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THE TAGUCHI'S PERFORMANCE STATISTIC TO OPTIMIZE THEOPHYLLINE BEADS PRODUCTION IN A HIGH-SPEED GRANULATOR

P. Wehrlé, G.F. Palmieri and A. Stamm

Laboratoire de Pharmacotechnie - Faculté de Pharmacie de Strasbourg
74, route du Rhin, B.P.24 F67401 Illkirch Cedex - France.

ABSTRACT

An original process using a simple procedure is developed to produce theophylline active pellets. In order to improve this process, an optimization approach is applied. But rather than only trying to bring the process to the target optimal values, attempt is made to find operating conditions leading also to stable and non-sensitive pellets characteristics. In this purpose, the classic experimental design approach and response surface methodology are completed by using Taguchi's philosophy.

INTRODUCTION

The aim of this work is to develop theophylline active pellets suitable for a controlled release oral drug delivery system. Different well known techniques including building up cores in a conventional coating pan, extrusion and spheronization, fluidized bed granulation or pellets growing in a specific rotogranulator already exist. An original and simple method for theophylline beads production using a common high-speed granulator dedicated to conventional granulates is studied in this work.

In order to improve the process, an optimization approach is chosen. But rather than only trying to bring the process to the target values, attempt is made to find optimal operating conditions leading also to stable and non-sensitive pellets characteristics. In this purpose, the classic experimental design methodology is completed by using the Taguchi's philosophy.

STATISTICAL METHODOLOGY

Dr. Genichi Taguchi, a Japanese engineer and quality consultant has developed original ideas and statistical procedures which have been used in Japan for decades, but it was the mid-1980s when the Western world became aware of his views toward process control and quality improvement (1). The purpose of his approach is to reduce system variability while simultaneously decreasing costs and increasing productivity. The general methodology is based on:

- separation of factors by role,
- extensive use of experimental design,
- use of measures of variability as responses,
- dual objectives of process centering and noise minimization.

Problem Analysis

The original Taguchi's approach consists in the organizational structure of the data-gathering which explicitly separates the factors by role. These factors can be divided into 3 categories (9):

- noise factors:
  They affect the process or product variability.
  External noise are variations in environmental variables such as temperature, humidity, dust and vibrations.
  Internal noise factors are the deviations of the actual characteristics of a process or product from the corresponding nominal settings. Manufacturing imperfections and product deterioration are the primary internal sources of noise.
  These noise factors, difficult or expensive to set precisely, are allowed to vary in the production stage. They are controlled only during the process improvement using specific experimental designs described below.

- signal factors or control parameters:
  They do not influence the process or the product variability but have a significant influence on the mean. Attempt is usually done to adjusted them in order to reach a target characteristic and to reduce the sensitivity of the target to variations in the noise factors.

- sensitivity factors:
  They share the characteristics of both noise and controlled factors and have influence on both the mean and the variability.

The second step of the initial analysis is to identify the responses of interest and to determine the level to be reached. Does the response need to match a specified value or must it be as large or as small as possible?

Taguchi's design of experiments

Instead of varying one factor at a time which is experiments consuming and can lead to completely wrong interpretation when variables interact, Taguchi generalized the use experimental design. A classical experimental design consists in changing more than one factor from one experimental run to the next in an organized and rationalized way so that a maximum of informations can be collected with a minimum of experiments.

But analyses of the Taguchi's specific method in the statistical literature have revealed some weaknesses (3-5). Taguchi's approach based on the use of orthogonal arrays and linear graphs has received considerable criticism in that it is somewhat complicated from a formal point of view and often inferior to the best known fractional factorial design. Moreover, Taguchi's procedures are analytical tools without a strong modeling framework, they can not be considered as optimization methods, mathematically speaking.

Nevertheless Taguchi's specific design has two main interesting components:

inner arrays and
outer arrays.

Both arrays are experimental designs. The inner array is an experimental design built up for the control factors. The outer array takes into account the noise factors (the control factors are fixed on the outer array). The methodology requires running an outer array for each experimental run of the inner array.

Data analysis

The Taguchi's approach has a dual objective that parallels the dual factor roles and the linked double design structure. The first objective is the traditional one of matching the nominal specification. The second objective is to minimize the sensitivity of the response to changes in the noise factors while fulfilling the first objective (6).
To reach this goal, Taguchi developed the use of signal-to-noise ratios which should be rather called performance statistics or criteria as there is no "signal" in some of these ratios (3). A performance statistic is a function of all the response values in an outer array and act as a response for the inner array. It is not a directly measurable output of the system. This statistic incorporates information about both the location and the spread of the response over the outer array into only one composite measure. Taguchi has defined 3 main "signal-to-noise" ratios:

- **{SNT}, "target-is-better"** criterion:

$$\{SN_T\} = 10 \cdot \log_{10}\left(\frac{\bar{y}^2}{s^2}\right)$$

with

$$\bar{y} = \frac{1}{n} \cdot \sum_{i=1}^{n} y_i$$

and

$$s = \left\{\frac{1}{n-1} \cdot \sum_{i=1}^{n} \left(y_i - \bar{y}\right)\right\}^{1/2}$$

This performance statistic is employed when the objective is closeness to target. When the variance is small compared to the mean, the target-is-best statsistic is large an positive. Practically, the goal is to find settings of the control factors (used in the inner array) that maximize this statistic which is calculated with the results of the outer array built with the noise factors.

- **{SN_L}, "Larger-is-better"** criterion:

$$\{SN_L\} = -10 \cdot \log_{10}\left[\frac{1}{n} \cdot \sum_{i=1}^{n}\left(\frac{1}{y_i}\right)^2\right]$$

This statistic is used when the objective is to make the response as large as possible. When all the responses in an outer array are large and positive, this larger-is-better performance statistic is as large as possible.

- **{SN_S}, "Smaller-is-better"** criterion:

$$\{SN_S\} = -10 \cdot \log_{10}\left[\frac{1}{n} \cdot \sum_{i=1}^{n} y_i^2\right]$$

Taguchi suggests to use this "smaller-is-better" performance statistic when the objective is to bring the value of the response as close to zero as possible. When all the responses in an outer array are near zero, this statistic is as large as possible.

The logarithmic transformation has different advantages. It tends to normalize data that have not a strong normal distribution (the logarithm of the standard deviation is more nearly normal than the standard deviation itself). The variance of the standard deviation typically will be larger as the standard deviation gets larger and in that case a logarithmic transformation is variance stabilizing.

The main interest of these performance statistic is that they give, in only one type of response, information about the location and the spread of the studied characteristic.

But, the analyst of the data should be aware that if the location and the spread of the response are not closely coupled in the process, the performance statistics lose information compared to separate measures and analyses of the location and the spread.

EXPERIMENTAL

Materials

- anhydrous theophylline, Boehringer Ingelheim (Germany),
- lactose E.F.C., Sucre de Lait sa. (France),
- microcrystalline cellulose, Avicel PH101, FMC (Ireland),

- hydroxypropylmethylcellulose, Pharmacoat 603, Shin Etsu (Japan),
- set of sieves, Prolabo (France),
- tamisor, vibrotronic VE1, Retsch, (Germany),
- high-speed granulator, Stephan UMC5, (Germany),

Composition of the active Beads

Anhydrous theophylline	20.0%
Lactose E.F.C	30.0 %
Microcrystalline cellulose, Avicel PH101	50.0%

The granulating liquid is a 15% hydro-alcoholic solution (ethanol/water, 30/70, V/V) of hydroxypropylmethylcellulose (Pharmacoat 603).

Equipment - Operating Conditions

After a 5 minutes dry-blending phase at 300 rpm in the high speed Stephan granulator, the granulating liquid is added with a peristaltic pump and a flow rate of 30 ml/min. During this stage, the impeller is rotating at different high-speed levels, precisely set near a target value. Different amounts of granulating liquid and kneading times are also tested. The granulates are then dried in the granulator shell by vacuum take-off and heating at 50°C, the impeller working at the lower rotation speed (300 rmp).

Preliminary study

During a previous study performed with the purpose of producing a classical theophylline granulate, a nearly over-wetted mass but constituted of approximately spherical agglomerates (figure 1) which particle size was mainly between 200 and 1000 µm (figure 2) has been obtained. These "pellets" were produced with 230 ml of granulating liquid, an impeller rotation speed of 1200 rmp without an additional kneading after wetting the mass.

Experimental design

Attempt is then made to analyse the effects of two main parameters that are well known to affect the granules characteristics (7).These

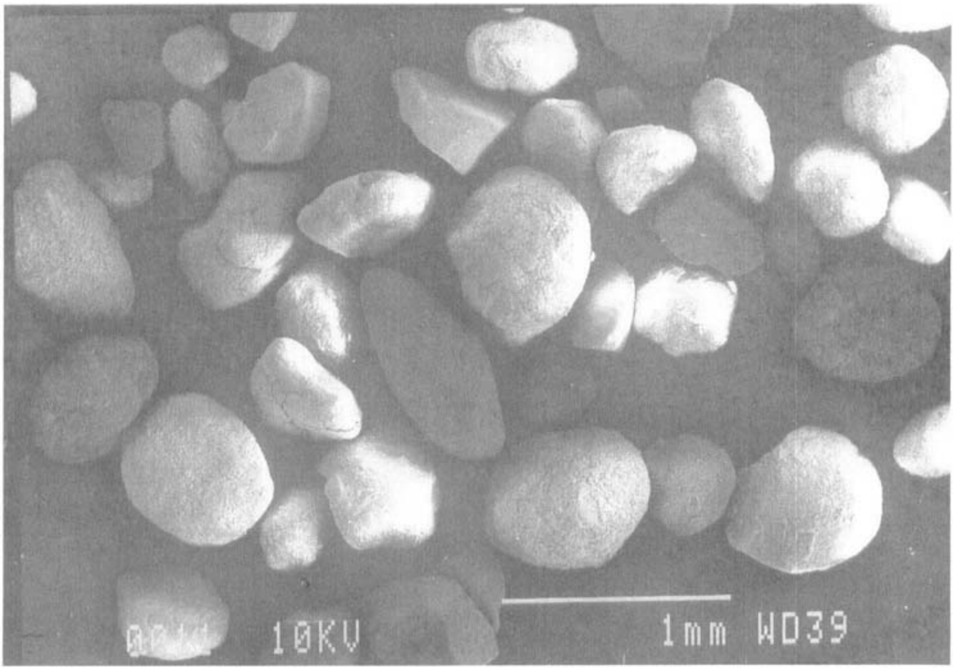

FIGURE 1
Photograph by Scanning Electron Microscopy.

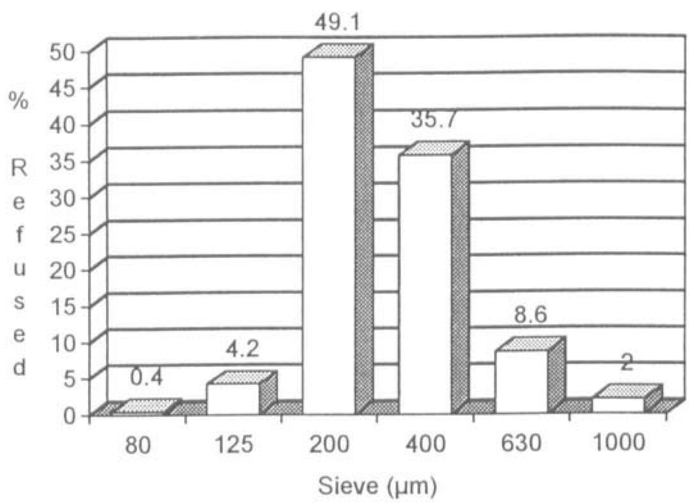

FIGURE 2
Particle Size Distribution.

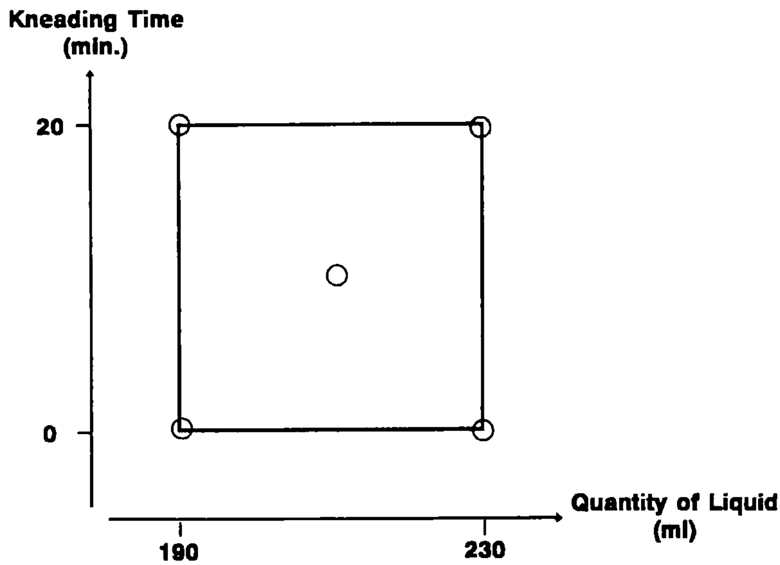

FIGURE 3
Classical Experimental Design $2^k + 1$.

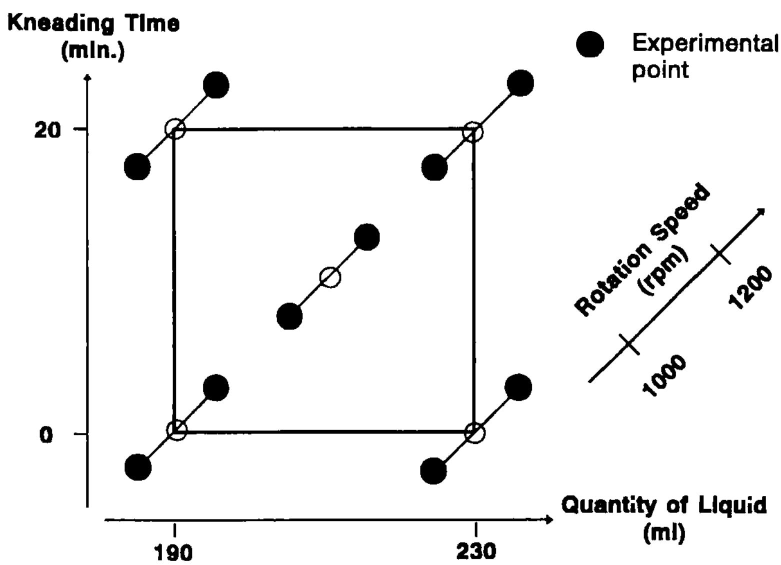

FIGURE 4
Experimental Design including a Noise Factor.

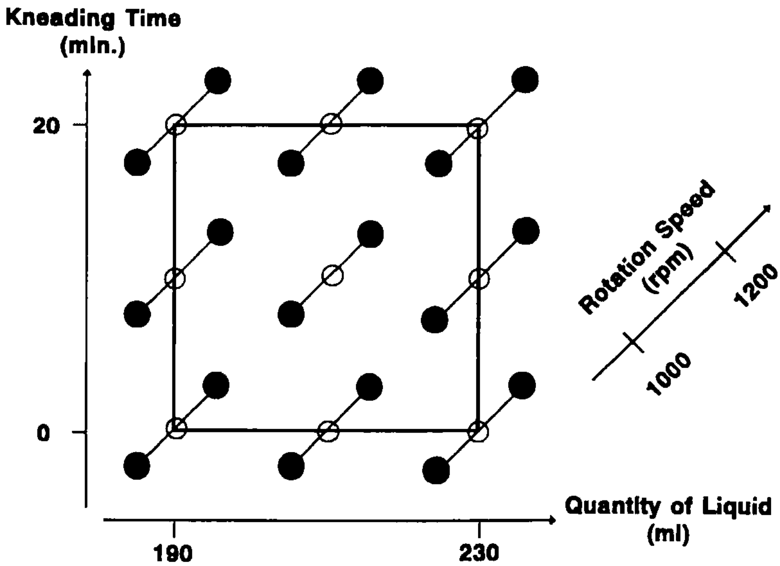

FIGURE 5
Experimental Design (3^k type) with a Noise Factor.

TABLE 1
Raw Data of the first Experimental Design.

	Factors			Responses		
Exp. #	**Liquid**	**Time**	**Speed**	**Yield**	**Mean diam.**	**Flowability**
1	190 ml	0 min.	1000 rpm	48 %	215 μm	4.06 s.
2	190 ml	20 min.	1000 rpm	84 %	322 μm	5.90 s.
3	230 ml	0 min.	1000 rpm	82 %	475 μm	6.74 s.
4	230 ml	20 min.	1000 rpm	21 %	980 μm	8.37 s
5	190 ml	0 min.	1200 rpm	66 %	275 μm	3.48 s.
6	190 ml	20 min.	1200 rpm	79 %	320 μm	5.95 s.
7	230 ml	0 min.	1200 rpm	85 %	380 μm	6.88 s.
8	230 ml	20 min.	1200 rpm	53 %	590 μm	8.01s.
9	210 ml	10 min.	1000 rpm	86 %	365 μm	7.18 s.
10	210 ml	10 min.	1200 rpm	88 %	370 μm	6.47 s.

TABLE 2
Performance Statistics.

Liquid	Time	Yield (Mean)	Perform. Statistic	Mean diameter	Perform. Statistic	Flowab. (Mean)	Perform. Statistic
190 ml	0 min.	57.4 %	34.86	245 µm	1800	3.77 s.	-11.6
190 ml	20 min.	81.2 %	38.17	321 µm	0.5	5.92.s	-15.4
230 ml	0 min.	83.4 %	38.42	427.5 µm	4512	6.81 s.	-16.7
230 ml	20 min.	36.7 %	28.78	785 µm	76050	8.19 s	-18.3
210 ml	10 min.	86.8 %	38.76	367.5 µm	13	6.82 s.	-16.7

TABLE 3
Significance of the Effects.

Response variable	Probability of no-effect (%) (according to the Student t-test)				R^2	ANOVA Prob.H_0
	1	Q	T	Q.T		
Yield	64.6	77.5	86.2	82.7	0.819	23.0
Performance	50.4	90.6	65.0	60.4	0.897	19.1
Mean diameter	67.0	56.7	61.6	55.6	0.966	22.6
Variance S^2	90.4	89.3	35.1	31.8	0.889	16.5
Flowabillity	24.8	16.8	51.6	62.6	0.968	14.7
Performance	36.5	18.5	41.7	48.0	0.954	16.4

TABLE 4
Results for the additional Experiments.

	Factors			Responses		
Exp. #	Liquid	Time	Speed	Yield	Mean diam.	Flowability
11	210 ml	0 min.	1000 rpm	74 %	300 µm	6.03 s.
12	210 ml	20 min.	1000 rpm	50 %	580 µm	8.54 s.
13	190 ml	10 min.	1000 rpm	84 %	305 µm	5.33 s.
14	230 ml	10 min.	1000 rpm	56 %	535 µm	7.26 s.
15	210 ml	0 min.	1200 rpm	83 %	305µm	5.41 s.
16	210 ml	20 min.	1200 rpm	75 %	486 µm	7.50 s.
17	190 ml	10 min.	1200 rpm	76 %	290 µm	4.44 s.
18	230 ml	10 min.	1200 rpm	36 %	725 µm	7.40 s.

TABLE 5
Performance Statistics.

Liquid	Time	Yield (Mean)	Perform. Statistic	Mean diam.	Perform. Statistic	Flowab. (Mean)	Perform. Statistic
210 ml	0 min.	78.5 %	37.87	302.5 µm	13	5.72 s.	-15.2
210 ml	20 min.	62.3 %	35.37	533 µm	4418	8.02.s	-18.1
190 ml	10 min.	79.6 %	38.17	297.5 µm	113	4.89 s.	-13.8
230 ml	10 min.	46.1 %	32.63	630 µm	18050	7.33 s	-17.3
210 ml	10 min.	86.8 %	38.76	367.5 µm	13	6.82 s.	-16.7

TABLE 6
Statistical Analysis of the quadratic Models.

	Probability of no-effect (%) (according to the Student t-test)							
Response variable	1	Q	T	Q.T	Q^2	T^2	R^2	ANOVA Prob.H_0 (%)
Yield	21.4	20.6	5.0	4.7	21.8	62	0.867	14.7
Performance	8.6	6.4	1.0	1.0	6.8	34.3	0.958	2.7
Mean diameter	10.8	10.0	2.3	1.4	8.1	85.2	0.992	0.3
Variance S^2	18.9	19.1	6.8	6.5	19.3	42.5	0.899	10.0
Flowabillity	0.9	0.1	6.9	13.5	1.3	69.0	0.994	0.2
Performance	0.001	0.003	0.1	0.2	0.1	66.3	0.998	0.02

TABLE 7
Regression Coefficients of the validated Models.

	Regression Coefficients					
Response variable	1	Q	T	Q.T	Q^2	T^2
Yield	-1320.27	12.899	18.678	-0.0880	-0.0296	-0.0421
Performance	-217.71	2.371	3.430	-0.016	-0.005	-0.009
Mean diameter	4821.16	-47.77	-63.75	0.352	0.125	0.039
Variance S^2	1699090	-16147.8	-19696.7	91.67	38.18	84.07
Flowabillity	-87.24	0.813	0.289	-0.00097	-0.00176	0.00059
Performance	-136.05	1.313	0.782	-0.0030	-0.0028	-0.0004

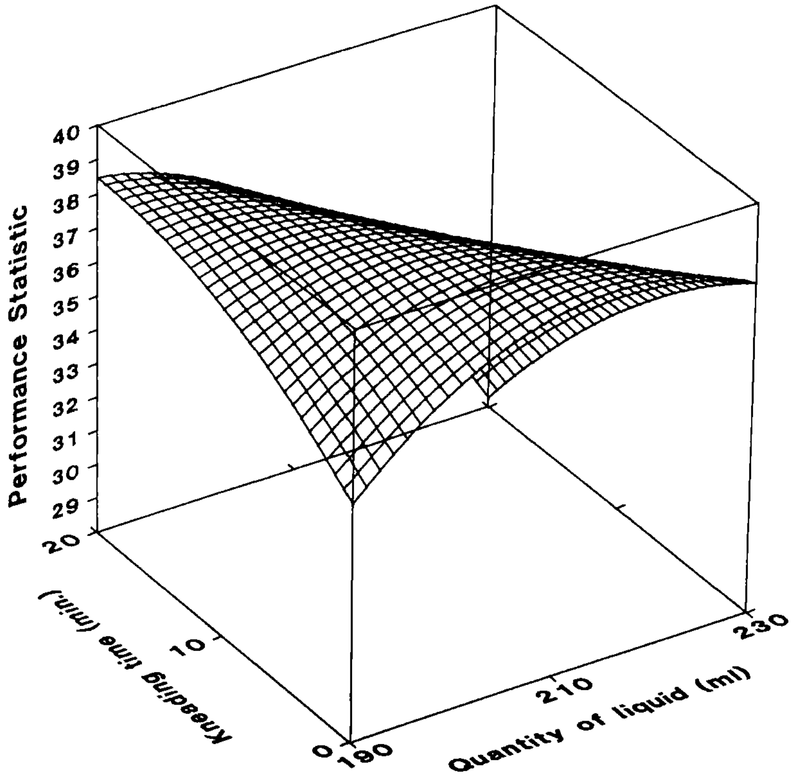

FIGURE 6.
Response Surface for the Yield Performance Statistic.

controlled variables are the quantity of granulating liquid and the kneading time after wetting the mass. The studied response variables are different pellets charactéristics such as their flowability, the mean particle size and also the process yield defined as the cumulative pourcentage of particules refused on the 200, 400 and 630 µm sieves. An 2^k type experimental design is first built in order to calculate a first order polynomial including a constant, two terms of main "linear effects" and a rectangle term of interaction:

$$Y = b_0 + b_1Q + b_2T + b_{12}QT$$

Y : Response variable,
Q : Quantity of granulating liquid,

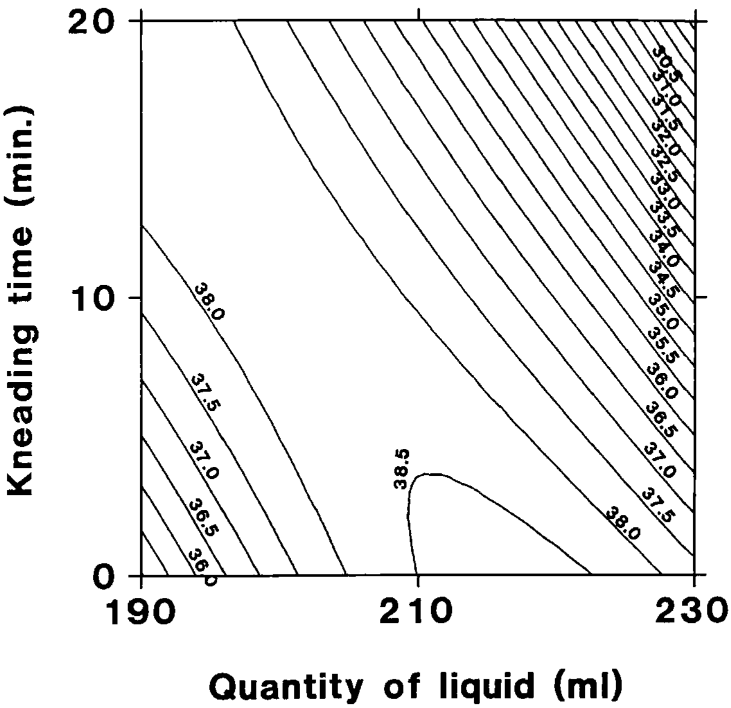

FIGURE 7.
Contourplot for the Yield Performance Statistic.

T : Kneading time,
b_0 : Constant,
b_1 ,b_2, b_{12} : Regression coefficients.

The experimental field is represented on figure 3. The limits for the kneading time are set to 0 and 20 minutes. For the quantity of liquid, no more than 230 ml is expected since the mass is almost over-wetted, the lower limit is fixed at 190 ml.

If the impeller rotation speed can theoritically be fixed at precise levels, in reality it may be subject to small random variations and therefore affect the pellets characteristics. In this granulating operation, the quantity of granulating liquid and the kneading time are the main factors supposed to modify the mean of the different studied responses and small variations of the impeller rotation speed appears to influence

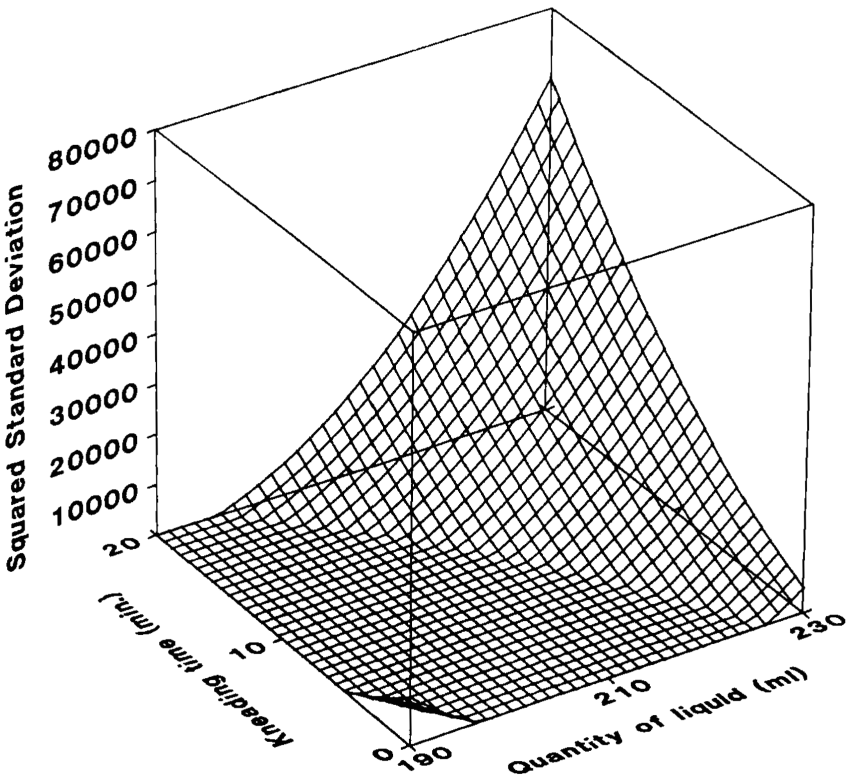

FIGURE 8.
Response Surface for the Mean Particle Size Performance Statistic.

the response variability. In order to find the operating conditions leading not only to pre-defined target characteristics (such as highest pellets flowability or highest yield) but also to define a robust process not sensible to noise factors, the classical experimental design is completed using the general Taguchi methodolgy. The inner array according to Taguchi's approach is therefore corresponding to the 2^2 experimental design built with the 2 main controlled variables while the outer array is consituted of a 2^1 experimental design performed for each point of the inner array with two levels for the impeller rotation speed close to the target value of 1100 rpm. The final resulting experimental design is represented on figure 4.

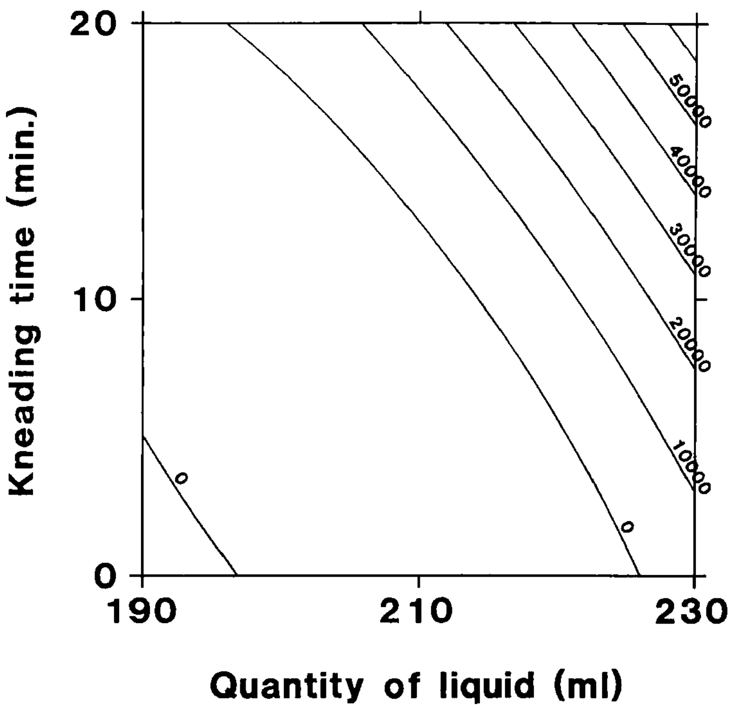

FIGURE 9.
Contourplot for the Mean Particle Size Performance Statistic.

The model is calculated by multiple regression and validated by performing an additional experiment in the centre of the experimental field. The result obtained for this experiment must correspond to the expected one according to the model, if not, the response surface is not plane. In this case, the response surface curvature can be described by a model of the second order:

$$Y = b_0 + b_1Q + b_2T + b_{12}QT + b_{11}Q^2 + b_{22}T^2$$

Such a model can be evaluated after performing a 3^k experimental design which can be simply built by adding experiments to the previous experimental design at the middle of the sides or edges of the experimental field. Here again, the outer array points are tested for

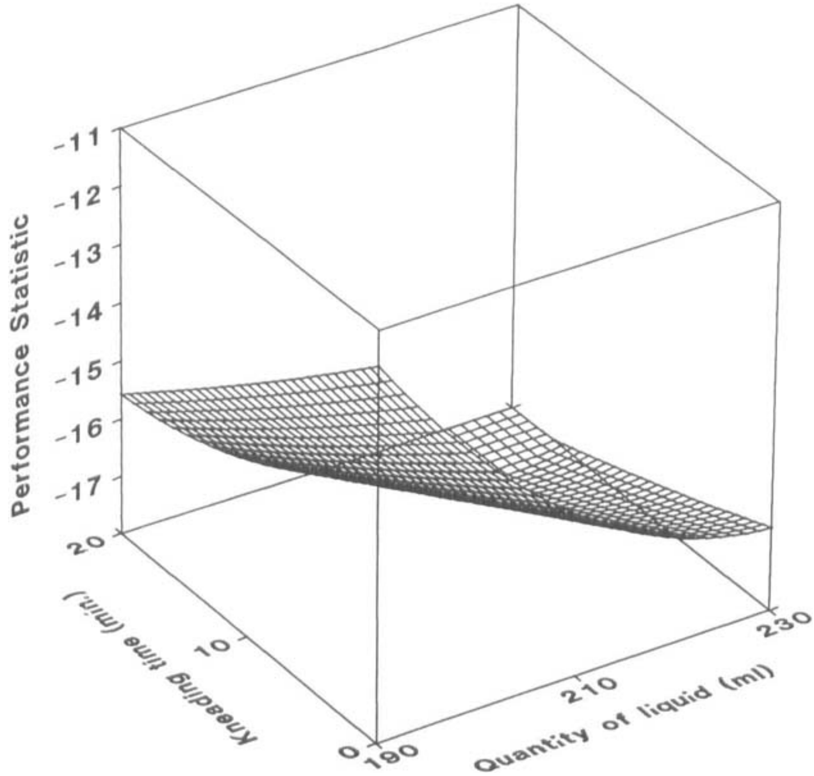

FIGURE 10.
Response Surface for the Flowability Performance Statistic.

each point of the inner experimental design (figure 5). The whole design needs 18 experiments to be performed.
The corresponding models are validated by an analysis of variance.

RESULTS AND DISCUSSION

The results obtained for the first set of experiments are reported in table 1. The couple of results for each point of the inner array are used to calculate performance statistics. Depending on the objective to be reached, different performance statistics are evaluated.
Because the process must be able to reach a maximum percentage of beads which size is between 200 and 1000 µm avoiding dust or big agglomerate production, the Taguchi's "larger-is-better" criterion is

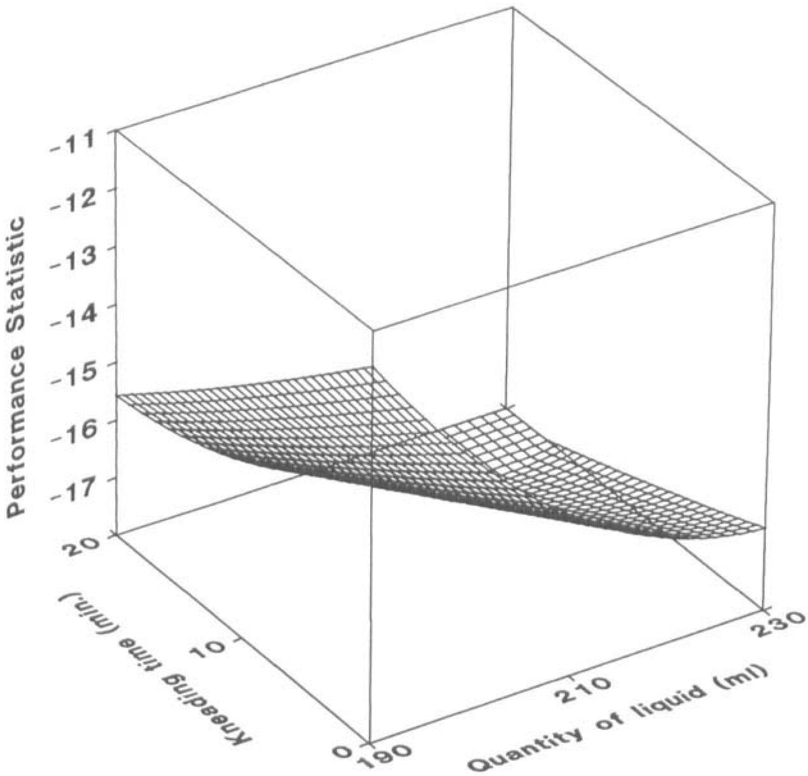

FIGURE 11.
Contourplot for the Flowability Performance Statistic.

adopted to define the operating conditions leading to the highest yield and but also not sensible to small impeller rotation speed variations. On the opposite, the "smaller-is-better" criterion is used for the flowability which must be low because the pellets must flow in the minimum rate of time. The mean particle size itself and an estimate of the variance are directly used without any other performance statistic calculations since no specific target are to be reached, the objectif is just to describe this response and its variability. The calculated data corresponding to the statistic to be modelized are reported in table 2.

The significance (according to the Student t-test) for each term of the first order model as well as the multiple correlation coefficient and the result of the analysis of variance are reported in table 3. One can see that no term has a significant effect. If a risk $\alpha = 0.10$ is taken for

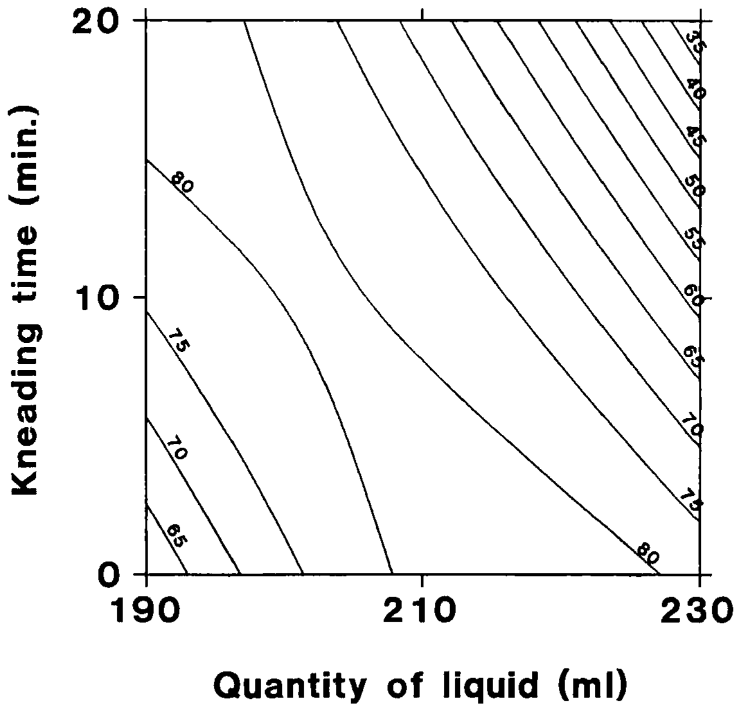

FIGURE 12.
Contourplot for the Yield (%).

the analysis of variance, no "linear" model is validated showing that the response surfaces are not plane. The curvatures must be evaluated by a quadratic model after performing a 3^k type experimental design. The obtained results are reported in table 4 and the performance statistics in table 5.

Statistical analysis of the different models is given in table 6. All the models reveal a multiple correlation coefficient greater than 0.85. If a risk α= 0.15 is fixed as a limit, the analysis of variance shows that all the models are validated. The corresponding polynomial expression are reported in table 7 containing the regression coefficients.

Because the models are calculated with the original controlled variables units (the data are not centered and reduced) and also because these models include quadratic terms, the analysis of the regression coefficients is not easy or even not possible. Drawing the response surfaces and the corresponding contourplots is much more speaking.

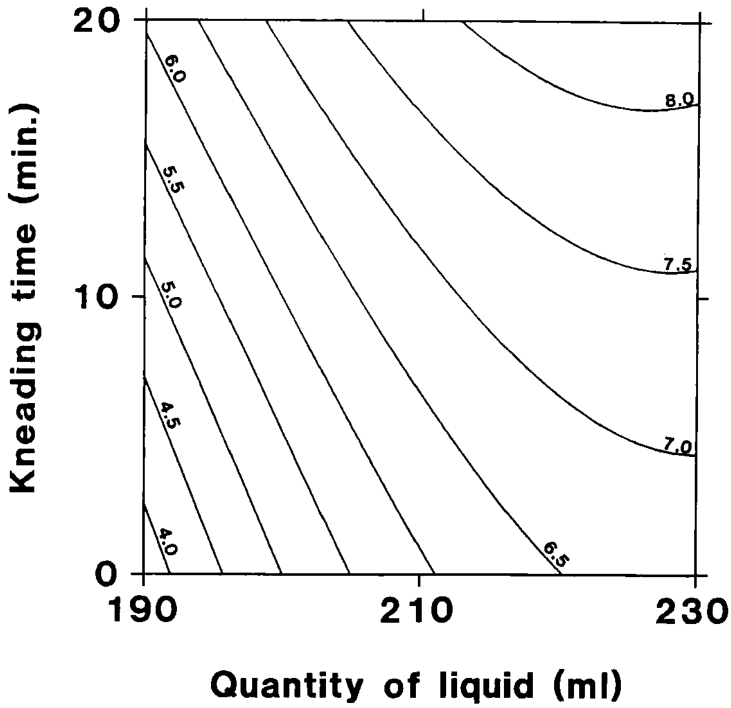

FIGURE 13.
Contourplot for the Flowability.

According to the Taguchi's approach, the performance statistics only should be studied because they give at the same time information about the location and the spread of the response. The corresponding surfaces and contourplots are represented in the figures 6 to11.

The performance statistic for the yield displays no single optimum but a typical ridge.with a "minimax" (figures 6 and 7). This ridge gives the optimal operating conditions leading to a yield level which is maximum and stable because not sensitive to small impeller rotation speed variations. The optimal operating conditions can be found out graphically or precisey defined by caculating the derivative function of the model. By differentiating the model equation with respect to first Q and then T, and equating the results to zero, the two equations to determine the minimax are:

$$T + 0.677.Q = 146.466$$
$$T + 0.917.Q = 194.228$$

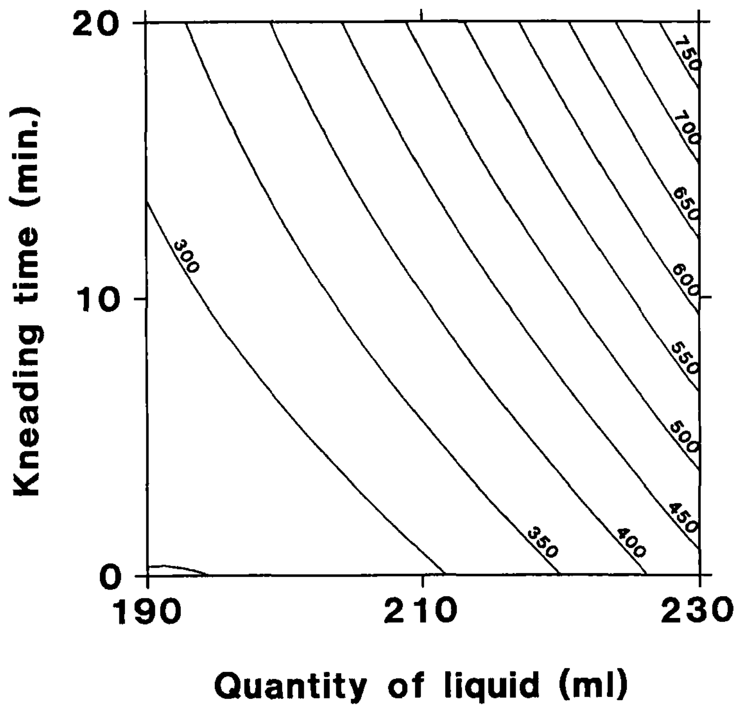

FIGURE 14.
Contourplot for the Mean Particle Size.

The solution of these equations is: Q=199 ml ant T= 11.7 min.The operating conditions corresponding to small amounts of liquid and a short kneading time as well as great amounts of liquid and a long period of wet-mixing give the worst results, highly sensitive to impeller rotation speed variations. (figures 6 and 7).

Like the performance for the yield, the mean particle size performance surface and contourplot display a stationary region corresponding to a minimum particle size variance.(figures 8, 9). The highest performance statistic level for the flowability is observed at the lower limit (190 ml, 0 min.) which leads to bad results for the yield. (figure 10, 11).

In order to select the optimal operating conditions, the contourplots for the initial response variables are also analysed (figures 12, 13, 14).

It can be seen (figure 12) that for the minimax, corresponding to the point less sensible to impeller rotation speed variations, a very good yield is reached, 82% calculated with the model equation. Working at 1100 rmp 85% have been obtained. If the flowability is not maximum for this point (figure 13), it is quite good (6 seconds for 100g of granules). The mean particle size is around 340 micrometers (figure 14).

CONCLUSION

This work proves that it is possible to produce active pellets with a non-specific granulator using a simple procedure. The sequential response surface methodology appears to be efficient to optimize the process. Completing this approach with the Taguchi's philosophy and using performance statistics seems to be particularly interesting to define operating conditions leading to a process which is robust and non-sensitive to noise factors.

The optimized pellets will be further tested for coating in a fluidized air bed in order to obtain a controlled release system.

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