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A FACTORIAL APPROACH TO PROCESS VARIABLES OF EXTRUSION-SPHERONISATION OF WET POWDER MASSES

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INTRODUCTION

The purpose of the present work was to investigate a pharmaceutical process using an experimental design that generated a maximum of information for a minimum of experimental runs.

Optimisation has been studied by different authors since Plackett and Burman in 1946 (1). Factorial designs were applied first in preformulation studies (2, 3) and further in pharmaceutical studies (4, 5, 6, 7, 8, 9, 10). Phan Tan Luu has studied experimental research methodology in chemistry and in the optimisation of industrial processes (11, 12, 13).

This work is an application of fractional factorial methods to the pharmaceutical process of the manufacture of microgranules by extrusion-spheronisation.

Spheronisation or marumerisation is a technique of Japanese origin for the production of spherical dosage forms (14). Invented in 1964 by Nakahara, the technique involves a massing stage, in which the powders are mixed with water to form a heavy plastic mass; an extrusion stage in which the mass is shaped into cylinders of uniform diameter; and a spheronisation stage in which the cylinders are cut and rolled into spheres.

For a given formulation, the production of spheres is determined by the experimental conditions employed. The procedure to study the problem using experimental design techniques (15) consists of:

- selection of the parameters to be studied.
- choice of the level to be assigned to each parameter.
- definition of a model taking into account the different parameters and their interactions.

- selection of the optimum experimental matrix for calculation of the model coefficients.
- selection of a response variable.
- determination by experiment of the values of the response variable corresponding to the experimental matrix.
- analysis of the results obtained using the coded variables.

FORMULA AND MANUFACTURING PROCESS

The formulation was lactose : microcrystalline cellulose : water, (30:30:40). Wet granulation performed in a planetary mixer (Hobart & Cie., Paris, France) produced a plastic mass which was then shaped into cylinders by passage through the screen of an extruder (Fuji Paudal EXDS 60, Collette, Belgium). Cylinders were then cut and rolled into spheres on the grooved horizontal plate of a spheroniser (Caleva Ltd., Newcastle, England) rotating at high speed.

EXPERIMENTAL DESIGN : INITIAL STUDY

Construction of experimental design involves the selection of the parameters to be studied and the choice of desired effects.

Five parameters, each at two levels, were studied

X1 : spheronisation time
X2 : spheroniser speed
X3 : rate of extrusion
X4 : spheroniser load
X5 : extrusion screen

The response selected was the yield of granules of the desired size, this being defined as the size of the screen used for the extrusion of the wet mass.

The aim of the study was an evaluation of the variation of experimental response passing from one limit of the experimental plan to the other.

It was postulated that some interactions would exist, for example between the spheronisation time and the spheroniser rate, or between the spheronisation time and the spheroniser load, fitting a first degree model. A complete factorial plan studying all interactions would include $2^5 = 32$ experiments.

Initially only 8 experiments were envisaged, affording a fractional factorial design 2^{5-2} with a generator $I \equiv 234 \equiv 235 \equiv 1245$, the purpose being to study the main effects and the two-factor interactions.

The factorial design with coded variables is represented in table 1.

TABLE 1

Parameters	X1	X2	X3	X4	X5	Response
Experiments						
1	-	-	-	+	+	Y1
2	+	-	-	+	-	Y2
3	-	+	-	-	+	Y3
4	+	+	-	-	-	Y4
5	-	-	+	-	-	Y5
6	+	-	+	-	+	Y6
7	-	+	+	+	-	Y7
8	+	+	+	+	+	Y8

TABLE 2

Parameters	X1 (min)	X2 (rpm)	X3 (rpm)	X4 (kg)	X5 (mm)	Response (Yield %)
Experiments						
1	2	650	15	4	1.5	11.1
2	5	650	15	4	0.8	92.8
3	2	1350	15	1	1.5	19.7
4	5	1350	15	1	0.8	55.5
5	2	650	59	1	0.8	75.5
6	5	650	59	1	1.5	45.4
7	2	1350	59	4	0.8	46.5
8	5	1350	59	4	1.5	55

Levels of each parameter are represented by a sign: (-) for the low level, (+) for the higher level.

Results are shown in table 2, with the variables for each parameter studied being identified.

Coefficients bi representing the effect of the parameters Xi can be estimated. bi will be the mean difference of the response when Xi varies from level 0 to level + 1. In other words, response varies by about 2bi when the corresponding factor changes from one limit of the experimental plan to the other.

bi values are calculated as follows:

$$b1 = \frac{-Y1 + Y2 - Y3 + Y4 - Y5 + Y6 - Y7 + Y8}{8}$$

$$b2 = \frac{-Y1\ -Y2\ +Y3\ +Y4\ -Y5\ -Y6\ +Y7\ +Y8}{8}$$

$$b3 = \frac{-Y1\ -Y2\ -Y3\ -Y4\ +Y5\ +Y6\ +Y7\ +Y8}{8}$$

$$b4 = \frac{+Y1\ +Y2\ -Y3\ -Y4\ -Y5\ -Y6\ +Y7\ +Y8}{8}$$

$$b5 = \frac{+Y1\ -Y2\ +Y3\ -Y4\ -Y5\ +Y6\ -Y7\ +Y8}{8}$$

The construction of the matrix, with a generator I≡234≡135≡1245 implies the combination of effects with interactions.

Calculations produce the following equations:

$b1 = \beta 1 + \beta 35$ $\quad$ $b4 = \beta 4 + \beta 23$

$b2 = \beta 2 + \beta 34$ $\quad$ $b5 = \beta 5 + \beta 13$

$b3 = \beta 3 + \beta 24 + \beta 15$

where βi represents the real value of the coefficient and bi the estimation. Thus $\beta 1$, and $\beta 35$ are "aliases".

Some interactions can also be quantified. Interaction exists between two parameters when the effect of one parameter depends on the level of another at the same time.

In this case, each response is affected by a sign which is the product of the levels of both parameters. We can calculate b values for two interactions:

$$b14 = \frac{-Y1\ +Y2\ +Y3\ -Y4\ +Y5\ -Y6\ -Y7\ +Y8}{8}$$

$$b12 = \frac{+Y1\ -Y2\ -Y3\ +Y4\ +Y5\ -Y6\ -Y7\ +Y8}{8}$$

These estimations, as for principal effects, are combinations of effects.

$b14 = \beta 14 + \beta 25$ $\quad$ $b12 = \beta 12 + \beta 45$

Results are shown in table 3.

TABLE 3

b1 = 12	b14 = 10.5
b2 = - 6	b12 = - 0.9
b3 = 5.4	
b4 = 1.2	
b5 = - 17.4	

Some factors seem to be important : 1 (spheronisation time) and 5 (extrusion screen). Interaction between 1 (spheronisation time) and 4 (spheroniser load) is apparently important too.

However, it can be assumed that the values obtained for some coefficients are influenced by interactions : β 35 (interaction between rate of extrusion and extrusion screen) for b1; β 24 (interaction between spheroniser speed and spheroniser load) for b3.

EXPERIMENTAL DESIGN : COMPLEMENTARY MATRIX

It is possible to improve interpretation by separating effects and interactions.

Building a complementary matrix with a generator I≡-234≡-135≡1245 will give estimations b'i:

$b'1 = \beta 1 - \beta 35$

$b'2 = \beta 2 - \beta 34$

$b'3 = \beta 3 - \beta 24 - \beta 15$

$b'4 = \beta 4 - \beta 23$

$b'5 = \beta 5 - \beta 13$

The coefficients β i can be isolated by grouping the results of the first and second matrices.

The second factorial design is represented in table 4 with coded variables .

Results are shown in table 5.

b' values corresponding to this new matrix are given below.

β values are obtained as follows:

$$\beta 1 = \frac{b1 + b'1}{2} \qquad \beta 35 = \frac{b1 - b'1}{2}$$

$$\beta 2 = \frac{b2 + b'2}{2} \qquad \beta 34 = \frac{b2 - b'2}{2}$$

$$\beta 3 = \frac{b3 + b'3}{2} \qquad \beta 23 = \frac{b4 - b'4}{2}$$

$$\beta 4 = \frac{b4 + b'4}{2} \qquad \beta 13 = \frac{b5 - b'5}{2}$$

$$\beta 5 = \frac{b5 + b'5}{2}$$

TABLE 4

Parameters	X1 (min)	X2 (rpm)	X3 (rpm)	X4 (kg)	X5 (mm)	Response
Experiments						
1'	-	-	-	-	-	Y'1
2'	+	-	-	-	+	Y'2
3'	-	+	-	+	-	Y'3
4'	+	+	-	+	+	Y'4
5'	-	-	+	+	+	Y'5
6'	+	-	+	+	-	Y'6
7'	-	+	+	-	+	Y'7
8'	+	+	+	-	-	Y'8

TABLE 5

Parameters	X1 (min)	X2 (rpm)	X3 (rpm)	X4 (kg)	X5 (mm)	Response (Yield %)
Experiments						
1'	2	650	15	1	0.8	62.5
2'	5	650	15	1	1.5	34.9
3'	2	1350	15	4	0.8	56.9
4'	5	1350	15	4	1.5	29
5'	2	650	59	4	1.5	1.2
6'	5	650	59	4	0.8	78.7
7'	2	1350	59	1	1.5	10.2
8'	5	1350	59	1	0.8	47

TABLE 6

b'1 = 7.3	b'14 = 5
b'2 = - 4.3	b'12 = - 5.1
b'3 = - 5.8	
b'4 = 1.4	
b'5 = - 21.2	

TABLE 7

Parameters	Interactions
β1 = 9.7	β 35 = 2.3
β2 = - 5.1	β 34 = - 0.8
β3 = - 0.2	β 23 = - 0.1
β4 = 1.3	β 13 = 1.9
β5 = - 19.3	β 24 + β 15 = 5.6
	β 12 + β 45 = - 3
	β 14 + β 25 = 7.7

Other interactions cannot be isolated:

$$\beta 24 + \beta 15 = \frac{b3 - b'3}{2}$$

β 12 + β45

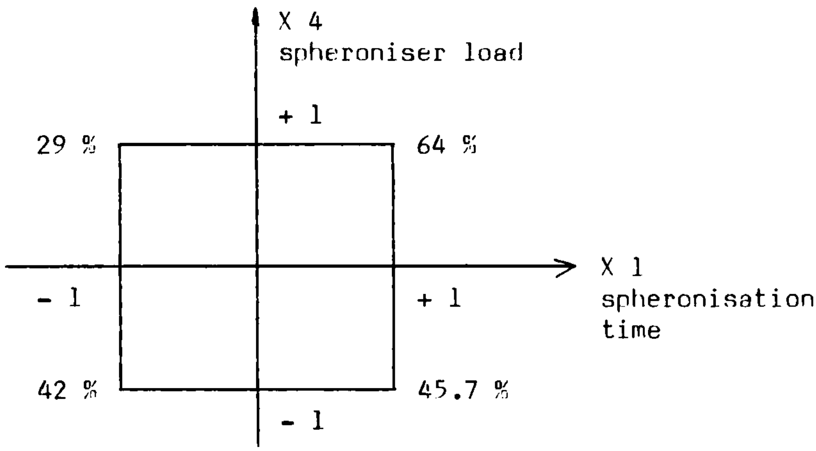
β 14 + β25

β values are reported in table 7

DISCUSSION OF RESULTS

Spheronisation time has a positive effect on the production of spheres: increasing the time from 2 to 5 minutes improves the yield about 20 % (β 1 = 9.7). However, there is a strong interaction β 14 + β 25, which, based on our non published results is probably mainly due to β 14 (β 14 + β 25 = 7.7). Thus spheronisation time and load must be considered together.

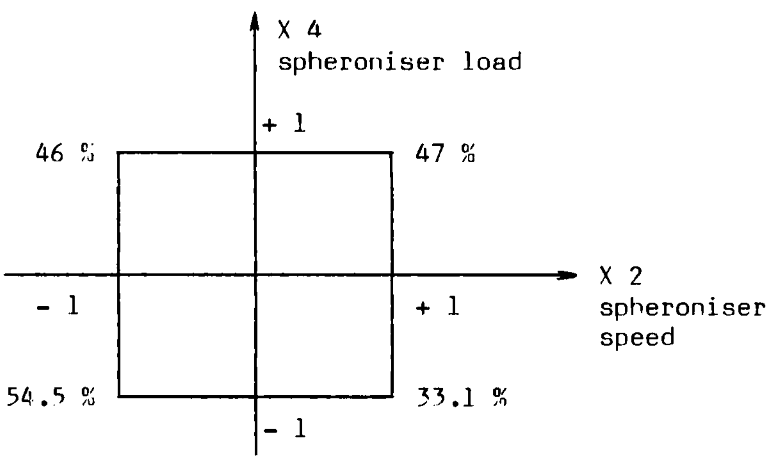
Mean values for 1 (-) 4 (-), 1 (+) 4 (-), 1 (-) 4 (+) and 1 (+) 4 (+) can be reported on a diagram.



The effect of increased spheronisation time is demonstrated at higher load (4 kg) but not at the lower value (1 kg).

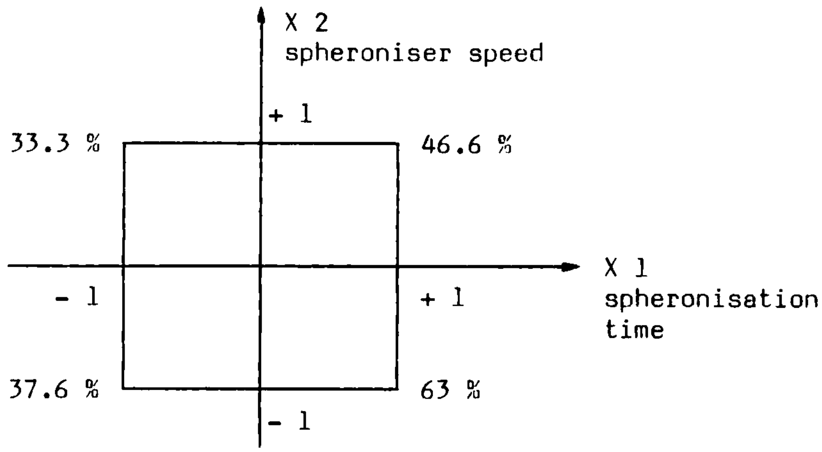
Spheroniser speed has a negative effect on the yield which is 10 % lower on passing from 650 to 1350 rpm (β 2 = - 5.1).

There is an important interaction β 24 + β 15 (+ 5.6). If it is considered that the interaction between spheronisation time and the extrusion screen is low, β 24 + β 15 can be considered as the interaction between spheroniser speed and spheroniser load.



The negative effect of spheroniser speed is important only at the lower load.

There exists also an important interaction between spheroniser speed and spheronisation time, if it is considered that interaction β 45 is negligeable.



Effect of spheronisation time is more evident at lower speed, improving the yield by about 25 %.

Extrusion speed has no effect on the yield (β 3 = - 0.2) and no significant interactions with the process variables.

Spheroniser load has little effect on the yield (β 4 = 1.3) but there are strong interactions with spheroniser speed (β 24 ≃ 5.6) and spheronisation time (β 14 ≃ 7.7), so that these variables cannot be considered separately.

Extrusion screen has a very strong negative effect on the yield: about 40 % lower on going from 0.8 to 1.5 mm (β 5 = - 19.3). There are no interactions with other variables.

The first plan gave a relatively good estimation of the importance of factors; b values were:

b1 = 12	(β1 = 9.7)
b2 = - 6	(β2 = - 5.1)
b4 = 1.2	(β4 = 1.3)
b5 = - 17.4	(β5 = - 19.3)

The second alternative plan permitted the calculation of the factors in an unambiguous manner and the separation of main effects from second order interactions. β value so obtained is about 0 instead of 5.4 at first for parameter X 3.

CONCLUSION

1. The results obtained enabled optimum ranges for process variables to be defined.

2. A fractional factorial design allows the evaluation of main effects and interactions when only 16 experiments were performed through two successive plans.

3. Definition of objectives and preliminary calculations showed predictable results for both plans. The complementary plan was known to be helpful if ambiguity existed.

4. Interpretation of results permitted the definition of the limits of the experimental zone.

5. Solving problems with this method is of real interest for quantification of effects and interactions, and possible extrapolation to a wider zone. Consideration of different response variables would permit many different interpretations and choice of conditions to be defined.

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