A Systematic Evaluation of the Compression and Tablet Characteristics of Various Types of Lactose and Dibasic Calcium Phosphate

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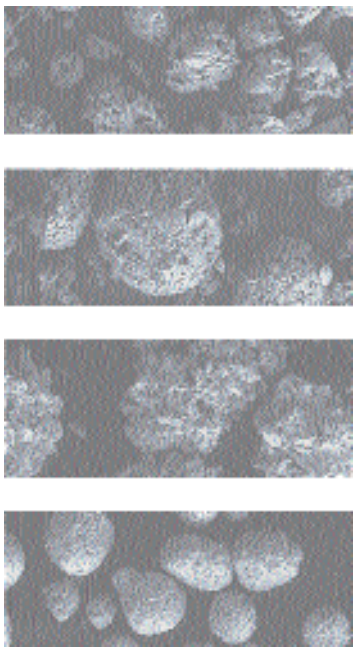

The most commonly used fillers for tablets and capsules are lactose, microcrystalline cellulose, starch, and dibasic calcium phosphate(DCP) (1). These compressible fillers have distinct differences in physicochemical characteristics to fulfill different formulation requirements. In this study, the authors evaluated two types of lactose and two types of DCP and studied the effects of the lubricant level, the lubrication time, and the compression speed for each filler.

According to a 1993 survey by Shangraw and Demarest, direct compression is the preferred manufacturing process for pharmaceutical tablets (1). The major characteristics of a good, directly compressible filler are physical and chemical compatibility, compactibility, flowability, lubricity, and the ability to blend uniformly with the active pharmaceutical ingredients (APIs) and other excipients. The most commonly used fillers are lactose, microcrystalline cellulose (MCC), starch, and dibasic calcium phosphate (DCP). Various types of MCC, lactose, and DCP exist with distinct differences in their particle properties. These differences affect the compression and tablet characteristics.

The various types of MCC have been thoroughly investigated and are well understood (2–5). The compression characteristics of lactose, another of the most commonly used fillers, also have been thoroughly evaluated (6,7). For direct-compression formulations, Fast Flo lactose (lactose monohydrate, spray-dried; Foremost, Baraboo, WI) is among the first choice of compressible fillers because of its compressibility and flowability. Super-Tab (lactose monohydrate, spray-dried; FMC, Philadelphia, PA) has larger particle sizes than Fast Flo lactose and is de-

Table I: Characteristics of various types of lactose and DCP.

Powder	Lactose		DCP	
Characteristics	Fast Flo Lactose	Super-Tab	Di-Tab	Fujicalin
Moisture (LOD, %)	0.30	0.10	<0.5*	<0.5
Particle size (μm)	103	168	127	113
Bulk density (g/cm^3)	0.67	0.60	0.83	0.43

Free moisture: <0.5%; LOD ~25% from the dihydrate.

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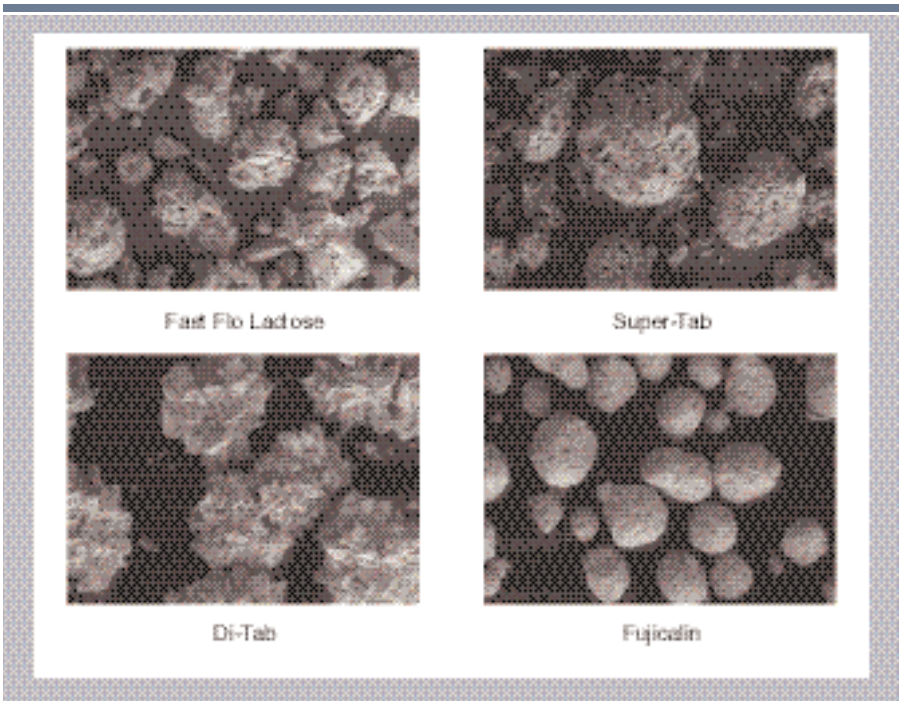

Figure 1: SEM pictures (×200 magnified, Hitachi S3500N) of different types of lactose and DCP.

Table II: Factors and responses.*

Factors	Levels		Responses
	−	+	Compression force RSD
			Ejection force
X_1: Lubricant level	0.2%	1.0% (lactose)	Tablet weight RSD
	1.0%	2.5% (DCP)	
X_2: Lubrication time	1 min	3 min	Hardness
X_3: Compression speed	30 rpm	60 rpm	Friability

*Types of lactose: Fast Flo and Super-Tab; types of DCP: Di-Tab and Fujicalin.

signed to have better flowability. Di-Tab (dibasic calcium phosphate, dihydrate; Rhône-Poulenc, Chicago Heights, IL) is known for its good flowability but has a segregation potential with many APIs and other excipients mainly because of its high density. Fujicalin (dibasic calcium phosphate, anhydrous; Fuji, Kamiichi, Japan) has a density of about half of Di-Tab's density and is more spherical in particle shape (as illustrated in the scanning electron microscopy image [SEM], see Figure 1). Table I lists these products' physical characteristics, which the authors obtained from the manufacturers' product brochures.

In this study, these various types of lactose and DCP were evaluated by a direct-compression process that incorporated the lubricant level, lubrication time, and compression speed as three factors. Magnesium stearate (Mallinckrodt, St. Louis, MO) was used as the lubricant because it was the most commonly used lubricant (1). For each excipient, a three-factor, two-level full factorial experimental design was used to evaluate the effects of these three factors on the compression characteristics (compression force RSD and ejection force) and tablet characteristics (tablet weight RSD, hardness, and friability). The data were statistically analyzed to evaluate the effects of three factors (lubricant level, lubrication time, and compression speed) on the five responses (compression force RSD, ejection force, tablet weight RSD, hardness, and friability). Statistical analysis also was performed to compare Fast Flo lactose, Super-Tab, Di-Tab, and Fujicalin. The information obtained from this study is important for a formulation scientist to choose the proper type of lactose and DCP and to optimize the lubricant level, lubrication time, and compression speed when developing tablet formulations.

Experimentation

The formulations evaluated in this study consisted only of the compressible filler and a lubricant. The various types of fillers included Fast Flo lactose, Super-Tab, Di-Tab, and Fujicalin.

Factors and responses. Magnesium stearate was used as the lubricant in this study, and the lubricant levels evaluated were 0.2 and 1.0% for lactose and 1.0 and 2.5% for DCP (DCP requires more lubricant because of its brittle-fracture characteristics). Lubrication time usually affects the mechanical strength of tablets, so two lubrication times (1 and 3 min) were evaluated. Because the quality of tablets can significantly depend on the compression speed for some formulations (8), the compression speed also was evaluated as a factor. Therefore, the three factors investigated for each excipient were the lubricant level (X_1), lubrication time (X_2), and the compression speed (X_3). Table II summarizes the ranges of the factors that were evaluated. The major response variables were compression force RSD, ejection force, tablet weight RSD, hardness, and friability (see Table II).

Design of experiment (DOE). For each filler, the study was conducted using a three-factor, two-level, full factorial experimental design that required eight experiments (see Table III). The sequence of these experiments was randomized. The purpose of using a full factorial experimental design was to conduct a comprehensive comparison for different types of lactose and DCP under various practical conditions and to evaluate the effects of various formulation and process variables on the compression and tablet characteristics based on an objective statistical analysis.

Method. For each experiment, the authors prepared a 1-kg batch of powder blend using a 4-qt V-blender (Patterson-Kelley, East Stroudsburg, PA) according to the lubrication time specified in the DOE. Following lubrication, the powder blend was compressed into 150-mg tablets using a tablet press (Korsch PH100, Korsch America, Somerset, NJ) equipped with 0.25-in. standard concave punches. The tablets were compressed at approximately 8 kN at 30 and 60 rpm, and the compression profiles (among them, the compression force RSD and ejection force were the major re-

Table III: DOE for each filler.

Run	X_1 Lubricant Level	X_2 Lubrication Time	X_3 Compression Speed
1	–	–	–
2	–	–	+
3	–	+	–
4	–	+	+
5	+	–	–
6	+	–	+
7	+	+	–
8	+	+	+

Table IV: DOE to compare two types of filler.

Run	X_4 Type of Filler	X_1 Lubricant Level	X_2 Lubrication Time	X_3 Compression Speed
1	–	–	–	–
2	–	–	–	+
3	–	–	+	–
4	–	–	+	+
5	–	+	–	–
6	–	+	–	+
7	–	+	+	–
8	–	+	+	+
9	+	–	–	–
10	+	–	–	+
11	+	–	+	–
12	+	–	+	+
13	+	+	–	–
14	+	+	–	+
15	+	+	+	–
16	+	+	+	+

sponses) were recorded by a compression research system (Korsch America).

The authors then tested the tablets for tablet weight, hardness, and friability. For each filler, they analyzed the results using computer software (JMP.3.1.6, SAS Institute, Cary, NC). The data of Fast Flo and Super-Tab lactose and Di-Tab and Fujicalin DCP were then analyzed by the DOE model shown in Table IV for a comprehensive comparison. The full factorial experimental design has the resolution power to analyze not only the main effects but also the two-factor interaction effects. Therefore, the statistical analysis was conducted to include both main effects and two-factor interaction effects. The results of the statistical analysis included the effects and their probability values (p-values). These effects were then summarized and compared for a thorough evaluation of the various types of fillers.

Results and discussion

Tables V–VIII show the results and effect summaries for the various types of lactose and DCP evaluated in this study. The compression force RSD and ejection force were the averages of the multiple measurements recorded throughout the compression process; the tablet weight RSD and hardness were calculated from 10 tablets; and the friability was measured from ~50 tablets. Among these responses, compression force RSD and tablet weight RSD were used as indicators of the flowability of a blend (note: the compression force RSD and tablet weight RSD also may be affected by particle uniformity). The ejection force was used to evaluate lubricity, and tablet hardness and friability were used to assess compactibility. An ideal tablet formulation should have low compression force RSD, low ejection force, low tablet weight RSD, high tablet hardness, and low friability.

When the data were statistically analyzed, the main effects, the interaction effects, and their corresponding p-values were calculated (except for the three-factor interaction). The effects that are more significant have lower p-values. The effects with p-values <0.05 are usually considered statistically significant. In this study, the effects with p-values <0.2 were considered directionally significant and were treated as substantial effects. To illustrate the main effects and interaction effects graphically, the effect plots for the tablet hardness of Fast Flo lactose were constructed (see Figures 2–7). According to Figures 2–4, tablet hardness decreased when the lubricant level (X_1), lubrication time (X_2), or compression speed (X_3) was increased. And the effects of X_1, X_2, and X_3 on tablet hardness were -22.66, -2.49, and -5.82%, respectively. These three factors all were considered substantial because their p-values were <0.2

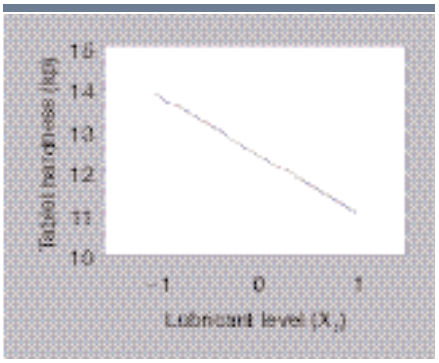

Figure 2: Effect plot for X_1 on tablet hardness (Fast Flo lactose).

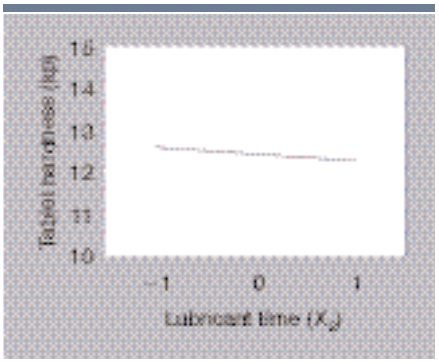

Figure 3: Effect plot for X_2 on tablet hardness (Fast Flo lactose).

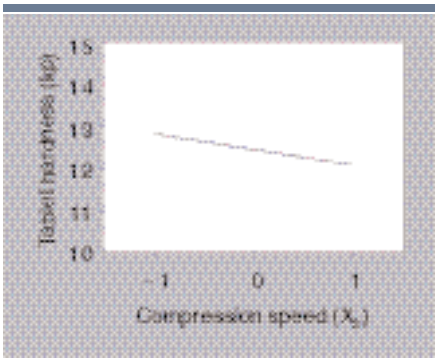

Figure 4: Effect plot for X_3 on tablet hardness (Fast Flo lactose).

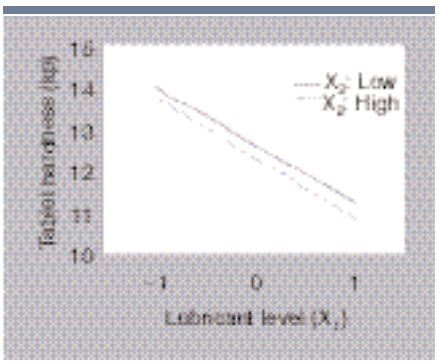

Figure 5: X_1X_2 interaction effect plots on tablet hardness (Fast Flo lactose).

Table V: Results and effect summary for Fast Flo lactose.

Run		Compression Force RSD (%)	Ejection Force (N)	Tablet Weight RSD (%)	Hardness (kp)	Friability (%)
1		5.508	273.39	0.85	14.13	0.030
2		5.234	301.60	0.78	13.87	0.045
3		5.248	340.38	1.00	13.76	0.061
4		4.904	317.09	1.00	13.76	0.060
5		6.387	278.43	1.14	12.05	0.061
6		4.908	274.66	0.95	10.44	0.046
7		5.414	255.65	0.84	11.38	0.030
8		4.554	260.67	0.74	10.35	0.060
Average		5.2696	287.7338	0.9125	12.4675	0.0491
X_1	Effect	0.0923	−40.7625	0.0100	−2.8250	0.0003
	%Effect	1.75	−14.17	1.10	−22.66	0.61
	p-value	0.6870	0.2255	0.2952	0.0180	0.9896
X_2	Effect	−0.4793	11.4275	−0.0350	−0.3100	0.0073
	%Effect	−9.10	3.97	−3.84	−2.49	14.87
	p-value	0.2197	0.5870	0.0903	0.1608	0.7175
X_3	Effect	−0.7393	1.5425	−0.0900	−0.7250	0.0073
	%Effect	−14.03	0.54	−9.86	−5.82	14.87
	p-value	0.1457	0.9351	0.0353	0.0700	0.7175
X_1X_2	Effect	−0.1843	−29.8125	−0.2200	−0.0700	−0.0158
	%Effect	−3.50	−10.36	−24.11	−0.56	−32.18
	p-value	0.4786	0.2980	0.0145	0.5424	0.4897
X_1X_3	Effect	−0.4303	−0.9175	−0.0550	−0.5950	0.0003
	%Effect	−8.17	−0.32	−6.03	−4.77	0.61
	p-value	0.2424	0.9613	0.0577	0.0851	0.9896
X_2X_3	Effect	0.1373	−10.6775	0.0400	0.2100	0.0073
	%Effect	2.61	−3.71	4.38	1.68	14.87
	p-value	0.5717	0.6076	0.0792	0.2317	0.7175
$X_1X_2X_3$	Effect	0.1723	15.0725	0.0050	0.0800	0.0153
	%Effect	3.27	5.24	0.55	0.64	31.16
	p-value	NA	NA	NA	NA	NA

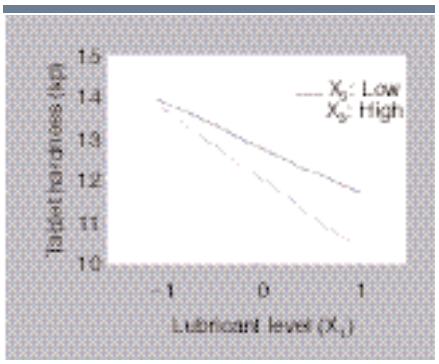

Figure 6: X_1X_3 interaction effect plots on tablet hardness (Fast Flo lactose).

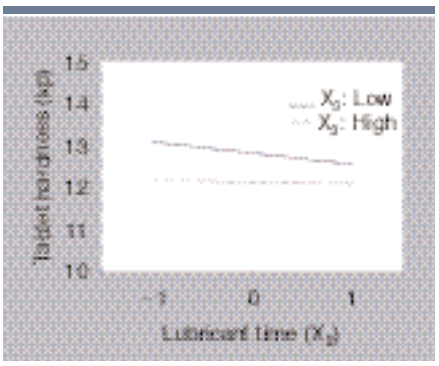

Figure 7: X_2X_3 interaction effect plots on tablet hardness (Fast Flo lactose).

(0.0180, 0.1608, and 0.0700 for X_1, X_2, and X_3, respectively). According to Figure 5 (X_1X_2 interaction effect), tablet hardness decreased when the lubricant level (X_1) was increased, and the effects were similar for the lubrication times (X_2) at 1 and 3 min (these two effect lines were almost parallel). That means that the effect of X_1 on tablet hardness was not affected by X_2. In other words, X_1 and X_2 had no interaction effect (p-value = 0.5424). According to Figure 6 (X_1X_3 interaction effect), tablet hardness decreased when the lubricant level (X_1) was increased, and the effects were different at the two different compression speeds (X_3) (these two effect lines had significantly different slopes). Tablet hardness decreased (average hardness from 13.82 to 10.40 kp when the tablets were made at high compression speed (X_3: high), and this decrease in tablet hardness was less (average hardness from 13.95 to 11.72 kp) at low compression speed (X_3: low). That means that the effect of X_1 on tablet hardness was affected by X_2. In other words, X_1 and X_3 had an interaction effect (p-value = 0.0851). According to Figure 7 (X_2X_3 interaction effect), tablet hardness decreased only slightly when the lubrication time (X_2) was increased, and the effects were similar for the two different compression speeds (X_3) (these two effect lines had similar slopes). That means that the effect of X_2 on tablet hardness was not affected by X_3. In other words, X_2 and X_3 did not have a significant interaction effect (p-value = 0.2317). When interaction effects exist, the interaction terms must be incorporated into the optimization process. For example, the equation to describe tablet hardness for Fast Flo lactose should include X_1, X_2, X_3, and X_1X_3 terms (hardness = $aX_1 + bX_2 + cX_3 + dX_1X_3$, where a, b, c, and d are constants calculated by curve fitting).

In this study, both the main effects and interaction effects were analyzed for each filler in the same manner as described previously. However, the focus of the discussion was on the main effects because the objective of this study was to compare different fillers, not to optimize the formulation or process. The authors made the following observations (see Tables V–VIII).

Fast Flo lactose. When the lubricant level was increased, tablet hardness decreased (worse compactibility). When the lubrication time was increased, the tablet weight RSD and tablet hardness decreased (better flowability but worse compactibility). When the compression speed was increased, the compression force RSD, tablet weight RSD, and tablet hardness decreased (better flowability but worse compactibility).

The lubricant level and lubrication time (X_1X_2) had an interaction effect on tablet

weight RSD. The lubricant level and compression speed (X_1X_3) had interaction effects on tablet weight RSD and tablet hardness. The lubrication time and compression speed (X_2X_3) had an interaction effect on tablet weight RSD.

Super-Tab. When the lubricant level was increased, the ejection force, tablet hardness, and friability decreased (better lubricity but worse compactibility with lower friability). When the lubrication time (X_2) was increased, tablet hardness decreased (worse compactibility). When the compression speed (X_3) was increased, tablet hardness decreased (worse compactibility).

The lubricant level and lubrication time (X_1X_2) had interaction effects on compression force RSD, tablet hardness, and friability. The lubricant level and compression speed (X_1X_3) had an interaction effect on tablet hardness. The lubrication time and compression speed (X_2X_3) had interaction effects on compression force RSD and tablet hardness.

Di-Tab. When the lubricant level (X_1) was increased, the tablet weight RSD and tablet hardness increased (worse flowability but better compactibility). When the lubrication time was increased, tablet hardness increased (better compactibility). When the compression speed was increased, tablet hardness decreased (worse compactibility).

The lubricant level and compression speed (X_1X_3) had an interaction effect on tablet hardness. The lubrication time and compression speed (X_2X_3) had an interaction effect on tablet hardness.

Fujicalin. When the lubricant level was increased, the ejection force and tablet hardness decreased and the tablet friability increased (better lubricity, but worse compactibility). When the lubrication time was increased, the ejection force and friability increased (worse lubricity and compactibility). When the compression speed was increased, the ejection force increased (worse lubricity).

The lubricant level and compression speed (X_1X_3) had an interaction effect on tablet friability.

On the basis of these observations, the authors compared the four fillers (see Table IX). For both types of lactose, compactibility became worse when the lubricant level, lubrication time, or compression speed was increased. Fast Flo lactose and Super-Tab had affected flowability and lubricity differently. The flowability of Fast Flo lactose was enhanced when the lubrication time or compression speed was increased, but this effect was not significant for Super-Tab. The use of Super-Tab resulted in better lubricity when the lubricant level was increased, but this effect was not significant when Fast Flo lactose was used. This demonstrated that Fast Flo lactose had substantial differences in compression and tablet characteristics because of its different particle characteristics.

Di-Tab and Fujicalin appeared to have significant differences in the effects of all three factors on the flowability, lubricity, and compactibility. When Di-Tab was used and the lubricant level was increased, the flowability became worse but the compactibility became better. When Fujicalin was used, the lubricity improved but the compactibility became worse. When Di-Tab was used and the lubrication time was increased, the compactibility improved. However, the lubricity and compactibility became worse when Fujicalin was used. For Di-Tab, when the compression speed was increased, the compactibility became worse. For Fujicalin, the lubricity became worse when the compression speed was increased. This demonstrated that Di-Tab and Fujicalin also had substantial differences in compression and tablet characteristics because of their different particle characteristics. The significant differences between these fillers demonstrates the importance of selecting the most proper filler(s) and optimizing the formulation and manufacturing process when developing tablet formulations (see Table IX).

To further evaluate the differences between these fillers, the effects of particle size of lactose and particle density of DCP

Table VI: Results and effect summary for Super-Tab.

Run		Compression Force RSD (%)	Ejection Force (N)	Tablet Weight RSD (%)	Hardness (kp)	Friability (%)
1		2.560	445.56	1.13	9.94	0.120
2		2.692	345.34	0.79	9.99	0.140
3		2.609	305.55	0.88	9.32	0.140
4		2.304	291.26	1.14	8.58	0.180
5		2.265	266.70	0.77	7.63	0.150
6		2.640	268.39	0.89	7.19	0.120
7		3.139	276.51	0.83	8.77	0.090
8		2.734	265.44	0.45	7.31	0.110
Average		2.6179	308.0938	0.8600	8.5913	0.1313
X_1	Effect	0.1533	−77.6675	−0.2500	−1.7325	−0.0275
	%Effect	5.86	−25.21	−29.07	−20.17	−20.94
	p-value	0.3248	0.1958	0.5303	0.0211	0.1695
X_2	Effect	0.1573	−46.8075	−0.0700	−0.1925	−0.0025
	%Effect	6.01	−15.19	−8.14	−2.24	−1.90
	p-value	0.3178	0.3088	0.8413	0.1848	0.7952
X_3	Effect	−0.0508	−30.2375	−0.0850	−0.6475	0.0125
	%Effect	−1.94	−9.81	−9.88	−7.54	9.52
	p-value	0.6598	0.4282	0.8092	0.0564	0.3440
X_1X_2	Effect	0.3268	50.2375	−0.1200	0.8225	−0.0325
	%Effect	12.48	16.31	−13.95	9.57	−24.75
	p-value	0.1634	0.2906	0.7381	0.0444	0.1444
X_1X_3	Effect	0.0358	26.2825	−0.0450	−0.3025	−0.0175
	%Effect	1.37	8.53	−5.23	−3.52	−13.33
	p-value	0.7485	0.4799	0.8967	0.1196	0.2578
X_2X_3	Effect	−0.3043	18.2925	0.0250	−0.4525	0.0175
	%Effect	−11.62	5.94	2.91	−5.27	13.33
	p-value	0.1749	0.5938	0.9423	0.0805	0.2578
$X_1X_2X_3$	Effect	−0.0858	−24.6725	−0.2750	−0.0575	0.0075
	%Effect	−3.28	−8.01	−31.98	−0.67	5.71
	p-value	NA	NA	NA	NA	NA

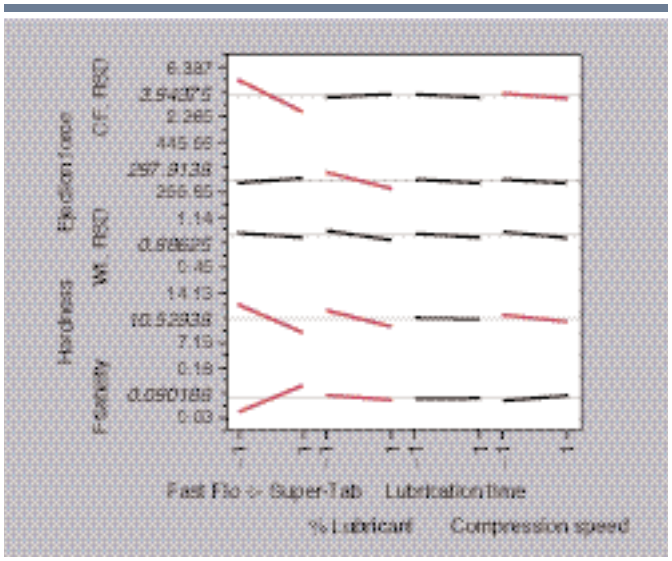

Figure 8: Effect plots for Fast Flo and Super-Tab lactose.

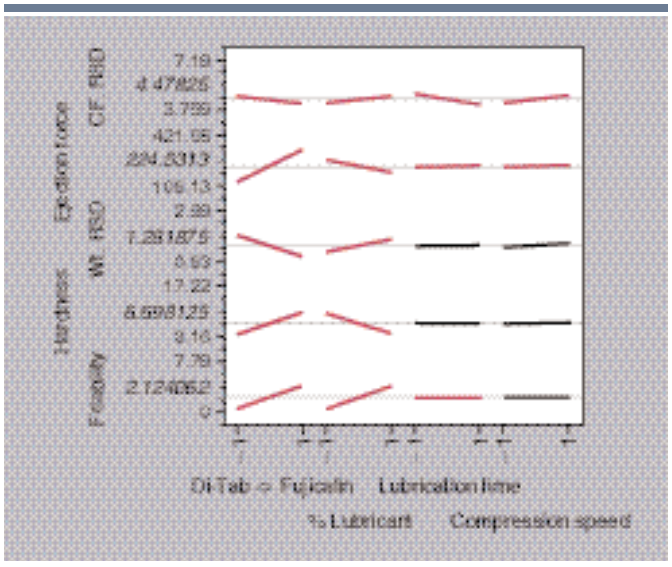

Figure 9: Effect plots for Di-Tab and Fujicalin DCP.

Table VII: Results and effect summary for Di-Tab.

Run		Compression Force RSD (%)	Ejection Force (N)	Tablet Weight RSD (%)	Hardness (kp)	Friability (%)
1		5.107	122.58	1.38	3.59	0.320
2		4.152	124.65	1.43	3.32	0.300
3		4.022	120.09	0.81	3.47	0.380
4		3.834	137.59	1.42	3.54	0.300
5		4.799	105.13	2.56	3.87	0.380
6		7.190	115.96	1.93	3.16	0.360
7		3.901	112.67	1.92	3.78	0.350
8		4.608	110.87	2.99	3.44	0.350
Average		4.7016	118.6925	1.8050	3.5213	0.3425
X_1	Effect	0.8458	-15.0700	1.0900	0.0825	0.0350
	%Effect	17.99	-12.70	60.39	2.34	10.22
	p-value	0.3992	0.2774	0.1628	0.0577	0.3305
X_2	Effect	-1.2208	3.2250	-0.0400	0.0725	0.0050
	%Effect	-25.97	2.72	-2.22	2.06	1.46
	p-value	0.2962	0.7257	0.9112	0.0656	0.8440
X_3	Effect	0.4888	7.1500	0.2750	-0.3125	-0.0300
	%Effect	10.40	6.02	15.24	-8.87	-8.76
	p-value	0.5714	0.4939	0.5114	0.0153	0.3743
X_1X_2	Effect	-0.5193	-2.0000	0.2500	0.0225	-0.0250
	%Effect	-11.05	-1.69	13.85	0.64	-7.30
	p-value	0.5525	0.8232	0.5416	0.2048	0.4296
X_1X_3	Effect	1.0603	−2.6350	−0.0550	−0.2125	0.0200
	%Effect	22.55	−2.22	−3.05	−6.03	5.84
	p-value	0.3336	0.7713	0.8786	0.0225	0.5000
X_2X_3	Effect	−0.2293	0.7000	0.5650	0.1775	−0.0100
	%Effect	−4.88	0.59	31.30	5.04	−2.92
	p-value	0.7721	0.9367	0.29745	0.0269	0.7048
$X_1X_2X_3$	Effect	−0.6128	−7.0150	0.2850	0.0075	0.0200
	%Effect	−13.03	−5.91	15.79	0.21	5.84
	p-value	NA	NA	NA	NA	NA

were statistically analyzed per the DOE shown in Table IV. The results were summarized in Tables X and XI (only the substantial effects were indicated in the tables). Figures 8 and 9 show the effects plots.

The authors concluded that larger particle sizes of lactose improved flowability (lower compression force RSD) but reduced compactibility (lower hardness and higher friability). When both types of lactose were considered, the higher lubricant level increased lubricity but decreased compactibility (with lower friability), and the higher compression speed resulted in lower compression force RSD and tablet hardness. Less-dense particles of DCP enhanced flowability (lower compression force RSD and tablet weight RSD) and tablet hardness, but reduced lubricity (higher ejection force) and increased friability. When both types of DCP were considered, the higher lubricant level decreased flowability and compactibility but increased lubricity; the longer lubrication time resulted in better flowability but worse lubricity and compactibility; and a higher compression speed resulted in a higher compression force RSD and ejection force.

To comprehensively compare the compression and tablet characteristics of various types of lactose and DCP, the authors calculated the average responses from the eight experiments indicated in Table III. Figures 10–14 show the comparative charts. (The median, 25–75% quartiles, and the ranges from the eight experimental conditions are indicated on the

Table VIII: Results and effect summary for Fujicalin.

Run		Compression Force RSD (%)	Ejection Force (N)	Tablet Weight RSD (%)	Hardness (kp)	Friability (%)
1		4.181	389.62	0.53	15.81	0.000
2		4.209	401.24	0.64	15.70	0.015
3		3.759	393.23	0.95	14.17	0.460
4		4.543	421.08	0.57	17.22	0.290
5		4.049	243.53	0.64	3.97	7.410
6		4.981	259.53	0.97	4.17	7.590
7		3.773	259.45	0.63	3.72	7.690
8		4.544	275.28	1.14	4.24	7.79
	Average	4.2549	330.3700	0.7588	9.8750	3.9056
X_1	Effect	0.1638	−141.8450	0.1725	−11.7000	7.4288
	%Effect	3.85	−42.94	22.73	−118.48	190.21
	p-value	0.6051	0.0184	0.4906	0.0386	0.0022
X_2	Effect	−0.2003	13.7800	0.1275	−0.0750	0.3038
	%Effect	−4.71	4.17	16.80	−0.76	7.78
	p-value	0.5429	0.1841	0.5858	0.9330	0.0549
X_3	Effect	0.6288	17.8250	0.1425	0.9150	0.0313
	%Effect	14.78	5.40	18.78	9.27	0.80
	p-value	0.2226	0.1439	0.5512	0.4201	0.4448
X_1X_2	Effect	−0.1563	2.0550	−0.0475	−0.0150	−0.0638
	%Effect	−3.67	0.62	−6.26	−0.15	−1.63
	p-value	0.6191	0.7042	0.8241	0.9866	0.2487
X_1X_3	Effect	0.2228	−1.9100	0.2775	−0.5550	0.1088
	%Effect	5.24	−0.58	36.57	−5.62	2.79
	p-value	0.5092	0.7225	0.3457	0.5776	0.1508
X_2X_3	Effect	0.1488	4.0150	−0.0775	0.8700	−0.0663
	%Effect	3.50	1.22	−10.21	8.81	−1.70
	p-value	0.6336	0.5067	0.7241	0.4358	0.2402
$X_1X_2X_3$	Effect	−0.2293	−4.1000	0.1675	−0.7100	0.0263
	%Effect	−5.39	−1.24	22.07	−7.19	0.67
	p-value	NA	NA	NA	NA	NA

Table IX: Effect summary for the fillers.

Factors	Characteristics	Fast Flo Lactose	Super-Tab Lactose	Di-Tab DCP	Fujicalin DCP
X_1: Lubricant	Flowability			Worse	
level	Lubricity		Better		Better
(0.2–1.0%)	Compactibility	Worse	Worse	Better	Worse
X_2: Lubrication	Flowability	Better			
time	Lubricity				Worse
(1–3 min)	Compactibility	Worse	Worse	Better	Worse
X_3: Compression	Flowability	Better			
speed	Lubricity				Worse
(30–60 rpm)	Compactibility	Worse	Worse	Worse	

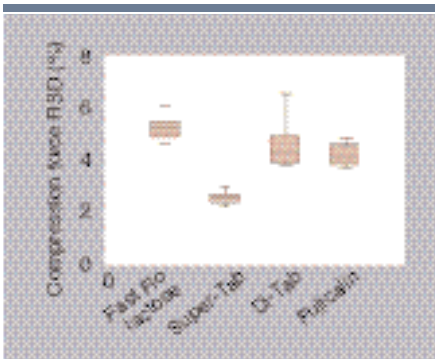

Figure 10: Compression force RSD chart.

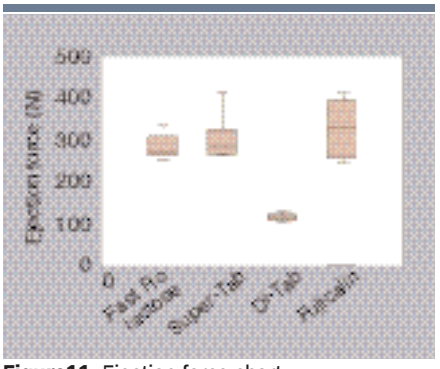

Figure11: Ejection force chart.

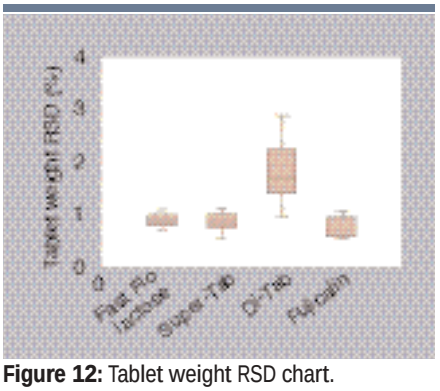

Figure 12: Tablet weight RSD chart.

charts). Super-Tab had the lowest compression force RSD (best flowability), and Di-Tab had the highest tablet weight RSD (see Figures 10 and 12, respectively). Di-Tab had better lubricity than Fujicalin, and Fujicalin had comparable lubricity as lactose, even when higher levels of lubricant were used in Fujicalin (see Figure 11). Fast Flo lactose had better compactibility than Super-Tab, and Fujicalin resulted in harder (but more friable) tablets than Di-Tab (see Figures 13 and 14, respectively). The tablet hardness and friability for Fujicalin appeared to be quite variable throughout the various experimental conditions. Di-Tab seemed to be more consistent and not as process dependent as Fujicalin.

Conclusion

The authors concluded from this study that various types of lactose and DCP did possess different properties that affected compression and tablet characteristics. Super-Tab's larger particle size resulted in better flowability but softer tablets than did Fast Flo lactose. Fujicalin's less dense, more spherical particles resulted in better flowability and harder (but more friable) tablets with less lubricity than did Di-Tab. For lactose in general, the higher lubricant level increased lubricity but decreased compactibility, and the higher compression speed resulted in lower compression force RSD and tablet hardness. That meant

Table X: Effect summary for lactose.

Factors	Compression Force RSD (%)	Ejection Force (N)	Tablet Weight RSD (%)	Hardness (kp)	Friability (%)
X_4: Type of Filler	Decreased			Decreased	Increased
Fast Flo–Super-Tab	($p < 0.0001$)			($p < 0.0001$)	($p < 0.0002$)
X_1: Lubricant level (0.2–1.0% for lactose, 1.0–2.5% for DCP)		Decreased ($p = 0.0431$)		Decreased ($p = 0.0003$)	Decreased ($p = 0.1491$)
X_2: Lubrication time (1–3 min)					
X_3: Compression speed (30–60 rpm)	Decreased ($p = 0.0964$)			Decreased ($p = 0.0454$)	
Interaction effects	X_2X_4		X_1X_2	X_1X_3	X_1X_2
	X_3X_4			X_1X_4	X_1X_4
					X_2X_3

Table XI: Effect summary for DCP.

Factors	Compression Force RSD (%)	Ejection Force (N)	Tablet Weight RSD (%)	Hardness (kp)	Friability (%)
X_4: Type of filler	Decreased	Increased	Decreased	Increased	Increased
Di-Tab–Fujicalin	($p = 0.2000$)	($p < 0.0001$)	($p = 0.0037$)	($p < 0.0001$)	($p < 0.0001$)
X_1: Lubricant level (1.0–2.5%)	Increased ($p = 0.1563$)	Decreased ($p < 0.0001$)	Increased ($p = 0.0269$)	Decreased ($p < 0.0001$)	Increased ($p < 0.0001$)
X_2: Lubrication time (1–3 min)	Decreased ($p = 0.0658$)	Increased ($p = 0.0299$)			Increased ($p = 0.0023$)
X_3: Compression speed (30–60 rpm)	Increased ($p = 0.1242$)	Increased ($p = 0.0069$)			
Interaction Effects	X_1X_3	X_1X_4	X_1X_4	X_1X_4	X_1X_2
	X_2X_4	X_2X_4		X_2X_3	X_1X_3
		X_3X_4		X_3X_4	X_1X_4
					X_2X_4

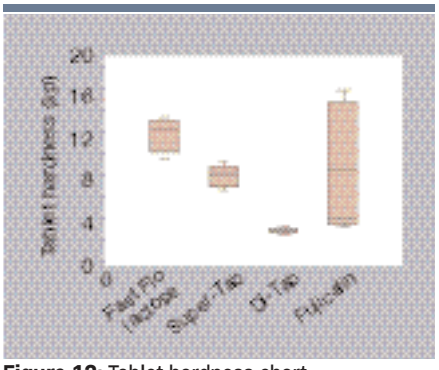

Figure 13: Tablet hardness chart.

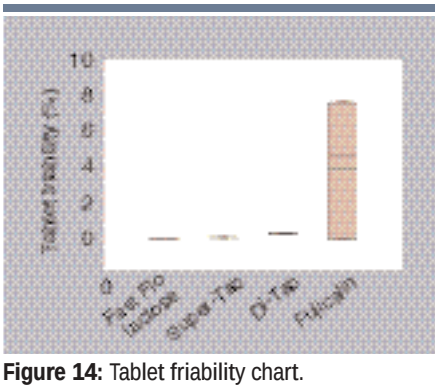

Figure 14: Tablet friability chart.

the hardness of tablets made by lactose was sensitive to the lubricant level and compression speed, but the flowability was sufficient to accommodate the increase in compression speed. For DCP, the higher lubricant level decreased flowability and compactibility, but increased lubricity; the longer lubrication time resulted in better flowability but worse lubricity and compactibility; and a higher compression speed resulted in higher compression force RSD and ejection force. Therefore, the compression and tablet characteristics of DCP were significantly affected by formulation and process variables. A thorough study usually is needed to optimize a formulation and manufacturing process when formulation- or process-sensitive fillers (e.g., DCP) are used. The information obtained from this study is systematic and comprehensive and can be used to facilitate an efficient formulation development for pharmaceutical tablets.

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