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RESEARCH PAPER

Influence of Tableting Forces and Lubricant Concentration on the Adhesion Strength in Complex Layer Tablets

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ABSTRACT

The strength of adhesion in complex two-layer tablets is assessed using statistical methods with respect to the applied tableting forces for the first layer and for applying the second layer on the first, as well as regarding the fraction of the lubricant. These results, obtained on a single-punch tablet press, are compared with the results for three-layer tablets produced on a rotary press at production scale. The strongest negative influence on adhesion strength was exerted by the amount of lubricant in the central layer. As expected, compression forces for central-layer tableting also had a negative effect, whereas the compression forces for complex layer tableting exerted a positive effect on layer adhesion. The validity of the derived model equation was proved by experiments: It was shown that the adhesion strength in complex layer tablets produced in production scale can be predicted from laboratory-scale experiments. This makes optimization of the formulation and parameter settings at an early stage of development possible.

Key Words: *Adhesion strength; Central composite design of experiments; Compression force; Layer tablet; Lubicant; Shear apparatus; Smartrix®.*

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INTRODUCTION

In the past years, interest in developing new oral controlled-release systems has increased. The need for reduction of production costs caused a revival of layer tableting as an alternative to multiparticulate and coating systems. Several technologies with sophisticated layer tablets have been presented, such as Smartrix® (1), Geomatrix® (2), and others (3–5).

Smartrix tablets belong to a group of new layer tablets called complex layer tablets, which have layers that are shaped individually. The individual shaping of the layers is achieved by the geometry and direction of one precompressed layer (''core tablet'') that is inserted as a central layer in the tablet. Upper and lower layers are pressed onto the central layer in a second step. This can be done on a specially designed two-station rotary tablet press. By this, the new technology of complex layer tableting allows the compression of outer layers on precompressed central-layer tablets in a single process, which is allied to compression coating. The goal of complex layer tableting is the design of different controlled-release profiles (e.g., through the shaping of the central-layer tablet, the geometry of which controls drug release), together with the concurrent erosion of the outer layers, as was demonstrated for Smartrix tablets elsewhere (1,6). The main advantage of this technology is the possibility to achieve different release profiles easily through only the variation of the tablet geometry.

Technical problems caused by delamination in normal tablets, and particularly in layered tablets, are well known. In complex layer tablets, it is even more delicate to secure a good layer adhesion for the following reasons: First, the outer layers control the rate of drug release from the central layer of the tablet (7,8) only by erosion; second, the central layer is already a compressed tablet, a fact that makes adhesion even more difficult to achieve. To quantify the effects of the maximum forces used in tableting of the various layers and the fraction of the lubricant in the formulations on the strength of adhesion in complex layer tablets, experiments of the present study were statistically designed. Flat-face complex layer tablets were produced in laboratory scale and studied as a model. The quantitative results from the model tablets were evaluated and compared with the results from complex layer tablets that were produced in production scale. Furthermore, the aim of this study was to determine the possibilities of prediction of adhesion strength in complex layer tablets produced in production scale from results obtained from laboratory-scale model experiments. This would give an opportunity to optimize formulations and parameter settings at an early stage in the development process.

METHOD

Complex Layer Tablets

Central layers consisted of Microcelac® (Meggle, Wasserburg, Germany), a coprocessed mixture of 75% alpha-lactose monohydrate and 25% microcrystalline cellulose. To make a macroscopic differentiation of the layers possible, the central-layer material contained 0.05% of a color pigment (Grünlack E104 + E132, Dragoco, Holzminden, Germany). Central-layer tablets contained 0.25%, 0.5%, or 0.75% calcium behenate (Synopharm, Barsbüttel, Germany) as a lubricant. The outer layers consisted of Spherolac 100 (sieved alpha-lactose monohydrate, Meggle) with 0.25% calcium behenate as a lubricant. For all formulations, calcium behenate was sieved onto the powder through a 160-μm sieve. Afterward, the powder was mixed for 5 min in a Turbula mixer at 42 rpm (Turbula T2C, W. Bachofen, Basel, Switzerland). The containers were filled to two-thirds of the volume with the powder. The batch sizes were 500 g each.

For the laboratory-scale experiments, flat-face complex two-layer tablets (Fig. 1a) with a diameter of 10 mm were compressed on an instrumented single-punch tablet press (Korsch EK-0 DMS, Korsch Pressen, Berlin, Germany). The first layers (central-layer tablets) were tableted with compression forces of 5, 8, 10, or 15 kN at a speed of approximately 24 cycles per min. Complex two-layer tablets were produced on the single-punch tablet press by the following procedure: The 10-mm die was filled with the second-layer material; the central-layer tablet was inserted manually into the die; and the complex two-layer tablet was tableted with compaction forces of 10, 15, or 20 kN. The compression was performed by turning the hand wheel manually with a velocity corresponding to approximately 24 cycles per min. All

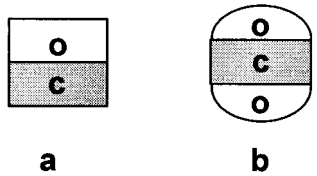

Figure 1. a, complex two-layer tablet (laboratory scale); b, complex three-layer tablet (production scale); c, central-layer tablet; o, outer layer.

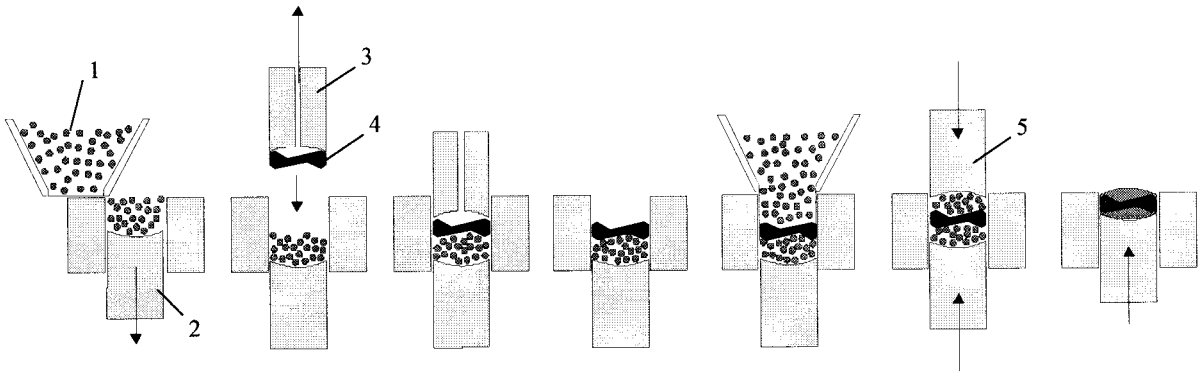

Figure 2. Complex layer tableting (schematic): 1, filling cam; 2, lower punch; 3, vacuum punch; 4, central-layer tablet; 5, upper punch.

compression forces have maximum variations of about 0.5 kN.

For the production-scale experiments, convex-shape complex three-layer tablets (Fig. 1b) with the same flat-face central-layer tablets as described above were produced on a special compression-coating machine for complex layer tableting with a new core-insertion system (9,10) that allows the precise radial positioning of the central-layer tablets (diameter 10 mm) into the 10-mm die (PH 848.3C, Korsch Pressen, Berlin, Germany). The material of the outer layers (Spherolac 100) is filled into the die before and after the insertion of the central-layer tablet (Fig. 2). The compression forces for production-scale complex-layer tableting are 15 kN. For the first three batches, the compression forces were within the limits of 13 to 17 kN (sliding average) and 12 to 18 kN (single compression forces). For the fourth batch, compression force limits were narrower, between 14 and 16 kN for both the sliding average and single compression forces.

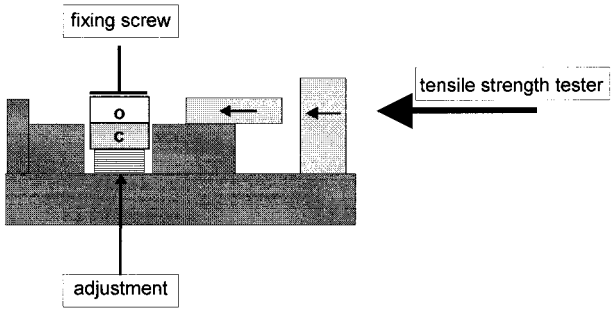

Figure 3. Shear apparatus for adhesion strength measurements (schematic): c, central-layer tablet; o, outer layer.

Measuring Adhesion Strength in Complex Layer Tablets

The shear forces needed to separate the layers in the radial direction are measured with a shear apparatus, described elsewhere (7,8), that is inserted into a commercially available tensile strength tester (TBH 30, Erweka, Heusenstamm, Germany) (Fig. 3). The complex layer tablets were inserted into the shear apparatus, and the level of the plane between the layers was adjusted to the level shear plane. On the top, the tablet was held by a screw with a constant torque of 6.5 N. The shear forces

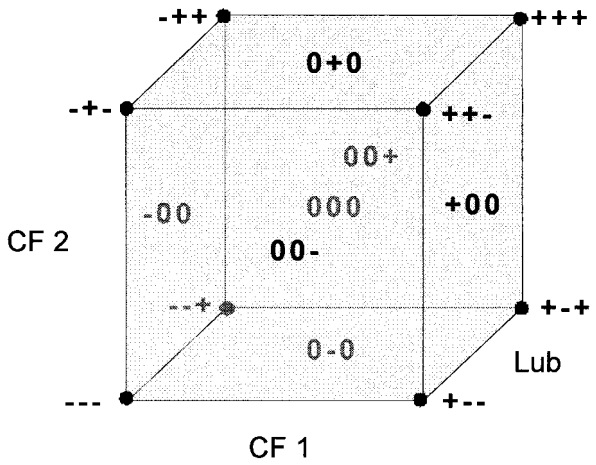

Figure 4. Central composite face design of experiments: +, high level of parameter settings; −, low level of parameter settings; 0, medium level of parameter settings; CF 1/2, compression force for central-layer/complex layer tableting; Lub, lubricant concentration in central-layer tablet.

needed to separate the layers were taken as a measure of adhesion strength. The values were obtained in newtons.

Design of Experiments

The influences of the applied compression forces for central-layer tableting, the lubricant concentration in the central-layer tablets, and the applied compression forces for complex layer tableting on the adhesion strength in complex layer tablets were assessed. The experiments were designed statistically following a central composite face design (Fig. 4) (11–13), which is commonly used for optimizations. All calculations were performed using JMP® statistical software (SAS Institute, Heidelberg, Germany).

RESULTS AND DISCUSSION

Adhesion Strength in Complex Two-Layer Tablets

The results for adhesion strength measurements are displayed in Table 1. For all those complex layer tablets that contained a central-layer tablet compressed at 5 kN, good layer adhesion was achieved irrespective of the lubricant fraction levels and the compression forces applied during complex layer tableting. In contrast, using central-layer tablets that were compressed with 15 kN, no sufficient adhesion strength in the resulting complex layer tablets could be achieved under any of the experimental conditions.

For all main effects and interaction effects, a first model for the estimation of adhesion strength in complex layer tablets was calculated. Table 2 gives a summary of the regression parameters and variance analysis for the model equation fitted to the results. The analysis of variance (ANOVA), which assesses model relevance, shows the significance of the model with a ratio of the variances of the residues of measurements compared to the model and the variance of all the measured data (FRatio) of 59.9, which is much higher than the critical value (FCrit) of 2.10. The lack-of-fit variance test evaluates if the variance caused by a lack of fit (LOF) is significantly greater than the experimental error (PE) expressed as the variance of the measured values. In this model, $FRatio_{LOF}$ (2.946) exceeds $FCrit_{LOF}$ (2.84) (Table 2). This means that the goodness of fit is not sufficient on the significance level of $\alpha = 5\%$. Nonsignificant parameters, therefore, have to be eliminated from the model. The *t* test of significance of the parameter estimates showed no significance for the interaction of compression force for complex layer tableting and lubricant concentration in the central-layer tablet and for the quadratic interaction of lubricant concentration. Prob $> t|$(Table 2) is the proba-

Table 1

Central Composite Design of Experiments and Results of Adhesion Strength Measurements

CF 1[a] (kN)	CF 2[b] (kN)	Lub[c] (%)	Adhesion Strength in Complex Layer Tablets (N)						Mean + SD (N)
5	10	0.25	126	131	116	123	91	101	115 ± 16
5	10	0.75	93	104	97	94	97	94	
			98	103	103	98			98 ± 4
5	20	0.25	240	208	252	242	229	253	237 ± 17
5	20	0.75	235	220	226	221	238	206	224 ± 12
15	10	0.25	0	0	0	0	0	0	0
15	10	0.75	0	0	0	0	0	0	0
15	20	0.25	0	0	0	0	0	0	0
15	20	0.75	0	0	0	0	0	0	0
5	15	0.50	139	143	154	135	143	145	143 ± 6
15	15	0.50	0	0	0	0	0	0	0
10	10	0.50	0	0	0	0	0	0	0
10	20	0.50	0	0	0	0	0	0	0
10	15	0.25	45	116	120	138	0	0	70 ± 63
10	15	0.75	0	0	0	23	0	0	4 ± 9
10	15	0.50	0	0	0	0	0	0	0

[a] CF 1=compression force for central-layer tableting.
[b] CF2=compression force for complex layer tableting.
[c] Lub=lubricant concentration in central-layer tablet.

Table 2

Analysis of Variance and Regression Parameters of Central Composite Design for All Effects

	Analysis of Variance					
	df	Sum of Squares	Mean Square	FRatio	FCrit	Prob > *F*
Model	9	352,108.11	39,123.1	59.6076	2.10	<.001
Error	44	28,879.15	656.3			
Total	53	380,987.26				
	Lack of Fit					
	df	Sum of Squares	Mean Square	FRatio	FCrit	Prob > *F*
LOF	3	5121.748	1707.25	2.9463	2.84	.044
PE	41	23,757.4	579.45			
Total error	44	28,879.148				

	Parameter Estimates									
	Intercept	CF 1	CF 2	Lub	$(CF\ 1)^2$	CF 2 ∗ CF 1	$(CF\ 2)^2$	Lub ∗ CF 1	Lub ∗ CF 2	$(Lub)^2$
Estimate	95.14	−27.95	32.78	−441.88	1.8900	−1.47	−0.44	−13.67	−0.18	476.98
Prob > |*t*|	0.309	0.0221	0.021	0.0166	0.0005	0.0002	0.3275	0.0418	0.9637	0.0043

RSquare = 0.924199; observations = 54; mean of response = 106.2963.

bility of getting a *t* ratio greater than the computed value by pure chance. A value below .05 is interpreted as evidence for a parameter being significantly different from zero. For this reason, the two nonsignificant effects, $(CF\ 2)^2$ and Lub ∗ CF 2, have to be eliminated from the model. All the other parameters showed a significant contribution to the model.

The model was recalculated for the significant effects only. Results are given in Table 3. Now, the LOF test expressed a significant dependence of the model from the parameters (FRatio = 1.99, which is below FCrit = 2.45). All parameters in this model had a significant influence on the adhesion strength (all Prob > |*t*| values are below .05). The analysis of variance still proved the model relevance (FRatio = 78.23, which is above FCrit = 2.22).

Model Equation

The model equation for the adhesion strength in complex layer tablets was derived from the above results. The values for the parameter estimates were put into an equation following $y = a + b_1x_1 + \ldots + b_ix_i$, with *a* being the intercept and b_i the parameter estimates. The equation for the adhesion strength in complex layer tablets is shown in Table 4.

First, the influence of the single parameters is discussed: The strongest negative effect (estimate − 370) on the adhesion strength in complex layer tablets was exerted by the lubricant concentration in the central layer. As expected, the compression force for central-layer tableting also had a negative influence (estimate −23), whereas the compression force for complex layer tableting affected the adhesion strength positively (estimate +20).

Interactions of the parameters in general had a smaller impact on adhesion strength. The only exception was (Lub^2), derived from the lubricant fraction, which was already found to have the strongest impact. The interaction between compression force of the first layer and lubricant fraction was also of some relevance. Correlation between the calculated and the measured values for adhesion strength is shown in Fig. 5. The horizontal line represents the overall mean; the fit is displayed together with the 95% confidence interval. The graph shows good correlation between the calculated and the experimental values for the adhesion strength in complex layer tablets. Ideally, all measured values would be located on the fit. Yet, it has to be considered that no experimental values for the adhesion strength lower than zero can be obtained in contrast to the calculated negative values.

Response Surface Plots

With help of the model equation, response surfaces were calculated; they visualize the effects and interac-

Table 3

Analysis of Variance and Regression Parameters of Central Composite Designs for All Significant Effects

	Analysis of Variance					
	df	Sum of Squares	Mean Square	FRatio	FCrit	Prob > *F*
Model	7	351,464.1	50,209.2	78.2308	2.22	<.001
Error	46	29,523.16	641.8			
Total	53	380,987.26				
	Lack of Fit					
	df	Sum of Squares	Mean Square	FRatio	FCrit	Prob > *F*
LOF	5	5765.763	1153.15	1.9901	2.45	.1005
PE	41	23,757.4	579.45			
Total error	46	29,523.164				

	Parameter Estimates							
	Intercept	CF 1	CF 2	Lub	(CF 1)^2	CF 2 ∗ CF 1	Lub ∗ CF 1	(Lub)^2
Estimate	152.74	−23.14	19.58	−370.41	1.64	−1.47	−13.07	398.77
Prob > |*t*|	0.0158	0.0328	<0.0001	0.0162	0.0004	<0.0001	0.0472	0.0051

RSquare = 0.922509; observations = 54; mean of response = 106,2963.

tions of two parameters at a fixed level of a third parameter.

At a low level of lubricant concentration in the central-layer tablet (Fig. 6), the adhesion strength was higher than 100 N over the whole range of compression forces. At low applied compression forces for central-layer tableting, the increase of compression forces for complex layer tableting from 10 to 15 kN led to an increase of adhesion strength from about 150 N to 250 N.

If large amounts of lubricant were used in the central-layer tablet (Fig. 7), insufficient adhesion strength was achieved when the central-layer compression forces exceed about 10 kN. At low compression forces for central-layer tableting, increasing applied compression pressures for complex layer tableting (from 10 to 20 kN) led, as expected, to an increase in adhesion strength from about 100 N to about 200 N.

These results confirm the expectation that an increased amount of lubricant leads to higher sensitivity of layer adhesion to the applied compression forces during central-layer tableting. Sufficient adhesion strength in complex layer tablets, in which the central-layer tablets contain high amounts of lubricant, can only be expected when the central-layer tablets are compressed with low compression forces.

When low compaction pressures during complex layer tableting were applied (Fig. 8), sufficient adhesion forces of about 100 N were only obtained with central-layer tablets, which were compressed with low compression forces. When central-layer tablets were compressed with forces greater than 10 kN, no layer adhesion could be expected if compression forces in complex layer tableting were applied that were in a reasonably low range (under 20 kN) unless the lubricant fraction was very low (0.25%).

Table 4

Model Equation for Adhesion Strength in Complex Layer Tablets

$$\text{Adhesion strength [N]} = 152.7 - 23.1 \cdot \text{CF 1} + 19.6 \cdot \text{CF 2} - 370.4 \cdot \text{Lub} + 1.6 \cdot (\text{CF 1})^2 + 398.8 \cdot (\text{Lub})^2 - 1.5 \cdot (\text{CF 1} \cdot \text{CF 2}) - 13.1 \cdot (\text{CF 1} \cdot \text{Lub})$$

CF 1/2 = compression force for central-layer/complex layer tablets, Lub = lubricant concentration in central-layer tablet.

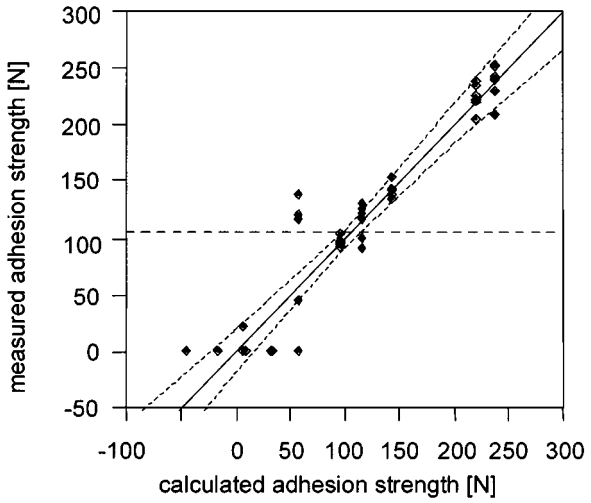

Figure 5. Measured values versus calculated values for adhesion strength in complex two-layer tablets.

When the compression forces during complex layer tableting were set at a high level of 20 kN (Fig. 9), the strong negative influence of the central-layer compaction forces on the adhesion strength were observed. When central-layer tablets tableted with 5 to 10 kN were used, adhesion strength ranged between 200 and 100 N. When the central-layer tablets were tableted with a compression force of 10 to 15 kN, only 100 to 20 N adhesion strength could be expected. The amount of lubricant in the central-layer tablets exerted an observable negative influence on the adhesion strength in this range of compression forces.

The positive influence of the compression forces applied during complex layer tableting on the adhesion strength in complex layer tablets improved with lower applied tableting forces for the central layers. When central-layer tablets compressed with higher compression pressures were inserted, the negative influence of the lubricant concentration on the adhesion strength was more obvious.

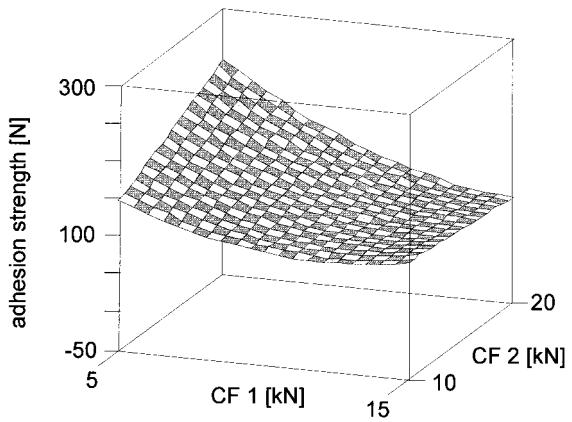

Figure 6. Contour plot for influence of compression forces on adhesion strength in complex layer tablets at low level of lubricant concentration in central-layer tablet. CF 1/2, compression force for central-layer/complex layer tableting.

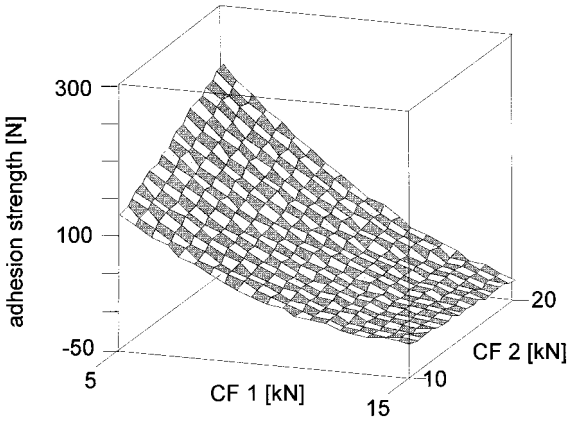

Figure 7. Contour plot for influence of compression forces on adhesion strength in complex layer tablets at high level of lubricant concentration in central-layer tablet. CF 1/2, compression force for central-layer/complex layer tableting.

Experiments to Confirm the Validity of the Model Equation

On central-layer tablets containing 0.2% of the lubricant, which were compressed with 8 kN on the same tab-

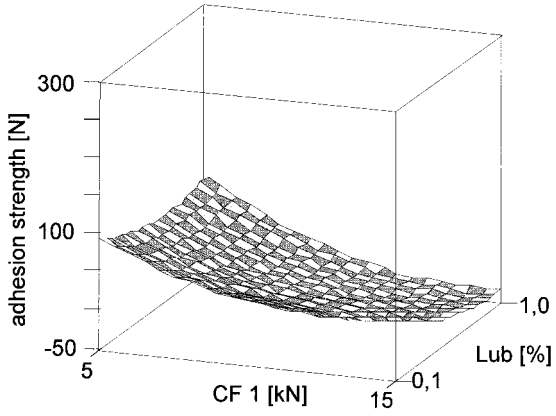

Figure 8. Contour plot for influence of compression force and lubricant concentration of central-layer tablet on adhesion strength in complex layer tablets at low compression forces for complex layer tableting. CF 1, compression force for central-layer tableting; Lub, lubricant concentration in central-layer tablet.

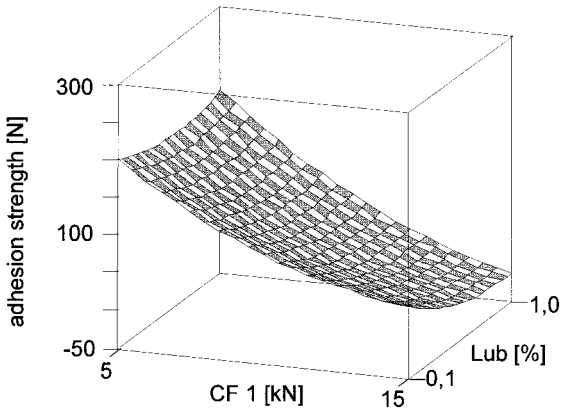

Figure 9. Contour plot for influence of compression force and lubricant concentration of central-layer tablet on adhesion strength in complex layer tablets at high compression forces for complex layer tableting. CF 1, compression force for central-layer tableting; Lub, lubricant concentration in central-layer tablet.

let press as above, complex layer tableting was performed with 15 and 20 kN, and the adhesion strength was measured. The expected adhesion strength was calculated from the model equation and compared with the experimental values. The chosen settings represent a good compromise between (*a*) sufficient tablet strength and sufficient resistance to friability and (*b*) lowest possible compression forces for the central-layer tablet.

The measured adhesion strengths are 113 N ± 7 N for those complex layer tablets compressed with 15 kN compression force; the model predicted 111 N. The second measurements resulted in adhesion strengths of 131 N ± 18 N for complex layer tablets compressed with 20 kN; the model predicted 150 N. In both cases, the theoretical values correlated well with the measured values. These results show that a good prediction of adhesion strength is possible within the limits of the chosen design. With a small number of statistically designed experiments, a good prediction of adhesion strength over a wide range of parameter settings is possible. With minimum effort, it is already possible, at an early stage in development, to optimize formula and production parameters with regard to adhesion strength.

As expected, ideal parameter settings to achieve high adhesion strength are low lubricant concentrations, low compression forces for central-layer tableting, and high compression forces for compaction of complex layer tablets.

Adhesion Strength in Complex Three-Layer Tablets

To validate if the results obtained on a laboratory scale for complex two-layer tablets can be transferred to production scale, four batches of one formula were produced as complex three-layer tablets in a large scale on the rotary press. The central-layer tablets contained 0.2% lubricant and were tableted with 8 kN compression force. The complex-layer tableting was carried out with 15 kN, which would then lead to a predicted adhesion strength of 111 N. The experimental results are listed in Table 5. There were no significant differences in the adhesion strength among the batches. For all batches, adhesion strength was 113 N ± 37 N (n = 392) (Table 5). The smaller variability of the maximum compression forces with batch 4 had no significant effect on adhesion strength or on its variability. No significant difference was found between adhesion of the upper (109 N ± 40 N) and the lower (116 ± 34 N) outer layers on the central layer.

Compared with the results from complex two-layer tablets (113 N ± 7 N) in the small scale, the values measured for adhesion strength for complex three-layer tablets are within the same range (113 N ± 37 N). Their higher variability is presumably attributed to a higher variability in compression force due to technical reasons.

Table 5

Batch Sizes and Adhesion Strength in Complex Three-Layer Tablets

Batch No.	Batch Size	Adhesion Strength, Upper Layer [N]	Adhesion Strength, Lower Layer [N]	Mean Adhesion, Strength [N]
1	400	95 ± 23 (n = 28)	131 ± 38 (n = 28)	113 ± 36 (n = 56)
2	200	95 ± 29 (n = 10)	139 ± 42 (n = 10)	118 ± 42 (n = 20)
3	200	84 ± 20 (n = 28)	110 ± 26 (n = 28)	97 ± 26 (n = 56)
4	1000	96 ± 26 (n = 98)	138 ± 38 (n = 98)	117 ± 38 (n = 196)
Overall mean		109 ± 40 (n = 169)	116 ± 34 (n = 169)	113 ± 37 (n = 392)

The results presented show that, within the model studied, it is possible to predict the adhesion strength achieved on a production-scale rotary tablet press from a small number of laboratory-scale experiments.

CONCLUSIONS

As expected, the ideal parameter settings to achieve high adhesion strength in complex layer tablets were low lubricant concentration, low compression forces for central-layer tableting, and high compression forces for complex layer tableting. Yet, this demand was limited for practical reasons:

1. Lubricant concentration has to be sufficient to avoid sticking.
2. Compression force for central-layer tablets has to be high enough to achieve sufficient crushing strength and resistance to friability.
3. Compression force for complex layer tableting cannot be increased infinitely because of (*a*) limitations of the tablet press and tooling and (*b*) the asymptotic approach toward a final density of the tablet, as described by Heckel (14). When the central-layer tablet was already highly condensed by high applied compression forces, an increase in compression force for complex layer tableting cannot reduce its volume further.

By means of a central composite design of experiments, a model equation to calculate and predict the adhesion strength in complex two-layer tablets was derived. The validity of the model equation was confirmed by the experiments.

The strongest negative influence on layer adhesion was exerted by the main and quadratic interaction effects of the lubricant concentration in the central-layer tablet: Larger fractions of lubricant led to reduced adhesion strength. This effect was more pronounced when high compression forces were applied already during central-layer tableting. If large fractions of lubrication in the central-layer tablet were used, adhesion strength could only be obtained with low compression forces during central-layer tableting. Furthermore, the positive effect on adhesion strength of higher compression forces during complex layer tableting increased with central-layer tablets that were tableted with lower compaction forces at all lubricant fraction levels.

Experiments in the production scale of complex three-layer tablets proved the validity of the model equation derived from laboratory-scale experiments within the range of parameter settings chosen, which cover the range that would commonly and preferably be used in pharmaceutical tableting of the formulation studied. It is possible to predict the adhesion strength and to optimize the production parameters with respect to the production scale in the laboratory scale with only a minimum number of experiments.

Considering the differences in compaction mechanisms of the various excipients (15), it is necessary to carry out the same set of experiments for each new formulation. Yet, with 15 or fewer runs within a statistical design of experiments, the effort is small compared to the general statements that can be derived from the obtained results. Critical parameter settings can be determined at an early stage in development. This is important as regards time and financial aspects in industrial research and development.

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