Original Article

Effects of lubricants on binary direct compression mixtures

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ABSTRACT: The objective of this study was to investigate the effects of conventional lubricants including a new candidate lubricant on binary direct compression mixtures. Magnesium stearate (MGST), stearic acid (STAC), glyceryl behenate (COMP) and hexagonal boron nitride (HBN) were tested. The binary mixtures were 1:1 combinations of spray dried lactose (FlowLac 100), dicalcium phosphate dihydrate (Emcompress), and modified starch (Starch 1500) with microcrystalline cellulose (Avicel PH 102). Tablets were manufactured on a single-station instrumented tablet press with and without lubricants. In the case of unlubricated granules, the modified starch-microcrystalline cellulose mixture provided the highest percent compressibility value at 8.25%, spray dried lactose-microcrystalline cellulose mixture was 7.33%, and the dialcium phosphate dihydrate-microcrystalline cellulose mixture was 5.79%. Their corresponding tablet crushing strength values were: 104 N, 117 N, and 61 N, respectively. The lubricant concentrations studied were 0.5, 1, 2, and 4%. Effects of lubricant type and lubricant concentration on crushing strength were analyzed using a factorial ANOVA model. It was found that the Avicel PH 102-Starch 1500 mixture showed the highest lubricant sensitivity (110 N *vs.* 9 N), the least affected formulation was FlowLac-Avicel PH 102 mixture (118 N *vs.* 62 N). The crushing strength *vs.* concentration curve for MGST showed a typical biphasic profile, a fast drop up to 1% and a slower decline between 1 and 4%. The STAC, COMP, and HBN for all formulations showed a shallow linear decline of tablet crushing strength with increasing lubricant concentration. The HBN was as effective as MGST as a lubricant, and did not show a significant negative effect on the crushing strength of the tablets. The COMP and STAC also did not interfere with the crushing strength, however, they were not as effective lubricants as MGST or HBN.

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1. Introduction

For a wide range of drugs, tablets are the preferred form of delivery. There are many reasons for this preference. Tablets have a high level of patient acceptability and compliance, they provide an accurate dosage and are easy to swallow. The form is distinctive and identifiable as tablets come in a variety of shapes and colors. Tablets taste bland, are less prone to tampering than other dosage forms and they offer advantages in manufacturing speed and cost (*1,2*). Before the 1960s, tablet manufacturing often required a wet granulation process to convert the active ingredients into flowable and compressible granules. With the introduction of carriers such as microcrystalline cellulose, tablet manufacturing *via* direct compression has become a convenient option (*2,3*). In contrast to wet granulation, direct compression methods are rather simple. In fact, the three step process, involving screening and/or milling, final mixing and compression, can often save labor, time, equipment and space (*4,5*). Although direct compression may seem to be a simple method for making tablets, the selection of appropriate excipients and their levels in the formulation are crucial for successful manufacturing (*6,7*). The compressibility and flowability of an excipient must be considered when developing a direct compression formula. The lubricants are pharmaceutical excipients that decrease friction at the interface between a tablet and the die wall during ejection. Without external lubricant addition the modern tableting operations can not be carried out. Inadequate lubrication due to friction and adhesion among powder particles leads to troubles in the manufacturing process and deterioration of productivity (*8,9*). Friction will damage the machine and tablet during the ejection phase. Moreover, high temperature generated during compression can affect drug stability (*10*). Because of the aforementioned reasons, determining the type and level of lubricants are among the critical parameters in direct compression. If the concentration of a lubricant is too high, or the mixing time is too long, the potential problem will be a decrease

in tablet hardness, inability to compress into tablets, increase in tablet disintegration time, and a decrease in dissolution rate (*11-14*). In our previous studies (*9,15*), we reported that magnesium stearate (MGST), and a newly introduced lubricant, hexagonal boron nitride (HBN) provided the smallest lower punch ejection forces (LPEF) during tableting for a wet granulation process. While stearic acid (STAC) and glyceryl behenate (COMP) resulted in a much higher LPEF. This study was designed based on that information. In this study, selected binary direct compression mixtures spray dried lactose-microcrystalline cellulose (DC1), dicalcium phosphate dihydrate-microcrystalline cellulose (DC2), and modified starch-microcrystalline cellulose (DC3) were used to assess the effect of lubricant type and concentration on directly compressed tablets' mechanical properties. A two-way ANOVA design was used to evaluate these effects.

2. Materials and Methods

2.1. *Materials*

Microcrystalline cellulose (Avicel PH 102) was donated by FMC, Brussels, Belgium. Spray dried Lactose (FlowLac 100) was obtained from Meggle AG, Wasserburg, Germany. Dibasic calcium phosphate dihydrate (Emcompress), and Starch 1500 were donated by Select Chemie AG, and Colorcon Ltd., Istanbul, Turkey. MGST (0.43 m^2/g) , STAC (0.03 m^2/g), COMP (0.23 m^2/g), and HBN (1.13 m^2/g) were obtained from Mallinckrodt, St. Louis, MO, USA, Sherex, Dublin, OH, USA, Gattefose, Cedex, France, and ITU, High Technology Ceramics and Composites Research Center, Istanbul, Turkey, respectively.

2.2. *Powder mixtures*

A 1:1 mixture of Avicel PH 102-FlowLac 100, Avicel PH 102-Emcompress, and Avicel PH 102-Starch 1500 were used as the master mixtures without a drug. Binary mixtures were mixed for 20 min in a laboratory size V-blender. All lubricants were added to those binary mixtures depending on their studied concentrations and mixed further for 3 min.

2.3. *Bulk and tapped densities*

Twenty grams of binary mixtures DC1, DC2, and DC3 were mixed separately in a V-blender for 10 min, the mixtures were poured into a 100 mL graduated cylinder. Their bulk volumes were recorded. The cylinder was directly mounted onto a tapping machine which had a tapping speed of 100 taps/min. After 3 min tapped volumes were recorded. Measurements were made in triplicate. Average d_b and d_t were calculated from M/V_b and M/V_t where M was the weight of the binary mixture, V_b was the bulk volume and V_t was the tapped volume. The bulk density was d_b and d_t was the tapped density. Percent compressibility (Carr Index) was calculated for each mixture as: $1– d_b/d_t \times 100$.

2.4. *Tablet preparation*

For lubrication performance, 48 batches (B1-B48) of tablets were manufactured using a single-station instrumented tablet press (Korsch EK0, Berlin, Germany) with a 9 mm flat faced punch set. Study design is given in Table 1. A 250 mg direct compression mass was filled into the die cavity and 6 perpetual compressions were made. Tablet weight and the upper punch compression pressure were kept constant for each binary mixture for 0.5, 1, 2, and 4% lubricant concentrations. However, when the tableting operation was changed to the next formulation (*i.e.,* DC2), the tablet weight was kept constant but the compression pressure was adjusted to obtain approximately 110-120 N crushing strength for the

Table 1. Study design

Formulation DC 1 [Spray dried lactose/Avicel PH 102 (1:1)]			Formulation DC 2 [Emcompress/Avicel PH 102 (1:1)]			Formulation DC 3 [Starch 1500/Avicel PH 102 (1:1)]		
Batches	Lubricant type	Lubricant concentration (%)	Batches	Lubricant type	Lubricant concentration (%)	Batches	Lubricant type	Lubricant concentration (%)
B1	MGST	0.5	B17	MGST	0.5	B33	MGST	0.5
B2	MGST	1	B18	MGST	1	B34	MGST	1
B3	MGST	2	B19	MGST	2	B35	MGST	2
B4	MGST	4	B20	MGST	4	B36	MGST	4
B5	HBN	0.5	B21	HBN	0.5	B37	HBN	0.5
B6	HBN	1	B22	HBN	1	B38	HBN	1
B7	HBN	2	B23	HBN	2	B39	HBN	2
B8	HBN	4	B24	HBN	4	B40	HBN	4
B9	COMP	0.5	B25	COMP	0.5	B41	COMP	0.5
B10	COMP	1	B26	COMP	1	B42	COMP	1
B11	COMP	2	B27	COMP	2	B43	COMP	2
B12	COMP	4	B28	COMP	4	B44	COMP	4
B13	STAC	0.5	B29	STAC	0.5	B45	STAC	0.5
B14	STAC	1	B30	STAC	1	B46	STAC	1
B15	STAC	2	B31	STAC	2	B47	STAC	2
B16	STAC	4	B32	STAC	4	B48	STAC	4

Mixing time: 3 min in V-blender.

manufactured tablets at 0.5% lubricant concentration to be able to observe the decline of crushing strength with increasing lubricant level from the same starting point.

2.5. *Tablets of unlubricated powder mixtures*

The compression pressure and tablet weight adjustment were made once for DC1 and no further change was made during the compaction of the DC2 and DC3. An unlubricated, 250 mg binary powder was filled into the die cavity and 6 perpetual compressions were made for each batch and the average of the data was calculated.

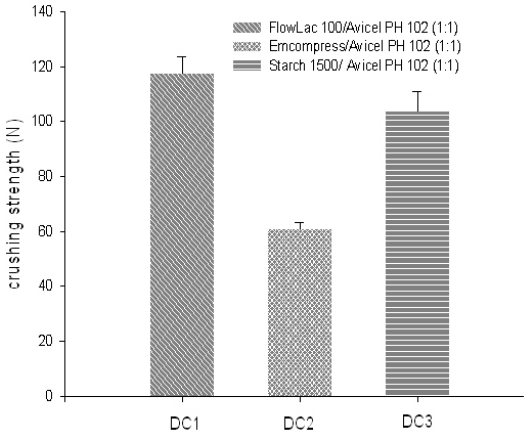

Figure 1. The case of no lubricant. Average tablet crushing strengths for DC1, DC2, and DC3 (250 mg tablet weight, 1,000 kg.f compression force).

Table 2. Bulk/tapped densities and compressibility of binary mixtures

	d-Bulk (g/mL)	d-Tapped (g/mL)	% Compresibility (CI)
DC1	0.43 ± 0.03	0.46	7.33
DC2	0.52 ± 0.03	0.55	5.79
DC3	0.47 ± 0.05	0.51	8.25

CI = Carr Index.

2.6. *Measurement of tablet properties*

The weight variation of tablets was determined according to the USP 24. The diametrical tablet crushing strength was evaluated using a tablet hardness tester (Model C 50, I-Holland, Ltd., Nottingham, UK).

2.7. *Statistical analysis*

The effect of lubricant type and lubricant concentration on the crushing strength of tablets were tested using a factorial ANOVA model, specifically, a two-way analysis of variance (two-way ANOVA) procedure for the main effects (SPSS 13.0 for windows).

3. Results and Discussion

Study design is summarized in Table 1. Trials were made with four levels (0.5, 1, 2, and 4%) of MGST, HBN, COMP, and STAC for all direct compression formulations (Batches 1 to 48). Figure 1 presents the crushing strength values of unlubricated binary mixtures (DC1, DC2, and DC3), the crushing strength values were found to be 117 N for DC1, 61 N for DC2, and 104 N for DC3, respectively (Figure 1). These values correlated well with the bulk densities of the binary powders. The values were 0.43 g/mL for DC1, 0.52 g/mL for DC2, and 0.47 g/mL for DC3, respectively (Table 2). In the case of unlubricated granules, DC3 showed the highest compressibility value of 8.25%, DC1 was 7.33%, and DC2 provided a value of 5.79% (Table 2). Table 3 and Figures 2-4, show

Table 3. Weight and crushing strength variation of tablets including different lubricants

Lubricant type	Lubricant amount (%)	Formulation DC1 [FlowLac/Avicel PH 102 (1:1)] Batches (B1 to B16)		Formulation DC2 [Emcompress/Avicel PH 102 (1:1)] Batches (B17 to B32)		Formulation DC3 [Starch 1500/Avicel PH 102 (1:1)] Batches (B33 to B48)	
		Weight (mg)	Crushing Strength (N)	Weight (mg)	Crushing Strength (N)	Weight (mg)	Crushing Strength (N)
MGST	0.5	245.17 ± 2.64	101.53 ± 9.71	247.65 ± 0.87	71.61 ± 3.53	243.75 ± 1.77	59.65 ± 4.31
	1	247 ± 1.79	78.38 ± 4.70	247.53 ± 2.08	54.74 ± 3.13	241.38 ± 1.35	49.84 ± 6.86
	2	246.17 ± 2.64	70.14 ± 5.98	248.48 ± 1.64	48.65 ± 2.94	244.33 ± 3.27	27.76 ± 2.84
	4	245 ± 2.68	62.19 ± 3.92	248 ± 2.63	40.02 ± 3.33	245.72 ± 2.26	8.93 ± 1.66
HBN	0.5	246.67 ± 1.64	117.32 ± 6.37	246.65 ± 0.35	102.61 ± 7.75	241.77 ± 3.21	104.18 ± 7.75
	1	245.33 ± 1.41	114.18 ± 6.27	250.33 ± 1.48	100.55 ± 3.72	242.97 ± 2.49	99.76 ± 4.51
	2	245.23 ± 2.7	113.20 ± 11.77	247.53 ± 3.06	88.68 ± 7.84	244.65 ± 1.91	98.88 ± 5.49
	4	246.65 ± 3.49	102.02 ± 6.47	247.97 ± 2.9	79.95 ± 3.23	242.82 ± 3.78	89.17 ± 10.20
COMP	0.5	245.42 ± 0.28	118.40 ± 4.70	245.6 ± 2.75	90.84 ± 7.75	243.6 ± 3.58	103.10 ± 12.65
	1	245.75 ± 0.56	117.03 ± 3.63	245.7 ± 1.12	89.27 ± 5.59	243.15 ± 1.78	92.01 ± 7.45
	2	244.83 ± 1.73	109.48 ± 5.98	245.23 ± 2.05	89.07 ± 2.74	244.4 ± 3.07	80.34 ± 3.23
	4	243.35 ± 1.42	96.04 ± 4.12	246.6 ± 1.61	86.52 ± 4.90	243.27 ± 3.17	68.57 ± 5.98
STAC	0.5	241.63 ± 2.4	111.83 ± 7.25	247.12 ± 2.99	97.41 ± 6.96	246.43 ± 2.2	109.57 ± 5.10
	1	243.37 ± 2.43	108.30 ± 4.12	246.83 ± 3.55	96.62 ± 7.25	243.55 ± 5.37	100.94 ± 6.37
	2	243.72 ± 1.74	105.35 ± 8.63	247.08 ± 1.44	95.942 ± 6.57	245.02 ± 4.22	86.62 ± 8.92
	4	244.72 ± 2.01	97.41 ± 4.70	247.08 ± 1.6	92.99 ± 1.86	245.33 ± 2.74	69.55 ± 3.92

lubricant concentration *vs.* crushing strength profiles. MGST resulted in a biphasic curve, up to 1% lubricant concentration and a fast drop in crushing strength was observed for DC1, DC2, and DC3. From 1% to 4% lubricant concentration the curve was shallow (Figures 2-3) except for DC3 where the mechanical strength of tablets fell drastically (Figure 4). It was well known from the literature that surface covering properties of lubricants are more drastic in the case of plastically deformed particles that are unable to create new clean surfaces during compression (*16*). The other three lubricants, HBN, COMP, and STAC showed a shallow linear decline in tablet crushing strength *vs.* lubricant concentration curves. The binary mixture Starch 1500/Avicel PH 102 showed a steeper decline when compared to DC1 and DC2. This observation correlates well with less effective lubricant behavior. However, in one of our previous reports (*9*) it was found that hexagonal boron nitride was as affective as MGST in terms of lower punch ejection force. In the same study, COMP and STAC were much inferior in lowering the ejection forces (*9*). Based on the data obtained from Figures 2-4, 0.5% MGST addition as a lubricant with 3 min mixing time was not appropriate for mechanically acceptable tablets regardless of binary combination in direct compression. Either less MGST should be used, or another effective lubricant such as HBN could be considered. It can be concluded that STAC or COMP will not be satisfactory lubricants at those concentrations. For the statistical analysis, a two-way analysis of variance (Two-way ANOVA) was separately performed for spray dried lactose-microcrystalline cellulose (DC1), dicalcium phosphate dihydrate-microcrystalline cellulose (DC2), and modified starch-microcrystalline cellulose (DC3). The crushing strength was the dependent variable. Lubricant type and lubricant concentration were selected as the fixed factors. The general linear model/univariate analysis of variance, main effects were evaluated. The Bonferroni method was chosen for the post hoc test. It was found that for all cases (DC1, DC2, and DC3) there was a significant difference among the lubricants ($p < 0.0001$). In terms of lubricant concentration the most significant case was DC3 ($p < 0.0001$) and the least significant case was DC2 ($p < 0.033$) with DC1 in between ($p < 0.003$) (Tables 4-7). Therefore, it seemed that the dicalcium phosphate dihydrate-microcrystalline cellulose binary mixture showed the least lubricant sensitivity, and modified starch-microcrystalline cellulose binary mixture showed the highest lubricant sensitivity. The effect of MGST on tablet crushing strength was significantly different than the other lubricants, the difference among the other three lubricants (STAC,

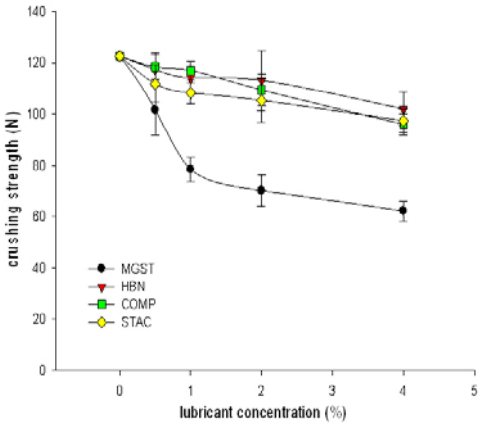

Figure 2. Effect of lubricant concentration on tablet crushing strength for DC1 [FlowLac 100/Avicel PH 102 (1:1)].

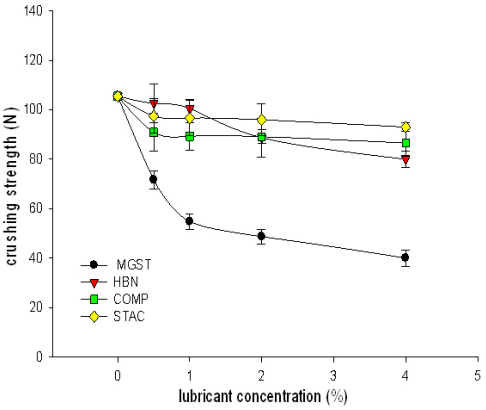

Figure 3. Effect of lubricant concentration on tablet crushing strength for DC2 [Emcompress/Avicel PH 102 (1:1)].

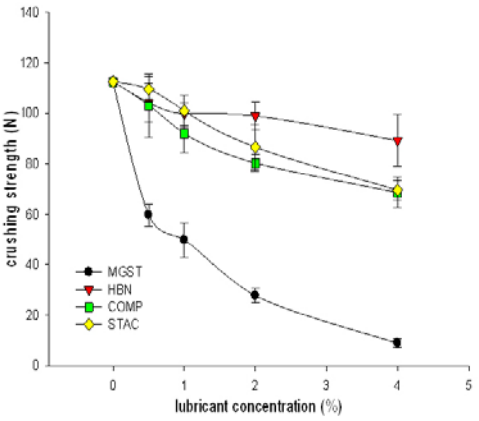

Figure 4. Effect of lubricant concentration on tablet crushing strength for DC3 [Starch 1500/Avicel PH 102 (1:1)].

Table 4. Factors and their levels for ANOVA.

		N
Lubricant	1	4
	2	4
	3	4
	4	4
Concentration	0.5	4
	1.0	4
	2.0	4
	4.0	4

Table 5. Effects of factors on dependent variable (DC1) [Spray dried lactose/Avicel PH 102 (1:1)]

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	42.480[a]	6	7.080	18.664	0.000
Intercept	1,710.443	1	1,710.443	4,508.936	0.000
Lubricant	31.061	3	10.354	27.293	0.000
Concentration	11.419	3	3.806	10.034	0.003
Error	3.414	9	0.379		
Total	1,756.337	16			
Corrected Total	45.894	15			

Dependent Variable: Crushing strength. [a] *R* Squared = 0.926 (Adjusted *R* Squared = 0.876).

Table 6. Effects of factors on dependent variable (DC2) [Emcompress/Avicel PH 102 (1:1)]

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	53.477[a]	6	8.913	21.861	0.000
Intercept	1,141.088	1	1,141.088	2,798.805	0.000
Lubricant	47.863	3	15.954	39.132	0.000
Concentration	5.614	3	1.871	4.590	0.033
Error	3.699	9	0.408		
Total	1,198.235	16			
Corrected Total	57.174	15			

Dependent Variable: Crushing strength. [a] *R* Squared = 0.936 (Adjusted *R* Squared = 0.893).

Table 7. Effects of factors on dependent variable (DC3) [Starch 1500/Avicel PH 102 (1:1)]

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	127.536[a]	6	21.256	39.836	0.000
Intercept	1,012.990	1	1,012.990	1,898.444	0.000
Lubricant	29.031	3	9.677	18.136	0.000
Concentration	98.505	3	32.835	61.536	0.000
Error	4.802	9	0.534		
Total	1,145.328	16			
Corrected Total	132.339	15			

Dependent Variable: Crushing strength. [a] *R* Squared = 0.964 (Adjusted *R* Squared = 0.940).

Table 8. Multiple comparison of lubricant types among each other as a post hoc test/ Bonferroni

(I) Lubricant	(J) Lubricant	Mean Difference (I-J)	Std. Error	Sig.
MGST	STAC	-3.4275*	0.43551	0.000
	COMP	-3.2800*	0.43551	0.000
	HBN	-2.8200*	0.43551	0.000

Dependent variable: Crushing strength. Based on observed means.
* The mean difference is significant at the 0.05 level.

HBN, COMP) was not significant (Table 8). The FlowLac-Avicel binary mixture (DC1) was found to be the best candidate for further evaluation as a direct compression formula based on lubricant sensitivity and tablet mechanical strength. However, the DC3 mixture gave the highest compressibility value. Furthermore, a lubricant concentration lower than 0.5% for MGST and more preferably selecting HBN between 0.5-1% would result in mechanically acceptable tablets.

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