DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(4), 917-930 (1985)

THE GRANULATION OF A TABLET FORMULATION IN A HIGH-SPEED MIXER, DIOSNA P 25

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ABSTRACT

The impeller speed, the loss-on-drying of starch, and the added amount of water significantly influenced these response variables: granule fractions of less than 0.150 mm and more than 2.00 mm; and granule median diameter. The influence of the drug concentration on the response variables was less important. All the response variables showed significant interactions.

At a fixed impeller speed, the fine fraction was reduced when the loss-on-drying of starch increased, and when water was added in increasing amounts. The coarse fraction and granule median diameter increased along with an increasing moisture content in the starch. Increasing amounts of added water had the same effect.

The response surface contours of a fraction less than 0.150 mm, and a fraction exceeding 2.00 mm, were plotted. So was the granule median diameter. Suitable

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levels for the processing variables involved in obtaining a granulation of the desired proportions - fine or coarse fraction - can be read from the contour plots.

Heat was generated in the mixer during kneading, which caused some evaporation of water.

The change in the rotation rate of the impeller during the addition of the granulating liquid can be used as an indication of the fraction percentages below 0.150 mm and above 2.00 mm, but not of the median diameter.

INTRODUCTION

Factorial experiments have been performed during studies of the granulation process in high-speed mixers[1-3].

In an earlier factorial experiment, the influence of six variables on the following factors was investigated: fractions below 0.150 mm or above 2.00 mm; the granule median diameter; the change in the rotation rate of the impeller shaft; and the heat generation in the mass. The aim of that study was to obtain a placebo formulation as a preparation for the formulation with the drug[3]. The six variables were the main-impeller and chopper speeds; the method of fluid addition; the way of adding the binder; the volume of granulating liquid added; and the wet massing time. The dominating variables were the volume of granulating liquid and the impeller rate. The humidity of the starch has previously been reported to affect the granulation process[3]. This circumstance, together with the two factors mentioned above and the drug concentration in the powder mixture, formed the set of variables in the experiment presented here, the experiment in which the dependence on the fraction dimension - less than 0.150 mm and larger than

2.00 mm - and on the granule median diameter was studied.

MATERIALS AND METHODS

Materials

A freely soluble drug, solubility in water 260g/l, lactose 100 mesh[4], corn starch[5] and povidone[6] according to Table 1.

Where starch with a normal humidity was concerned the loss-on-drying (LOD) was 9.5 - 10.9 %. When starch with a low humidity level was used, the material was dried at 60° C to a LOD of 4.3 - 5.0 %. Starch with a high humidity level - close to the limit of Ph Eur[10] - was obtained by mixing with water in a planetary mixer to a LOD of 14.3 - 15.3 %.

The LOD of starch was measured according to Ph Eur[10].

Granulation

A $3 \cdot 2^3$ factorial experiment was performed; see Table 2. All the experiments were replicated once.

With regard to factor x_3, the levels were selected so that granulations fit for use were obtained.

The powder mixtures according to Table 3 were granulated with water in a recording Diosna P 25[11]. The amount of water was added during 4 mins, but the wet massing was continued for another 2 mins. This meant that water was added at a flow rate of 212.5 ml/min on the low level and at 262.5 ml/min on the high level.

The impeller speed was varied at two levels, but the chopper speed was fixed at 4200 rpm; the method of fluid addition was non-atomized throughout; and binder was added in dry form.

Samples of approximately 0.1 kg were withdrawn by means of a scoop from the granule stream in the vicinity of the chopper. The samples, taken after the ad-

TABLE 1
Powder characteristics

Characteristics	Drug	Lactose	Starch	Povidone
Geometric mean diameter by weight, µm	90	103	-	88
Geometric standard deviation	2.5	1.4	-	1.7
Volume-surface mean diameter[7], µm	-	-	12.7	-
Apparent density[8], kg/m^3	620	740	530	430
Tap density[9], kg/m^3	760	850	680	510

TABLE 2
Factors and factor levels

Factor	Factor levels		
	0	1	2
x_1 Rotation rate of main impeller shaft, rpm	1500	3000	-
x_2 Loss-on-drying of corn starch, %	5	10	15
x_3 Added amount of water, kg	0.85	1.05	-
x_4 Drug concentration, mg drug per g powder mixture	91	182	-

TABLE 3

Granule compositions

	kg	
Component	Drug level: Low	High
Drug	0.750	1.500
Lactose	4.690	3.940
Corn starch	2.560	2.560
Povidone	0.250	0.250

dition of the water and after the subsequent kneading, were immediately dried in a hot-air oven at 50° C. Sieve analyses of the dried samples were performed through sieves measuring 2.00, 1.50, 1.00, 0.750, 0.500, 0.300 and 0.150 mm[12]. The duration of the sieving process was 2 mins.

The change in the rotation rate of the main impeller shaft was recorded during the granulation.

The moisture content of the massed granulation was immediately measured after the kneading. About 1.00 g of wet mass was dried for 18 h at 105° C.

RESULTS AND DISCUSSION

The experimental design employed here made it possible to test the existence of all main effects and interactions.

The responses from the 48 experiments were measured and tabulated. An account of the extensive data volume is hardly necessary here, as most of it bears little relevance to the present discussion.

The impact of the formulation and process variables on the following response variables was studied: the change of rotation on the part of the impeller shaft during the liquid addition (y_1), the wet massing

(y_2), and the liquid addition and wet massing (y_3); the granule fraction of less than 0.150 mm - fines - after the liquid addition (y_4), and after liquid addition and wet massing (y_5); the granule fraction exceeding 2.00 mm - lumps - after the liquid addition (y_6), and after liquid addition and wet massing (y_7); the granule median diameter - d50% - after the liquid addition (y_8), and after liquid addition and wet massing (y_9); and the difference between measured and theoretical moisture content after wet massing (y_{10}).

The results obtained when the experiments were subjected to an analysis of variance are summarized in Table 4.

For the response variables y_1 and y_3 - y_9, the significant main effects were x_1, x_2 and x_3. Almost throughout, factor x_4 had no significant influence. Although factor x_4 was significant at $P < 0.05$ for y_4, y_6 and y_7, this influence of drug concentration was judged as unimportant.

With regard to all the response variables y_1 - y_9, there were significant interactions which indicate that the influence on the response variables of the studied processing variables is complex and cannot be studied by varying one processing variable at a time.

Predictably, the change in the rotation rate of the impeller shaft during wet massing (y_2) was influenced by the rotation rate of the impeller shaft (x_1), and this dependence is not affected by the other processing variables. The LOD of starch and the amount of water added also affected the change in the impeller-shaft rotation rate, but they did so in an interactive manner.

The measured moisture content of the granulation was lower than the theoretical, indicating evaporation

TABLE 4
Analysis of variance

Factor, interaction	Level of significance									
	y_1	y_2	y_3	y_4	y_5	y_6	y_7	y_8	y_9	y_{10}
x_1	***	***	***	***	***	***	***	***	***	***
x_2	***	NS	***	***	***	***	***	***	***	**
x_3	***	NS	***	***	***	***	***	***	***	NS
x_4	NS	NS	NS	*	NS	NS	*	NS	NS	NS
x_1x_2	***	NS	***	***	***	NS	*	***	***	NS
x_1x_3	***	NS	***	***	**	*	**	***	***	NS
x_1x_4	NS	NS	NS	*	NS	*	*	NS	NS	NS
x_2x_3	NS	**	*	***	***	***	***	***	***	*
x_2x_4	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
x_3x_4	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

NS Not significant
* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

of water during the process due to the generation of heat in the mixer.

The difference between measured and theoretical granule moisture content (y_{10}) was significantly influenced by the impeller speed (x_1) and by the LOD of starch (x_2). The evaporation was smaller at a low impeller-speed level, which agrees with a recent report[2].

In order to model the effects of the factors on the response variables, a second-order, multiple linear regression model was fitted to the datapoints.

The following complete model was valid for this experiment design.

TABLE 5

Regression coefficients of the final models

b_i	Regression coefficient values									
	y_1	y_2	y_3	y_4	y_5	y_6	y_7	y_8	y_9	y_{10}
b_0	-22	-7.1	-7.1	$1.2\cdot10^{2}$	92	22	72	2.4	5.9	$8.7\cdot10^{-1}$
b_1	$6.0\cdot10^{-3}$	$5.2\cdot10^{-3}$	$1.6\cdot10^{-2}$	$-2.1\cdot10^{-2}$	$-1.3\cdot10^{-2}$	$8.6\cdot10^{-4}$	$-3.4\cdot10^{-3}$	$-6.0\cdot10^{-4}$	$-1.7\cdot10^{-3}$	$-7.6\cdot10^{-4}$
b_2	-2.1	-	-5.4	-3.2	-2.5	-6.6	-13	$-2.4\cdot10^{-1}$	$-5.4\cdot10^{-1}$	$1.5\cdot10^{-1}$
b_3	-42	-	-62	-82	-66	-30	-85	-2.0	-5.2	-
b_4	-	-	-	$-2.4\cdot10^{-1}$	-	-	$2.7\cdot10^{-1}$	-	-	-
b_5	$5.6\cdot10^{-2}$	-	$6.6\cdot10^{-2}$	$-3.4\cdot10^{-2}$	$-3.7\cdot10^{-2}$	$1.5\cdot10^{-1}$	$2.3\cdot10^{-1}$	$4.5\cdot10^{-3}$	$8.9\cdot10^{-3}$	$-5.5\cdot10^{-3}$
b_6	$1.2\cdot10^{-3}$	-	$1.3\cdot10^{-3}$	$4.4\cdot10^{-4}$	$2.7\cdot10^{-4}$	-	$3.9\cdot10^{-4}$	$1.4\cdot10^{-5}$	$4.2\cdot10^{-5}$	-
b_7	$4.5\cdot10^{-2}$	-	$3.9\cdot10^{-2}$	$1.2\cdot10^{-2}$	$7.7\cdot10^{-3}$	$1.1\cdot10^{-2}$	$1.7\cdot10^{-2}$	$5.9\cdot10^{-4}$	$1.6\cdot10^{-3}$	-
b_8	-	-	-	$8.3\cdot10^{-5}$	-	$-4.9\cdot10^{-5}$	$-1.8\cdot10^{-4}$	-	-	-
b_9	-	$1.3\cdot10^{-1}$	3.1	1.7	1.6	4.9	9.7	$1.6\cdot10^{-1}$	$3.6\cdot10^{-1}$	$-1.2\cdot10^{-1}$
b_{10}	-	-	-	-	-	-	-	-	-	-
b_{11}	-	-	-	-	-	-	-	-	-	-

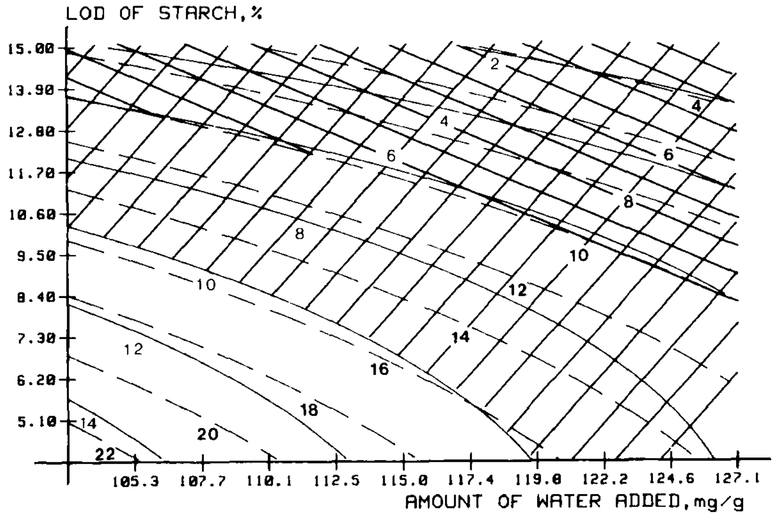


FIGURE 1

The fraction below 0.150 mm, expressed as a percentage, versus LOD of starch (y-axis) and added amount of water (x-axis) at impeller shaft speed of 1500 rpm — — — and 3000 rpm ——— just after the addition of the liquid. The added amount of water is expressed as mg water per g powder mixture.

Granulations with less than 10 % of the fines are obtained in the shaded area for 3000 rpm and in the cross-hatched area for 1500 rpm impeller-shaft speed.

$$y_k = b_1x_1 + b_2x_2 + b_3x_3 + b_4x_4 + b_5x_2^2 + b_6x_1x_2 + b_7x_1x_3 + b_8x_1x_4 + b_9x_2x_3 + b_{10}x_2x_4 + b_{11}x_3x_4 + b_0 + e, \qquad k = 1, \ldots, 10$$

where b_i are the regression coefficients and e is the random error.

Those insignificant factors and interactions on the part of the different response variables that are contained in Table 4 were deducted from the model.

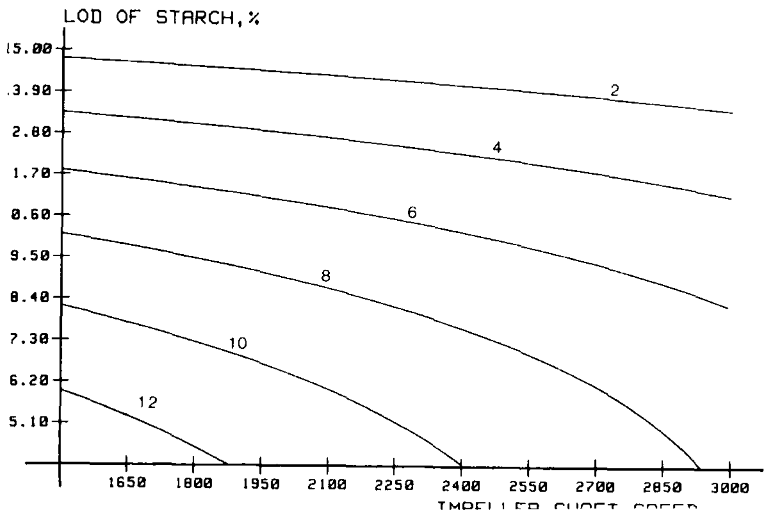


FIGURE 2

Fraction of less than 0.150 mm, percentage, versus LOD of starch (y-axis) and impeller-shaft speed (x-axis) at the high water level after liquid addition and massing.

The regression coefficient values for the final models are supplied in Table 5.

The model was used in order to depict the response surface contours.

By means of fixing one of the three significant main factors, the calculated plots of one of the response variables as a function of the second and the third significant main factors were obtained. These response surface contour plots are given in Figs 1 - 4.

At a fixed impeller speed (x_1), the fines decreased along with increasing starch LOD (x_2) and an added amount of water (x_3); see Fig 1. When the amount of water added was fixed (x_3), the fines decreased with an increasing LOD on the part of the starch (x_2) and

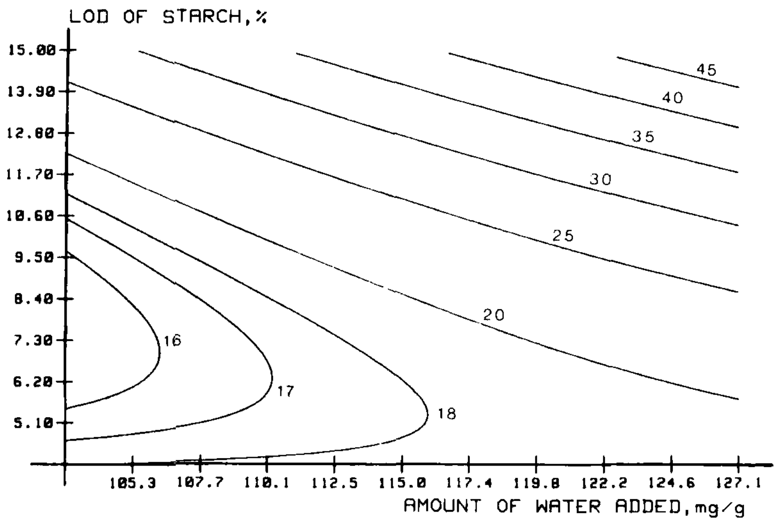
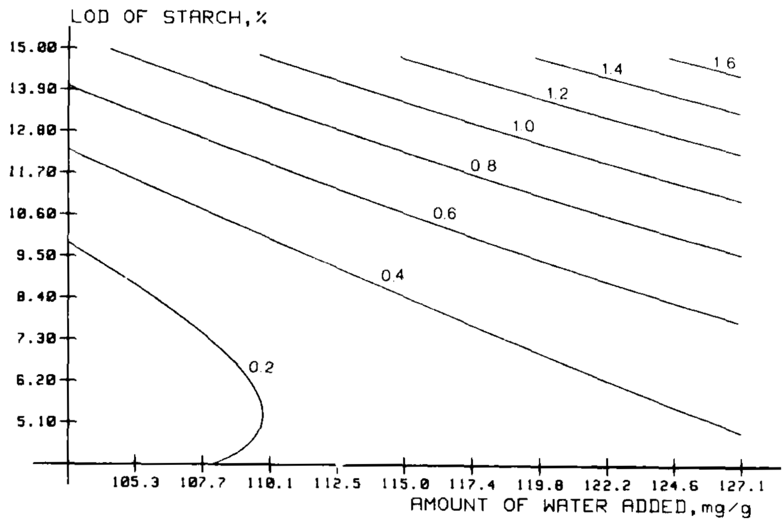


FIGURE 3

Fraction larger than 2.00 mm, as a percentage, versus LOD of starch (y-axis) and added amount of water (x-axis) at high impeller speed and low level of drug concentration after liquid addition and massing.

an augmented impeller speed (x_1); see Fig 2. At a fixed impeller speed (x_1), the lumps increased along with an increasing starch moisture (x_2) and an added amount of water (x_3); see Fig 3. However, in cases involving starch with a low LOD, approximately less than 7 %, and low amounts of water, approximately less than 116 mg/g, the lumps decreased with an increasing starch moisture. When the granule median diameter was calculated as a function of the starch LOD (x_2) and the amount of water added (x_3) at a fixed main impeller speed (x_1), it was obvious that d50% increased at higher levels of x_2 and x_3; see Fig 4. Where the median diameter was concerned, a low starch moisture also entailed a decrease. These results stress the unsuitability of using a fixed



Granule median diameter, in mm, versus LOD of starch (y-axis) and added amount of water (x-axis) at high impeller speed after liquid addition and wet massing.

amount of granulating liquid when a powder mixture containing a large proportion of starch is granulated.

When the impeller speed is at the high level, the outcome is less fines; see Fig 1. The amount of fines is a suitable indicator of granule growth. When the dried granulation is comminuted, more fines will be generated. It is important to limit the fraction below 0.150 mm, as it will influence the flow properties of the granulation. Not more than 10 % of fines has appeared to be a suitable limit in the dried but uncomminuted granulation. These requirements are fulfilled in the shaded area of Fig 1 for the high impeller speed and in the cross-hatched area for the low impeller speed.

In addition, the response variable y_1 was included as a co-variate in the final models for y_4, y_6 and y_8. In the same way, y_3 was included as a co-variate of the final model for y_5, y_7 and y_9.

There was a relationship between y_1 and y_4 ($P < 0.05$), y_1 and y_6 ($P < 0.01$) but not between y_1 and y_8. This means that the change in the rotation rate of the main impeller shaft - and of the impeller too - during the addition of the liquid can be used as an indication of the percentages of fines and lumps but not of d50%. Recently the change in the rotation rate of the main impeller shaft was made to indicate the end-point during the addition of the granulating solution[13].

CONCLUSIONS

The response variables, that is, fractions that are smaller than 0.150 mm and larger than 2.00 mm and the granule median diameter, were influenced by the impeller speed, the LOD of starch, and the added amount of water. The drug concentration was of less importance. The dependence on the studied processing variables was found to be complex; the effect of a variable depends on the levels of the other variables.

Water evaporated during the kneading because of the generation of heat in the mixer. The evaporation increased at a high impeller speed.

Mathematical models were fitted, and the response surface contours were plotted.

At a fixed impeller speed, the less-than-0.150-mm fraction decreased. The fraction exceeding 2.00 mm and the median diameter increased along with an increasing LOD on the part of the starch and with an added amount of water.

The influence on the response variables of impeller speed, LOD of starch, and amount of added water is supplied in Figs 1 - 4.

Granulations fulfilling the requirements with regard to fines were obtained in the shaded and cross-hatched area of Fig 1.

The change in the rotation rate of the impeller can be used as an indication of fines and lumps during the addition of liquid.

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