind. Pharm., 14, 2535-2556 (1988)
8. A. Pena Romero, F. Nevoux, M. Poncet and J.C. Jinot, S.T.P. Pharma, 5, 88-95 (1989)
9. N-O. Lindberg, C. Jonsson and B. Holmquist, Drug Dev. Ind. Pharm., 11, 917-930 (1985)
10. D. Mathieu and R. Phan-Tan-Luu, Program NEMROD, L.P.R.A.I., Universitè d'Aix, Marseille, 1986