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Research paper

Influence and optimisation of operating parameters with a new binder in wet granulation. I: use in powder form

P. Soyeux[a], A. Delacourte[a,*], B. Delie[b], P. Lefevre[b], B. Boniface[c]

[a]*Laboratoire de Pharmacotechnie Industrielle, Lille, France*
[b]*Roquette Frères, Lestrem, France*
[c]*Laboratoire de Biomathématiques, Lille, France*

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Abstract

It is very important to know the properties of a new binder in wet granulation because it involves the good or poor quality of the grain and the tablets. To estimate the effects of various procedural parameters on the tablet properties, to evaluate the optimal quantity of binder and solvent, the consequences of excess solvent or time mixing and to limit the number of experiments, the authors use the method of design of experiments. The experiments were carried out on a classical blend of lactose and maize starch and the binder was LYCATAB® DSH, a maltodextrin. In this first part the binder was used in powder form and three process factors were retained and controlled, the binder quantity, the quantity of wetting liquid and the mixing time after granulation. Different outcomes were measured and mathematical relationships between responses and operating factors were performed and discussed. A 4% binder concentration with 14–16% of solvent gives good results and an increase in mixing time improves the tablet hardness without increasing the disintegration time (the wetting liquid was water and the blender a LOEDIGE).

Keywords: Binder; Experimental design; Operating parameters; Wet granulation

1. Introduction

Binders are used to produce solid oral forms for their cohesive and adhesive properties. They have an important role with regard to the technology as well as the biodisponibility. They must give excellent properties to the grain and the tablets such as flowability, hardness and are not to hold up disintegration [1–4].

The aim of this study is to show clearly the binding properties of an excipient in wet granulation and to know in which technological conditions it has to be used for optimal results.

When a new binder exists, the manufacturer asks questions about its place facing classical binders, its action on hardness and disintegration of the tablets. When making grain, technological problems can occur and it is necessary to know the consequences of an excess of solvent, if the binder requires an important quantity of water to take effect which increases drying time and therefore cost. It is also desirable to know the consequences of an accidental increase in mixing time. We propose a methodology to answer these questions and test it on LYCATAB® DSH developed by Roquette fréres [5]. This binder is a maltodextrin and meets the requirements of the USP XXII monograph. Obtained by controlled hydrolysis of maize starch, it is characterised by total water solubility at room temperature [6].

It can be used in dry blend or in solution, like PVP and in this part our aim was to evaluate the influence of main parameters on the binding capacity when the binder is used in powder form, in order to define the limits and optimal conditions for the use of the product.

* Corresponding author. Laboratoire de Pharmacotechnie Industrielle, Faculté de Pharmacie, 3 rue du Pr Laguesse, B.P.83, 59006 Lille Cedex France.

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Among the numerous parameters influencing on the granulation process, the following three are of more particular interest:

- The quantity of wetting liquid already studied by many authors [2,7–9]. The liquid has to solubilise the binder, it can also solubilise a part of excipients and/or active agents, its quantity is difficult to determine. We chose water.
- The quantity of binder.
- The mixing time after wetting [6,10,11].
- We use the methodology of design of experiments to determine the effects of change in the chosen factors and to study their interaction [6,11].

2. Materials and methods

2.1. Formula

The formula chosen is that generally used in wet granulation studies [2]. This formula consists of: 81.4% lactose EFK (HMS, F59 Sains du Nord) and 18.6% maize starch (Roquette Frères, F62136 Lestrem). The batch numbers are 326062046 for lactose and E56580473 for the maize starch.

The binder is incorporated as a powder into the powder blend in varying proportions. The granulated powder is lubricated with 0.75% magnesium stearate (Cooper, France).

2.2. Operating parameters and granulated powder production controls

The operating parameters and the controls applied are given in Table 1.

2.3. Manufacture and tablet controls

The lubricated granulated powder is compressed on an instrumented single-punch press [2,12] equipped with 11.28 mm diameter flat punches (area 1 cm^2). The compression matrix is 1 cm deep.

The following is obtained using the equipment available:

- $Y_{1\ max}$, maximum force (N) measured at the upper punch;
- $Y_{2\ max}$, maximum force (N) measured at the lower punch;
- X_{max}, maximum penetration depth (10^{-5} m) of the upper punch.

The weight, thickness and hardness values are determined for each trial on a sample of 5 tablets, but only hardness will be studied.

In order to compare the different trials, we have examined the hardness values calculated by simulation [12,13] for a force Y_1 of 20 kN maximum as well as the friability and disintegration obtained on tablets for a maximum force Y_1 as close as possible to 20 kN.

2.4. Choice of experimental design

The study of the binding properties when dry-blended is based on an experimental design [10,11]. Planning experiments increases the information obtained and fewer experiments are needed. The selected factors vary at the same time and interaction effects can be estimated. Furthermore, a model equation can be established for the response on the influent factors in two ways. On one the hand, with the use of a proper code for the different levels of the varying factors we can obtain an equation where the value of the coefficients shows the importance of the effects. On the other hand the response can be regressed on the factors with real units.

Previous studies have indicated that the responses could be non-linear. So we had to choose at least three levels for each of the three factors.

The study of a complete model based on the simultaneous variation of three factors at three levels implies the running of 27 trials. In order to limit the number of trials, we decided in favour of a fractional factorial planning on three levels. But to determine all the possible main and interaction effects, this plan is saturated and we needed an extra trial for the model validation. The chosen design is thus the first block of the 3^3 factorial design composed of nine trials plus one, in the centre of the field, for validation (trial 10).

2.5. Choice of experimental field

The variables chosen for this study are: the quantity of binder (%): X_1; the quantity of water (%): X_2; the mixing time after wetting (min.s): X_3; and the investigation field is given in Table 2.

For the upper limits, the scope of the field studied is limited by feasibility problems. For a given formula, the amount of wetting solvent is limited. Beyond this limit the wet mass is saturated and changes from the capillary state (corresponding to the phase of particle-size growth) to the kneaded state [2,7].

Various tests have confirmed this saturation phenomenon of the wet mass when the wetting solvent is present in large amounts. In addition, the maximum amount of wetting solvent depends on the quantity of binder used. Where a large quantity of binder is used, saturation of the wet mass is obtained with a small quantity of solvent. Conversely, a small quantity of binder makes it possible to incorporate a large quantity of wetting solvent before the wet mass is saturated.

The choice of the upper limits is therefore the result of a compromise between experimental feasibility and the scope of the field studied. The lower limits were set when the beginning of granulation was observed. So the quantity of binder varied from 2 to 6% and the quantity of water from 5

Table 1

Manufacturing process and controls

Process	Commercial product	Operating conditions	Control
Dry blend	LOEDIGE 5l (Maschinenbau GmbH, Elsenest 7/9, Postfach, 2050 D4790, Paderborn)	Speed (250 rev./min) Time (5 min)	Humidity (%)
Wetting		Variable quantity added at one time	Wet mass humidity (%)
Granulation	Frewitt (Euraf, 55 rue E. Deschanel F92400, Courbevoie)	Sieve (1.6/0.5 mm)	
Drying	Aeromatic air bed (Farnsburgerstrasse 6, CH-4132, Muttenz)	Time (15 min) Temperature (40°C)	
Sieving	Frewitt	Sieve (1.6/0.5 mm)	On dry grain Humidity Rheology Flowability Compaction Diameter
Lubrification	Turbula (Willy A. Bachofen A.G. Maschinenfabrik, CH-4005, Basel)	Speed (52 rev./min) Time (5 min)	
Compression	Single-punch instrumented machine	Punches (11.28 mm) Depth (1 cm) Speed (1tablet/s)	On tablets Weight Thickness Hardness Friability Disintegration time

to 16%. As regards the mixing time, the limits were taken from a previous study (i.e. 1 min 30 s to 10 min) [10].

2.6. Experiments

The trials are those of the first block of the $3^3/3$ fractional factorial design and can be represented as a matrix (Table 3). For each variable we used the following code; −1 represents the lower limit, 0 the centre point of the field, + 1 the upper limit (noted Z_i with i varying from 1 to 3). The experiments were randomised.

2.7. Choice of responses studied

To point out binder influence on the properties of grain and tablets among the various controls carried out throughout the operating procedure (Table 1) the following are of interest:

On the granulated powder:

- The flowability using a standardised funnel [14].
- ($V10$–$V500$): measurement of the volume after 10 and 500 compactions under standard conditions [14].
- The statistical mean diameter of the granulated powder, calculated after particle size analysis [14].

On the tablets:

- The hardness or crushing strength of the tablets, obtained by means of a SODEXIM apparatus (F-51140 Muizon).
- The disintegration of the tablets [14], using distilled water at 37°C, measured on 6 tablets.
- The friability of the tablets [14], determined by means of an ERWEKA friabilator (Euraf Courbe-

Table 2

Investigation field of the variables

Z_i (i = 1,2,3) coded variable	X_1 quantity of binder %	X_2 quantity of water %	X_3 mixing time (min.s)
−1	2	5.0	1.30
0	4	10.5	5.45
+1	6	16.0	10.0

Table 3

Design matrix

Trials	Variables		
	Z_1	Z_2	Z_3
1	−1	−1	−1
2	0	0	−1
3	1	1	−1
4	0	−1	0
5	1	0	0
6	−1	1	0
7	1	−1	1
8	−1	0	1
9	0	1	1
10	0	0	0

voie), expressed as a percentage of weight loss in relation to initial weight.
- The weight and the thickness were simply noted down and not reported here.

2.8. Mathematical modelling

The chosen design enables us to postulate, for the responses studied, a model of the second degree:

$$Y = b_0 + \sum_i b_i X_i + \sum_{ij} b_{ij} X_i X_j$$

with i,j = 1,2,3.z

The coefficients b_0 b_i b_{ii} b_{ij} characterise respectively the constant, the linear and quadratic effects of the variable X_i and the interactions between X_i and X_j.

Nine trials enabled us to calculate only 9 of the 10 coefficients of this model, but we used multiple regression software for the results (SAS System) and a particular procedure that finds subsets of variables that best predict the response. The 3D presentation of results in the form of a surface area was made by STATGRAPHICS Software (Uniware Paris). Each response is expressed as a function of two parameters, the third being preset.

3. Results and interpretation

3.1. Test results

The results of the 10 trials of the design carried out to study the binder used in powder form are given in Table 4.

The mean diameter seems to increase with the quantity of water. It is about 200 μm with 5–10.5% water and reaches 400 μm with 16% water.

The values of flowability and compaction of granulated powder are all below or equal to the limits usually set at 10 s for flowability and 20 ml for compaction. The rheological behaviour is therefore completely satisfactory over the whole experimental field. This good result was confirmed during compression since the tablets obtained showed only very slight weight variations, that is why we did not modelise these parameters.

As on the mean diameter, the quantity of water seems to be the variable with the greatest influence on hardness. We obtained about 50 N with 5% water, 70 N with 10.5% and finally a maximum of 100 N in trial 9 (16% water).

Unlike the two previous responses, disintegration mainly varies with the quantity of binder. With 2% binder, the disintegration time is 2–3 min and reaches 8–12 min with 6% binder.

Tablet friability is about 1.3% with 4% binder and 16% water, but reaches 18% with minimum quantities of binder and water. Generally, hardness and friability are negatively correlated, when the first one is increasing the second is decreasing, therefore we only modelised hardness.

Interactions between the different variables limit any direct evaluation of test results. It is therefore indispensable to calculate a mathematical model of the responses. We have chosen to model the mean diameter, the hardness and the disintegration time, successively.

3.2. Mathematical modelling and analysis

Consequently, three responses were the subject of a mathematical modelling.

3.2.1. Mean diameter

Model. With coded variables, the best model with 9 coefficients is as follows:

$$MD = 231.67 + 32.5\,Z_1 + 96.7\,Z_2 - 14.7\,Z_3 - 18.33\,Z_1Z_2 + 21.67\,Z_2Z_3 + 15.83\,Z_1^2 + 50\,Z_2^2 - 0.83\,Z_3^2 \quad (1)$$

this does not take into account Z_1Z_3 interaction. The most influent factor is Z_2 the quantity of water followed by its quadratic term, then Z_1 the quantity of binder, the interactions Z_2Z_3, Z_1Z_2 and the quadratic term Z_1^2, only after the

Table 4
Results of the 10 trials of the design carried out to study the binder used in powder form

Trials	Binder in dry blend					
	MD (μm)	FGP (s)	CGP (ml)	H (N)	DT (mins)	FR (%)
1	185	5.0	14	50.0	2.15	18.50
2	245	8.5	18	74.0	5.30	2.25
3	400	10.0	15	85.8	12.00	2.20
4	185	4.5	17	56.5	4.15	14.40
5	280	8.0	16	87.6	10.00	2.10
6	380	8.0	13	71.4	2.45	3.70
7	215	6.0	20	52.4	6.30	7.75
8	200	6.0	17	74.9	3.30	3.81
9	385	10.0	17	102.8	8.30	1.30
10	245	5.0	16	76.0	6.15	3.15

MD, mean diameter; FGP, flowability of granulated powder; CGP, compaction of granulated powder; H, hardness; DT, disintegration time; FR, tablet friability.

main effect of mixing time. Furthermore, owing to the weak coefficient of Z_3^2, Eq. (2) can be retained to model the mean diameter.

With uncoded variables: (X_3 in min):

$$MD = 245.0 - 10.15\,X_1 - 15.09\,X_2 - 10.41\,X_3 - 2.24\,X_1X_2 - 0.19\,X_2X_3 + 1.25\,X_1^2 + 1.67\,X_2^2 \quad (R^2 = 0.99) \qquad (2)$$

Validation of the model. With the calculation method of the mean diameter, one can at best obtain an accuracy of ±15 μm.

The mean diameter observed in the confirmatory trial is 245 μm. The mean diameter calculated from the model chosen is 232 μm. The remainder (13 μm) obtained in the confirmatory trial is thus small enough to validate this model.

Interpretation. The graph (Fig. 1) clearly illustrates the almost exclusive influence of the quantity of water on mean diameter. This increases from about 150 μm with 5% of water to 400 μm with 16% water. The quantity of binder has very little effect on mean diameter, especially in the presence of a maximum quantity of water and maximum mixing times where the particle-size growth is only 20 μm with 2–6% binder.

A comparison of the two mean diameter surface areas obtained after 1 min 30 s and 10 min mixing time shows

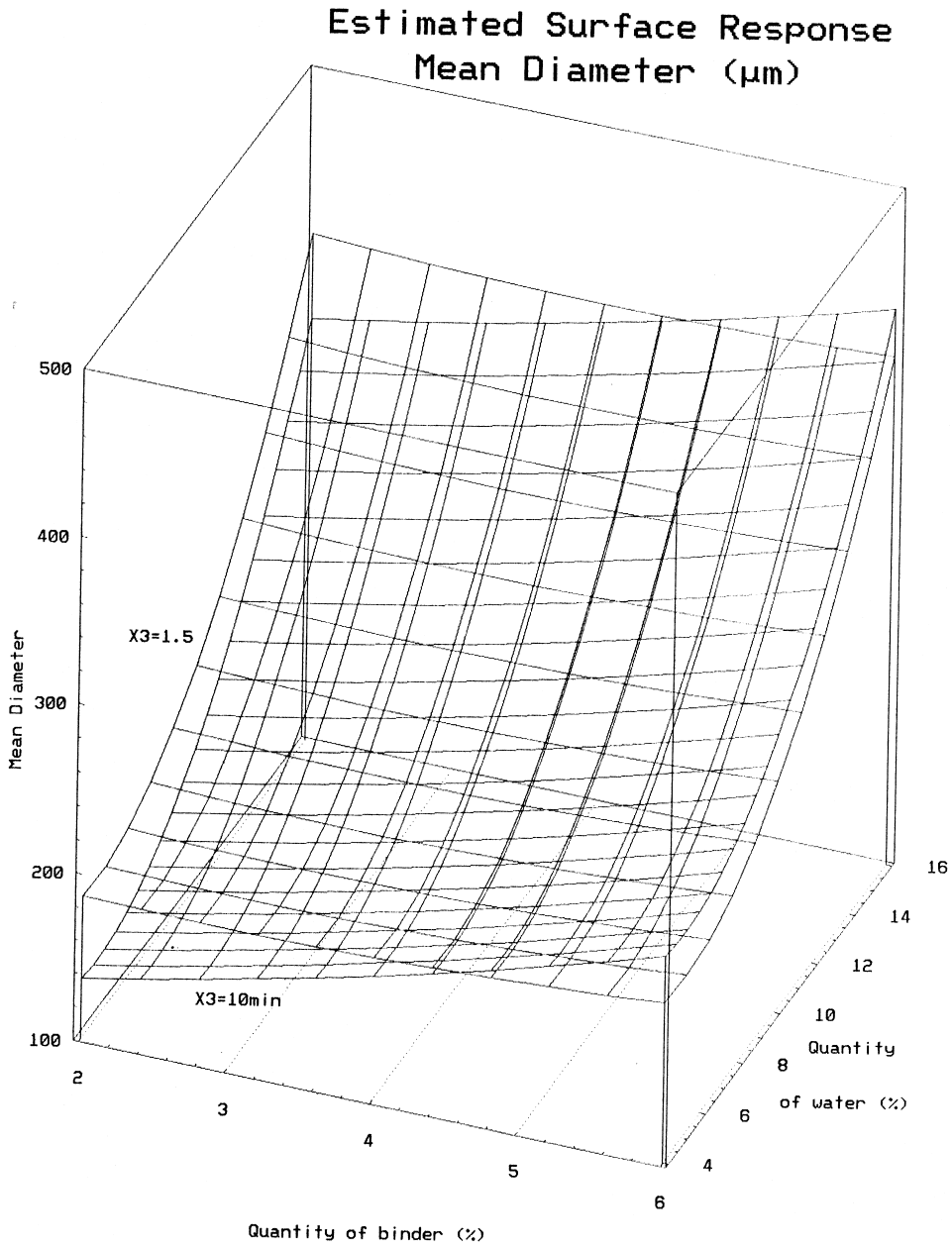

Fig. 1. Binder in dry blend. Response surface of mean diameter (μm) (mixing time after wetting fixed at 1 min 30 s and at 10 min).

that particle-size growth is about 30 μm over the whole experimental field. So, mixing time has little influence on mean diameter (the Z_3 coefficient is very low in Eq. (1)).

3.2.2. Analysis of hardness

Model. With coded variables (hardness in N):

$$H = 76.65 + 12.09\ Z_1 + 13.58\ Z_2 + 3.38\ Z_3 + 14.35\ Z_2Z_3 - 6.55\ Z_1Z_3 - 5.74\ Z_2^2 \quad (3)$$

With uncoded variables:

$$H = 23.93 + 10.26\ X_1 + 2.31\ X_2 - 2.96\ X_3 - 0.16\ X_2^2 - 0.71\ X_1X_3 + 0.62\ X_2X_3 \quad (R^2 = 0.998) \quad (4)$$

Validation of the model. With the method used to determine hardness, one can at best obtain an accuracy of ±5 N.

The hardness observed in the confirmatory trial is 76 N. With the equation obtained it is possible to calculate hardness mathematically, that is 76.65. The difference of 0.65 N between the observed and the calculated hardness is smaller than the margin of error fixed at 5 N. We can thus conclude that the hardness model is valid.

Interpretation. The coefficients of the model (Eq. (3)) show that the binder quantity, the water quantity and the interaction between quantity of water and mixing time have strong and positive effects with the same intensity. The effect of the interaction between the quantity of binder and the mixing time is weaker and has a negative influence.

Influence of mixing time. The influence of mixing time

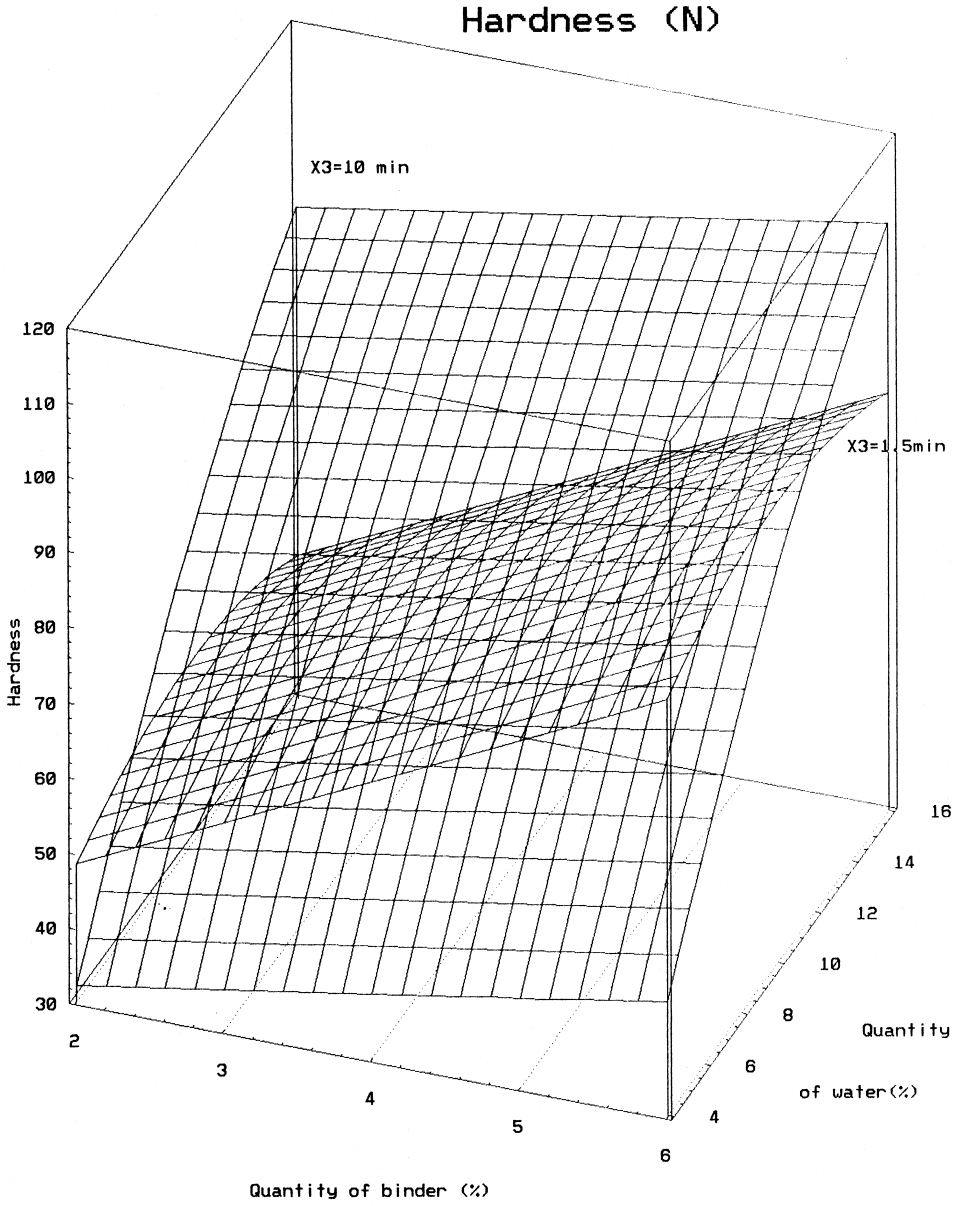

Fig. 2. Binder in dry blend. Response surface of hardness (N) (mixing time after wetting fixed at 1 min 30 s and at 10 min).

(Fig. 2) on the wet mass is illustrated by comparing the two graphs obtained after 1 min 30 s and 10 min, respectively. Between 1 min 30 s and 10 min mixing time, there is no increase in hardness with a small quantity of water (5%). The increase becomes significant when the quantities of water and binder are optimal. Consequently, a longer mixing time improves the effectiveness of the water/binder interaction on hardness.

Influence of the quantity of water and binder. The graph (Fig. 2) shows the significant influence of the quantity of water on hardness. Varying the quantity of water from 5 to 16%, with 6% binder, results in an increase in hardness from 50 to 110 N, i.e. an increase of 60 N. With 2% binder, hardness passes from 50 to 83 N, i.e. an increase of 33 N.

The quantity of binder has little influence on hardness with a small quantity of water (5%). With 2–6% binder and 5% water, hardness is about 50 N. The influence of the quantity of binder is greater with a quantity of water of around 16%: the increase in hardness is 30 N with 2–6% binder. However, it is only 7 N with 4–6% binder.

In an additional trial run with 0% binder and 16% water, the tablet hardness was 31 N. The increase in hardness due to the binder is thus significant between 0 and 4% binder, but smaller between 4 and 6%.

An analysis of the surface response demonstrates the optimum granulation conditions shown by the stabilisation obtained between 5 and 6% binder and between 14 and 16% water.

3.2.3. Analysis of the disintegration time

Model. With coded variables:

$$\mathrm{DST} = 6.333 + 3.333\,Z_1 + 1.708\,Z_2 + 0.667\,Z_3 + 1.75\,Z_1Z_2 - 0.292\,Z_2^2 \quad (5)$$

With uncoded variables:

$$\mathrm{DST} = 1.751 - 0.077\,X_1 - 0.248\,X_2 + 0.169\,X_3 - 0.0045\,X_2^2 + 0.163\,X_1X_2 \quad (R^2 = 0.997) \quad (6)$$

Validation of the model. The experimental value obtained in the confirmatory trial of this disintegration model is 6 min 15 s. The value calculated from this model is 6.32 min equal to 6 min 25 s.

The difference (10 s) between the observed and the calculated disintegration time is smaller than the margin of error fixed at 20 s. We can thus conclude that the disintegration model is valid.

Interpretation. No disintegration time exceeds the limit of 15 min fixed by the pharmacopoeia (Fig. 3). The quantity of binder has the most important effect, follows the effects of the quantity of water and the interaction quantity of water quantity of binder. With 16% water and 6% binder, the longest disintegration time is 13 min 30 s.

With a minimum quantity of water of 5% and a maximum quantity of binder of 6%, the disintegration time is 6 min 30 s. Conversely, with 2% binder and 16% water, it is only 3 min 10 s. This observation makes it possible to assert that the quantity of binder is the most influential variable.

Analysis of the hardness model has shown that the increase in hardness obtained with 4–6% binder is rather small (about 15 N). With an optimum quantity of water (14–16%), increasing the quantity of binder from 4 to 6% increases hardness only by 15 N. Its main effect is to prolong disintegration time by 60% (from 8 min 20 s to 13 min 30 s).

Comparison of the two surface responses obtained after 1 min 30 s and 10 min (Fig. 3) shows that they are superimposable and that the slight difference obtained is so close to the margin of error that the mixing time has no significant influence on disintegration.

4. Discussion

When a new binder has to be used, it is necessary to put it in relation with usual binders. In a previous study [2] the binder capacity of starch derived products and of the PVP K30 (polyvinyl pyrrolidone) was compared. These experiments allowed us to select the LYCATAB® DSH from the other starch derived because it yields good results. In the chosen experimental conditions (5% in dry powder), we verify that the results were nearly the same of those obtained with PVP K30. A study by Symecko et al. [15] confirms that PVP K30 and LYCATAB® DSH give practically the same results.

Moreover, excipient has not only to give good results easily transposable in industrial conditions, but also has to assure the robustness of the formula. So, we studied the optimal conditions of the binder, its behaviour with the increase of the quantity of water or of the mixing time.

LYCATAB® DSH is extremely soluble in water [5]. An increase of quantity of wetting solvent for a fixed binder concentration improves the tablet hardness and increases the grain diameter. The quantity of water does not overstep a limit like 16% with binder at 6% in our experimental conditions.

An increase of the mixing time facilitates the binder solubilisation, its repartition in the blend and its development in binding power.

5. Conclusion

The use of an experimental design has enabled us to study the influence of three important parameters in wet granulation (quantity of water, quantity of binder, mixing time) on the binding properties of LYCATAB® DSH used in powder form. The methodology can be useful to answer the questions arising when a new binder appears on the market and allows its use under optimum conditions.

In addition to an analysis of the influence of various para-

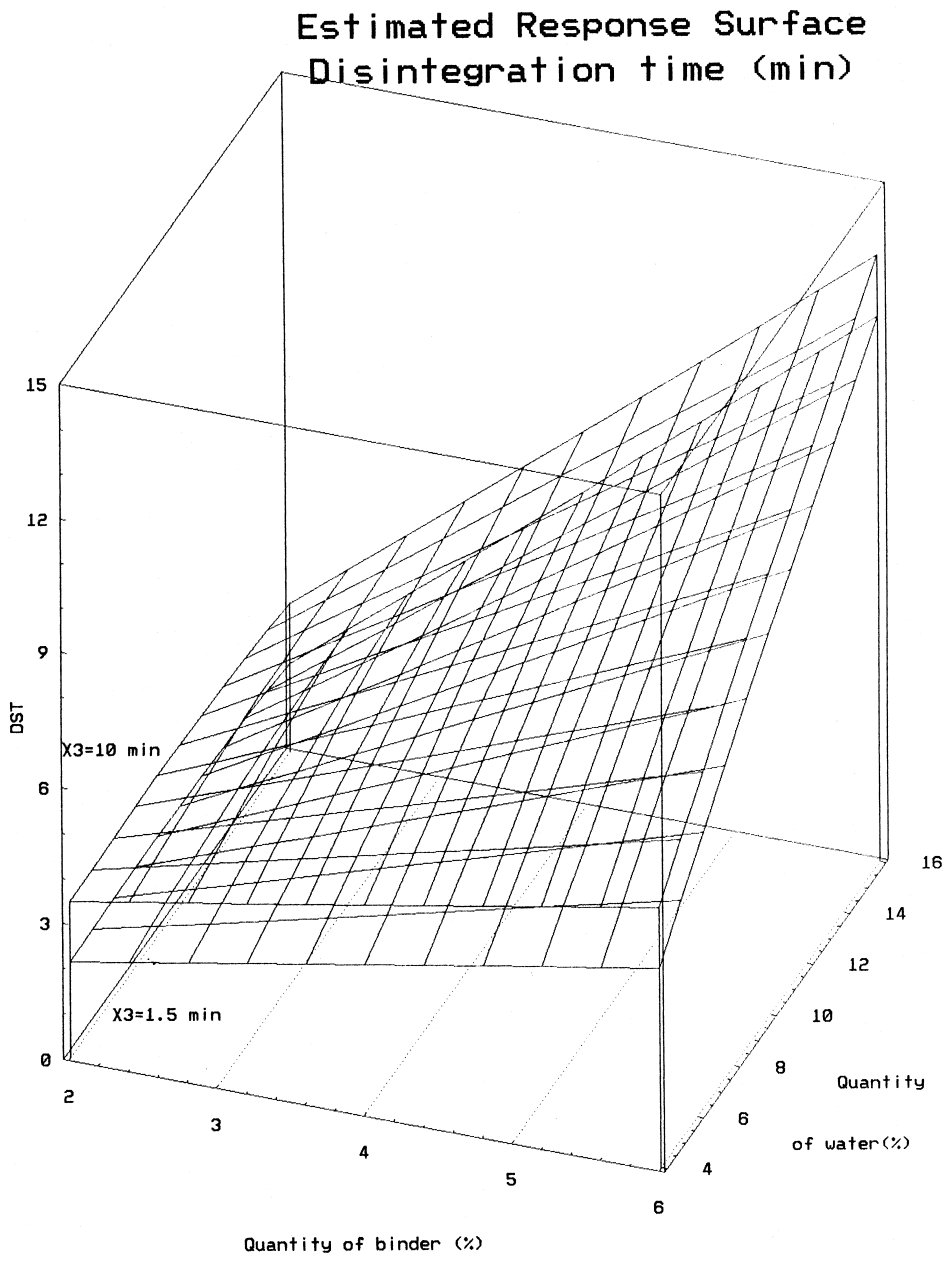

Fig. 3. Binder in dry blend. Response surface of disintegration time (min) (mixing time after wetting fixed at 1 min 30 s and at 10 min).

meters, this study determines an area corresponding to the optimum quality of the granulated powder and of the tablets. This area is defined by 14–16% water, 4% binder and 10 min mixing time.

Increasing the quantity of water leads to a significant increase in the mean diameter of size-graded granulated powder, increased hardness and longer disintegration time.

A quantity of binder larger than 4% affects hardness moderately, but extends disintegration time considerably. It is therefore absolutely essential to optimise the proportion of binder to obtain the best hardness/disintegration ratio. The mean diameter of size-graded granulated powder is independent of the quantity of binder.

Finally, mixing time has no significant influence on mean diameter or on disintegration time, but its increase, in the case where binder is used in powder form is beneficial because the binder is more soluble and there is an increase in hardness (by more than 25% here) without any change in the disintegration time.

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