DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(4), 931-943 (1985)

OPTIMIZATION OF DISINTEGRATION TIME AND CRUSHING STRENGTH OF A TABLET FORMULATION

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ABSTRACT

In an experiment with a factorial design, the following aspects were scrutinized: the impact on disintegration time and crushing strength caused by the loss-on-drying of the granulation; the granule-size distribution; the lubricant concentration; the compression force; and the pre-compression. Both with regard to disintegration time and crushing strength, these factors were found to have a significant influence: the loss-on-drying of the granulation; the fraction less than 0.150 mm; the concentration of magnesium stearate; and the compression force. A reduction of the tablet disintegration time was obtained by means of an increase of the granulation moisture; by an increase of the fine fraction; or by a reduction of the lubricant concentration or the compression force. The tablet crushing strength was increased by reducing the deviation of the granulation loss-on-drying from

0363-9045/85/1104-0931$3.50/0

approximately 4.6 %; by a reduction of the fine fraction; by decreasing the lubricant concentration; or by increasing the compression force. The fraction larger than 0.300 mm had no significant influence; nor did the pre-compression. Further, there were no significant interactions.

By means of superimposing contour plots of disintegration time and crushing strength, a region was obtained where the requirements of disintegration time and crushing strength could be satisfied by controlling the processing variables.

INTRODUCTION

The development of tablet formulations is particularly well suited to factorially designed experiments, as there are many factors which affect one or several response variables. In the formulator's search for the best possible solution to a particular problem, optimization techniques form valuable implements. Both factorially designed experiments and optimization techniques have been used during the development of tablet formulations and in the establishing of suitable ranges for the in-process variables during tablet production[1-9].

The influence of one formulation and four process variables on the disintegration time and crushing strength of a tablet formulation was investigated in order to improve the product. This meant establishing a suitable lubricant concentration as well as suitable ranges for the processing variables.

MATERIALS AND METHODS

Materials

A freely soluble drug, solubility in water 260 g/l, lactose 100 mesh[10], corn starch[11], povidone[12], cellulose[13], and magnesium stearate[14], according to Table 1.

TABLE 1
Tablet composition

Component	%
Drug	8.2
Lactose	51.2
Starch	27.9
Povidone	2.7
Starch	4.2; 4.1
Cellulose	5.5; 5.4
Magnesium stearate	0.25; 0.50

Granulation

Drug, lactose, a part of the starch and PVP - a total of 8.25 kg powder - were all granulated with water in a 25-liter high-speed mixer[15]. After drying in a hot-air oven at 50° C to the desired loss-on-drying (LOD) level, 2 - 6%, the granulations were comminuted to the required granule-size distribution. A fine granulation was obtained by means of comminuting in a hammer mill[16] through a 0.69 mm sieve at 2700 rpm. When the dried granulation was milled through a 0.75 mm screen in a granulating machine[17], a coarse granulation was obtained.

LOD values were determined with the aid of a moisture balance[18], and the weight loss was read directly from the instrument.

Tableting

Cellulose and the rest of the starch were blended with the milled granulations for 8 mins in a 25-liter planetary mixer. Magnesium stearate was mixed for 2 mins.

Tablets - 8 mm standard, biconvex with monogram and a weight of 183 mg - were compressed with a high-speed rotary tablet machine[19]. The machine rate was 60 000 tablets/h. Three different compression-force ranges were used. The force was measured with a commercial instrument[20].

When pre-compression was used, the pre-compression setting was adjusted so that tablets of a 4.00 mm thickness were obtained when the final pressure was zero.

The disintegration time in water of 6 tablets was determined after one day according to Ph Eur[21].

The crushing strength was determined[22] one day after the compression. For each determination, 10 tablets were tested and the mean value calculated.

The tablet weight was averaged from 10 tablets.

The tablet thickness of 10 individual tablets was measured with a micrometer[23] and the mean value calculated.

The ratio of mean weight to mean thickness was calculated, yielding an indirect measure of the tablet density.

Design

A design of the fractional-replication type was used, with 36 experimental points and 10 replicates according to Morrison[24]. The factor levels are stated in Table 2.

The actual levels of factor x_1 were 1.6 - 2.4, 3.5 - 4.2 and 5.8 - 6.4%.

Factor x_2 was divided into two subfactors, the fractions less than 0.150 mm (fines) and larger than 0.300 mm.

With regard to factor x_4, the actual levels were 630 -770, 860 - 1050 and 1080 - 1320 kp (or 6.2 - 7.5, 8.4 - 10.2 and 10.6 - 12.9 kN).

TABLE 2
Factors and factor levels

Factor	Factor levels 0	1	2
x_1 Loss-on-drying of dried granulation, %	2	4	6
x_2 Comminuted granulation,			
$x_{2,150}$; < 0.150 mm, %	14-20	21-38	——
$x_{2,300}$; > 0.300 mm, %	31-42	5-16	——
x_3 Magnesium stearate, %	0.25	0.50	——
x_4 Compression force, kp (kN)	700(6.9)	950(9.3)	1200(11.8)
x_5 Pre-compression	0	+	——

The results were analyzed by means of multiple linear regression models. A mathematical model was fitted to the datapoints and used to depict the response surface contours.

RESULTS AND DISCUSSION

When applying fractional replication, it is - in certain circumstances - possible to use only a portion of all conceivable factor-level combinations and still be able to test hypotheses concerning the existence of all main effects and all two-factor interactions[24]. A design of this type was employed.

The responses from the 46 experiments were measured and tabulated. The large volume of data is rather too unwieldy to be presented here; besides, most of it is not directly relevant to the present discussion.

With regard to the two response variables disintegration time (y_1) and crushing strength (y_2), the

TABLE 3

Regression coefficients of the reduced models

Coefficients	Factors, interactions	Regression coefficient values	
	Response variables:	y_1	y_2
b_1	x_1	—	2.6
b_2	$x_{2,150}$	$-1.4 \cdot 10^{-2}$	$-3.5 \cdot 10^{-2}$
b_3	x_3	1.4	-4.8
b_4	x_4	$5.4 \cdot 10^{-3}$	$8.8 \cdot 10^{-4}$
b_5	x_1^2	$-4.0 \cdot 10^{-3}$	$-2.7 \cdot 10^{-1}$
b_0	mean level	$9.9 \cdot 10^{-2}$	1.0

following independent variables exercised a significant influence: LOD of dried granulation (x_1); granule fraction of less than 0.150 mm ($x_{2,150}$); lubricant concentration (x_3); and compression force (x_4). "Significant influence" refers to results where $P < 0.05$. The factors consisting in granule fraction exceeding 0.300 mm ($x_{2,300}$) and pre-compression had no significant influence, though. Significant interactions were absent.

The analysis resulted in the following models:

$$y_1 = b_2x_{2,150} + b_3x_3 + b_4x_4 + b_5x_1^2 + b_0 + \text{random error}$$

$$y_2 = b_1x_1 + b_2x_{2,150} + b_3x_3 + b_4x_4 + b_5x_1^2 + b_0 + \text{+ random error}$$

In both cases, the multiple correlation coefficient was larger than 0.80. Consequently, 80% of the total variation seen in the response variables could be explained as being caused by the independent variables in the way described by these equations.

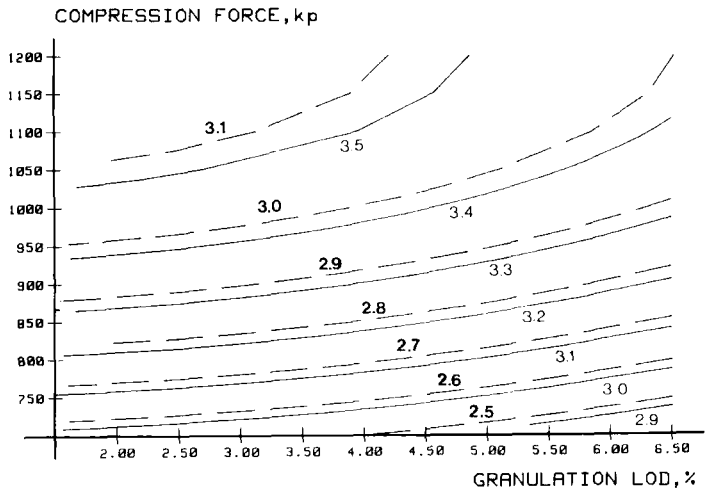

FIGURE 1

Tablet disintegration time, mins, versus compression force (y-axis) and granulation LOD (x-axis) at a lubricant concentration of 0.25 % and with a fraction of less than 0.150 mm 10 % —— or 40 % —— —— ——.

The model coefficients are stated in Table 3, with the number of significant digits that are warranted considering the accuracy in the measurements of the responses.

By fixing the lubricant concentration and the fraction less than 0.150 mm, the calculated plots of tablet disintegration time and crushing strength as a function of compression force and granulation LOD were obtained. These response surface contour plots of disintegration time and crushing strength are given in Figs 1 and 2.

The ratio of mean tablet weight to mean tablet thickness was included as a co-variate in the models of both disintegration time and crushing strength. However, the ratio had no significant influence on either of the two response variables.

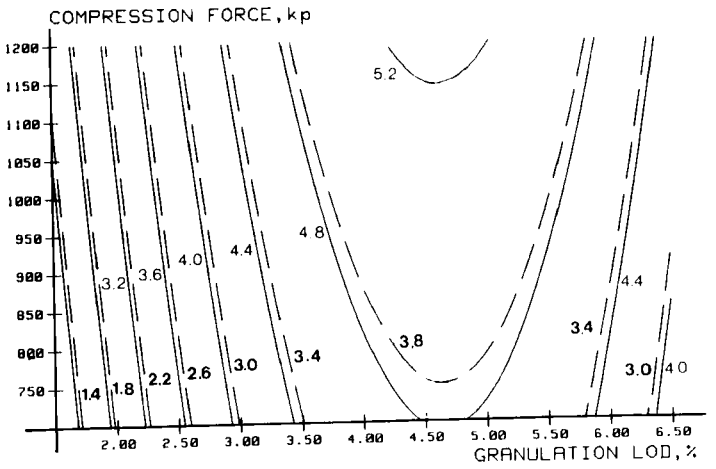

FIGURE 2

Tablet crushing strength, kp, versus compression force (y-axis) and granulation LOD (x-axis) at a lubricant concentration of 0.5 % and a fraction of less than 0.150 mm 10 % ——— or 40 % — — — —.

The tablet disintegration time decreased along with a reduced compression force, an increasing granulation LOD and an increased percentage of fines; see Fig 1. Besides, decreased lubricant concentration brought about an almost linear reduction of the disintegration time。

There was a maximum of tablet crushing strength at a granulation LOD of approximately 4.6%. In other words, the strength decreased both with reduced and increased granulation moisture, see Fig 2. Reduction of the lubricant concentration and increase in compression force did increase the crushing strength; cf。 Figs 2 and 3. In addition, a reduction of the less-than-0.150-mm fraction percentage led to an increase of the crushing strength; see Fig 2.

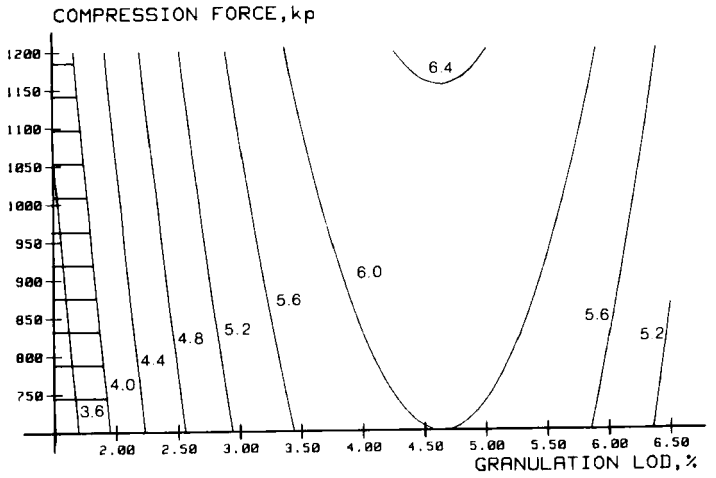

FIGURE 3

Tablet crushing strength, kp, versus compression force (y-axis) and granulation LOD (x-axis) at a lubricant concentration of 0.25 % and a less-than-0.150-mm fraction of 10 %.

Tablets with a disintegration time of at most 5 mins and a crushing strength of at least 4 kp are obtained within the unshaded area.

A short tablet disintegration time also entails a low crushing strength. Hence, the ambition to make tablets with short disintegration time and high crushing strength, is a contradiction in itself. Consequently, suitable ranges for the formulation and processing variables must be established with regard to the desired limits of tablet disintegration time and crushing strength.

When contour plots of disintegration time and crushing strength were superimposed, the influence of the process variables was clearly seen. Tablets with, for instance, a disintegration time of at most 3 mins

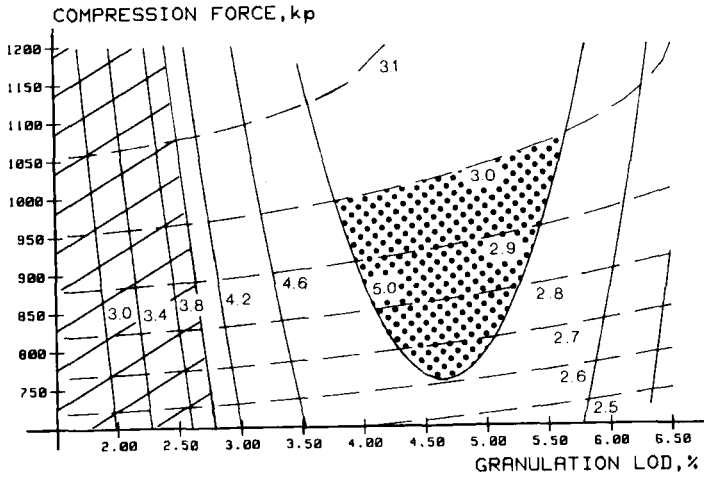

FIGURE 4

Contour overlay of disintegration time, mins, — — — and crushing strength, kp, ——— for compression force (y-axis) and granulation LOD (x-axis) at a lubricant concentration of 0.25 % and a less-than-0.150-mm fraction of 40 %.

Tablets with a disintegration time of at most 3 mins and a crushing strength of at least 5 kp are obtained in the dotted area.

Tablets with a disintegration time of at most 5 mins and a crushing strength of at least 4 kp are obtained within the dotted and the unshaded areas.

and a crushing strength of at least 5 kp (49 N) were obtained within the dotted area of Fig 4.

The specifications for the formulation were a disintegration time that did not exceed 5 mins, and a crushing strength of at least 4 kp (39 N). As other tests with high-speed tablet machines and monogram punches have shown that the lower magnesium stearate level was sufficient in respect to lubrication efficiency, there was no reason to increase the lubricant

concentration to 0.5%. A granulation with not more than 40 % of the fines will flow easily in the hopper and feeder of a rotary tablet machine; this has been investigated in earlier tests. To produce tablets with the requested disintegration time and crushing strength, the granulation LOD must thus be at least 2.0 % with reference to the conditions prevailing in Fig 3. As for Fig 4, tablets according to the specifications are obtained with a granulation LOD of at least 2.8 %, this is, within the dotted and unshaded areas.

CONCLUSIONS

A reduction of the tablet disintegration time was obtained by increasing the granulation LOD; by increasing the fines; by reducing the magnesium stearate concentration; and finally by decreasing the compression force. The tablet crushing strength was increased by reducing the deviation of the granulation LOD from approximately 4.6 %; by reducing the proportion of fines; by decreasing the lubricant concentration; and by increasing the compression force.

0.25 % of magnesium stearate was a suitable lubricant concentration.

Pre-compression did not influence the tablet properties significantly.

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

Tablets fulfilling the specifications for the disintegration time and crushing strength were obtained in the unshaded area of Fig 3 and the dotted and unshaded areas of Fig 4.

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