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Optimization of a Granulation Procedure for a Hydrophilic Matrix Tablet Using Experimental Design

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ABSTRACT

An experimental design was used in order to optimize a granulation procedure in a high-shear mixer for a hydrophilic matrix tablet formulation. The parameters tested were the amount of water in the hydroalcoholic granulation liquid, the amount of granulation liquid, and the massing time. The amount of granulation liquid was the most important parameter, followed by the amount of water in the granulation liquid. The influence of the massing time was negligible. A granule with a friability below 20% was obtained.

INTRODUCTION

A granulation procedure for the production of a hydrophilic matrix tablet formulation based on a mixture of 95% pregelatinized starch and 5% polyacrylic acid (w/w) was developed (1). Production was performed in a high-shear mixer using a hydroalcoholic granulation liquid.

Several authors have reported on the optimization of wet granulation in a high-shear mixer (2, 4) and the application of an experimental design to this granulation process (7, 8). They examined especially the amount of granulation liquid, massing time, and impeller speed as variables during the granulation process.

In this work the influence of three granulation process parameters on the quality of the granules was studied in order to obtain an optimal formulation: the amount of water in the granulation liquid, the amount of granulation liquid, and the massing time.

MATERIALS AND METHODS

Materials

A mixture consisting of 95% pregelatinized starch [drum-dried waxy maize starch (DDWM), Cerestar, Vilvoorde, Belgium] and 5% polyacrylic acid (Carbopol 974P, B. F. Goodrich Co., Cleveland, OH, USA) was granulated by using an hydroalcoholic solution containing an amount of water ranging from 0% to 25% water (v/v) (parameter x_1)

Methods

Wet granulation is performed in an 8 liter capacity high-shear mixer (Gral 10, Collette Machines, Wommelgem, Belgium). The spherical bowl of this apparatus is equipped with a three-part impeller with a profile similar to that of the inside wall of the bowl. A chopper avoids the growth of oversized aggregates during wetting. The granulating liquid can be introduced at the top of the bowl. The double jacket was water cooled.

Granulation Procedure

A total amount of 750 g powder was brought into the bowl and mixed during 5 min with the impeller set at 430 rpm. A varying volume of granulation liquid (300–900 ml:parameter x_2) was poured on the powder mixture over a 30-sec period with the impeller and chopper set at 650 and 3000 rpm, respectively. The granulation occurred at the same speed during a variable time period between 1 and 10 min (parameter x_3). The granules were dried overnight at room temperature. Next the dried granules were passed through a 1-mm screen of an oscillating sieve (Erweka, Type FGS, Frankfurt, Germany).

Evaluation of the Granulate

Sieve Analysis

A 100-g sample was sieved using 1000-, 710-, 500-, and 250-μm sieves. The sieves were placed on a vibrating shaker (Retostat, Germany) for 5 min at the maximal vibrational capacity. The fraction retained on each screen was weighed and the yield of granules between 250 and 1000 μm and the amount of dust were calculated and expressed as a percentage of the total weight.

Bulk and Tap Density

The 250- to 1000-μm fraction of the granules was poured into a 100-ml graduated cylinder. The amount of the granules was noted before and after 100 taps on a tap density apparatus (J. Engelsman, Ludwigshafen, Germany) and expressed in percentage.

Friability

The friability of the granules was examined by introducing 10 g of the granules with a particle size between 250 and 500 μm together with 200 glass beads (mean diameter 4 mm) in an Erweka friabilator during 10 min at a rotational speed of 25 rpm (5). After 10 min the glass beads were removed and the granules were sieved over a 250-μm screen for 15 sec on a vibrating shaker (Retostat, Germany). The weight of the amount retained on the 250-μm screen was recorded and the percentage friability was calculated.

Tablet Quality

The visual aspect of the tablets was considered as an important evaluation parameter. Tablets were made with the 250- to 1000-μm granule fraction on an eccentric compression machine (Korsh, Type EKO, Frankfurt, Germany) with a pressure of 150 MPa. The tablets had an average weight of 100 mg and a diameter of 7 mm. The tablets were visually evaluated for hard particles and scored as good (G), acceptable (A), or poor (P).

Statistical Evaluation

Three process variables were studied: x_1, the amount of water in the hydroalcoholic granulation liquid (%); x_2, the amount of granulation liquid (milliliters); and x_3, the massing time (minutes).

All other parameters were kept constant during processing. To be able to obtain second-degree models, describing the responses as a function of the process variables, a central composite design was first applied. In the expected optimal zone, derived with these models, a 3^3 design was then used. All experiments were replicated to obtain a sufficient number of degrees of freedom to decide whether the coefficients of each of the parameters were significant. The results were calculated using Statgraphics (Statistical Graphics Corporation, USA). The results are shown as mean values.

RESULTS AND DISCUSSION

In order to obtain an optimal formulation during the granulation process, the influence of several parameters had to be studied. Recently, great interest has raised in the application of an experimental design on the granulation process (8). In this study an experimental design was used to optimize the granulation procedure and to examine the influence of three parameters on the granule quality. The results are shown in Tables 1 and 2. The results of the reproducibility tests are shown in Table 3.

As the average tap density for all granulations was 90% (range 87–93%), this parameter was not considered in the evaluation of the granulation procedure. The granule quality was evaluated using the following parameters: the amount of dust (defined as the fraction

Table 1

Process Parameters and Testing Results for Each Granulation (central composite design)

% Water in the Granulation Liquid (x_1)	Volume of Granulation Liquid (ml; x_2)	Total Granulation Time (min; x_3)	Tablet Quality[a]	Friability (%)	Amount of Granules (%) Within 250–1000 μm	Amount of Dust (%; fraction below 250 μm)
5.87	381	2′50″	G	59.0	69.0	30.8
20.13	381	2′50″	A	85.8	50.0	49.6
5.87	619	2′50″	G	26.5	76.4	23.2
20.13	619	2′50″	P	28.5	76.4	22.9
5.87	381	8′10″	G	70.5	67.8	31.8
20.13	381	8′10″	A	70.5	59.0	40.7
5.87	619	8′10″	G	21.5	72.5	23.4
20.13	619	8′10″	P	16.25	83.2	16.6
1	500	5′30″	G	34.0	74.0	24.6
25	500	5′30″	P	38.2	70.4	28.8
13	700	5′30″	G	90.0	41.4	58.6
13	300	5′30″	A	19.5	72.2	22.2
13	500	1′	G	50.0	73.4	26.5
13	500	10′	G	51.8	74.4	22.8
13	500	5′30″	G	61.5	74.8	22.2

[a]G: good; A: acceptable; P: poor.

Table 2

Process Parameters and Testing Results for Each Granulation

% Water in the Granulation Liquid (x_1)	Volume of Granulation Liquid (ml; x_2)	Total Granulation Time (min; x_3)	Tablet Quality[a]	Friability (%)	Amount of Granules (%) Within 250–1000 μm	Amount of Dust (%; fraction below 250 μm)
0	450	5′30″	G	38.5	74.4	25.1
0	675	5′30″	G	22.8	76.9	18.9
0	900	5′30″	—	—	—	—
1	450	5′30″	G	52.5	72.1	26.9
1	675	5′30″	G	16.8	74.6	22.7
1	900	5′30″	—	—	—	—
1	900	1′	—	—	—	—
1	900	10′	—	—	—	—
6.5	450	5′30″	G	59.5	75.9	23.7
6.5	675	5′30″	G	18.5	75.0	21.5
6.5	900	5′30″	—	—	—	—
13	450	5′30″	G	49.5	77.6	22.1
13	675	5′30″	A	11.5	83.6	12.3
13	900	5′30″	—	—	—	—

[a]G: good; A: acceptable; P: poor, cannot be processed.

Table 3

Reproducibility Experiments on the Granulation Procedure with the Following Parameter Values: x_1 = 15%; x_2 = 500 ml, and x_3 = 5 min

	Granule Size Distribution (%)					
Experiment	>1000 µm	1000–710 µm	710–500 µm	500–250 µm	< 250 µm	Friability (%)
1	0.91	23.64	17.24	37.15	21.06	49
2	1.80	18.57	18.98	39.26	21.39	54
3	3.06	17.08	18.1	38.66	23.10	46
4	3.72	20.15	18.83	36.45	20.85	55
5	3.01	19.95	17.77	37.88	21.39	49
Average	2.50	19.87	18.18	37.88	21.55	50.6
SD	1.13	2.44	0.73	1.13	0.89	3.8

below 250 µm), the friability, and the visual tablet quality. The visual tablet quality was poor for all situations with a high percentage of water in the granulation liquid, combined with a high volume of granulation liquid. The granule friability and the amount of dust after sieve analysis were highly correlated. The friability value increased for an increasing amount of dust. The correlation coefficient was 0.84 and highly significant ($p <$ 0.00001, t test). The regression equation for the amount of dust is given by:

$$y_1 = 120.81 + 3.37x_1 - 0.39x_2 - 0.0056x_1x_2 + 0.00038x_2 - 0.06x_1x_3$$

Only the significant parameters were retained in the equation. The t values for the equation with the coefficients are given in Table 4.

The model fits the data well (r^2 = 0.956). The parameter massing time (parameter x_3) had little or no

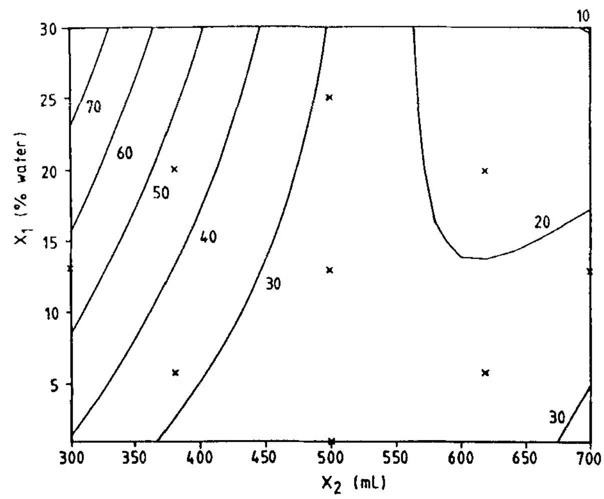

Figure 1. Contour plot for the evaluation of the amount of dust after sieve analysis (x_3 = 5.5 min).

Table 4

Coefficients (± SD), t Values and Significance Levels for the Parameters in the Evaluation of the Amount of Dust in the Granules

Independent Variable	Coefficient	Standard Error	t Value	Significance Level
Constant	120.81	10.84	11.14	0.00
x_1	3.37	0.40	8.32	0.00
x_2	-0.39	0.040	-9.60	0.00
x_1x_2	-0.0056	0.00078	-7.11	0.00
x_2x_2	0.00038	0.000039	9.77	0.00
x_1x_3	-0.060	0.014	-4.48	0.0002

influence. Figure 1 shows the contour plot at $x_3 = 5.5$ min (mean value).

The lowest amount of dust was obtained at high x_1 and x_2 values. From the results shown in Tables 1 and 2 it can be seen that visually a poor tablet quality was obtained for this combination. Therefore it can be concluded that for an optimal amount of dust a high x_2 value is required, possibly in combination with a not too low x_1 value.

The regression equation for the friability is given by:

$$y_2 = 28.34 + 10.26x_1 - 0.13x_1^2 - 0.013x_1x_2$$

Again only significant parameters were retained in the equation. The t values for the equation with the coefficients are given in Table 5.

The model fits the data well ($r^2 = 0.8634$), except for the low x_1 and the high x_2 values, which predicted values were much higher than the ones observed experimentally. Figure 2 gives the contour plot at $x_3 = 5.5$ min (mean value). Again the high x_1, x_2 combination gives the best friability results, but as mentioned previously, unfortunately, also a poor visual tablet quality (Tables 1 and 2). The best results are obtained at high x_2. The influence of x_1 appears to be less important but it appears that low x_1 is slightly preferable. Again x_3 is not important.

Table 6 shows the results for the granulations which are supposed to be in the optimal zone.

This optimal zone concerns high x_2 values and, because the combination of high x_2 and x_1 leads to a poor visual tablet quality, the zone is restricted to medium-high x_1 values. From these results it can be seen that a good visual quality was obtained throughout the zone. Without the addition of water in the granulation liquid, good results were obtained for friability and dust. With increasing amounts of water in the granulation liquid,

Table 5

Coefficients (± SD), t Values and Significance Levels for the Parameters in the Evaluation of the Friability of the Granules

Independent Variable	Coefficient	Standard Error	t Value	Significance Level
Constant	28.34	5.63	5.04	0.00
x_1	10.26	1.09	9.41	0.00
x_1x_1	-0.13	0.036	-3.57	0.0014
x_1x_2	-0.013	0.0010	-13.11	0.00

Table 6

Process Parameters and Testing Results for Each Granulation in the Optimal Zone

% Water in the Granulation Liquid (x_1)	Volume of Granulation Liquid (ml; x_2)	Total Granulation Time (min; x_3)	Tablet Quality[a]	Friability (%)	Amount of Granules (%) Within 250–1000 µm	Amount of Dust (%; fraction below 250 µm)
0	500	5′30″	G	24.0	74.6	22.4
0	575	5′30″	G	15.0	79.0	19.0
0	650	5′30″	G	12.0	74.7	23.0
5	500	5′30″	G	36.5	73.3	24.5
5	575	5′30″	G	17.0	78.1	19.2
5	650	5′30″	G	13.0	75.4	21.6
10	500	5′30″	G	49.0	80.7	19.1
10	575	5′30″	G	18.0	82.0	17.1
10	650	5′30″	G	17.0	77.4	19.9

[a]G: good; A: acceptable; P: poor.

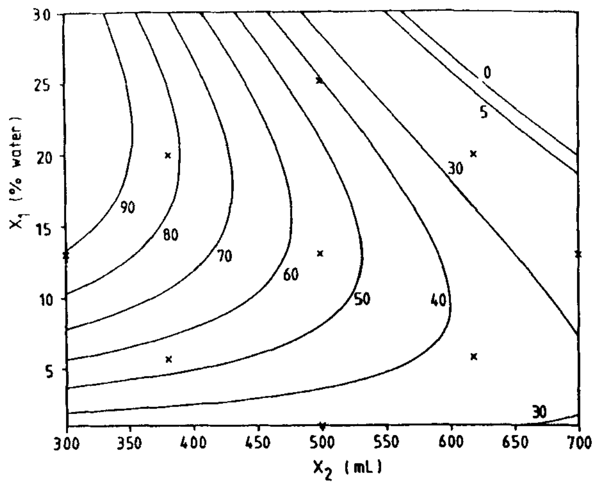

Figure 2. Contour plot for the evaluation of the friability (x_3 = 5.5 min).

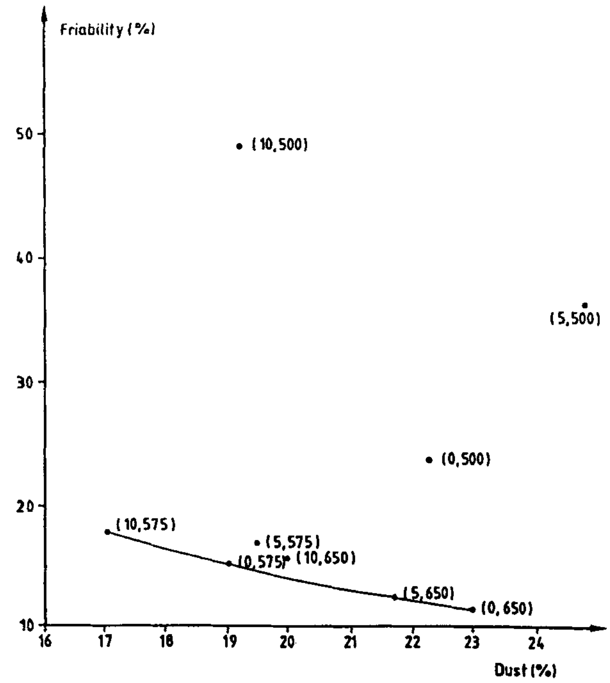

Figure 3. Pareto plot.

a decrease in the results for friability became progressively worse. Adding more granulation liquid leads to better results. The effect is clearest when going from 500 to 575 ml. The amount of dust is less affected. It seems that the medium x_2 value is slightly better. The results are also somewhat better at higher x_1.

Since several criteria (i.e., tablet quality, friability, and amount of dust) are studied in order to find the optimal working conditions, the Pareto-optimality principle (3,6) was applied. This decision-making technique is used to find an optimal trade-off when the optima for two criteria are not the same. It defines a set of working conditions to be Pareto-optimal if there is no other set exhibiting a better result on one criterion, without having a worse result on any other. The method is especially useful when only two criteria are considered, since a simple graphical representation is then possible. In this case only experiments leading to a good visual tablet quality were retained, and the plot of Fig. 3 results when friability is plotted against the amount of dust for every experiment. The Pareto-optimal conditions are found when both parameters have low values, i.e., on the line connecting the border points in the lower left corner. The experiment with 0% water and 575 ml

Table 7

Process Parameters and Testing Results for Each Granulation

% Water in the Granulation Liquid (x_1)	Volume of Granulation Liquid (ml; x_2)	Total Granulation Time (min; x_3)	Tablet Quality[a]	Friability (%)	Amount of Granules (%) Within 250–1000 μm	Amount of Dust (%; fraction below 250 μm)
0	575	1′	G	23.0	79.8	19.9
0	575	2′30″	G	23.0	79.3	19.8
0	575	5′	G	20.0	80.6	18.6
0	575	7′30″	G	20.0	79.3	19.0
0	575	10′	G	18.0	79.9	18.7

[a]G: good; A: acceptable; P: poor.

granulation liquid was then retained. Table 7 gives the effect of massing time on the results at that combination of variables.

There seems to be a slight trend in the friability result: longer granulation time led to better results. However, the effect is slight and confirms our earlier conclusion that time is not an important parameter.

From these data it can be concluded that the optimal zone is obtained for the combination of a x_1 value (amount of water in the granulation liquid) between 0 and 10% water and a x_2 value (amount of granulation liquid) between 575 and 650 ml. The massing time (x_3) had little or no effect and therefore no average massing time of 5.5 min can be used.

The experimental design as used allowed us to stress that the influence of the amount of granulation liquid in the granulation procedure was the most important parameter, next to the amount of water in the granulation liquid. The influence of the massing time was negligible.

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