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THE GRANULATION OF A TABLET FORMULATION IN A HIGH-SPEED MIXER, DIOSNA P25. INFLUENCE ON INTRA-GRANULAR POROSITY AND LIQUID SATURATION.

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ABSTRACT

Intragranular porosity and liquid saturation were influenced by the impeller speed, the loss-on-drying of starch, the added amount of water and the drug concentration. A reduction of the impeller speed and the drug concentration decreased the porosity and increased the liquid saturation. Response surface contours were plotted.

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INTRODUCTION

A report regarding the granulation of a tablet formulation in a Diosna P25 was recently published[1]. The liquid saturation[2] and the intragranular porosity[3] of the granules are affected by the process conditions[3], i.e. intensity of agitation, processing time, and the amount of binder solution.

Now the earlier response variables - which were granule fractions less than 0.150 mm and more than 2.00 mm as well as granule median diameter - are completed with further variables: intragranular porosity and liquid saturation.

METHODS

The granules from a recent study[1] were used in this test.

The granule density, ρA, of 0.250-1.00 mm granules was measured by a pycnometric method where mercury was used as the penetration liquid according to Jaegerskou et al[3]. Calculation of the intragranular porosity, ϵ was performed according to:

$$\epsilon = \left(1 - \frac{\rho A}{\rho T} \right) \cdot 100 \qquad \text{Eq 1}$$

where ρT is the density of the granules, measured with the aid of the Beckman pycnometer[4].

The liquid saturation, S, was calculated according to Kristensen et al[2]

$$S = \frac{H\ (1 - \epsilon)\ \cdot \rho T}{\epsilon} \qquad \text{Eq 2}$$

where H is the percentage of moisture content on a dry-weight basis. 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 results obtained when the experiments were subjected to an analysis of variance are summarized in Table 1.

Intragranular Porosity

The impact of the formulation and process variables on the intragranular porosity (Y_{12}) was studied.

The porosity was in the range 12-25%.

The significant main effects were the impeller speed, X_1; the loss-on-drying of starch, X_2; and the drug concentration, X_4; see Table 1. Factor X_3, the added amount of water, had no significant influence except for the interactions X_1X_3, X_2X_3, and X_3X_4. The influence on the response variables of the studied process variables is complex and cannot be studied by varying one process variable at a time.

TABLE 1
Analysis of variance

Factor, interaction	Factor	Level of significance	
		Y_{12}	Y_{13}
X_1	Rotation rate of main impeller shaft	**	**
X_2	Loss-on-drying of corn starch	*	*
X_3	Added amount of water	NS	NS
X_4	Drug concentration	***	***
X_1X_2		NS	NS
X_1X_3		**	NS
X_1X_4		NS	NS
X_2X_3		***	***
X_2X_4		*	NS
X_3X_4		**	NS

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

Y_{12} is also indicated as ϵ, while Y_{13} is also designed as S in the text.

The analysis of variance supplies information on significant main effects and interactions but does not determine the degree of dependence on these factors. In order to establish a model for this dependence, a complete second-order regression model was assumed and then reduced, using a backward elimination technique[5], to the model:

$$Y_{12} = 0.00089X_1 + 7.28X_3 + 0.965X_4 - 0.0538X^2_2 + + 1.12X_2X_3 - 0.715X_3X_4 \quad \text{Eq 3}$$

The squared correlation coefficient was 0.46, which means that 46% of the total variation can be explained by the independent variables in this model.

The porosity decreased with decreasing impeller speed and drug concentration; see Fig 1.

This response surface model gives us information about the nature and degree of dependence in respect of the main effects as well as of the interactions. We cannot, however, expect identical answers from the two different tests, as more assumptions are made in the regression model.

The change in the rotation rate of the impeller-shaft during liquid addition and wet massing (Y_3), and the difference between measured and theoretical moisture content after wet massing (Y_{10}), were included as co-variates in the model. Model reduction resulted in the following model:

$$Y_{12} = 0.00777X_1 - 1.86X_2 + 0.889X_4 + 2.22X_2X_3 - - 0.636X_3X_4 - 0.104Y_3 \quad \text{Eq 4}$$

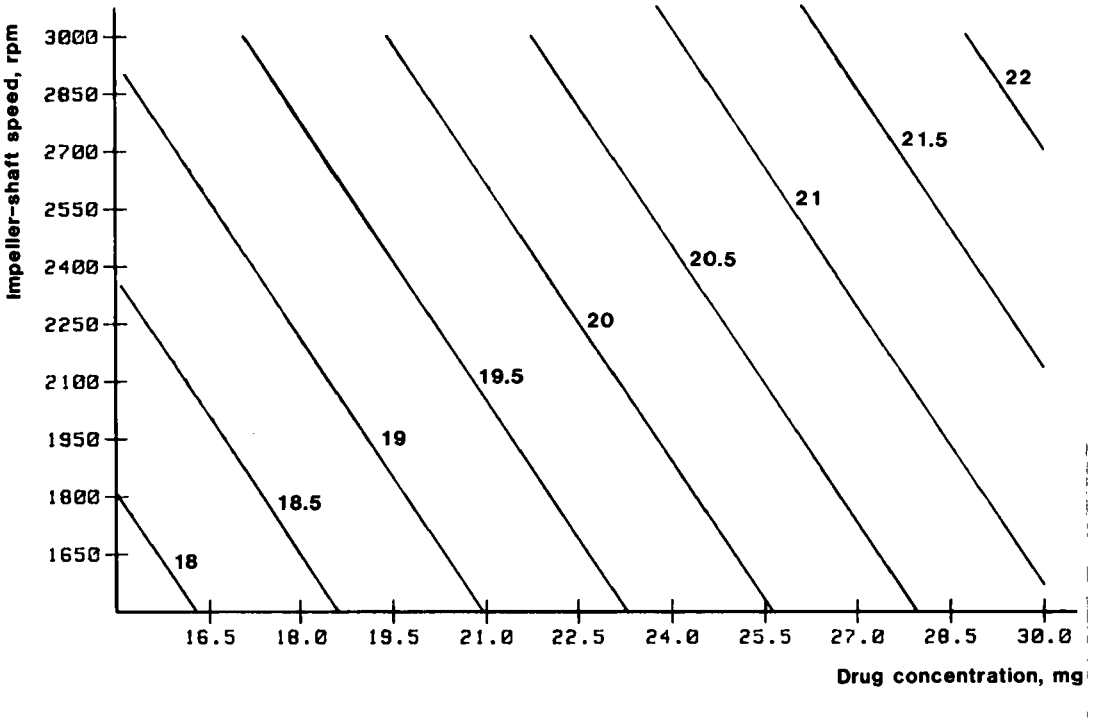

FIGURE 1

Intragranular porosity, percentage, versus impeller-shaft speed (Y-axis) and drug concentration (X-axis) at a high LOD of starch and a high water level after liquid addition and massing.

with a squared correlation coefficient of 0.47. Thus, Y_{10} was without any significant influence, while Y_3 had a significant influence.

It is known that there is a relationship between the electric power input of an impeller and a change of rotation rate[6]. Besides, the power consumption is influenced by the porosity[7]. Therefore, a significant influence of Y_3 on Y_{12} is to be expected.

Liquid Saturation

The influence of the independent variables on liquid saturation (Y_{13}) - which expresses the degree of filling of the intragranular voids with the liquid phase - was investigated.

The liquid saturation was in the range of about 60 - 200%. Values larger than 100% are theoretically incorrect. In the calculations, it was assumed that the liquid phase was only water. However, povidone and - in part - lactose dissolve during the granulation process, which consequently influences both the volume of binder solution and the porosity of the dried granulation. These conditions can explain S-values larger than 100%. In any case, the values can be used when comparing the influences of the different factors on this formulation.

The significant main effects were X_1, X_2 and X_4, Table 1. There were significant interactions too.

The results were similar to those obtained with regard to intragranular porosity, which is only to be expected as porosity and liquid saturation are interrelated; see Eq 2.

The complete multiple linear regression model was reduced in a backward elimination procedure to:

$$Y_{13} = 171.2 - 0.0116X_1 + 1.87X_2 - 2.52X_4 \qquad \text{Eq 5}$$

Thus there is no interaction with this model. The squared multiple correlation coefficient is 0.45.

Liquid saturation increased with a reduction of the impeller speed and the drug concentration; see Fig 2. This is obvious from Eq 5, too, which also indicates increased liquid saturation with increasing loss-on-drying of corn starch.

As could be seen from Fig 3, liquid saturation increased with increasing LOD of starch and reduced impeller speed.

When Y_3 was included as a co-variate in the model, it was reduced as insignificant. This was unexpected in view of its influence on intragranular porosity.

There was no significant influence of Y_{13} on Y_3 when Y_{13} was included as a co-variate in the model of Y_3.

Liquid saturation was included as a co-variate in the model of Y_5 (the fraction less than 0.150 mm during wet massing), Y_7 (the fraction more than 2.00 mm during kneading) and Y_9 (the granule median diameter during wet massing).

For Y_5 there was a significant influence, which was expected[2]. The complete model was reduced to:

$$Y_5 = 90.0 - 0.0119X_1 - 2.59X_2 - 67.2X_3 - 0.0420X_2^2 + \\ + 0.00026X_1X_2 + 0.00688X_1X_3 + 1.83X_2X_3 + 0.0167Y_{13} \quad \text{Eq 6}$$

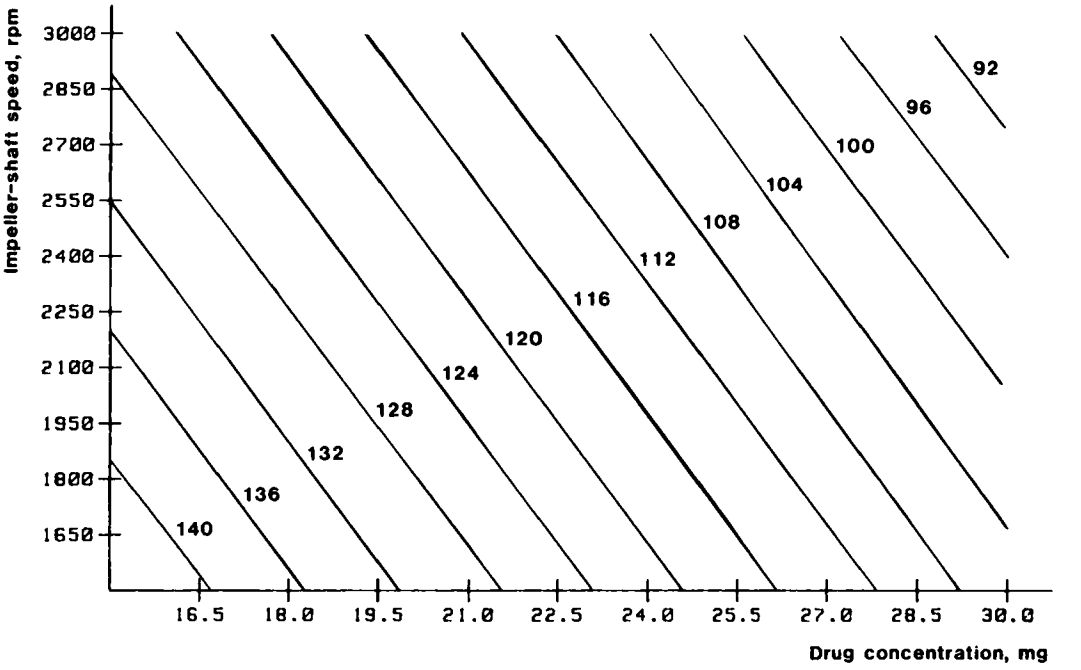

FIGURE 2

Liquid saturation, percentage, versus impeller-shaft speed (Y-axis) and drug concentration (X-axis) at a high level of starch LOD after liquid addition and massing.

by a step-down procedure. The squared multiple correlation coefficient was 0.97.

In respect of Y_7 and Y_9 there was no significant influence; this was an unexpected result.

CONCLUSIONS

Intragranular porosity and liquid saturation, which are interrelated, were found to be influenced by the impeller speed, the LOD of starch,

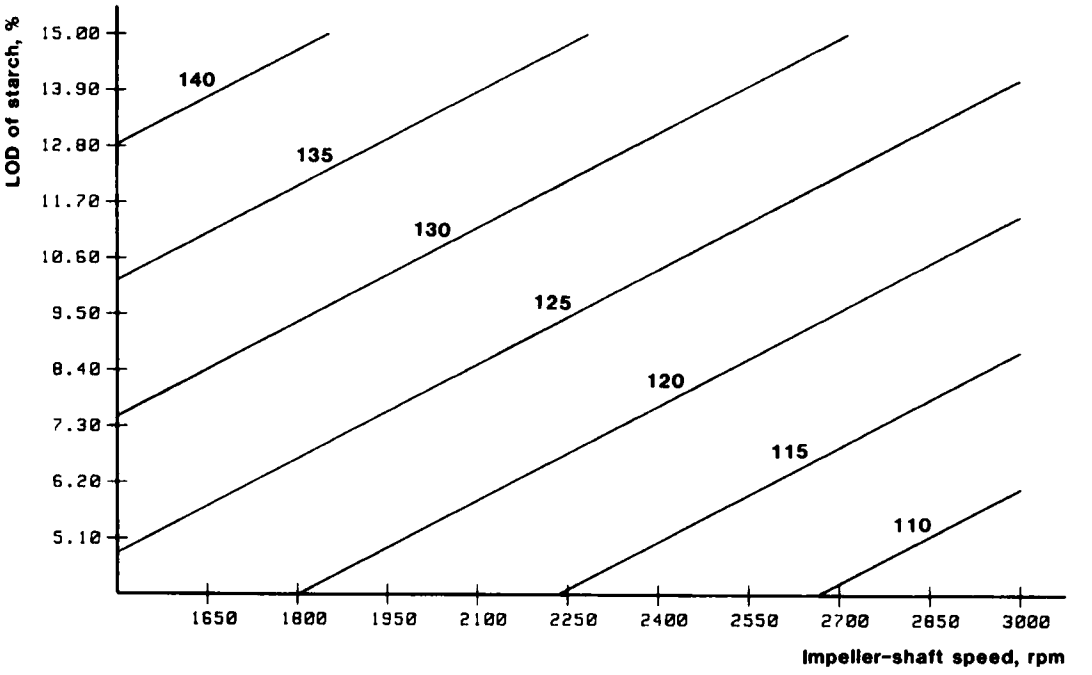

FIGURE 3

Liquid saturation, percentage, versus LOD of starch (Y-axis) and impeller-shaft speed (X-axis) at a low drug-concentration level after liquid addition and massing.

the added amount of water and the drug concentration, either by main effects or interactions.

When the change of the impeller shaft was considered, intragranular porosity could be more satisfactorily explained. This was to be expected, as there are known interrelations between the power consumption of the mixer motor and the impeller rate on the one hand and power consumption and porosity on the other.

Porosity decreased with decreasing impeller speed and drug concentration, while liquid saturation increased with a reduction of impeller speed and drug concentration. The response surface contours of the mathematical models were plotted.

The results emphasize the importance of the process variables. This is valuable information, for instance during the up-scaling, as Diosna P25 is a very intensive mixer compared to the larger Diosna mixers[8].

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