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PLANNING EXPERIMENTS USING AN INSTRUMENTED TABLET MACHINE IN FORMULATION

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SUMMARY

For a few years, we have been in possession of a methodology for the formulation of tablets. It is based on an experimental planning design of rational development work using an instrumented tablet machine. On the other hand, it is possible to organize mathematically the scientific studies in various fields so that we can reach the best result as fast as possible, i.e. to carry out an optimal number of experiments giving the maximum amount of information : this is the application of the statistical experimental designs. The aim of this study is to associate these two concepts.

The major principle is to study the variations of well-chosen answers (tablet crushing strength...) according to the percentages of vehicles chosen as variables (diluent, disintegration agent...) while the methodology of mixing remains fixed. An experimental design is built, a well-defined number of experiments are carried out, and then we try to put into equation the responses as a poly-

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nomial function of the percentages of vehicles. The best mathematical models are statistically determined by multilinear regression and used to plot the response surfaces. This mathematical treatment associated with the objectives of the pharmacist allows us to determine the optimal formula. And so, carrying out the theoretical optimal experiment we can verify the accordance of the experiment with the model.

A first approach with wet granulation showed all the difficulties in fixing all the parameters. But it has already shown all the advantages of the experimental designs and that this technique can be very helpful in building the experimental planning design.

With direct compression, two experimental designs were built to determine the optimal formula as fast as possible : these were a Scheffe design and a Mac Lean and Anderson design.

When the constraints on vehicle percentages lead to a triangular experimental field, Scheffe designs are recommanded. For any other configuration Mac Lean and Anderson designs will be useful.

The responses were :

1. Y1/D, where Y1 is the maximal pressure measured at the upper punch and D the crushing strength of the tablet.
2. (V10 - V500), where V10 and V500 are the volumes of 100 grammes of the final mix of powder after 10 and 500 tamping taps given by a standardized apparatus. Their difference (V10 - V500) should not exceed 20 ml.
3. td, the disintegration time of tablets measured by way of the European Pharmacopea test.

In both cases, the results were excellent considering the differences between the response values given by the mathematical models and the corresponding experimental values.

INTRODUCTION

For a few years, we have been in possession of a methodology for the formulation of tablets (1, 2, 3).

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It is based on an experimental planning design of rational development work using an instrumented tablet machine (4).

On the other hand, it is possible to organize statistically the scientific studies so that we can reach the best result as fast as possible in a well-defined experimental field, i.e. to carry out an optimal number of experiments providing the maximum amount of information : this is the application of the statistical experimental designs (5, 6, 7, 8).

The aim of this study is to associate these two concepts.

1. BASIS OF THIS METHOD

1.1. Statistical designs

Statistical designs have been used by pharmaceutical development scientists in parametric studies of equipments or processes concerning a given formula (9, 10, 11, 12), whereas this work is specifically a formulation study (13). The designs we have performed be long to one particular group of statistical experimental designs :

- The Response Surface Methodology ;

"... 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..." (14).

One such type of those design is the Extreme Vertices Design which have been specially developed for experiments with mixtures (15). It does not incorporate any process variables, which implies that the process should remain strictly fixed.

Two of these designs were realized :

- a Scheffe design,
- a Mac Lean and Anderson design which derives from the first (13, 15).

When the constraint on vehicle percentages lead to a triangular experimental field, Scheffe designs are recommended. For any other configuration Mac Lean and Anderson (13) designs will be useful.

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The principle is to study the variations of well-chosen responses, tablet crushing for example, according to the percentages of vehicles chosen as variables (diluent, disintegration agent...). Nothing else but those values has to vary during the experiments. This implies a careful preparative work described in the next paragraph.

1.2. Modelling the responses

The general polynomial equation of the response model is the following one for a three component mixture and for a degree up to three.

$$Y = b_1X_1 + b_2X_2 + b_3X_3 \quad \text{(1st degree model)}$$

$$+ b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 \quad \text{(2nd degree)}$$

$$+ b_{123}X_1X_2X_3 \quad \text{(incomplete 3rd degree)}$$

$$+ b'_{12}X_1X_2(X_1 - X_2) + b'_{13}X_1X_3(X_1 - X_3) +$$

$$b'_{23}X_2X_3(X_2 - X_3) \quad \text{(3rd degree)}$$

where - Y is the measured response,
- X_i the percentage of ingredient i,
- b_i, b_{ij}, b_{ijk}, b'_{ij} are the coefficients of the model.

Evidently, the minimal number of experiments to be performed, i.e. the number of coefficients to determine, depends on the variable number and the model degree. Therefore our experimental study is limited to the influence of no more than four parameters.

1.3. Data Analysis

Statistical tools can be classified into three sections.

1.3.1. The Principal Component Analysis (PCA) which is used mainly when numerous assays are performed.

1.3.2. The classical Analysis of Variance (ANOVA) and its derivatives (MULTINOVA).

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1.3.3. The Multilinear Regression Techniques which is used for Response Surface Methodology.

The details of data analysis have already been described (7, 11, 14) and their discussion is not within the scope of this text. Its general principle is the following : the analysis of experimental data, according to the chosen model is tested on a computer by multilinear regression using a statistical package. The global efficiency of the model is measured from a correlation coefficient. When this coefficient is superior to 0.95, the fitting is satisfactory ; it is excellent if the coefficient is superior to 0.99.

Moreover 2 tests can be performed :

1) Lack of adequacy of the model is tested using an F-test
2) The significance of the estimated coefficients of the model is tested using the variance-covariance matrix of the coefficients and a student t-test. The purpose is to determine the probability of the coefficients not to have a zero value.

All these tests allow us to choose the best model. It is used to plot the different response surface contours where each contour line connects responses of equal value.

1.4. Optimization

Then, we can see if it is possible or not to define an optimal area in the experimental field. So we use the model to predict the responses corresponding with the optimal mixture, i.e. with the optimal formula. The prediction is tested by carrying out an experiment and comparing its results with the calculated values.

2. PROPOSED METHOD

The tablet formulation methodology using statistical experimental designs and instrumented tablet machines is described in table I.

First, we have the preformulation requirements : the basis of the formulation work must be the careful study of preliminary data, problems to be solved, and requirements such as physico-

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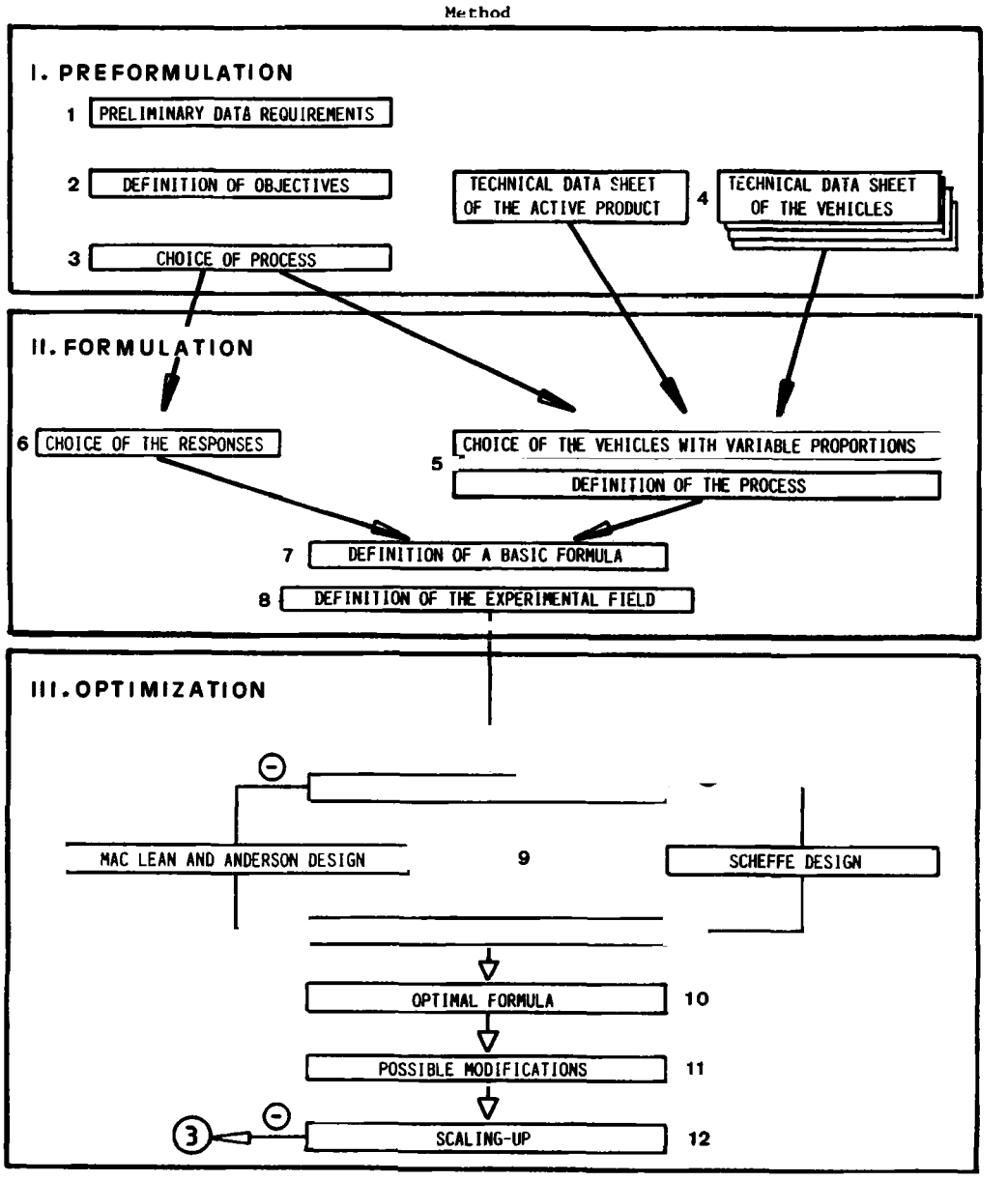

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chemical properties of materials, equipment facilities, marketing necessities... (1).

It is necessary to set up the objectives of the study (2) : for example the percentage of active powder in the tablets, the properties of this active powder in relation to the compression, the requirements of the tablets and of its production conditions.

The type of process (direct compression or granulation...) (3) is a preliminary datum. During the preformulation phase we study the behaviour of the active powder in response to compression and of each vehicle used in compression at the laboratory on an instrumented tablet machine. On the "technical data sheet" of each product (4) we report all the compressional characteristics of the materials, but also their technological properties such as flowability, density, size distribution... (3, 16).

All those preformulation requirements lead us to the formulation phase. The technical data sheet of the active product gives all the information necessary for choosing the vehicles with variable proportions (5) with the assistance of our methodology of formulation (1,4). This methodology is based on the properties of the materials measured with an instrumented tablet machine and at the same time permits the definition of the process that will have to remain fixed during the following steps of the study. This leads to a basic formula (7) where some of the proportions of its ingredients are fixed when the rest is available for the variables.

In addition, the choice and the definition of the responses (6) allow us to define the experimental field easily (8). The responses may be for example :

- Y1/D, where Y1 is the maximal pression measured at the upper punch and D the crushing strength of the tablet. It is calculated for a given value of D (80 N for example).
- (V10 - V500), where V10 and V500 are the volumes of 100 grammes of the final mix of powder after 10 and 500 tamping taps given by a stamp volumer (a). Their difference (V10 - V500) should not exceed 20 ml.

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- t_d, the disintegration time of the tablet measured by the way of the European Pharmacopoea test.

The third part of this table consists in the choice of the statistical experimental design and its realization. According to the constraints related to each vehicle percentage in a ternary mixture, the experimental field may be either a triangle or any other geometric figure such as a hexagon or a trapezium.

When the experimental field is a triangle, it is easy to transform it into an equilateral triangle, the summits of which correspond to pure pseudo-components. Then, Scheffe designs are well adapted for modelling the responses.

For other cases, the experimental optimal strategy corresponds to designs reported by Mac Lean and Anderson.

Hence the shape of the experimental field is fundamental for determining the pertinent design to be used.

The treatment of the results permits :

1) The definition of a model for each response,
2) The plotting of the response surface contours,
3) The determination whether an optimal area exists or not according to the objectives.

Experiments are then performed to verify the predictions of the model. If the model is unvalid it is necessary to develop new hypotheses to define a new basic formula.

Step number (11) consists in a possible improvement of the optimal formula and then we may be interested in the scaling up (12).

3. EXAMPLE OF APPLICATION

We had to study whether a direct compression formulation of tablets containing 20 per cent of an active powder with bad compressibility, was possible or not. The final tablet had to be disintegrated within 5 to 10 minutes. Such a study is typical of the field of statistical experimental designs.

The type of process (direct compression) (5) was here a preliminary datum.

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The three vehicles the proportions of which will vary are : Avicel pH 102® (b), Dicalcic phosphate and wheat starch. The first two vehicles were chosen because of their good compressional characteristics and notably their power to provide hardness to the tablets. Wheat starch was tested as a flowability agent (17) and as a disintegration agent.

Te experimental field is determined by selecting the upper and lower limits of the variables. It was defined as follows :

$$5\ \% < X_1 < 23\ \%$$
$$0\ \% < X_2 < 63{,}9\ \%$$
$$0\ \% < X_3 < 63{,}9\ \%$$
$$\text{and } \Sigma X_i = 68{,}9\ \%$$

where X_1 = percentage of wheat starch
X_2 = percentage of Avicel pH 102
X_3 = percentage of Dicalcic phosphate

The experimental field is here a trapezium and so a Mac Lean and Anderson design is recommended. Such a design is easy to realize by graphical means for three or four components, but a general method is available for designing (13).

Here, the chosen design includes :

- The summits of the trapezium, required for determining the coefficients of a 1st degree model,
- The middles of all the sides, required with the previous points for determining the coefficients of a 2nd degree model,
- The central point needed for the 3rd degree incomplete model.

So nine experiments have to be performed. The representative contour graphs of the response surfaces are given in Fig. 1, 2, 3 and the optimal area in Fig. 4.

In that example, we needed :

$$Y1/D < 100$$
$$Dt > 4{,}5\ \text{mns}$$
$$V10 - V500 < 25\ \text{ml}$$

Three experiments were there performed to verify the predictions of the models. The results presented in Table 2 were good

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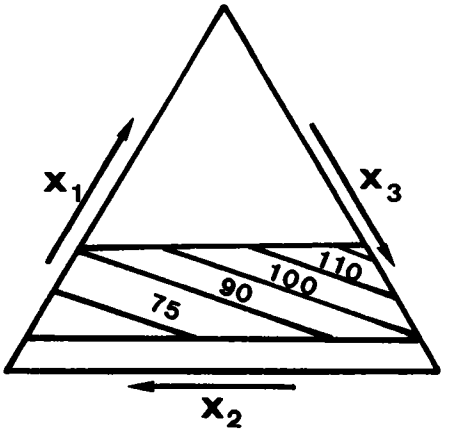

FIGURE 1
Diagram of Y1/H = f (X1, X2, X3)

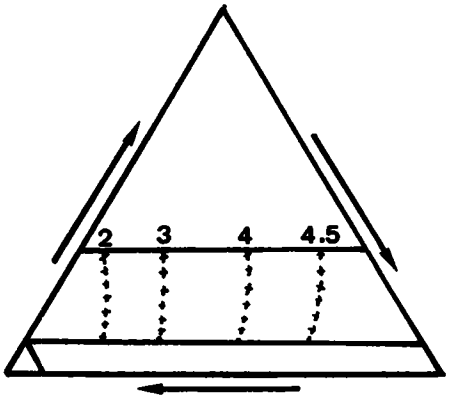

FIGURE 2
Diagram of Dt = f (X1, X2, X3)

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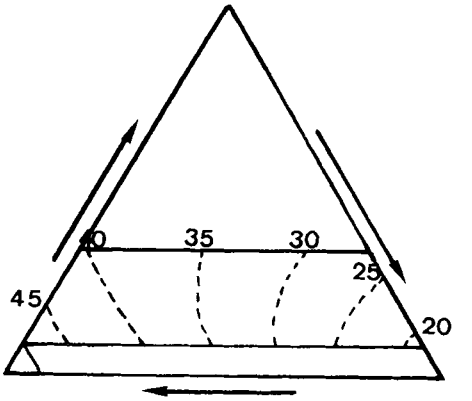

FIGURE 3

Diagram of (V10 - V500) = f (X1, X2, X3)

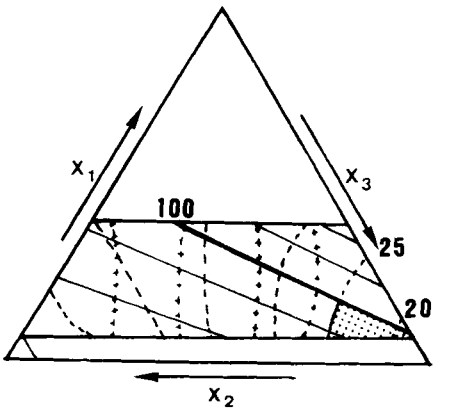

FIGURE 4

Definition of the optimal area

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TABLE 2

Comparison between experimental results and the predictions of the models

			Y1/H	(V10 - V500)	Dt
	Experimental	Model	Relative error% Absolute error	Relative error% Absolute error	Relative error% Absolute error
01	Y1/H =94 V10-V500 = 20 Dt = 6.25	96.2 20 4.71	-2.34% -2.2	0% 0	24.64% 1.54
02	Y1/H = 84.6 V = 28 Dt = 5.5	90 24.3 4.64	-6.38% -5.4	13.2% 3.7	15.64% 0.86
03	Y1/H = 94.5 V = 26 Dt = 5.4	96.9 22.3 4.64	-2.54% -2.4	13.2% 3.7	15.38% 0.72
Maxi of absolute error of the model			- 7.55 to 7.93	-3.54 to 4.06	1.08
Maxi of relative error of the model			10.3%	15%	54%

TABLE 3

Experimental design and experimental value of the responses

	Variables			Responses		
Experiment	X1	X2	X3	Y1/H	V10-V500	Dt
1	1	0	0	137	28	3.5
2	0	1	0	60	50	1.5
3	0	0	1	91	20	7
4	1/2	1/2	0	99	30	2
5	1/2	0	1/2	133	24	4
6	0	1/2	1/2	77	34	4

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according to the experimental design methodology but they showed that the experimental field we had chosen was not good. That is why we decided to replace starch with Tablettose® (c) and to make its percentages vary within the same range as the other ingredients (we kept 5 % of starch in the formula as a glidant). So we performed a Scheffe design.

The experimental results are reported in Table 3. We can notice that experiments n° 2, 3 and 6 had already been performed in the previous study.

The models are :

$$Y1/D = 137\ X_1 + 60\ X_2 + 91\ X_3 + 2\ X_1X_2 + 76\ X_1X_3 + 6\ X_2X_3$$

$$(V10 - V500) = 28\ X_1 + 50\ X_2 + 20\ X_3 - 36\ X_1X_2 - 4\ X_2X_3$$

$$Dt = 3{,}5\ X_1 + 1{,}5\ X_2 + 7\ X_3 - 2\ X_1X_2 - 5\ X_1X_3 - X_2X_3$$

A seventh experiment was carried out to verify the 2nd degree models. This experiment was chosen among the ones included in the optimal design for studying an incomplete 3rd degree model (Table

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TABLE 4

Experimental results to verify the models of the second degree

	Variables			Responses		
	X1	X2	X3	Y1/H	V	Dt
exp. n° 7	1/3	1/3	1/3	102	30	2.5
model				105.33	28.22	3.11
difference				- 3.33	+ 1.8	- 0.6
%				- 3.2%	- 5.9%	-24.4%

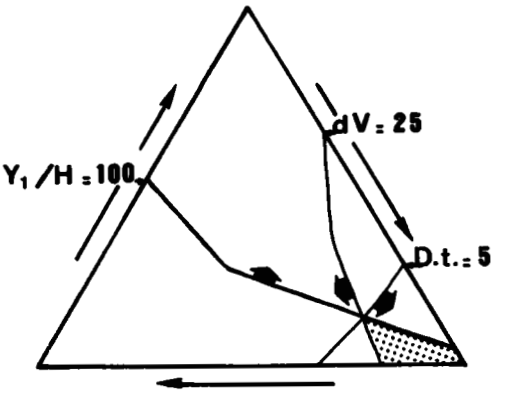

FIGURE 5

Optimal area and experimental field

4). The models were verified so we plotted the response surface contours (Figure 5) and we determined the optimal area.

Two points were realized, O_1 and O_2, respectively the extreme point considering the Tablettose® percentages and the central point. The final results are reported in Table 5.

N.B. : Those 2 formulae showed excellent flow ability properties.

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TABLE 5

Final results : comparison between experimental values and the predictions

	X1	X2	X3	Y1/H	V	Dt
01	12.25	17.50	70.25	99.9	26	4.5
Model				98.53	25	5.01
Δ				1.4	1	- 0.5
%				1.4	3.85	11.3
02	4.04	9.05	86.91	98.8	23	5.8
Model				95.2	22.6	6.1
Δ				5.6	+ 0.4	- 0.3
%				5.7	+ 1.7	5.2

The adequacy of the models to the experimental results is quite satisfactory. It seems that poor flowability was the principal factor of variation in the first part of the study.

So we chose O_2 as the best formula.

CONCLUSION

This work points out that a satisfactory modelling may be obtained for each response from a small number of well chosen experiments.

These models allow us to draw the representative contour graphs of the response surfaces.

The surimposition of these contour plots leads to an area corresponding to the optimal formula.

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FOOTNOTE

(a) Engelsman - Ludwighaven
(b) FMC Philadelphia
(c) Meggle Wasserburg

BIBLIOGRAPHY

1. J.C. Guyot, A. Delacourte and M. Traisnel, Sci. Techn. Pharm,, 9, 459-558 (1980)
2. J.C. Guyot, A. Delacourte, B. Devise and M. Traisnel, Labo Pharm., 263, 209-214 (1977)
3. A. Delacourte, J.C. Guyot and M. Traisnel, Sci. Techn. Pharm., 11, 131-140 (1982)
4. J.C. Guyot, A. Delacourte, P. Bleuse and P. Leterme, Sci. Techn. Pharm., 11, 427-432 (1982)
5. O.L. Davies, "The design and analysis of industrial experiments", Longman Group Ltd, New York, 1978
6. V.L. Anderson and R.A. Mac Lean, "Design of experiments : a realistic approach", Marcel Dekker Inc., New York, 1974
7. P. Ozil, J.P. Caire, "Initiation aux plans d'expériences." Lecture of Industrial Pharmacy DEA, Faculté de Pharmacie de Lille, 1986
8. G. Romier, Plans d'expériences, in Galenica, Vol. 3, Lavoisier Techn. et Doc., Paris, 1982
9. B. Delerue, Les plans d'expériences et les applications en formulation. Thèse de Doctorat en Pharmacie, Lille, 1985
10. B. Jimenez, D. Chulia-Clément, C. Jeannin, P. Lemaître and A. Verain, Pharm. Acta Helv., 60, 149-156 (1985)

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11. B. Jimenez, D. Chulia, C. Jeannin, B. Lemaître, P. Ozil and A. Verain, Pharm. Acta Helv., 61, 282-291 (1986)
12. Z.T. Chow-Han, I.C. Yang, A.A. Azuro and Lihua Chi, J. Pharm. Sci., 71, 1371-1375 (1982)
13. P. Billardon, Intégration des plans d'expérience dans la méthodologie de formulation assistée des comprimés, DEA de Pharmacie Industrielle et Génie Pharmaceutique, Lille, 1986
14. G. Stetsko, Drug Dev. Ind. Pharm., 12, 1109-1123 (1986)
15. R.A. Mac Lean and V.L. Anderson, Technometrics, 17, 149 (1975)
16. M. Minet, A. Delacourte, J.C. Guyot and M. Traisnel, Sci. Techn. Pharm., 12, 1, 17-35 (1983)
17. F. Jaminet and A. Denoel, Formes médicamenteuses destinées à la voie orale, Presses Universitaires de Liège, 1971

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