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RESPONSE SURFACE METHODOLOGY: AN INTERESTING STATISTICAL TOOL FOR PROCESS OPTIMIZATION AND VALIDATION:

EXAMPLE OF WET GRANULATION IN A HIGH-SHEAR MIXER

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ABSTRACT

The Response Surface Methodology is used to study the wet granulation in a high-speed mixer, granulator and dryer. By building sequential experimental designs, it is possible to quantify the influence of different process parameters on the characteristics of the final produced granules and tablets. The computed mathematical models are statistically tested and verified by experimentation. In order to facilitate the analysis of the regression coefficients, the response surfaces and the corresponding contourplots are drawn pointing out interesting levels for the operating conditions. Finally the chosen statististical approach appears to be efficient not only to optimize but also to validate the operation of wet granulation.

INTRODUCTION

Because of the development of new granulation equipment such as high-speed or high-shear mixers, the operations of mixing, wetting, kneading and drying can be performed in the same machine avoiding dust problems and contamination risks. This leads also to a saving of time, equipment, energy, space and machine operators.

Since the earlier research of Rumpf (1), Newitt and Conway-Jones (2), the theory of granulates formation and growth is well known. Nevertheless, the process of wet granulation, above all with the modern technology, is not completely elucidated witness the abundant literature on this subject (2-13). This work using a statistical method is a contribution to the best knowledge of this operation.

MATERIALS

Composition of the granules

The starting product used for granulation is a standard powder made up of lactose (150 mesh, DMV, France), corn starch (Roquette, France) and polyvinylpyrrolidone (PVP K30, BASF, Germany). The amount of each component is kept constant.

Lactose .... 75.0 %
Corn Starch .... 20.0 %
PVP K30 .... 5.0 %

The chosen wetting liquid is an hydro-alcoholic solution (ethanol/water, 30/70, V/V) in order to hasten the drying phase.

Equipment

Wet granulation in performed in a 10l capacity mixer Turbosphère TS10 (Moritz, France). The spherical bowl of this apparatus is equipped with a three shaped impeller which profile is similar to that of the inside wall of the bowl. This impeller, working at a speed varying from 10 rpm. to 450 rpm., gives to the powder to be granulated a spherical and vertical movement. This movement

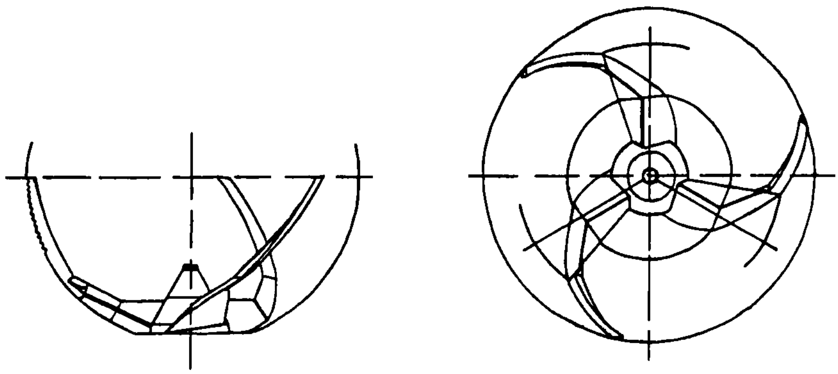

FIGURE 1. Impeller Profile of Turbosphère TS10.

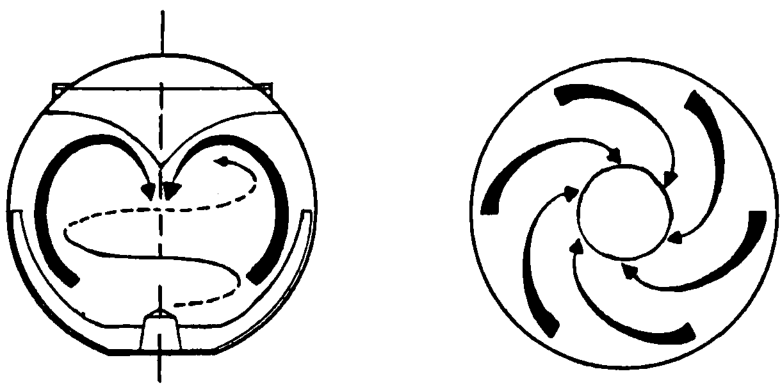

FIGURE 2. Movement of the Powder in the Turbosphère TS10.

is centrifugal up to the equator of the bowl and becomes then centripetal feeding the impeller again, so that mixing and kneading is very efficient (fig.1 and fig.2).

The granulating liquid can be introduced through the hole on the top of the bowl using a peristaltic pump. A chopper, rotating at 1500 rpm or 3000 rpm, avoids the growth of too big aggregates during wetting. Turbospère TS10 is a twin-shell blender equipped with a heated jacket and a vacuum air-pump so that dry mixing of the powder, wetting, kneading and drying can be performed in the same apparatus.

METHODS

Operating conditions

Controlled variables or factors

Two main parameters vary during this study: quantity of granulating liquid and kneading time after wetting the mass. All other parameters are kept constant as described below.

Constant operating conditions

The quantity of powder is set to 3.4 kg. The impeller speed is fixed to 200 rpm in order to avoid uncontrolled vortex-ring. After a dry-blending phase of 10 min. the granulating liquid is added. The flow rate is fixed to 60 ml/min.kg. During wetting and the following kneading phase the chopper works at 3000 rpm. Drying occurs directly in the shell by vacuum take-off and heating at 60°C until the granules humidity reaches 3%. Granules are then sieved through the 0.71 mm screen of an oscillating calibrator (Frewitt, Switzerland).

Response variables

In order to collect the maximum of information, a great number of response variables is measured before, during and after compression of the granules.

The flow time of 100g of granules through a standardized funnel set upon a test-tube is measured. Height of granules in the test-tube indicates the bulk volume. The graduated test-glass is then submitted to vertical taps. Differences between volumes after 10 and 500 taps are determined (14). A set of sieves permits to calculate the mean diameter and the uniformity of size distribution (the higher the value, the less homogeneous the granules (15). Friability is evaluated by shaking granules with little balls and measuring the fine particles produced.

Granules are then mixed with 0.5% of magnesium stearate and compressed with a single punch press instrumented with strain gauges and displacement transducers on both upper and lower punches. This equipment allows to control the force applied and to measure the energy displayed by the upper punch, force transmission index, residual and ejection forces and expansion energy of the tablet in the die wall (16).

The obtained tablets are characterized by their weight, thickness, hardness, friability and disintegration time.

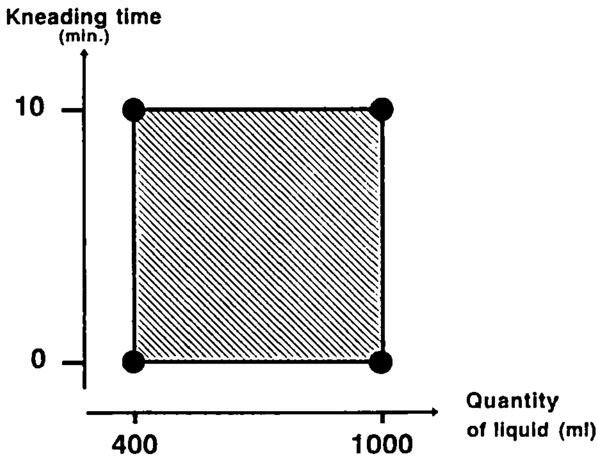

FIGURE 3. Experimental Field.

Statistical methodology

Until recently, formulation and development investigations were realized proceeding just by trial and error and varying one factor a time. Needless to say that this approach is time, energy and money spending. In the worst case, completely wrong conclusions are built, above all when different variables interact. Due to multiple requirements, the modern designer can no more be satisfied with a method leading to uncertain and nonvalidated results. The use of a statistical approach is necessary. The Response Surface Methodology (17-22) using experimental designs is an economical method leading to collect a maximum of information with a minimum of experiments.

Preliminary study

Before building an experimental design, the experimental field must be defined precisely. This experimental field must not be too large, leading to non realistic experiments and not too small, far from an optimal region. In this work, lower limits correspond to the minimum of granulating liquid quantity and kneading time which can produce granules although not very different from the starting product but flowing through the standardized funnel. Quantity of liquid and kneading time leading to an overwetted mass but not pasty and able to be compressed set the upper limits (fig.3).

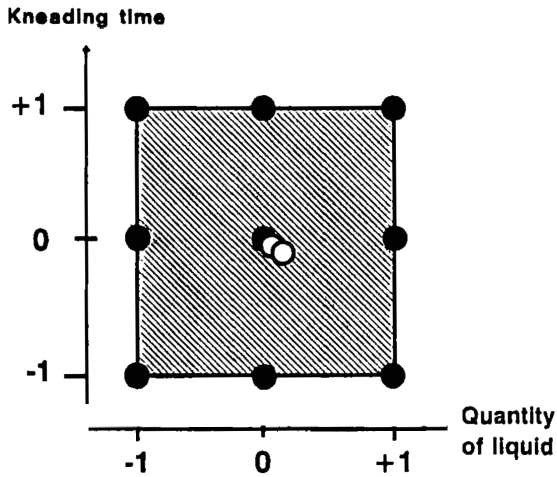

FIGURE 4. Experimental Design $3^2 + 2$.

Sequential experimental designs

The extreme vertices of the experimental field do constitute a typical 2^2 experimental design. The theory of least squares is then applied to the four obtained results so that a linear model with interaction can be calculated for each response variable:

$$Y = a + b.Q + c.T + d.Q.T$$

(Y: response variable; Q: quantity of liquid; T: kneading time; a: constant; b,c,d: regression coefficients).

This model is verified by performing an additional experiment in the centre of the experimental field. Difference between the experimental response in this point and the evaluated value according to the linear model must be zero, if not, an other model must be tested.

To describe the response surface curvature, a 3^2 experimental design (fig.4) can be built by adding only four experiments to the previous one, so that a quadratic model can be calculated:

$$Y = a + b.Q + c.T + d.Q.T + e.Q^2 + f.T^2$$

(Y: response variable; Q: quantity of liquid; T: kneading time; a: constant, b,c,d,e,f: regression coefficients).

TABLE 1
Statistical Model Validation

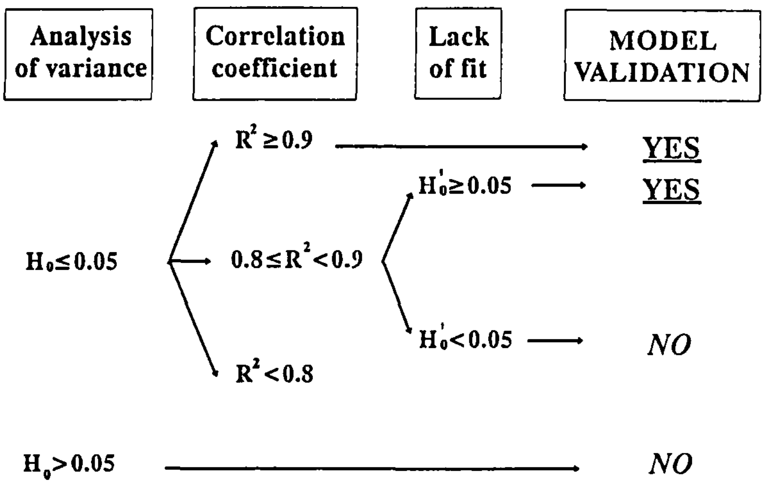

TABLE 2
Correlation Coefficients of the linear Models with Interactions.

Response Variables	r^2
Flow time	0,385
Bulk volume	0,666
V10 - V500	0,962
Mean diameter	0,458
Uniformity of size distribution	0,746
Granules friability	0,947
Upper punch energy	0,670
Force transmission index	/
Residual force	0,990
Ejection force	0,978
Expansion energy	0,999
Tablets weight	0,728
Tablets hardness	0,833
Tablets friability	0,865
Disintegration time	0,866

The experimental error is quantified by collecting the results of 2 additional central experiments.

The complete model is statistically validated by analysis of variance, calculation of the multiple correlation coefficient and estimation of lack of fit (Table 1).

TABLE 3
Regression Coefficients of the Models.

Response Variables	Regression coefficients				r^2
	1	Q	T	Q.T	
V10-V500	18,8	*	*	*	0
Granules friability	31,4	-7,25	*	*	0,770
Residual force	98,0	7,5	2,5	-7,5	0,990
Ejection force	306,0	*	*	*	0
Expansion energy	1,802	-0,015	0,130	0,035	0,999
Tablets hardness	13,2	1,0	*	*	0,833
Friability	1,158	-0,125	*	*	0,733
Disintegration time	7,146	*	*	*	0

* : non significant term, $\alpha>0,1$.

RESULTS AND DISCUSSION

Linear models with interaction are calculated for the studied response variables. The corresponding correlation coefficients are reported in table 2.

For the models displaying a correlation coefficient greater than 0.8 the step by step method of regression is applied. According to the Student T-test non significant terms of the model are withdrawn, the model is recalculated and so on, until only high significant terms ($\alpha<0.1$) are selected for the model. The following results are obtained (Table 3).

If 8 models among the 15 calculated ones display a correlation coefficient higher than 0.8, only 3 of them still keep a satisfying coefficient when the step by step method is applied. The linear model seems to be adapted to describe the effect of the quantity of granulating liquid and kneading time on the residual force an expansion energy during compression and the tablets hardness. No linear model is selected for the variables characteristic of the granules.

So, to calculate more suitable models for these variables and also to confirm and verify the few selected linear ones, the initial experiments are completed in order to build a 3^2 design and to calculate quadratic models. Experimental validation by performing an additional experiment is no more necessary because the number of experiments of the whole design (11 trials) is higher than the

TABLE 4
Regression Coefficients of the validated Models.

RESPONSE VARIABLES	VALIDATED MODELS					
	CONST.	Q	T	Q^2	T^2	Q.T
Flowability	4.24	-0.03	-0.22	0.56	*	*
Bulk volume	155.60	-4.00	-3.67	9.73	*	3.50
Mean diameter	147.00	6.83	8.00	-17.83	*	*
Size distribution	2.80	0.28	*	-0.25	*	*
Granules friability	27.00	-7.08	*	5.75	*	*
Tablets weight	0.724	0.010	0.013	-0.027	*	-0.013
Tablets hardness	13.40	1.17	*	0.57	*	*
Tablets friability	1.10	-0.14	*	0.07	*	*
Disintegration time	7.55	0.72	0.38	*	-0.61	-1.04

* : non significant term, $\alpha>0,1$.

regression coefficients and constant to be estimated (6 terms). The step by step method is applied and the resulting models are statistically validated as described above. The results obtained for the completely validated models are reported in table 4.

After the second campaign of experiments, a greater number of models are definitely validated. This time, models are selected for the variables characteristic of the granules. On the contrary, the majority of the models kept after the first experimental design are not confirmed and quadratic models are not more efficient to describe the corresponding variables. This is particularly the case for the variables measured during the compression. Due to the great experimental error, the lack of fit is found statistically highly significant for these variables. Compression parameters are not suitable to study the characteristics of the different produced granules.

If table 4 shows clearly that the kneading time by the quadratic term is not influent on the great majority of the variables, precise analysis of the regression coefficients is not easy for a not expert person. Drawing the response surfaces and the corresponding contourplots is much more efficient to visualize the influence of the controlled variables on each response variable.

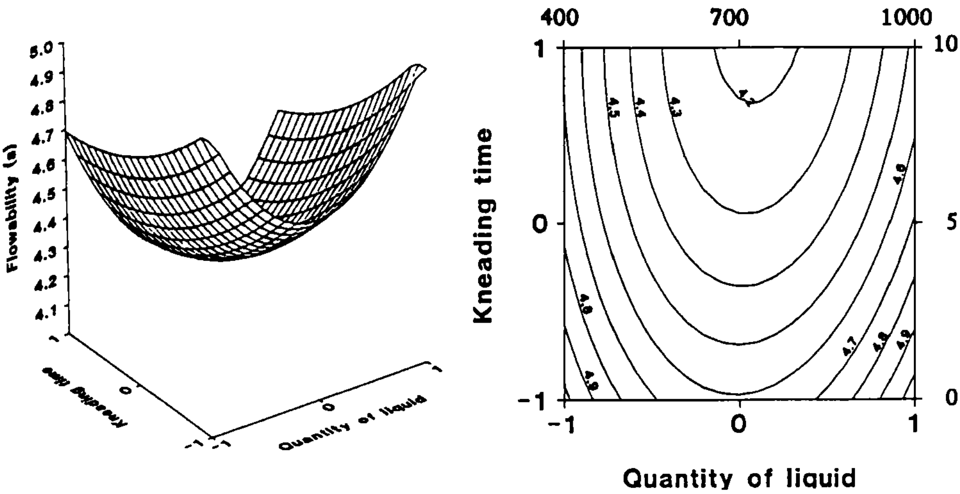

FIGURE 5. Response Surface and Contourplot for the Flow Time.

By the quadratic term, the quantity of granulating liquid produces an effect on the flowability of the granules due to the great response surface curvature (fig.5). The shortest flow time corresponds to around 730-740 ml for and optimal kneading time of 10 minutes. But whatever the operating conditions, the flow time of 100g of granules is always less than 5 seconds.

The response surface is particularly interesting to analyse for the bulk volume (fig.6). In fact, the interaction between the two controlled variables clearly appears. For the lowest quantity of liquid, the bulk volume decreases from 176 ml to 162 ml for a kneading time varying from 0 min. to 10 min. when this bulk volume is quite constant (160 ml) for the highest quantity and this whatever the kneading time. A minimum of bulk volume, corresponding to a maximum of densifying effect, is obtained with around 700 ml and 10 min.

The mean granules diameter is greatly affected by the quadratic effect of the quantity of granulating liquid. Increasing the kneading time leads to larger granules (fig.7). The maximum observed (155μm), corresponds to around 700 ml and 10 minutes.

Kneading time has statistically no effect on the uniformity of size distribution which is in relation only with the quantity of liquid. This surprising

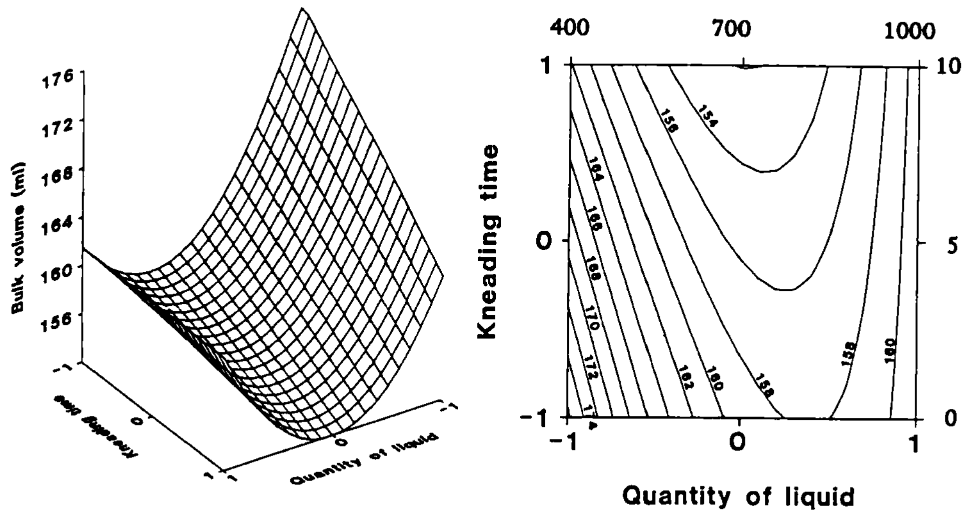

FIGURE 6. Response Surface and Contourplot for the Bulk Volume.

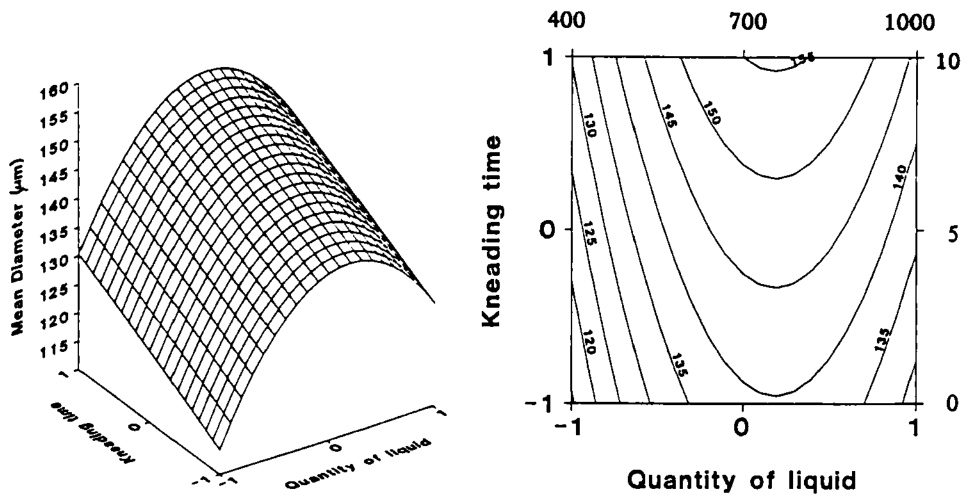

FIGURE 7. Response Surface and Contourplot for the mean Diameter.

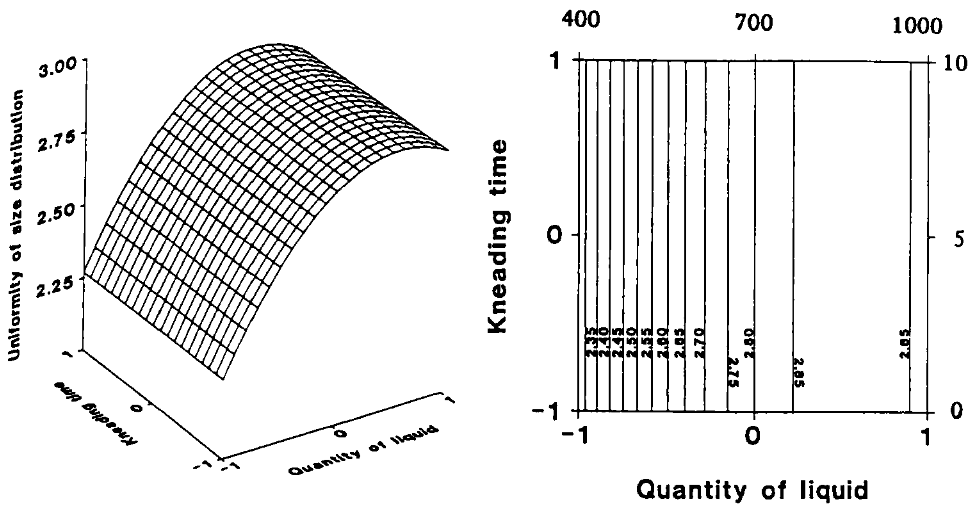

FIGURE 8. Response Surface, Contourplot: Uniformity of Size Distribution.

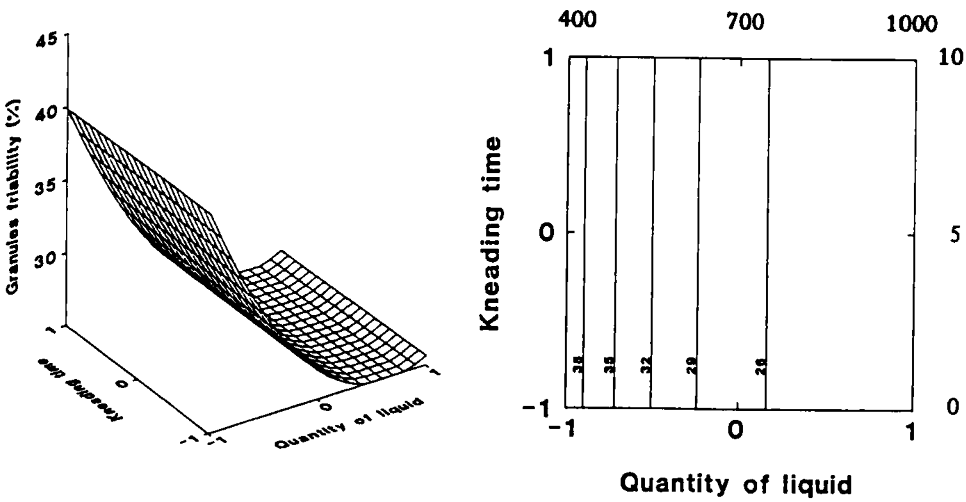

FIGURE 9. Response Surface and Contourplot for the Granules Friability.

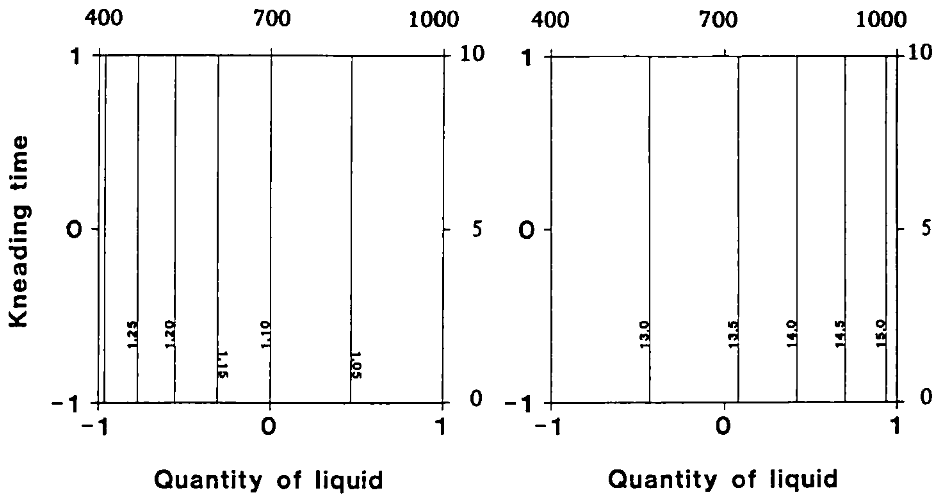

FIGURE 10. Contourplots for the Tablets Friability and Hardness.

result shows the great densifying effect of the granulator Turbosphère TS10. Prolonging the kneading time has no consequence for this variable.

A similar result is obtained with the granules friability (fig.9). Energy displayed by the high-shear granulator is great enough so that kneading time after wetting the mass has no influence. Granules friability is not varying significatively beyond 700-740ml of granulating liquid. Granules friability induces the tablets friability and harness as shown by the similarity of the contourplots (fig.9 and fig.10). Whatever the operating conditions, tablets friability, decreasing with the quantity of liquid, is around 1% and the hardness, increasing with the amount of liquid, is always greater than 12 kgp.

The response surface for the tablets weight (fig.11) is quite the negative image of the bulk volume. The controlled variables effects are opposite but the interaction also clearly appears. The maximum value (around 740mg) is reached with quite same optimal operating conditions.

The response surface for disintegration appears to be very elaborated showing linear and quadratic effects of the controlled variables as well as the interaction. Nevertheless a stationary region is present. The disintegration time is always lower than the 15 minutes required by the European Pharmacopeia.

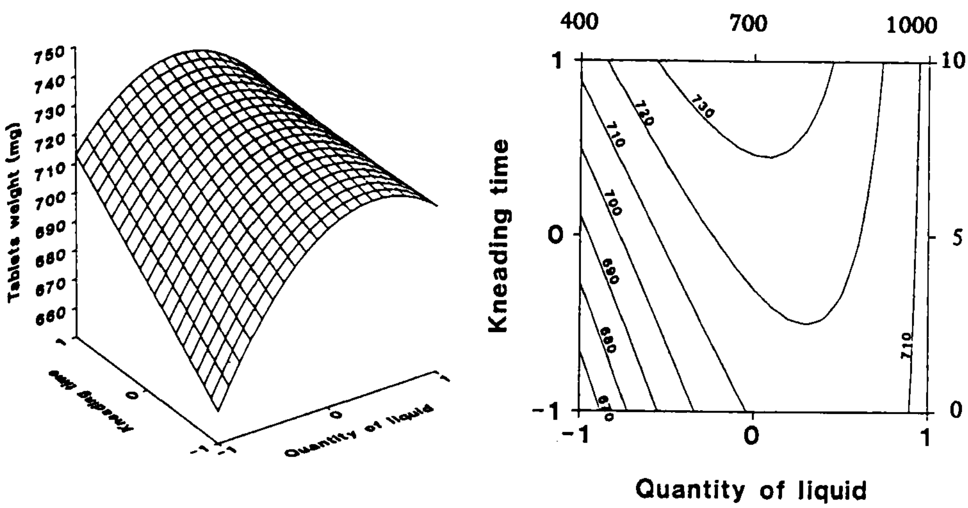

FIGURE 11. Response Surface and Contourplots for the Tablets Weight.

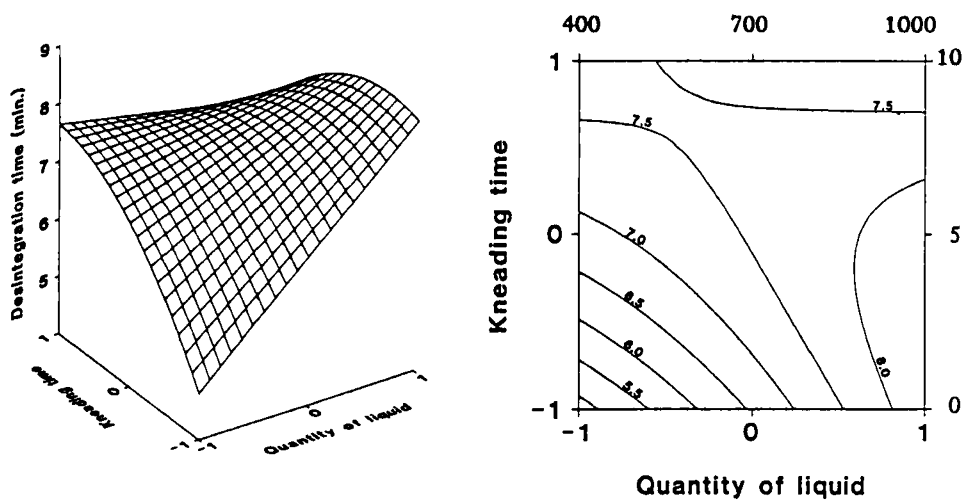

FIGURE 12. Response Surface and Contourplots for Disintegration Time.

TABLE 5.
Optimal Operating Conditions.

RESPONSE VARIABLES	OPTIMUM	QUANTITY (ml)	TIME (min.)	RESPONSE VALUE
Flowability	minimum	740	10	4 s.
Bulk volume	minimum	710	10	152 ml
Mean diameter	maximum	760	10	155 μm
Tablets weight	maximum	680	10	735 mg

TABLE 6.
Response Variables Variations
between 680 and 760 ml of granulating Liquid
for a kneading time of 10 minutes.

Flowability	4.02 - 4.04 s
Bulk volume	152.20 - 152.22 ml
Mean diameter	154.5 - 155.7 μm
Size distribution	2.78 - 2.85
Granules friability	27.5 - 25.8 %
Weight of tablets	735 - 731 mg
Hardness of tablets	13.2 - 13.6 kg
Tablets friability	1.10 - 1.07 %
Disintegration time	7.3 - 7.5 min.

Optimal operating conditions leading to a characteristic extremum (maximum or minimum) are collected in table 5.

For all the variables displaying a characteristic extremum the optimal kneading time is 10 minutes and the optimal quantity of granulating liquid varies from 680ml to 760ml which are quite narrow values.

It is very interesting to see that, in this range of variation for the quantity of granulating liquid and for 10 minutes of kneading, all the studied responses are not varying significatively as it is reported in table 6.

CONCLUSION

The modern pharmaceutical scientist in charge of process studies can no more waste time, energy and materials, proceeding just by trial and error and varying factors one by one. This traditional but still used approach leads to uncertain, nonvalidated and in the worst case wrong conclusions. A rational statistical methodology is nowadays necessary to solve problems of formulation or process development. The general Response Surface Methodology is an economical method allowing to collect a maximum of information with a minimum of experiments. Recent advances in computing greatly facilitates complicated and long calculations such as multiple regression used in this methodology.

This statististical approach was applied in this work to study the wet granulation process in a high-shear mixer, granulator and dryer. Building sequential experimental designs appeared to be efficient to describe the influence of the quantity of granulating liquid and kneading time on the characteristics of the produced granules and tablets. Because the first design proved its weakness, the initial experiments were completed in order to evaluate quadratic models, statistically tested. Helped by the response surfaces and the corresponding contourplots, it was possible to point out interesting operating conditions. Using the response surface methodology is was possible not only to optimize the process of wet granulation but also to validate it.

NOTES

Softwares used for multiple regression, statistical tests and graphics generation: RS/Discover, BBN Software Products, Cambridge, U.K.; SYSTAT, Intelligent Software, Evanston, U.S.A.

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