ELSEVIER

International Journal of Pharmaceutics 145 (1996) 203–213

international journal of pharmaceutics

Doehlert experimental design applied to optimization and quality control of a granulation process in a high shear mixer

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Received 2 August 1996; accepted 4 October 1996

Abstract

A quality control study on a placebo granulation prepared in a 10 l high shear mixer was carried out using a Doehlert design with the introduction of a noise factor (impeller speed). The response surface methodology was used to find the operating conditions leading to a product whose characteristics are not only included in the target range, but also non-sensitive to impeller speed variations. Based on the fact that the impeller speed is an important noise factor in the scale-up process, the above-mentioned operating conditions were chosen for preparation of the granules in 50 l high shear mixer. The tested operating conditions proved suitable for scaling-up from 10 to 50 l. Copyright © 1996 Elsevier Science B.V.

Keywords: Doehlert design; Granulation; High shear mixer; Quality control; Scale-up

1. Introduction

A common problem in the development and manufacture of a product is to find optimal settings of the process variables leading not only to the desired combination of product properties, but also to the minimization of product variability. An approach that proved to be very efficient in process control and quality improvement is the Taguchi's method (Phadke, 1989; Stone and Veevers, 1994). According to Taguchi, the quality of a product is measured in terms of the total loss to society due to variability about the expected functions and to harmful side effects. A high-quality product is one for which the total loss approaches zero. The key idea behind this methodology is to improve the quality of a product by minimizing the effect of the causes of variation without eliminating the causes. This can be achieved by optimizing the operating conditions, so as to obtain a product whose characteristics are minimally sensitive to the causes of

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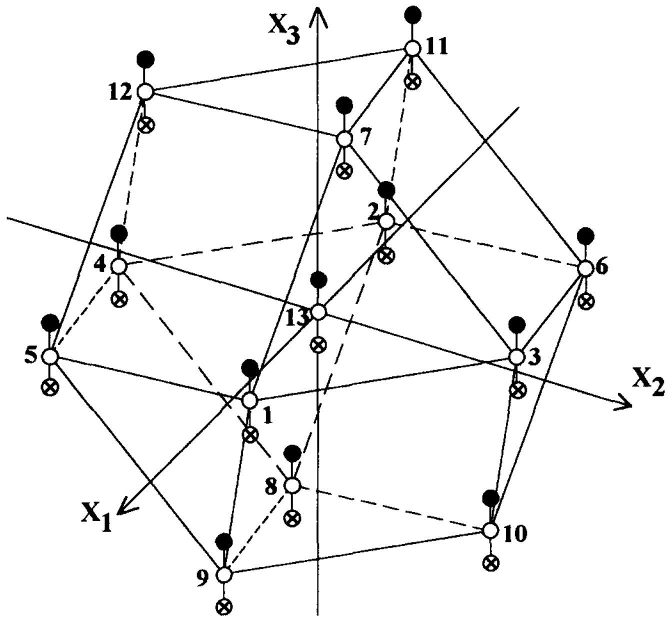
PII S0378-5173(96)04771-0



			noise factor		
Exp.	X_1	X_2	X_3 ○	X_3 ●	X_3 ⊗
1	0.943	0.236	0.236	1.179	-0.707
2	-0.943	-0.236	-0.236	0.707	-1.179
3	0.236	0.943	0.236	1.179	-0.707
4	-0.236	-0.943	-0.236	0.707	-1.179
5	0.707	-0.707	0.000	0.943	-0.943
6	-0.707	0.707	0.000	0.943	-0.943
7	0.236	0.236	0.943	1.886	0.000
8	-0.236	-0.236	-0.943	0.000	-1.886
9	0.707	0.000	-0.707	0.236	-1.650
10	0.000	0.707	-0.707	0.236	-1.650
11	-0.707	0.000	0.707	1.650	-0.236
12	0.000	-0.707	0.707	1.650	-0.236
13	0.000	0.000	0.000	0.943	-0.943

Fig. 1. Doehlert matrix-design including a noise factor (●, ⊗) and distribution of the experimental points in the space of three variables. The process variables (X_i) are expressed in terms of normalized values.

variation. The Taguchi's approach has a wide applicability, ranging from research to industrial production. Although it has been mostly used in engineering fields, this approach has also been applied in pharmaceutical technology with regard to tablet formulation (Diemunsch et al., 1993) and optimization of theophylline beads production in a high-speed granulator (Wehrlé et al., 1994).

In this work the effects of three process variables on some characteristics of a placebo granulation have been investigated. The aim was to find one or more optimal combinations of process variables that would lead, according to Taguchi's idea, not only to the required granules characteristics, but also to a stable product, whose properties are not sensitive to noise factors (causes of variation). The impeller speed was taken as the only noise factor, since this variable has the most important effect on the two studied responses, i.e. geometric mean diameter and percentage of particles smaller than 200 mm (Schaefer et al., 1990; Vojnovic et al., 1992). The Doehlert design was used for the planning of the experimental points, and unlike in the Taguchi's approach, a polynomial equation describing the responses as functions of process variables was achieved. The response surface methodology made it possible to outline a restricted zone of the experimental field, where the product characteristics were simultaneously optimized and the product quality was not altered by impeller speed variations.

Table 1
Process (independent) variables (X_i) with their levels, and measured responses (Y_i) for Doehlert design

Independent variables	Normalized level	Experimental value
X_1 Moisture level (%)	1	40.0
	0	30.0
	−1	20.0
X_2 Massing time (min)	1	7.0
	0	5.0
	−1	3.0
X_3 Impeller speed (rpm)	1	400
	0	300
	−1	200

Measured responses
Y_1 = Geometric mean diameter
Y_2 = Percentage in weight (w/w) of granules smaller than 200 μm

In previous studies (Vojnovic et al., 1993a; Ogawa et al., 1994) the impeller speed was found to be an important noise factor in the scaling-up of granulation processes. Therefore, the same operating conditions that gave rise to a product whose characteristics were not sensitive to impeller speed variations were used to investigate the feasibility of scaling-up.

2. Experimental design

A rotated Doehlert matrix (Doehlert, 1970) was used for the optimization of process variables and for quality control of granulation characteristics. This design is suitable for construction of a second order polynomial equation and for exploration of quadratic response surfaces. It also has particular characteristics, such as possibility of translation and rotation, so that each variable can take different number of distinct levels. These properties have already been described (Mathieu and Phan-Tan-Luu, 1992) and successfully exploited in preformulation studies of a granulation (Lewis and Chariot, 1992) and in wet pelletization of paracetamol (Vojnovic et al., 1993b) and theophylline (Vojnovic et al., 1995a) in a high shear mixer.

The design is composed of 13 uniformly distributed points in the experimental domain (Fig. 1). A quadratic polynomial model Eq. (1) was constructed for the description of the measured responses as functions of the process variables (Table 1).

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 \quad (1)$$

In order to find the optimal operating conditions leading to stable and non-sensitive granule characteristics, the impeller speed (X_3) was taken as noise factor. The rotated Doehlert experimental matrix and its three-dimensional representation together with the noise factor are shown in Fig. 1.

Table 2
Experimental plans and observed response values

Exp.	Process variables					Responses					
	X_1 (%)	X_2 (min)	X_3 (rpm)			Y_1 (μm)			Y_2 (%)		
			○	●	⊗	○	●	⊗	○	●	⊗
1	40.0	5.5	325	425	225	740	861	750	0.30	0.21	0.47
2	20.0	4.5	275	375	175	327	347	320	23.70	24.94	43.82
3	32.5	7.0	325	425	225	587	705	525	0.89	0.49	3.68
4	27.5	3.0	275	375	175	440	381	356	16.67	18.93	34.60
5	37.5	3.5	300	400	200	562	697	553	2.43	0.84	6.18
6	22.5	6.5	300	400	200	384	432	378	13.53	6.42	25.00
7	32.5	5.5	400	500	300	611	726	541	0.59	0.37	2.63
8	27.5	4.5	200	300	100	353	446	356	24.65	10.31	37.65
9	37.5	5.0	225	325	125	577	697	487	3.10	0.61	12.56
10	30.0	6.5	225	325	125	436	524	392	8.83	2.14	27.17
11	22.5	5.0	375	475	275	360	388	357	13.87	10.06	27.58
12	30.0	3.5	375	475	275	492	484	429	5.03	4.42	19.27
13	30.0	5.0	300	400	200	427	521	441	8.48	2.37	14.24
13a	30.0	5.0	300	400	200	414	510	445	10.46	2.43	14.65
13b	30.0	5.0	300	400	200	448	495	437	10.33	2.26	16.23
13c	30.0	5.0	300	400	200	454	543	453	9.18	1.91	13.87
13d	30.0	5.0	300	400	200	421	514	433	9.84	2.81	14.04

Points 13a, b, c and d are replicate of point 13.

3. Materials and methods

3.1. Materials

Lactose (Pharmatose, 200 mesh, Prodotti Gianni-Italy) and corn starch (Prodotti Gianni-Italy), microcrystalline cellulose (MC-Avicel PH 101, Faravelli-Milano, Italy) and saccharose (Faravelli-Milano, Italy) were used as starting materials.

3.2. Equipment

The 10 l (laboratory scale) Zanchetta Roto J granulator and the 50 l Zanchetta Roto P granulator, already described in a previous work (Vojnovic et al., 1993b), were used in the experiments.

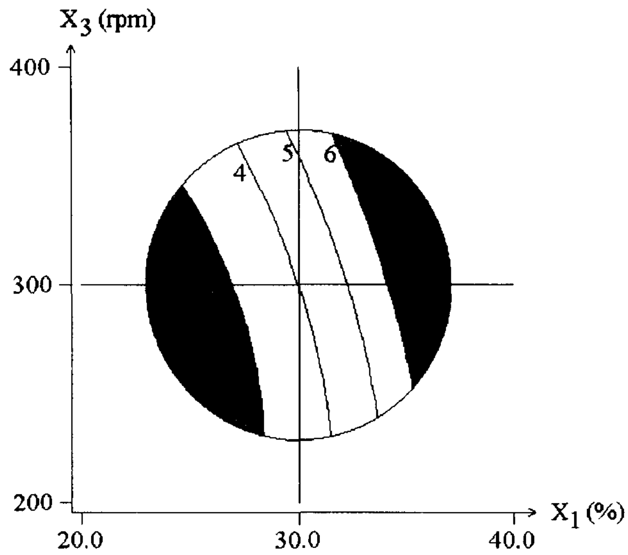
A vibrating apparatus (Octagon 200, Endecotts) and a set of sieves (1250, 800, 630, 500, 400, 315, 250 and 200 μm) were used for size distribution determinations.

3.3. Granulation manufacture

Preparation in 10 l Roto J granulator: 1.5 kg batches containing lactose (28%), microcrystalline cellulose (15%), corn starch (8%) and saccharose were mixed at an impeller speed of 80 rpm for 10 min. The mixture was granulated with water, which was added by spraying at a flow rate of 60 ml/min, a pressure of 4.0 bar and atomized by a pneumatic nozzle with a diameter of 0.5 mm. During this step the impeller speed was kept at 80 rpm. In the subsequent massing stage the impeller speed was increased, according to the experimental planes (Table 2).

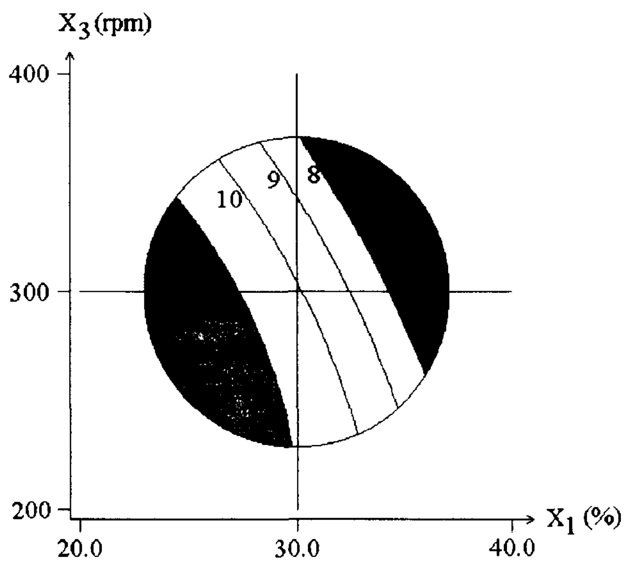
Preparation in 50 l Roto P granulator: the load was 7.5 kg. The water was atomized at a flow rate of 270 ml/min, so as to keep the spraying time constant with respect to the laboratory scale preparations.

The granulation samples were dried in a hot-air oven at 60°C for 4 h.



Contour number	Y_1 (μm)
3	402
4	440
5	477
6	515
7	552
8	590

(a)



Contour number	Y_2 (%)
6	2.22
7	3.32
8	4.96
9	7.41
10	11.06
11	16.51

(b)

Fig. 2. Contour plots obtained from experimental plane ○ for (a) Y_1 and (b) Y_2 as functions of moisture level (X_1) and impeller speed (X_3-noise factor). Massing time (X_2) = 3.5 min. The unshaded areas represent the operating conditions leading to the target range of the response values.

Table 3
Regression analysis results for the two measured responses fitted to the proposed model Eq. (1) at each level of the noise factor (○, ●, ⊗)

	Equations for Y_1			Equations for Y_2 [a]		
	○	●	⊗	○	●	⊗
b_0	432.80	516.60	441.80	0.9383	1.5320	3.8202
b_1 (X_1)	191.04	258.21	176.13	−0.8646	−2.1461	−2.6446
b_2 (X_2)	32.82	83.38	38.60	−0.3323	−1.1083	−0.9601
b_3 (X_3)	65.35	53.68	62.46	−0.4970	−0.5602	−1.4908
b_{11} (X_1^2)	81.62	78.07	79.59	−0.3860	0.9298	−0.0783
b_{22} (X_2^2)	60.12	4.23	−18.74	−0.2240	0.6645	0.3038
b_{33} (X_3^2)	27.12	39.90	−25.24	−0.2089	0.1324	0.5007
b_{12} (X_1X_2)	61.33	−13.50	13.44	−0.2504	1.2080	0.3800
b_{13} (X_1X_3)	37.33	66.17	93.94	−0.3518	0.1734	−0.7329
b_{23} (X_2X_3)	24.83	69.33	18.61	−0.2038	0.2956	−1.1574
R^2	0.9782	0.9919	0.9829	0.9868	0.9942	0.9973
R^2_{adj}	0.9501	0.9815	0.9610	0.9698	0.9867	0.9938

[a]The model coefficients of the equations for Y_2 were determined using the transformed values of Y_2 (○ = log Y_2; ●, ⊗ = $\sqrt{Y_2}$).

3.4. Granule characterization

The dry granulations were stored in well closed containers and the geometric mean diameter and the percentage in weight (w/w) of granules smaller than 200 μm have been evaluated. The methods employed have been described in a previous paper (Vojnovic et al., 1995b).

4. Results and discussion

Each of the 13 couples of X_1 and X_2 values was associated to three different levels (○, ●, ⊗) of the noise factor (X_3), according to the experimental plans (Table 2), and so a set of 39 experimental points was obtained. Four replicate of the central point (number 13) were carried out and considered for the variance estimate. The observed responses at each of the three levels of the noise factor are listed in Table 2.

An important requirement for the efficiency and validity of least-square estimation is that the variance of the response Y is independent of the magnitude of the response mean value. In our case this is not so for response Y_2, since the difference between the maximum and minimum value of Y_2 is very large. In such cases, in order to stabilize the variance, an appropriate transformation of the response variable is needed (Box and Draper, 1987). Such transformations are particularly important when dealing with quality control problems. The Y_2 variable was transformed into log Y_2 for the experimental plan ○ and into $\sqrt{Y_2}$ for the other two experimental plans (●, ⊗). The dependent and independent variables were than related using regression analysis, according to the proposed model Eq. (1) and the results are given in Table 3.

Isoresponse surfaces were drawn from the obtained equations for the two response variables using NEMROD program (Mathieu and Phan-Tan-Luu, 1992). In order to obtain a two-dimensional representation of the isoresponse surfaces, X_2 was chosen as constant variable and fixed at 3.5 min.

The subsequent step was to find, by means of the contour diagrams, a zone in the experimental field where the operating conditions lead to optimal values of both responses. The following constraint levels were set as limits of the optimal range of Y_1 and Y_2:

$$400 \leq Y_1 \leq 500\ \mu m$$

$$5 \leq Y_2 \leq 20\%$$

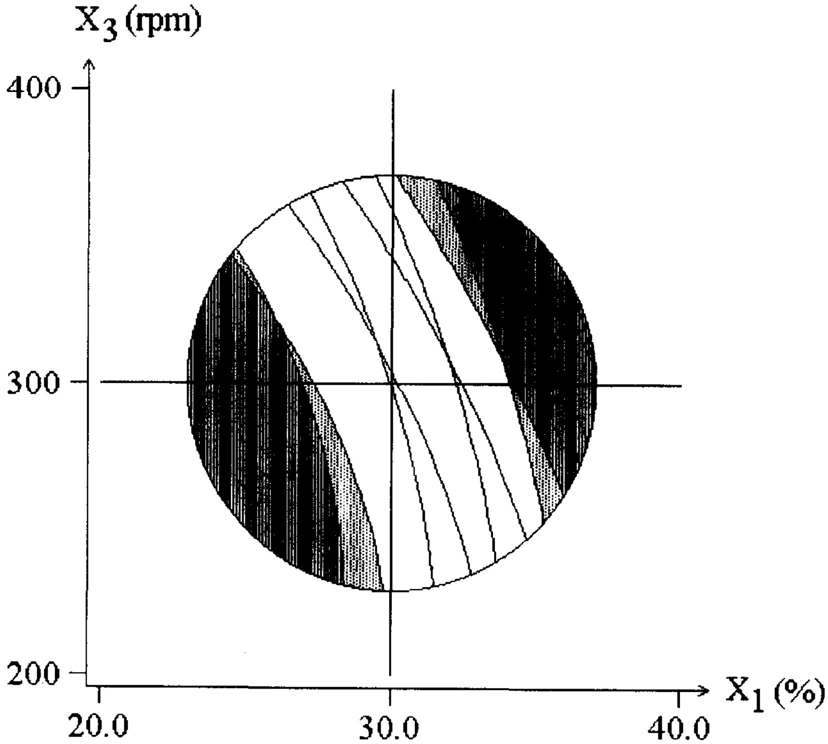


Fig. 3. Plot resulting from the superimposition of plots 2(a) and 2(b). The unshaded area represents the operating conditions leading to optimal values of both responses (Y_1 and Y_2).

Fig. 2a and b show contour plots for Y_1 and Y_2 respectively, at the middle level of the noise factor (experimental plane ○). The zone where both responses fall within the above-mentioned ranges was found by superimposing the two plots (Fig. 3).

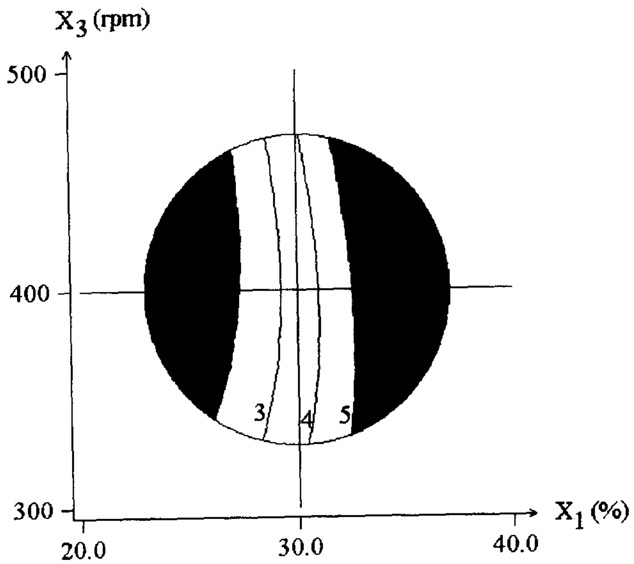
The contour plots for Y_1 and Y_2 obtained from experimental plans ● and ⊗ are represented in Figs. 4 and 5, respectively.

The superimposition of the plot in Fig. 2c with those obtained at the upper and lower levels of the noise factor (plots in Figs. 4 and 5) gave rise to an area where the operating conditions lead to a granulation which is not altered by impeller speed variations (Fig. 6).

In order to confirm the stability of the product characteristics in the resulting white area, three granulations were prepared at three different impeller speeds in one of the points included in this area (Fig. 6, point ■). The operating conditions corresponding to the chosen check point and the observed responses are shown in Table 4.

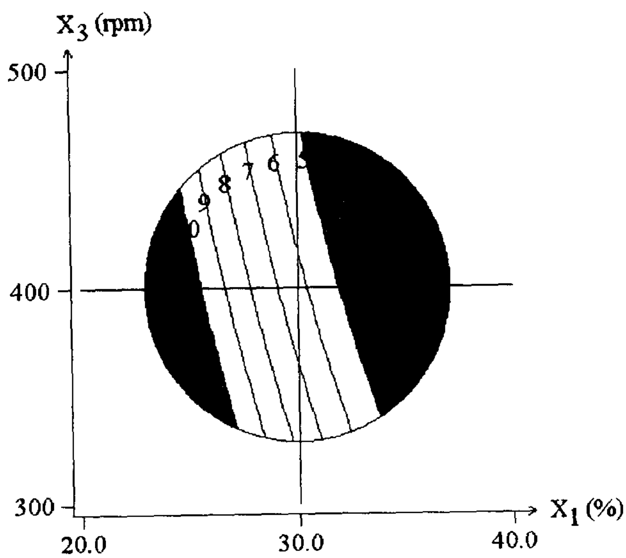
As can be seen in the Table 4, at constant moisture level (X_1) and massing time (X_2), the response values at different impeller speeds (X_3-noise factor) are all included in the target range, showing that at the selected operating conditions the quality of the product is not sensitive to impeller speed variations, if these variations are kept in the given range (200–400 rpm).

In previous studies (Vojnovic et al., 1993a) on scale-up of granulation processes in Zanchetta's Roto J and P granulators the impeller periferic rate was successfully used as a scaling-up parameter. Therefore, the point at which non-sensitive granulation characteristics were obtained in the 10 l granulator (check point ■) was chosen to test the feasibility of scaling-up to 50 l high shear mixer. The geometric mean diameter values obtained in the 50 l granulator (Table 4) confirmed



Contour number	Y_1 (μm)
1	347
2	394
3	440
4	487
5	534
6	581
7	627
8	674

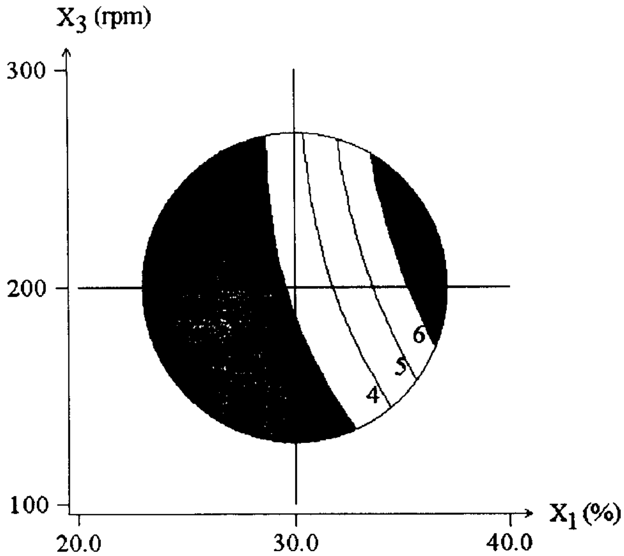
(a)



Contour number	Y_2 (%)
3	1.64
4	2.87
5	4.44
6	6.35
7	8.60
8	11.19
9	14.11
10	17.38
11	21.00

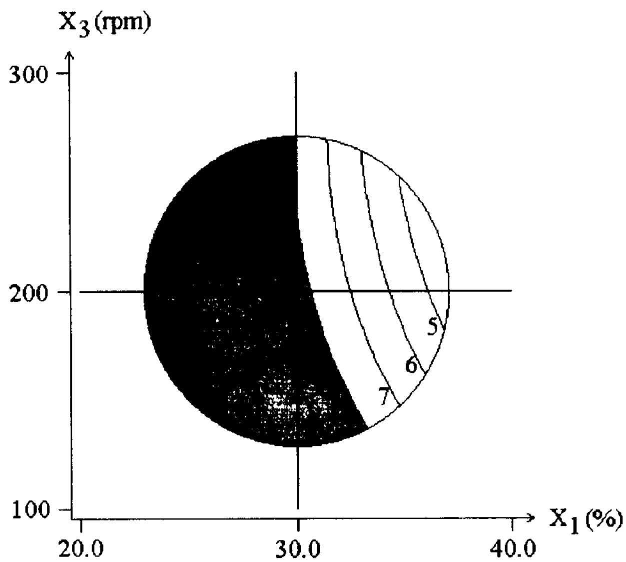
(b)

Fig. 4. Contour plots obtained from experimental plane ● for (a) Y_1 and (b) Y_2 as functions of moisture level (X_1) and impeller speed (X_3-noise factor). Massing time (X_2) = 3.5 min. The unshaded areas represent the operating conditions leading to the target range of the response values.



Contour number	Y_1 (μm)
2	359
3	398
4	437
5	476
6	515
7	554

(a)



Contour number	Y_2 (%)
5	8.08
6	11.44
7	15.38
8	19.91
9	25.01
10	30.70
11	36.97

Fig. 5. Contour plots obtained from experimental plane ⊗ for (a) Y_1 and (b) Y_2 as functions of moisture level (X_1) and impeller speed (X_3-noise factor). Massing time (X_2) = 3.5 min. The unshaded areas represent the operating conditions leading to the target range of the response values.

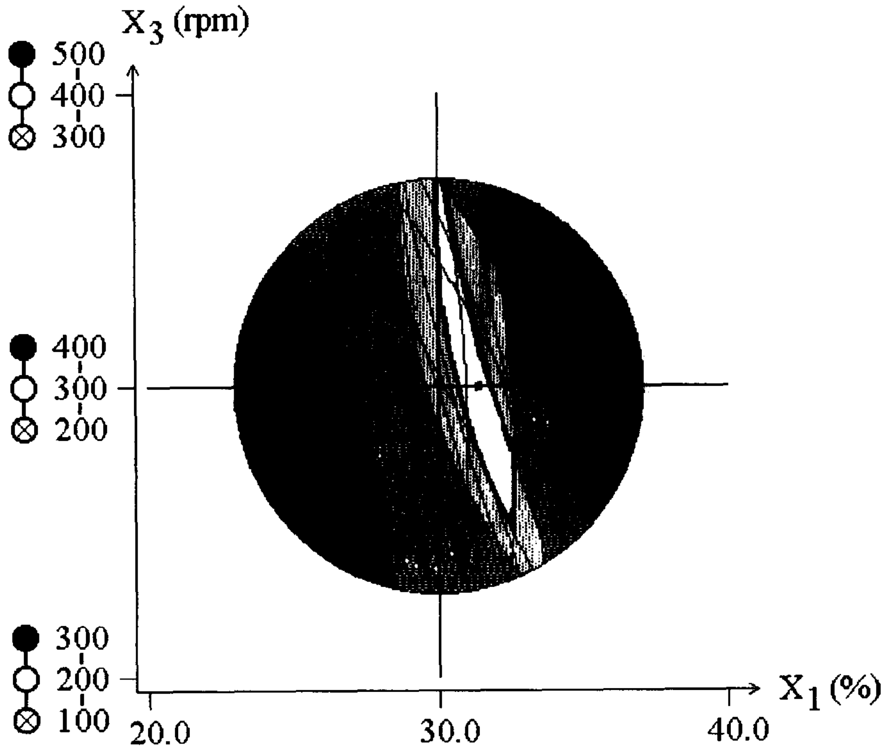


Fig. 6. Plot resulting from the superimposition of plots 3, 4(a), 4(b), 5(a) and 5(b). The white area represents operating conditions leading to a granulation whose characteristics fall within the target range and are not sensitive to impeller speed variations (point ■ = check point).

the hypothesis about suitability for scaling-up of the selected point. The percentage of particles smaller than 200 μm obtained in the 50 l granulator at the highest impeller speed value falls below the lower limit of the target range because of the different bowl structure of the two mixers, which promotes, in the 50 l granulator, a higher agglomeration of the particles.

5. Conclusions

In the product manufacturing one is frequently faced with the problem of finding the operating conditions leading to low product variability. In this work a quality control problem was handled using a Doehlert matrix with the introduction of a noise factor (impeller speed). Such an approach, in combination with the surface response methodology, allowed the finding of operating conditions giving a granulation whose characteristics do not only fall within the optimal range, but are also non-sensitive to impeller speed variations. It is noteworthy that the methodology applied in this work leads to a mathematical model which describes the effects of process variables on the studied response, and therefore the response behaviour can be predicted over the whole experimental field.

Moreover, the check point at which the impeller speed was found to have a very low effect on the product quality in the 10 l high shear mixer, led, in the 50 l mixer, to a granulation whose characteristics where still included in the optimal range, confirming that the approach suggested in this work can be a valid tool in quality control as well as in scaling-up studies.

Table 4
Observed response values in the check point ■ at different impeller speeds in 10 l granulator and at the tested impeller speeds in 50 l granulator

	X_1 (%)	X_2 (min)	X_3 (rpm)	Y_1 (μm)	Y_2 (%)
10 l high shear mixer	31.5	3.5	200	432	17.06
	31.5	3.5	300	464	8.97
	31.5	3.5	400	485	6.08
50 l high shear mixer	31.5	3.5	125	440	16.80
	31.5	3.5	188	471	8.02
	31.5	3.5	250	493	4.20

Acknowledgements

The authors wish to thank Silvano Coslovich and Diego Rota for their precious technical support.

References

Box, G.E.P. and Draper, E.P., *Empirical Model-building and Response Surfaces*, Wiley, New York, 1987, pp. 288-293.

Diemunsch, A.M., Pabst, J.Y., Constant, C., Mathis, C. and Stamm, A., Tablet formulation: Genichi Taguchi's approach. *Drug Dev. Ind. Pharm.*, 19 (1993) 1461-1477.

Doehlert, D.H., Uniform shell designs. *Appl. Stat.*, 19 (1970) 231.

Lewis, G.A. and Chariot, M., Flexible experimental design in pharmaceutical development: optimal designs for formulation and process optimization. *Pharm. Techol. Int.*, (1992) 46-51.

Mathieu, D. and Phan-Tan-Luu, R., *Program NEMROD*, L.P.R.A.I., Université d'Aix, Marseille, 1992.

Ogawa, S., Kamijima, T., Miyamoto, Y., Miyajima, M., Sato, H., Takayama, K. and Nagai, T., A new attempt to solve the scale-up problem for granulation using response surface methodology. *J. Pharm. Sci.*, 83 (1994) 439-443.

Phadke, M.S., *Quality Engineering Using Robust Design*, Prentice Hall, Englewood Cliffs, NJ, 1989.

Schaefer, T., Holm, P. and Kristensen, G., Wet granulation in a laboratory scale high shear mixer. *Pharm. Ind.*, 52 (1990) 1147-1153.

Stone, R.A. and Veevers, A., The Taguchi influence on designed experiments. *J. Chemometrics*, 8 (1994) 103-110.

Vojnovic, D., Moneghini, M., Rubessa, F. and Zanchetta, A., Simultaneous optimization of several response variables in a granulation process. *Drug Dev. Ind. Pharm.*, 19 (1993a) 1479-1496.

Vojnovic, D., Moneghini, M. and Masiello, S., Design and optimization of theophylline pellets obtained by wet spheronization in a high shear mixer. *Drug Dev. Ind. Pharm.*, 21 (1995a) 2129-2137.

Vojnovic, D., Moneghini, M., Rubessa, F., Experimental design for a granulation process with a priori criterias. *Drug Dev. Ind. Pharm.*, 21 (1995b) 823-831.

Vojnovic, D., Rupena, P., Moneghini, M., Rubessa, F., Coslovich, S., Phan-Tan-Luu, R. and Sergent, M., Experimental research methodology applied to wet pelletization in a high shear mixer. Part I. *S.T.P. Pharma Sci.*, 3 (1993b) 130-135.

Vojnovic, D., Selenati, P., Rubessa, F., Moneghini, M., Wet granulation in a small scale high shear mixer. *Drug Dev. Ind. Pharm.*, 18 (1992) 961-972.

Wehrlé, P., Palmieri, G.F. and Stamm, A., The Taguchi's performance statistic to optimize theophylline beads production in a high-speed granulator. *Drug Dev. Ind. Pharm.*, 20 (1994) 2823-2843.