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Experimentally Designed Optimization of Direct Compression Tablets

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ABSTRACT

The work reported here describes the improvement of an industrial production of tablets formed by direct compression. This formulation contained 50% active substance of plant origin as a nonhygroscopic powder. The first step was to evaluate a number of direct compression excipients in preformulation tests and then make up a basic formulation providing tablets with correct characteristics. The second step was the optimization of the initial formulation using a two-level factorial experimental design. This enabled the best formulations to be selected objectively.

INTRODUCTION

Direct compression is a simple technique for making tablets that is of particular value through the industrial manufacturing time it can save. However, this technique is problematic when the formulation contains a large amount of poorly compressible active substance (1).

The work described here concerns the improvement of industrial production of tablets containing 50% active substance in the form of plant extracts. The present formulation raises problems in industrial processing, due in particular to the poor flow properties of the powder mixture, requiring addition of a powered feed system upstream of the tablet production line. Also, the tablets obtained have (a) low resistance to crushing (5 daN), which allows only classical air suspension coating, and (b) relatively long disintegration times, between 40 and 45 minutes.

This study set out to improve the rheological and pharmacotechnical characteristics of the present formulation using an appropriate experimental design.

MATERIALS AND METHODS

First, various formulations were made up to afford a choice of excipients necessary for a correct basic formulation. Among the excipients tested, particular attention was focused on the choice of the direct compression excipient.

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Second, an experimental design was drawn up from the selected base formulation.

Raw Materials

Active Substances

The active substances were dry extracts of plant origin, nonhygroscopic under normal conditions of ambient air humidity (60 ± 10%), and displaying no fluidity.

Excipients tested

Diluent
- Lactose (French Pharmacopeia, 10th edition)

Direct compression excipients
- Lactose E.F.C.® (extrafine crystalline) (S.P.C.I.)
- Microcrystalline cellulose: Avicel PH 101 (Seppic)
- Dicalcium phosphate: Emcompress® (S.P.C.I.)

Glidant
- Amorphous hydrated precipitated silica: Levilite® (Rhône-Poulenc)
- Anhydrous colloidal silica: Aerosil 200® (Degussa)

Lubricants
- Glycerol behenate: Compritol 888® (Gattefossé)
- Magnesium stearate

Disintegration agent
- Reticulated sodium carboxymethylcellulose: Acdisol® (Seppic)

Choice of Excipients

For preformulation tests the excipients were selected using two criteria. They had to provide a correct reproducible basic formulation and have an acceptable cost that was compatible with the manufacturer's specifications.

Among the available direct compression excipients, three were pretested: Avicel PH 101, Emcompress, and Lactose E.F.C.

Avicel PH 101 was not finally selected since, although it only required a force of 1250 daN to obtain tablets with a hardness equivalent to that obtained with the other two direct compression excipients, the results of tests carried out during batch production of tablets were markedly less favorable: longer flow time, lower bulk density of the powder mixture, higher tapping test (V_{10}–V_{500}), and thicker tablets. Likewise, though Emcompress was pharmacotechnically attractive but it was not selected because it required a higher compression force (1600 daN) as well as a disintegration agent (such as Acdisol) to reduce the tablet disintegration time.

Lactose E.F.C. afforded the best results with a compression force near 1400 daN, and was accordingly selected as the direct compression excipient.

The choice of glidant was an association of two types of silica: Levilite, as this was already present in the existing formulation, and Aerosil 200, which can have a strong influence on compression, even at low concentrations, due to its physical characteristics.

As lubricants, Compritol 888 associated with magnesium stearate allowed the amount of the latter to be reduced; too much can be detrimental to disintegration rate and also tablet hardness. The amount of Compritol was first set at a reasonable value in terms of cost considerations. The effect of varying the level of magnesium stearate was then studied so as to reduce it optimally.

Basic Formulation

An initial tablet formulation was made up.

Nature	Constituents	mg
Drug	Plant extracts	250
Glidants	Amorphous hydrated precipitated silica	10
	Anhydrous colloidal silica	2.5
Diluents	Lactose	76
Direct compression excipient	Lactose E.F.C.	150
Lubricants	Glycerol behenate	10
	Magnesium stearate	1.5

The final weight of the tablets was 500 mg.

The constituents were screened at 500 μm before mixing in a Turbula mixer for 5 minutes. The compression was carried out on a Korsch-type E.K.O. tableting machine equipped with strain gauges and fitted with dies 10 mm in diameter with a radius of curvature of 8.5 mm.

Tests

The tests conducted during the manufacture of batches of tablets were to afford an assessment of the rheological and pharmacotechnical characteristics of the various formulations.

The tests set up comply with the French Pharmacopeia except for the mass regularity test where measure-

ment was carried out on 20 tablets instead of 10:

Measurements before compression
- Flow rate (in seconds)
- Tapping: V_{10}–V_{500} (in ml)
- Bulk density (in g/ml)

Measurements on tablets
- Mass regularity (in mg)
- Hardness: resistance to crushing (in daN)
- Friability (in %)
- Disintegration time (in minutes)

Optimization of the Formulation: Experimental Design

Out of several possible methods (2–4) the experimental design selected was a two-level nonrepeating factorial design, i.e., 2^k where k is the number of factors tested (5–8). The tablet formulation selected was that which gave the best results during tablet batch production, namely that containing Lactose E.F.C.

The three factors selected as variables were those most liable to affect the formulation:

Factor A = direct compression excipient: Lactose E.F.C.
Factor B = glidant: anhydrous colloidal silica: Aerosil 200
Factor C = lubricant: magnesium stearate

The zero level for these excipients corresponds to the basic formulation selected. The high and low levels were ±20% relative to this formulation for Lactose E.F.C. and anhydrous colloidal silica and ±33% for magnesium stearate.

	Lactose E.F.C. (mg)	Anhydrous Colloidal Silica (mg)	Magnesium Stearate (mg)
High level (+)	180	3	2
Zero level	150	2.5	1.5
Low level (–)	120	2	1

Test Matrix

The test matrix is presented in Table 1.

Choice of Response Criterion

The main problem lies in being able to predict the behavior of the powder during compression and the behavior of the resulting tablets. The response criterion should be able to assess these different behaviors. A mixed criterion (Y) was constructed on the basis of three subcriteria. It allows for flow (Y_1), tapping test (Y_2), which accounts for the behavior of the powder during the feed and compression phases, and tablet weight regularity (Y_3), which reflects the evenness of the production. These three factors were weighted to obtain identical contributions in Y. The practical calculation of the different subcriteria was as follows:

Table 1

Test Matrix

Symbol for Experiment	Lactose E.F.C. (A)	Aerosil 200 (B)	Mg Stearate (C)
Exp. 1: (*I*)	–	–	–
Exp. 2: *a*	+	–	–
Exp. 3: *b*	–	+	–
Exp. 4: *ab*	+	+	–
Exp. 5: *c*	–	–	+
Exp. 6: *ac*	+	–	+
Exp. 7: *bc*	–	+	+
Exp. 8: abc	+	+	+

Letters *a*, *b*, and *c* in the symbols for experiments represent high levels of each of the three factors A, B, and C. Eight experiments were planned without repetition to avoid extra cost. It was assumed for the statistical analysis that the three factors did not interact.

Y_1 = the flow time multiplied by 10 plus its standard deviation multiplied by 100 plus the flow evenness score (smooth flow 1, irregular 10, and intermittent 20). Multiplying coefficients provide numbers of the same magnitude.

Y_2 = the value (V_{10}–V_{500}) found for each formulation.

Y_3 = the coefficient of variation (in %) of the weight of the tablets for each formulation.

The final criterion is presented in the following equation: $Y = 1/10\ (Y_1 + Y_2 + 100Y_3)$; the factor 1/10 was applied to obtain convenient-sized numbers between 0 and 50.

A low value of Y indicated an optimal formulation.

Statistical Analysis

An analysis of variance was carried out. To analyze the interactions, repetitions would have been necessary. In the present case, the ABC interaction was taken as an estimation of the residual variation for the other factors (A, B, C, interactions AB, BC, AC). This implies that it cannot be processed and that it is neglected (starting assumption).

RESULTS AND DISCUSSION

Composition of the Different Formulations and Results of Dosage Form Tests

The unit compositions of the different formulations made up according to the experimental design are presented in Table 2 together with the corresponding dosage form tests. Formulation Y_0 is the starting formulation for the experimental design.

Effects Matrix

The values of the final criterion Y obtained for each formulation, together with the values of the effects and interactions, are given in Table 3.

Analysis of Variance

The analysis of variance is presented in Table 4. The coefficient of variation is 4.0%.

If no interaction is suspected a priori, the residual interaction can be taken as the sum of the different interactions. In this case the importance of factor A (Lactose E.F.C.) is even more marked ($p = 0.0063$), factor C (magnesium stearate) retains a comparable influence ($p = 0.0974$), and factor B (Aerosil 200) remains nonsignificant ($p = 0.2159$).

DISCUSSION

Influence of Lactose

The analysis of variance showed the predominant influence of the increase in Lactose E.F.C. or the decrease in lactose, the two factors being linked. However, the particle size characteristics of Lactose E.F.C. suggest that it is the increase in this material that is essential.

Influence of Magnesium Stearate

Magnesium stearate can have a negative role ($0.05 < p < 0.1$), especially when the Lactose E.F.C. content is low.

Influence of Anhydrous Colloidal Silica (Aerosil)

At the levels used in the experimental design, the differences found in the results are not very great. However, though at level +1 (*b*) flow is slightly improved, level -1 represents a necessary and sufficient value.

The absence of repetition in this experimental design was deliberate, to reduce experimentation time. The data obtained are therefore clearly limited. This is reflected in the analysis of variance by the ddl number of the residual variance, which lies between 1 and 4. However, the influence of Lactose E.F.C. and to a lesser extent magnesium stearate has been demonstrated.

Interactions

The experimental design setup shows a possible influence between Lactose E.F.C. and magnesium stearate. In fact, at level -1 of Lactose E.F.C. the influence of magnesium stearate is marked, while at this same level anhydrous colloidal silica reduces the unfavorable effect of magnesium stearate.

Given these results, an experimental point located to the right of the plane defined by Y_2, Y_4, Y_6, and Y_8 in Figure 1, e.g., a point Y'_0 opposite Y_0, would be expected to afford an even better result, i.e., a mixture displaying markedly better technological qualities. Such a point Y'_0 would have the coordinates Lactose E.F.C. = 226 mg; Aerosil 200 = 2.5 mg; magnesium stearate = 1.5 mg corresponding to a formulation without lactose.

Table 2

Unit Compositions and Dosage Form Tests Results

	Y_0	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8
Products									
Plant extracts	250	250	250	250	250	250	250	250	250
Levilite	10	10	10	10	10	10	10	10	10
Lactose	71	107	47	106	46	106	46	105	45
Lactose E.F.C.	150	120	180	120	180	120	180	120	180
Compritol 888	10	10	10	10	10	10	10	10	10
Magnesium stearate	1.5	1	1	1	1	2	2	2	2
Aerosil 200	2.5	2	2	3	3	2	2	3	3
Tablet weight (mg)	500	500	500	500	500	500	500	500	500
Results									
Flow									
Time (sec) ±S.D.	3.51 ± 0.60	2.77 ± 0.61	2.14 ± 0.15	2.87 ± 0.33	3.66 ± 0.09	4.23 ± 1.45	2.48 ± 0.17	5.31 ± 0.88	2.52 ± 0.18
Type	Regular	Irregular	Regular	Irregular	Regular	Intermittent	Regular	Intermittent	Irregular
Tapping test									
V_0 (ml)	158	165	156	168	160	167	160	166	160
V_{10}-V_{500} (ml)	28	30	25	26	27	31	26	30	25
M/V_0 (g/ml)	0.633	0.606	0.641	0.595	0.625	0.895	0.625	0.602	0.625
M/V_{1250} (g/ml)	0.806	0.813	0.833	0.813	0.826	0.819	0.819	0.813	0.819
Mass (20 tb)									
Mean (mg) ± S.D.	504.41 ± 4.93	497.40 ± 5.4	501.65 ± 3.6	497.65 ± 4.6	504.45 ± 2.3	504.99 ± 5.5	504.86 ± 3.8	503.01 ± 4.4	502.56 ± 2.5
C.V. (%)	0.976	1.087	0.727	0.931	0.455	1.093	0.754	0.876	0.501
Hardness (20 tb)									
Mean (daN) ± S.D.	15.871 ± 1.670	13.775 ± 1.369	15.390 ± 1.242	15.415 ± 1.511	16.185 ± 0.883	15.630 ± 1.690	14.500 ± 1.273	15.130 ± 1.210	15.250 ± 0.861
C.V. (%)	10.57	9.939	8.074	9.805	5.461	10.816	8.780	8.003	5.646
Friability (%)	0.204	0.234	0.208	0.194	0.212	0.232	0.244	0.233	0.209
Disintegration (6 tb)									
Mean	19 min 30 sec	18 min 30 sec	19 min 45 sec	20 min 10 sec	21 min 40 sec	19 min 40 sec	20 min 50 sec	22 min	21 min 10 sec
Standard deviation	1 min 10 sec	1 min 22 sec	16 sec	45 sec	1 min 30 sec	1 min 02 sec	1 min 36 sec	53 sec	45 sec
C.V. (%)	5.948	7.450	1.386	3.732	6.948	5.251	7.690	4.065	3.556

Table 3

Effects Matrix

Test Number	Mean	Factor A	Factor B	Factor C	Interact. A-B	Interact. A-C	Interact. B-C	Interact. A-B-C	*Y*
1	+	-	-	-	+	+	+	-	23.74
2	+	+	-	-	-	-	+	+	13.51
3	+	-	+	-	-	+	-	+	19.08
4	+	+	+	-	+	-	-	-	11.91
5	+	-	-	+	+	-	-	+	34.76
6	+	+	-	+	-	+	-	-	14.42
7	+	-	+	+	-	-	+	-	27.87
8	+	+	+	+	+	+	+	+	12.83
Divider	8	8	8	8	8	8	8	8	
Effects	19.76	- 6.59	- 1.84	2.70					

The main effects (A, B, C) can be calculated as the half sum of the difference between the means of the high and low levels. Thus for *A*:

$A = \frac{1}{2}[\frac{1}{4}(a + ab + ac + abc) - \frac{1}{4}((1) + b + c + bc)]$

Table 4

Analysis of Variance

Source	SCE	ddl	s^2	*F*	$P > F$
A	348.216	1	348.216	555.19	0.0270
B	27.158	1	27.158	43.30	0.0960
C	58.536	1	58.536	93.33	0.0657
A-B	8.736	1	8.736	13.93	0.116
A-C	40.410	1	40.410	64.43	0.0789
B-C	0.616	1	0.616	0.98	0.5029
Residual	0.627	1	0.627		
Total	484.30	7	484.30		

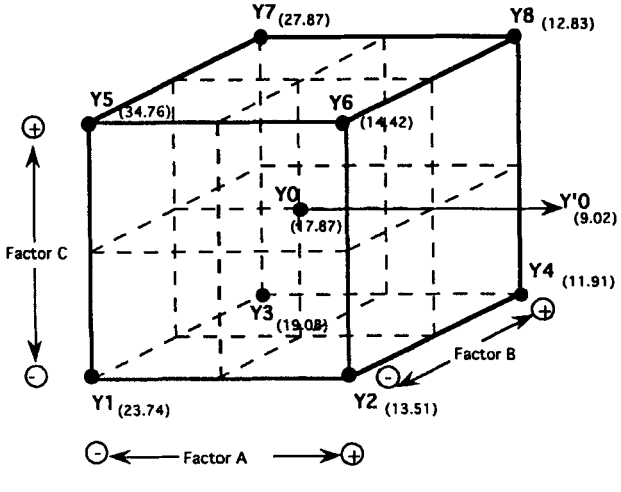

Figure 1. Graphical representation of effects matrix.

Preparation of this new formulation confirmed predictions, i.e., an even better response by the previous criteria, namely $Y'_0 = 9.02$.

This result is confirmed by the mathematical approach. If the different regressions are constructed stepwise, progressively adding the most informative parameter, we obtain:

Lactose E.F.C. alone: $Y = 52.8 - 0.22\ A$

Lactose E.F.C. and magnesium stearate:
$Y = 44.6 - 0.22\ A + 5.41\ C$

The three components: $Y = 53.9 - 0.22\ A + 5.41\ C - 3.69\ B$

In the last two equations, the slopes for C and B are not significantly different from zero at the threshold $\alpha = 0.05$.

Using the regression that includes only Lactose E.F.C., a quantity close to 240 mg gave optimal results. To keep a constant mass of 500 mg, a formulation containing 226 mg of this excipient was made up, with the other components constant. The theoretical response was close to 3.1 and the observed response obtained was $Y'_0 = 9.02$ (instead of 17.87 for the original formulation). The improvement is marked; the difference between the theoretical and observed responses may be due to the influence of the other factors.

The characteristics of this optimized formulation were as follows:

Mixture before compression
- Flow: 2.17 ± 0.08 seconds
- Tapping test: $V_{10} - V_{500} = 21$ ml
- Bulk density: 0.657 g/ml before and 0.819 g/ml after tapping

Tablets
- Mass regularity: 501.87 ± 0.02 mg
- Hardness/resistance to crushing: 14.80 ± 0.52 daN
- Friability: 0.16%
- Disintegration time: 20 min 50 sec ± 45 sec

In this study anhydrous lactose was always added, since (a) the resulting tablet characteristics were always correct, and (b) the cost of the formulation was obviously reduced—a significant factor for any manufacturer.

CONCLUSION

An improvement in the manufacture of direct compression tablets containing 50% plant extracts was obtained by a two-step experimental procedure.

First, preformulation tests were carried out to select the direct compression excipient, and subsequently the other excipients, lubricant, disintegration agent, and glidant to obtain an acceptable tablet formulation.

Second, in order to optimize this formulation by varying the levels of the different excipients while avoiding haphazard trial and error, a complete two-level experimental design was constructed. Three factors were tested: a compression agent (Lactose E.F.C.), a glidant (anhydrous colloidal silica), and a lubricant (magnesium stearate), i.e., 8 separate experiments. This revealed differences among the formulations, all of which gave good results, thus providing a sound basis for choosing the best ones.

This experimental design revealed a marked influence of Lactose E.F.C. and to a lesser extent magnesium stearate, and so allowed an optimization of the levels of these components. However, the best formulation, Y'_0, was not selected owing to its excessive industrial cost.

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