Tablet Relaxation and Physicomechanical Stability of Lactose, Microcrystalline Cellulose, and Dibasic Calcium Phosphate

Ruey-ching Hwang,* Gretchen R. Peck, Debra M. Besserman, Chris E. Friedrich, and Mary K. Gemoules

To evaluate the physicomechanical stability of pharmaceutical tablets, this study investigated three commonly used, directly compressible pharmaceutical excipients. The four factors evaluated were lubricant level, lubrication time, compression force, and compression speed. The responses evaluated were tablet thickness, hardness, and friability. A fifth factor, storage condition, later was incorporated to evaluate its effect on the physicomechanical stability of each excipient during a period of one month. The information obtained from this study clarifies the physicomechanical characteristics of major compressible excipients and the effects of formulation and processing variables on their physicomechanical stability.

Ruey-ching Hwang, PhD, MBA, is a senior research scientist–group leader of pharmaceutical development at Pharmacia Corporation, 7000 Portage Road, Kalamazoo, MI 49001, tel. 616.833.0411, fax 616.833.7290, ruey.c.hwang@pharmacia.com. **Gretchen R. Peck** is an associate scientist at Pfizer. **Debra M. Besserman** and **Chris E. Friedrich** are research technicians, and **Mary K. Gemoules** is a project manager of pharmaceutical R&D, all at Mallinckrodt Inc. Dr. Hwang is a member of *Pharmaceutical Technology*'s Editorial Advisory Board.

*To whom all correspondence should be addressed.

Tablets are the most popular dosage form of pharmaceutical products. A typical tablet formulation consists of the active pharmaceutical ingredient(s) (API), filler(s), disintegrant, lubricant, and other inactive ingredients (e.g., binder, glidant, and colorant). A formulation scientist must conduct a thorough study both to optimize a formulation so that it meets all specifications and to ensure safety and efficacy. The specifications for pharmaceutical tablets usually include appearance, weight, thickness, hardness, friability, disintegration, dissolution, content uniformity, assay, organoleptic characteristics, and other product-specific requirements. These specifications are established to ensure that the tablets will have sufficient mechanical strength to withstand packaging, shipping, and handling and are physically and chemically stable to deliver the accurate amount of drug at the desired dissolution rate when consumed by a patient. Any changes in these characteristics may significantly affect the safety and efficacy of the product.

It is a well-known phenomenon that the mechanical strength and the rates of disintegration and dissolution of tablets can change with time (1–10), and these changes often are referred to as part of the aging process of pharmaceutical tablets. In some cases, changes in the physicomechanical characteristics of tablets can result in different bioavailability (11–13). Therefore, one must understand the factors that affect tablet aging so that the aging process can be properly managed. The potential factors that could affect tablet aging have been thoroughly investigated. These factors include the API, formulations, manufacturing processes, and storage conditions (14–32).

The aging process of pharmaceutical tablets can be initiated by stress relaxation that results from compression and is facilitated by the stabilization of tablet structure and tablet bonds during storage. The stress relaxation behavior after compression mainly depends on the deformation mechanism that occurs during compression. A plastically deformed material (e.g., sodium chloride) usually undergoes immediate pressure decay

Table I: Factors and responses.

Factors	Levels		Responses
	–	+	Tablet thickness*
X_1 Lubricant level	0.2%	1.0%	Tablet hardness*
X_2 Lubrication time	1 min	3 min	Tablet friability*
X_3 Compression force	4.5 kN	9.0 kN	
X_4 Compression speed	30 rpm	60 rpm	
X_5 Storage condition	25 °C, 60% RH (H_2)	40 °C, 75% RH (H_4)	

*At time zero, 1 h, 24 h,1 week, and 1 month.

Table II: DOE (Fast Flo lactose and Avicel PH-102).

Run	X_1 Lubricant Level	X_2 Lubrication Time	X_3 Compression Force	X_4 Compression Speed	X_5 Storage Condition
1	–	–	–	–	–
2	–	–	–	–	+
3	–	–	–	+	–
4	–	–	–	+	+
5	–	–	+	–	–
6	–	–	+	–	+
7	–	–	+	+	–
8	–	–	+	+	+
9	–	+	–	–	–
10	–	+	–	–	+
11	–	+	–	+	–
12	–	+	–	+	+
13	–	+	+	–	–
14	–	+	+	–	+
15	–	+	+	+	–
16	–	+	+	+	+
17	+	–	–	–	–
18	+	–	–	–	+
19	+	–	–	+	–
20	+	–	–	+	+
21	+	–	+	–	–
22	+	–	+	–	+
23	+	–	+	+	–
24	+	–	+	+	+
25	+	+	–	–	–
26	+	+	–	–	+
27	+	+	–	+	–
28	+	+	–	+	+
29	+	+	+	–	–
30	+	+	+	–	+
31	+	+	+	+	–
32	+	+	+	+	+

after compression and therefore does not preserve substantial internal energy for long-term relaxation. During storage, the plastically deformed materials tend to harden with age if appropriate moisture is available to help heal the fractures or flaws present in the internal surface of the tablet (4). An elastically deformed material (e.g., polyethylene) usually possesses a significant internal pressure after compression, and this internal pressure will release with the passage of time (33). During storage, this excess internal pressure may reach equilibrium with the external condition (temperature and humidity) and result in various physicomechanical characteristics. In this study, several excipients with differing deformation characteristics were evaluated to understand their tablet relaxation process and physicomechanical stability.

Direct compression is the preferred manufacturing process for pharmaceutical tablets, according to the survey conducted by Shangraw and Demarest (34). The same survey revealed that the most commonly used fillers for tablets and capsules are lactose, microcrystalline cellulose, starch, and dibasic calcium phosphate. In this study, the authors used direct-compression processes to evaluate lactose, microcrystalline cellulose, and dibasic calcium phosphate. Magnesium stearate was used as the lubricant because it is the most commonly used lubricant for pharmaceutical tablets.

Because the mechanical strength of a pharmaceutical tablet not only is determined by its formulation, but also is affected by lubrication (35–37), compression force (38,39), and compression speed (40–43), these excipients were evaluated with the use of a direct-compression process that incorporated the lubricant level, lubrication time, compression force, and compression speed as the factors in the experimental design. Tablet thickness, hardness, and friability were tested during a period of time, and the initial tablet relaxation and physicomechanical stability for each excipient were evaluated. The data also were statistically analyzed to obtain critical factors affecting tablet relaxation and physicomechanical stability.

The information obtained from this study will help formulation scientists determine the proper type of excipients for formulating a pharmaceutical product and efficiently optimize the lubricant level, lubrication time, compression speed, and compression force to develop direct-compression tablet formulations with stable physicomechanical characteristics.

Experimentation

The formulations evaluated in this study consisted only of the excipient and a lubricant. Fast Flo lactose (lactose monohydrate, spray-dried; Foremost, Baraboo, WI), Avicel PH-102 (microcrystalline cellulose; FMC Corp., Philadelphia, PA), and Di-Tab (dibasic calcium phosphate, dihydrate; Rhône-Poulenc, Chicago Heights, IL) were evaluated using a direct-compression process that incorporated the lubricant level, lubrication time, compression force, and compression speed as the factors (see Table I). Magnesium stearate (Mallinckrodt Inc., St. Louis, MO) was used as the lubricant in this study. The lubricant levels (X_1) evaluated in this study were 0.2% and 1.0% for Fast Flo lactose and Avicel PH-102. The lubricant levels were fixed at 1.0% for Di-Tab, which required a significantly higher amount because of its brittle-

Table III: DOE (Di-Tab).

Run	X_2 Lubrication Time	X_3 Compression Force	X_4 Compression Speed	X_5 Storage Condition
1	−	−	−	−
2	−	−	−	+
3	−	−	+	−
4	−	−	+	+
5	−	+	−	−
6	−	+	−	+
7	−	+	+	−
8	−	+	+	+
9	+	−	−	−
10	+	−	−	+
11	+	−	+	−
12	+	−	+	+
13	+	+	−	−
14	+	+	−	+
15	+	+	+	−
16	+	+	+	+

fracturing nature. The lubrication times (X_2) evaluated in this study were 1 and 3 min. Because the tablet relaxation process may depend on the compression force (X_3) and compression speed (X_4), the compression force and compression speed also were evaluated as process factors in this study (4.5 and 9.0 kN and 30 and 60 rpm, respectively).

The designs of experiment (DOE) are summarized in Tables II and III. For Fast Flo lactose and Avicel PH-102, a four-factor, two-level, full factorial experimental design was used to evaluate the effects of these four factors on the initial tablet relaxation, and a five-factor (storage condition was the additional factor), two-level, full factorial experimental design was used to evaluate physicomechanical stability. For Di-Tab, a three-factor, two-level, full factorial experimental design was used to evaluate the effects of these three factors on the initial tablet relaxation, and a four-factor (storage condition was the additional factor), two-level, full factorial experimental design was used to evaluate physicomechanical stability. The sequence of these experiments was randomized when the study was conducted.

The purpose of using a full factorial experimental design in this study was to conduct a comprehensive evaluation with various practical conditions and to investigate the effects of various formulation and process variables on the initial relaxation and physicomechanical stability on the basis of an objective statistical analysis. For each experiment, a 1-kg batch of powder blend was prepared with a 4-qt V-blender (Patterson-Kelley Co., East Stroudsburg, PA) according to the lubrication time specified in the DOE. Following lubrication, the powder blend was compressed into 100-mg tablets for the Fast Flo lactose and Avicel blends and 150-mg tablets for the Di-Tab blends using a Korsch PH100 tablet press (Korsch America, Somerset, NJ) equipped with 8/32-in., standard concave punches. The tablets were compressed at ~4.5 kN (40% maximum punch load) and 9.0 kN (80% maximum punch load) at two speeds (30 and 60 rpm). The tablets then were tested for thickness ($N = 30$), hardness ($N = 30$), and friability (6.5 g of tablets).

For each experiment, tablets also were evaluated at time zero (within 15 min), 1 h, 24 h, 1 week (7 days), and 1 month (28 days). The 1-week and 1-month samples were packaged in HDPE bottles (550 tablets in a 300-cm^3 bottle) and stored under two conditions: 25 °C and 60% RH (H_2) and 40 °C and 75% RH (H_4). The time-zero through 1-month data were thoroughly evaluated to fully understand the tablet relaxation process and age-hardening process for each excipient. The effects of these formulation and process variables on the initial relaxation and physicomechanical stability of each excipient then were evaluated by statistical analysis. The initial relaxation characteristics were evaluated by calculating the time-zero to 24-h changes in tablet thickness, hardness, and friability, and the physicomechanical stability was evaluated by calculating the 24-h to 1-month changes. The changes in tablet thickness and hardness were calculated using the following equations:

$$\% \text{ Change in thickness} = 100 \times [(T_2 - T_1) \div T_1]\%$$

$$\% \text{ Change in hardness} = 100 \times [(H_2 - H_1) \div H_1]\%$$

in which T_1 and H_1 are the beginning values, and T_2 and H_2 are the ending values.

The changes in tablet friability were calculated by the following equation:

$$\text{Change in friability} = (F_2 - F_1)$$

in which F_1 and F_2 are the beginning and ending values, respectively.

The data were statistically analyzed by computer software JMP.3.1.6 (SAS Institute Inc., Cary, NC) to evaluate the effects of the lubricant level, lubrication time, compression force, compression speed, and storage condition on the initial tablet relaxation and physicomechanical stability. The results of the statistical analysis included the effects and their probability values (p-values). Although the full factorial experimental design has the resolution power to analyze not only the main effects but also the interaction effects, the statistical analysis in this study was focused on the main effects. The two-factor interaction effects that were considered substantial also were listed in the effect summary tables (see Tables VII–VIII, XI–XIII). The effects of all of the factors on all of the responses then were summarized and evaluated for a comprehensive comparison.

Results and discussion

Overall physicomechanical profiles. Table IV summarizes the results for Fast Flo lactose. In general, an initial increase in tablet thickness occurred in 1 h. Tablet thickness slightly decreased from 1 to 24 h and then slightly increased from 24 h to 1 month. Tablet hardness significantly increased initially and then showed mixed trends between 24 h and 1 month. In general, tablet hardness increased between 24 h and one month for the Fast Flo lactose containing 0.2% lubricant and decreased for the Fast Flo lactose containing 1.0% lubricant. For the Fast Flo lactose

Table IV: Tablet thickness, hardness, and friability for Fast Flo lactose.

				Thickness, Hardness, Friability						
				Time			1 week		1 month	
Lub%	LubT	Force	rpm	Zero	1 h	24 h	H_2	H_4	H_2	H_4
0.2	1 min	4.5 kN	30	0.1328 in.	0.1328 in.	0.1328 in.	0.1323 in.	0.1328 in.	0.1331 in.	0.1347 in.
				5.15 kp	5.23 kp	5.60 kp	6.36 kp	6.77 kp	6.95 kp	5.32 kp
				0.09%	0.15%	0.09%	0.00%	0.00%	0.00%	0.17%
			60	0.1327 in.	0.1340 in.	0.1336 in.	0.1331 in.	0.1333 in.	0.1337 in.	0.1333 in.
				5.05 kp	5.14 kp	5.25 kp	6.02 kp	6.41 kp	6.09 kp	6.59 kp
				0.11%	0.14%	0.06%	0.00%	0.00%	0.00%	0.14%
		9.0 kN	30	0.1247 in.	0.1246 in.	0.1248 in.	0.1247 in.	0.1246 in.	0.1248 in.	0.1253 in.
				11.07 kp	11.45 kp	11.71 kp	12.60 kp	13.28 kp	13.18 kp	9.64 kp
				0.00%	0.08%	0.06%	0.00%	0.00%	0.00%	0.09%
			60	0.1265 in.	0.1278 in.	0.1278 in.	0.1276 in.	0.1273 in.	0.1280 in.	0.1280 in.
				11.48 kp	11.94 kp	11.60 kp	12.38 kp	13.02 kp	13.38 kp	9.55 kp
				0.00%	0.08%	0.06%	0.00%	0.00%	0.00%	0.14%
	3 min	4.5 kN	30	0.1307 in.	0.1314 in.	0.1308 in.	0.1312 in.	0.1312 in.	0.1312 in.	0.1309 in.
				5.83 kp	6.18 kp	6.53 kp	6.32 kp	7.52 kp	7.85 kp	7.35 kp
				0.00%	0.00%	0.00%	0.00%	0.00%	0.06%	0.14%
			60	0.1323 in.	0.1319 in.	0.1321 in.	0.1319 in.	0.1326 in.	0.1322 in.	0.1327 in.
				5.67 kp	6.21 kp	6.66 kp	6.16 kp	7.02 kp	6.46 kp	6.64 kp
				0.00%	0.00%	0.00%	0.00%	0.00%	0.09%	0.18%
		9.0 kN	30	0.1258 in.	0.1257 in.	0.1253 in.	0.1253 in.	0.1251 in.	0.1258 in.	0.1256 in.
				10.30 kp	10.44 kp	11.85 kp	11.96 kp	13.13 kp	12.34 kp	8.36 kp
				0.00%	0.00%	0.00%	0.00%	0.00%	0.03%	0.17%
			60	0.1249 in.	0.1250 in.	0.1254 in.	0.1258 in.	0.1252 in.	0.1249 in.	0.1257 in.
				11.20 kp	11.37 kp	11.94 kp	12.11 kp	9.41 kp	6.77 kp	8.80 kp
				0.00%	0.00%	0.06%	0.00%	0.15%	0.15%	0.15%
1.0	1 min	4.5 kN	30	0.1305 in.	0.1312 in.	0.1308 in.	0.1311 in.	0.1311 in.	0.1315 in.	0.1318 in.
				4.64 kp	4.86 kp	5.15 kp	4.45 kp	7.25 kp	3.85 kp	4.94 kp
				0.00%	0.00%	0.00%	0.11%	0.23%	0.27%	0.21%
			60	0.1309 in.	0.1313 in.	0.1310 in.	0.1316 in.	0.1316 in.	0.1318 in.	0.1318 in.
				4.32 kp	4.36 kp	4.62 kp	3.95 kp	7.10 kp	4.88 kp	4.84 kp
				0.02%	0.00%	0.00%	0.11%	0.24%	0.00%	0.24%
		9.0 kN	30	0.1228 in.	0.1226 in.	0.1225 in.	0.1225 in.	0.1226 in.	0.1228 in.	0.1231 in.
				9.06 kp	9.63 kp	10.18 kp	10.44 kp	12.41 kp	12.66 kp	9.67 kp
				0.00%	0.00%	0.02%	0.11%	0.14%	0.03%	0.17%
			60	0.1223 in.	0.1221 in.	0.1220 in.	0.1220 in.	0.1218 in.	0.1224 in.	0.1224 in.
				10.23 kp	10.47 kp	10.69 kp	11.20 kp	12.32 kp	12.36 kp	9.09 kp
				0.00%	0.00%	0.00%	0.09%	0.12%	0.50%	0.18%
	3 min	4.5 kN	30	0.1302 in.	0.1306 in.	0.1307 in.	0.1308 in.	0.1314 in.	0.1310 in.	0.1310 in.
				5.34 kp	5.43 kp	6.90 kp	3.29 kp	3.54 kp	5.11 kp	5.79 kp
				0.00%	0.00%	0.00%	0.34%	0.29%	0.25%	0.18%
			60	0.1300 in.	0.1301 in.	0.1307 in.	0.1303 in.	0.1309 in.	0.1309 in.	0.1310 in.
				5.28 kp	5.26 kp	5.63 kp	6.50 kp	3.81 kp	5.08 kp	5.61 kp
				0.00%	0.00%	0.00%	0.00%	0.30%	0.26%	0.24%
		9.0kN	30	0.1230 in.	0.1232 in.	0.1231 in.	0.1230 in.	0.1236 in.	0.1235 in.	0.1237in.
				10.96 kp	11.12 kp	12.28 kp	12.84 kp	6.05 kp	6.61 kp	7.58 kp
				0.00%	0.00%	0.06%	0.08%	0.21%	0.18%	0.17%
			60	0.1233 in.	0.1235 in.	0.1235 in.	0.1242 in.	0.1243 in.	0.1237 in.	0.1240 in.
				8.79 kp	7.70 kp	5.42 kp	5.74 kp	5.72 kp	7.22 kp	6.77 kp
				0.09%	0.17%	0.20%	0.21%	0.24%	0.20%	0.20%

Table V: Tablet thickness, hardness, and friability for Avicel PH-102.

				Thickness, Hardness, Friability						
				Time			1 week		1 month	
Lub%	LubT	Force	rpm	Zero	1 h	24 h	H_2	H_4	H_2	H_4
0.2	1 min	4.5 kN	30	0.1318 in.	0.1335 in.	0.1337 in.	0.1341 in.	0.1347 in.	0.1341 in.	0.1347 in.
				10.71 kp	10.24 kp	10.37 kp	10.61 kp	10.71 kp	10.80 kp	10.94 kp
				0.09%	0.08%	0.00%	0.00%	0.00%	0.08%	0.11%
			60	0.1341 in.	0.1342 in.	0.1336 in.	0.1350 in.	0.1352 in.	0.1349 in.	0.1363 in.
				9.64 kp	9.68 kp	9.64kp	9.52 kp	9.91 kp	9.79 kp	9.69 kp
				0.09%	0.09%	0.03%	0.00%	0.00%	0.09%	0.11%
		9.0 kN	30	0.1218 in.	0.1219 in.	0.1219 in.	0.1226 in.	0.1227 in.	0.1226 in.	0.1231 in.
				9.50 kp	9.87 kp	9.72 kp	10.16 kp	10.86 kp	10.59 kp	10.81 kp
				0.17%	0.17%	0.12%	0.06%	0.09%	0.12%	0.17%
			60	0.1240 in.	0.1242 in.	0.1240 in.	0.1244 in.	0.1253 in.	0.1249 in.	0.1256 in.
				6.55 kp	6.74 kp	6.26 kp	6.36 kp	6.45 kp	6.71 kp	7.14 kp
				0.20%	0.25%	0.18%	0.14%	0.25%	0.20%	0.21%
	3 min	4.5 kN	30	0.1318 in.	0.1318 in.	0.1320 in.	0.1321 in.	0.1332 in.	0.1327 in.	0.1333 in.
				12.07 kp	12.33 kp	12.13 kp	12.04 kp	11.81 kp	12.39 kp	12.51 kp
				0.12%	0.06%	0.03%	0.05%	0.08%	0.12%	0.11%
			60	0.1316 in.	0.1315 in.	0.1321 in.	0.1324 in.	0.1332 in.	0.1322 in.	0.1336 in.
				11.38 kp	11.55 kp	11.21 kp	11.55 kp	11.61 kp	11.67 kp	11.77 kp
				0.09%	0.11%	0.06%	0.00%	0.03%	0.11%	0.11%
		9.0 kN	30	0.1223 in.	0.1226 in.	0.1228 in.	0.1229 in.	0.1236 in.	0.1235 in.	0.1239 in.
				12.31 kp	11.93 kp	12.09 kp	12.43kp	12.56 kp	12.24 kp	12.86 kp
				0.11%	0.11%	0.09%	0.08%	0.08%	0.11%	0.12%
			60	0.1250 in.	0.1249 in.	0.1246 in.	0.1253 in.	0.1263 in.	0.1255 in.	0.1265 in.
				7.93 kp	7.38 kp	7.61kp	7.92 kp	7.88 kp	7.90 kp	8.50 kp
				0.14%	0.21%	0.14%	0.14%	0.17%	0.18%	0.20%
1.0	1 min	4.5 kN	30	0.1376 in.	0.1382 in.	0.1396 in.	0.1375 in.	0.1393 in.	0.1385 in.	0.1404 in.
				6.08 kp	6.36 kp	6.21kp	7.30kp	6.61 kp	6.80 kp	6.39 kp
				0.20%	0.30%	0.21%	0.26%	0.27%	0.27%	0.30%
			60	0.1389 in.	0.1388 in.	0.1398 in.	0.1400 in.	0.1403 in.	0.1402 in.	0.1408 in.
				6.05 kp	6.02 kp	5.90 kp	6.02 kp	6.25 kp	6.07 kp	6.29 kp
				0.29%	0.27%	0.15%	0.20%	0.15%	0.26%	0.30%
		9.0 kN	30	0.1222 in.	0.1225 in.	0.1232 in.	0.1232 in.	0.1235 in.	0.1231 in.	0.1239 in.
				5.70 kp	5.54 kp	5.47 kp	5.30kp	5.33 kp	5.32 kp	5.06 kp
				0.41%	0.41%	0.29%	0.43%	0.41%	0.43%	0.44%
			60	0.1260 in.	0.1264 in.	0.1267 in.	0.1268 in.	0.1267 in.	0.1273 in.	0.1274 in.
				2.52 kp	2.50 kp	2.55 kp	2.56 kp	2.47 kp	2.46kp	2.40 kp
				1.07%	1.11%	1.11%	1.15%	1.27%	1.07%	1.39%
	3 min	4.5 kN	30	0.1332 in.	0.1330 in.	0.1334 in.	0.1332 in.	0.1343 in.	0.1334 in.	0.1345 in.
				5.08 kp	5.14 kp	5.33 kp	5.83 kp	5.71 kp	5.49 kp	5.66 kp
				0.20%	0.30%	0.33%	0.33%	0.46%	0.23%	0.24%
			60	0.1329 in.	0.1324 in.	0.1332 in.	0.1329 in.	0.1335 in.	0.1333 in.	0.1338 in.
				5.12 kp	5.20 kp	5.42 kp	5.57 kp	5.71 kp	5.22 kp	5.62 kp
				0.18%	0.23%	0.22%	0.35%	0.35%	0.15%	0.22%
		9.0 kN	30	0.1268 in.	0.1271 in.	0.1271 in.	0.1276 in.	0.1276 in.	0.1275 in.	0.1279 in.
				5.04 kp	4.81 kp	5.15 kp	4.83 kp	5.09kp	4.73 kp	4.81 kp
				0.35%	0.38%	0.38%	0.49%	0.54%	0.41%	0.49%
			60	0.1293 in.	0.1293 in.	0.1295 in.	0.1295 in.	0.1300 in.	0.1297 in.	0.1299 in.
				2.64 kp	2.73 kp	2.69 kp	2.75 kp	2.61 kp	2.70 kp	2.54 kp
				1.61%	1.57%	1.46%	2.06%	2.20%	1.52%	1.67%

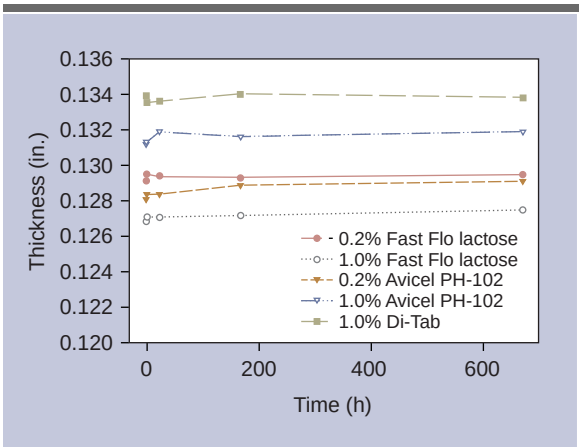

Figure 1: Thickness versus time.

containing 0.2% lubricant, tablet friability significantly increased for the first hour, decreased from 1 h to 1 week, and then slightly increased from 1 week to 1 month. Tablet friability increased gradually from time zero to 1 month for the Fast Flo lactose containing 1.0% lubricant.

Results for Avicel PH-102 are summarized in Table V. In general, tablet thickness increased from time zero to 24 h. For the Avicel PH-102 containing 0.2% lubricant, tablet thickness increased between 24 h and 1 week and then was stable between 1 week and 1 month. For the Avicel PH-102 containing 1.0% lubricant, tablet thickness decreased between 24 h and 1 week and was stable between 1 week and 1 month. Tablet hardness was reasonably consistent from time zero to 1 month for Avicel PH-102. With 0.2% lubricant, Avicel PH-102 showed a slight initial decrease in tablet hardness but then increased slightly between 24 h and 1 month. When the lubricant was increased to 1.0%, the hardness increased slightly between time zero and 1 week but then slightly decreased from 1 week to 1 month. Tablet friability of Avicel PH-102 did not have significant changes for the first hour, was decreased from 1 hour to 24 h, and was only slightly increased thereafter.

Results for Di-Tab are summarized in Table VI. In general, tablet thickness showed an initial decrease in 1 h, then the tablet thickness began to increase from 24 h to 1 week but decreased from 1 week to 1 month. Tablet hardness decreased initially and significantly increased thereafter. Tablet friability substantially increased from time zero to 1 week and slightly decreased from 1 week to 1 month. To compare the physicomechanical characteristics of these three excipients, the averaged physicomechanical profiles (from various lubrication times, compression forces, and compression speeds) for each excipient are plotted in Figures 1–3 (data from H_2 storage condition were used for the 1-week and 1-month characteristics).

As shown in Figure 1, Fast Flo lactose and Avicel PH-102 had an obvious initial increase in tablet thickness as a result of

Table VI: Tablet thickness, hardness, and friability for Di-Tab.

				Thickness, Hardness, Friability						
			Time			1 Week		1 Month	
Lub%	LubT	Force	rpm	Zero	1 h	24 h	H_2	H_4	H_2	H_4
1.0	1 min	4.5 kN	30	0.1358 in.	0.1355 in.	0.1359 in.	0.1358 in.	0.1351 in.	0.1359 in.	0.1356 in.
				1.57 kp	1.57 kp	1.50 kp	1.57 kp	1.55 kp	1.71 kp	1.68 kp
				0.53%	0.50%	1.05%	1.16%	1.44%	1.25%	1.35%
			60	0.1333 in.	0.1334 in.	0.1333 in.	0.1336 in.	0.1330 in.	0.1335 in.	0.1333 in.
				1.25 kp	1.24 kp	1.18 kp	1.15 kp	1.15 kp	1.23 kp	1.27 kp
				0.66%	0.75%	1.44%	1.51%	2.03%	1.57%	1.94%
		9.0 kN	30	0.1308 in.	0.1310 in.	0.1315 in.	0.1318 in.	0.1322 in.	0.1316 in.	0.1312 in.
				2.78 kp	2.91 kp	2.89 kp	2.98 kp	3.07 kp	3.53 kp	3.30 kp
				0.20%	0.26%	0.47%	0.52%	0.60%	0.47%	0.53%
			60	0.1309 in.	0.1280 in.	0.1287 in.	0.1305 in.	0.1318 in.	0.1303 in.	0.1284 in.
				2.93 kp	2.54 kp	2.34 kp	2.67 kp	2.99 kp	3.22 kp	2.93 kp
				0.28%	0.32%	0.37%	0.54%	0.61%	0.37%	0.55%
	3 min	4.5 kN	30	0.1392 in.	0.1389 in.	0.1391 in.	0.1394 in.	0.1385 in.	0.1382 in.	0.1389 in.
				1.75 kp	1.73 kp	1.63 kp	1.68 kp	1.57 kp	1.82 kp	1.85 kp
				0.39%	0.56%	0.73%	0.91%	2.51%	0.79%	1.22%
			60	0.1344 in.	0.1344 in.	0.1341 in.	0.1343 in.	0.1352 in.	0.1343 in.	0.1345 in.
				1.30 kp	1.29 kp	1.27 kp	1.21 kp	1.24 kp	1.38 kp	1.32 kp
				0.67%	0.76%	1.00%	1.55%	1.81%	1.28%	1.59%
		9.0 kN	30	0.1343 in.	0.1335 in.	0.1339 in.	0.1340 in.	0.1343 in.	0.1342 in.	0.1338 in.
				3.31 kp	3.30 kp	3.38 kp	3.44 kp	3.41 kp	3.90 kp	3.71 kp
				0.20%	0.22%	0.39%	0.46%	0.56%	0.38%	0.48%
			60	0.1302 in.	0.1310 in.	0.1301 in.	0.1303 in.	0.1311 in.	0.1302 in.	0.1300 in.
				3.15 kp	3.05 kp	2.94kp	3.13 kp	3.10 kp	3.58 kp	3.35 kp
				0.18%	0.23%	0.28%	0.58%	0.41%	0.43%	0.43%

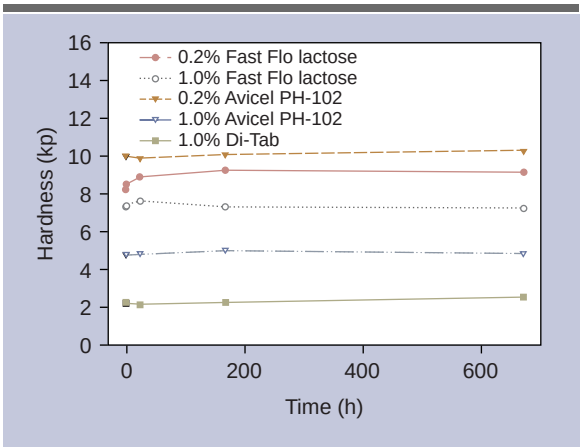

Figure 2: Hardness versus time.

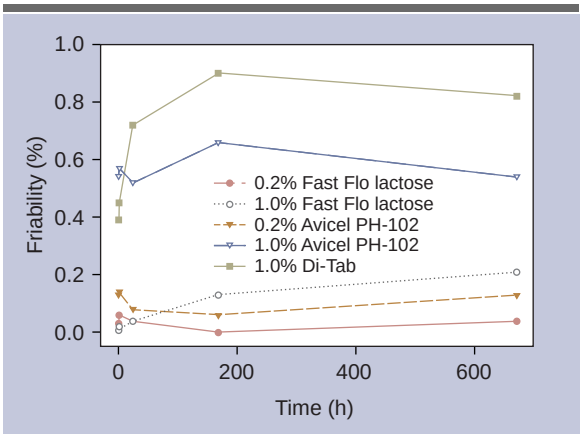

Figure 3: Friability versus time.

their substantial elasticity. Di-Tab's brittle-fracturing nature resulted in an initial decrease in tablet thickness. Figure 2 shows that the tablet hardness of Fast Flo lactose substantially increased initially but either increased or decreased thereafter depending on the concentration of lubricant. The tablet hardness for Di-Tab slightly decreased initially and then slightly increased thereafter. Avicel PH-102 had a very stable tablet hardness profile compared with those for Fast Flo lactose and Di-Tab because of microcrystalline cellulose's good compactibility and physicomechanical stability. Figure 3 shows that the friabilities for Fast Flo lactose and Avicel PH-102 slightly increased initially and either increased or decreased depending on the concentration of lubricant. The friability of Di-Tab increased substantially from time zero to 1 week and slightly decreased from 1 week to 1 month. Overall, Avicel PH-102 seemed to have the most stable physicomechanical characteristics, Fast Flo lactose had the most significant initial hardening, and Di-Tab's initially high friability seemed to increase substantially during the first week.

Effect analysis. To evaluate the effect of the lubricant level (X_1), lubrication time (X_2), compression force (X_3), compression speed (X_4), and storage condition (X_5) on tablet thickness, hardness, and friability, the 24-h and 1-month data from Tables IV–VI were analyzed statistically. The main effects and their corresponding p-values were calculated by the computer software JMP.3.1.6. The effects that are more significant have lower p-values. The effects with p-values of <0.05 are usually considered statistically significant. In this study, the effects with p-values of <0.2 were considered directionally significant and were treated as substantial effects. The effects and p-values for the 24-h and 1-month data are summarized in Tables VII and VIII (the substantial two-factor interaction effects are listed), and the effect plots are shown in Figures 4–6 (the significant effects are highlighted).

The 24-h data show that the lubricant level (X_1) had significant effects on the tablet thickness and hardness of Fast Flo lactose and Avicel PH-102 and the friability of Avicel PH-102. When the lubricant level was increased, the tablet thickness for Fast Flo lactose decreased but was increased for Avicel PH-102. Tablet hardnesses for both Fast Flo lactose and Avicel PH-102 decreased, and the friability of Avicel PH-102 increased as the lubricant level increased.

Lubrication time (X_2) had significant effects on the tablet hardness of Avicel PH-102 and the tablet thickness, hardness, and friability of Di-Tab, but it had no effects on Fast Flo lactose at 24 h. When the lubrication time was increased, the tablet

Table VII: Effects summary (24-h data).

		Fast Flo Lactose			Avicel PH-102			Di-Tab		
Factor	**Effect**	**Thickness**	**Hardness**	**Friability**	**Thickness**	**Hardness**	**Friability**	**Thickness**	**Hardness**	**Friability**
X_1	Effect	−0.0023 in.	−1.28 kp	−0.01%	+0.0035 in.	−5.04 kp	+0.44%	–	–	–
	p-value	0.0011	0.1692	0.7111	0.0091	<0.0001	0.0139	–	–	–
X_2	Effect	−0.0005 in.	+0.30 kp	+0.00%	−0.0010 in.	+0.69 kp	+0.08%	+0.0020 in.	+0.33 kp	−0.23%
	p-value	0.2354	0.7217	0.8233	0.2988	0.0065	0.5408	0.1131	0.0726	0.0750
X_3	Effect	−0.0073 in.	+4.92 kp	+0.04%	−0.0097 in.	−1.83 kp	+0.34%	−0.0046 in.	+1.49 kp	−0.68%
	p-value	<0.0001	0.0017	0.0593	<0.0001	<0.0001	0.0338	0.0489	0.0160	0.0258
X_4	Effect	+0.0007 in.	−1.05 kp	+0.02%	+0.0012 in.	−1.90 kp	+0.24%	−0.0036 in.	−0.42 kp	+0.11%
	p-value	0.1113	0.2465	0.2924	0.2051	<0.0001	0.1006	0.0626	0.0570	0.1526
Interaction Effects		X_1X_2 X_1X_3 X_1X_4 X_2X_3		X_1X_2 X_1X_3 X_2X_3 X_2X_4 X_3X_4	X_2X_3	X_1X_2 X_1X_4 X_3X_4	X_1X_3 X_1X_4 X_3X_4		X_2X_3	X_2X_3 X_3X_4

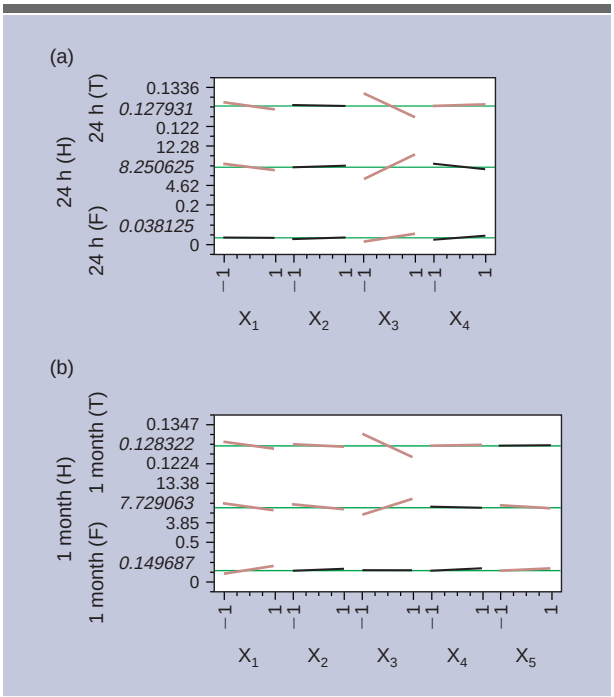

Figure 4: Effect plots for Fast Flo lactose (24-h and 1-month data).

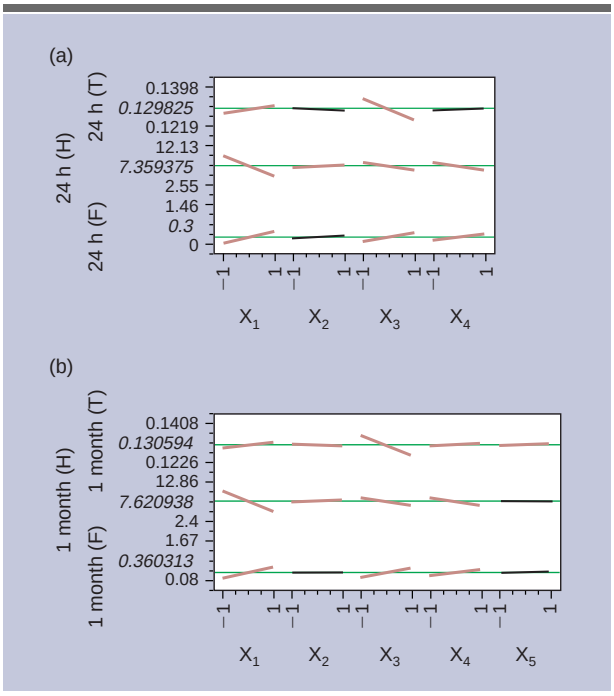

Figure 5: Effect plots for Avicel PH-102 (24-h and 1-month data).

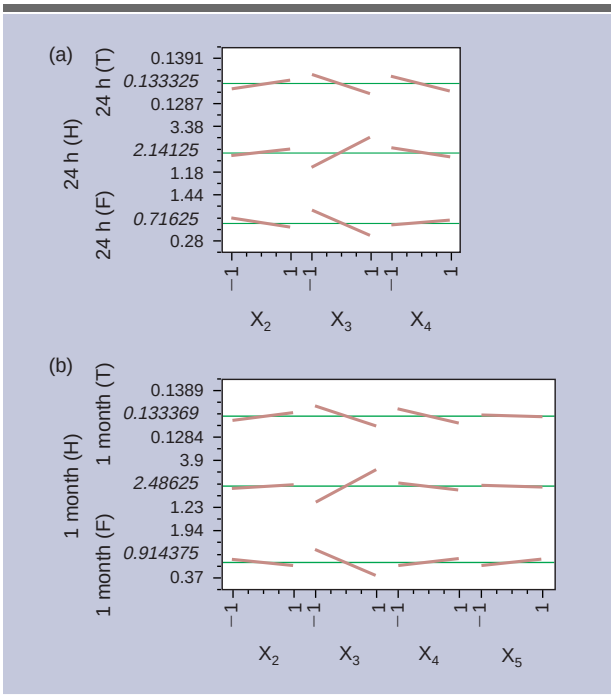

Figure 6: Effect plots for Di-Tab (24-h and 1-month data).

hardness of Avicel PH-102 increased slightly. With Di-Tab, both the tablet thickness and hardness increased, and friability decreased when the lubrication time was increased.

Compression force (X_3) had significant effects on the tablet thickness, hardness, and friability of Fast Flo lactose, Avicel PH-102, and Di-Tab at 24 h. A higher compression force certainly reduced tablet thickness, but compression force had significantly different effects on the hardness and friability of the excipients. When the compression force was increased, both the tablet hardness and friability increased for Fast Flo lactose; tablet hardness decreased and friability increased for Avicel PH-102; and tablet hardness increased and friability decreased for Di-Tab. The 9.0-kN compression force used in this study apparently exceeded the maximal compactibility for Avicel PH-102 and resulted in decreased hardness.

Compression speed (X_4) had significant effects on the tablet thickness of Fast Flo lactose; tablet hardness and friability of Avicel PH-102; and tablet thickness, hardness, and friability of Di-Tab at 24 h. When the compression speed was increased, tablet thickness increased for Fast Flo lactose. Tablet hardness decreased and friability increased for Avicel PH-102 at a higher compression speed. Tablet thickness and hardness decreased and friability increased when the compression speed was increased for Di-Tab.

The DOE used in this study is capable of analyzing the interaction effects. The interaction effects with p-values of <0.2 are listed in the effect summary (see Tables VII and VIII). Figures 7–9 illustrate the interaction effect plots for the 24-h tablet friability of Di-Tab.

As shown in Figure 7 (X_2X_3 interaction effect), the tablet friability of Di-Tab decreased when the lubrication time (X_2) was increased. This decrease was more significant when the compression force (X_3) was lower. That means that the effect of X_2 on tablet friability was affected by X_3. In other words, X_2 and X_3 had an interaction effect (p-value = 0.1173) on tablet friability.

As shown in Figure 8 (X_2X_4 interaction effect), the tablet friability of Di-Tab decreased when the lubrication time (X_2) was increased, and the effects were similar for the compression speeds (X_4) at 30 and 60 rpm. That means that the effect of X_2 on tablet friability was not affected by X_4. In other words, X_2 and X_4 had no interaction effect (p-value = 0.4471).

Table VIII: Effects summary (1-month data).

		Fast Flo Lactose			Avicel PH-102			Di-Tab		
Factor	**Effect**	**Thickness**	**Hardness**	**Friability**	**Thickness**	**Hardness**	**Friability**	**Thickness**	**Hardness**	**Friability**
X_1	Effect	−0.0021 in.	−1.45 kp	+0.11%	+0.0028 in.	−5.55 kp	+0.45%	–	–	–
	p-value	<0.0011	0.0013	0.0050	<0.0001	<0.0001	<0.0001	–	–	–
X_2	Effect	−0.0007 in.	−1.17 kp	+0.03%	−0.0010 in.	+0.58 kp	+0.03%	+0.0018 in.	+0.26 kp	−0.18%
	p-value	0.2888	0.0065	0.3625	0.0314	0.0001	0.6740	<0.0001	<0.0001	0.0092
X_3	Effect	−0.0074 in.	+3.79 kp	−0.00%	−0.0097 in.	−1.90 kp	+0.37%	−0.0043 in.	+1.91 kp	−0.92%
	p-value	<0.0001	<0.0001	0.8992	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
X_4	Effect	+0.0004 in.	−0.44 kp	+0.03%	+0.0016 in.	−1.93 kp	+0.25%	−0.0031 in.	−0.40 kp	+0.21%
	p-value	0.1522	0.2527	0.3271	0.0028	<0.0001	0.1014	<0.0001	<0.0001	0.0046
X_5	Effect	+0.0002 in.	−0.89 kp	+0.05%	+0.0008 in.	+0.13 kp	+0.05%	−0.0003 in.	−0.12 kp	+0.19%
	p-value	0.4186	0.0294	0.1870	0.1024	0.2710	0.4301	0.0952	0.0007	0.0066
Interaction		X_1X_2	X_2X_3	X_1X_5	X_2X_3	X_1X_2	X_1X_3	X_2X_4	X_2X_3	X_2X_3
Effects		X_1X_3	X_2X_4	X_3X_4	X_3X_4	X_1X_3	X_1X_4	X_2X_5	X_3X_4	X_3X_4
		X_1X_4	X_2X_5			X_1X_4	X_3X_4	X_3X_5	X_3X_5	X_3X_5
		X_2X_3	X_3X_5			X_3X_4				

Table IX: Optimal conditions for the highest mechanical strength for tablets.

	Fast Flo Lactose				
	Tablet Hardness (High)		Tablet Friability (Low)		
Factors	**24 h**	**I Month**	**24 h**	**1 Month**	**Optimal Level**
X_1 (0.2–1.0%)	0.2%	0.2%	–	0.2%	0.2%
X_2 (1–3 min)	–	1 min	–	–	1 min
X_3 (4.5–9.0 kN)	9.0 kN	9.0 kN	4.5 kN	–	9.0 kN
X_4 (30–60 rpm)	–	–	–	–	–
X_5 (H_2–H_4)	NA	H_2	NA	H_2	H_2
	Avicel PH-102				
	Tablet Hardness (High)		Tablet Friability (Low)		
Factors	**24 h**	**I Month**	**24 h**	**1 Month**	**Optimal Level**
X_1 (0.2–1.0%)	0.2%	0.2%	0.2%	0.2%	0.2%
X_2 (1–3 min)	3 min	3 min	–	–	3 min
X_3 (4.5–9.0 kN)	4.5 kN	4.5 kN	4.5 kN	4.5 kN	4.5 kN
X_4 (30–60 rpm)	30 rpm	30 rpm	30 rpm	30 rpm	30 rpm
X_5 (H_2–H_4)	NA	–	NA	–	–
	Di-Tab				
	Tablet Hardness (High)		Tablet Friability (Low)		
Factors	**24 h**	**I Month**	**24 h**	**1 Month**	**Optimal Level**
X_2 (1–3 min)	3 min	3 min	3 min	3 min	3 min
X_3 (4.5–9.0 kN)	9.0 kN	9.0 kN	9.0 kN	9.0 kN	9.0 kN
X_4 (30–60 rpm)	30 rpm	30 rpm	30 rpm	30 rpm	30 rpm
X_5 (H_2–H_4)	NA	H_2	NA	H_2	H_2

As shown in Figure 9 (X_3X_4 interaction effect), the tablet friability of Di-Tab decreased when the compression force (X_3) was increased. This decrease was more significant when the compression speed (X_4) was higher. That means that the effect of X_3 on tablet friability was affected by X_4. In other words, X_3 and X_4 had an interaction effect (p-value = 0.0801) on tablet friability. Although the DOE used in this study is capable of analyzing the interaction effects as illustrated, the focus of the discussion was on the main effects.

The effect analysis from the 1-month data (see Table VIII) was similar to the 24-h results as shown in Figures 4–6. Some effects were significant at 24 h but were not significant at 1 month and vice versa, but all of the effects were consistent in trends. In addition to X_1, X_2, X_3, and X_4, the effects of storage condition (X_5) also were evaluated from the 1-month data. The accelerated storage condition (H_4) resulted in a decrease in tablet hardness and an increase in friability for Fast Flo lactose and Di-Tab, an increase in tablet thickness for Avicel PH-102, and a decrease in tablet thickness for Di-Tab. From the effect summaries shown in Tables VII and VIII, the optimal conditions that generated the highest mechanical strength for tablets are listed in Table IX. From Table IX, the following conditions were found to be in favor of producing tablets with high hardness and low friability:

- Fast Flo lactose: lower lubricant level, shorter lubrication time, higher compression force, and room-temperature storage condition.
- Avicel PH-102: lower lubricant level, longer lubrication time, and lower compression speed (storage condition is not critical).
- Di-Tab: longer lubrication time, higher compression force, lower compression speed, and room-temperature storage condition.

Initial relaxation and physicomechanical stability. To further evaluate the stress relaxation processes for Fast Flo lactose, Avicel PH-102, and Di-Tab, the initial relaxation (from time zero to 24 h) and physicomechanical stability (from 24 h to 1 month) were calculated and summarized in Table X. The data in Table X were analyzed by the computer software JMP.3.1.6. The effects and p-values for the initial relaxation and physicomechanical stability data of Fast Flo lactose are summarized in Table XI, and the effect plots are shown in Figure 10 (the significant effects are highlighted).

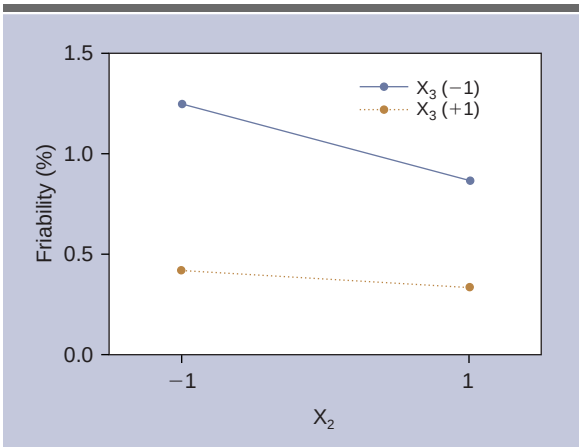

Figure 7: X_2X_3 interaction plot for Di-Tab 24-h friability.

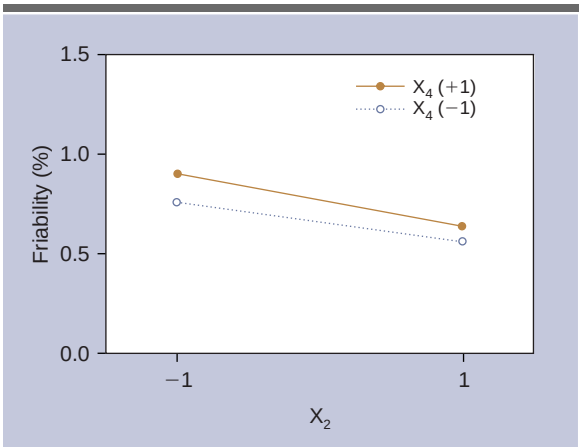

Figure 8: X_2X_4 interaction plot for Di-Tab 24-h friability.

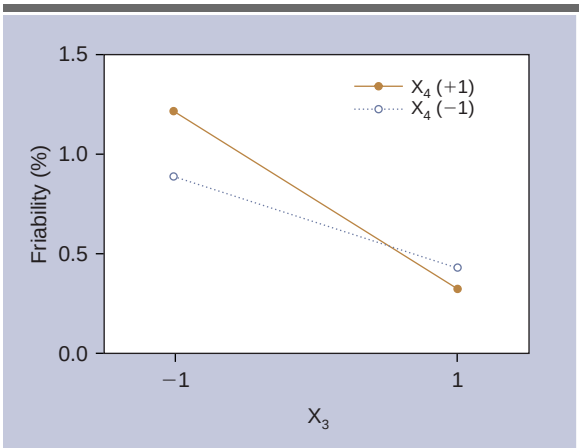

Figure 9: X_3X_4 interaction plot for Di-Tab 24-h friability.

An increase in the lubricant level (X_1) resulted in a more significant increase in tablet thickness and friability over time. An increase in the lubrication time (X_2) resulted in a less significant increase in tablet thickness and hardness over time and a more significant increase in friability in the first 24 h. An increase in the compression force (X_3) resulted in a less significant increase in tablet thickness and hardness and a more significant increase in friability in the first 24 h. A higher compression speed (X_4) resulted in a more significant increase in tablet thickness in the first 24 h but reduced the increase in tablet thickness between 24 h and 1 month and reduced the increase in tablet hardness during the first 24 h. The accelerated storage condition (X_5 : H_4) enhanced the increase in tablet thickness.

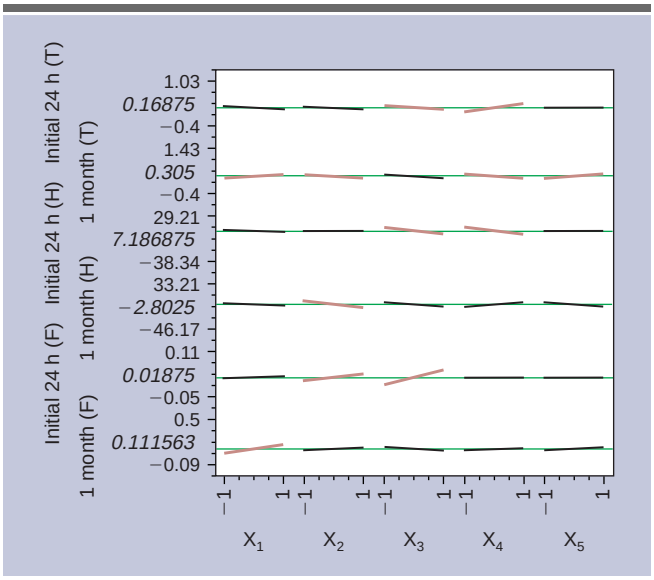

Figure 10: Effect plots for Fast Flo lactose (initial relaxation and physicomechanical storage stability).

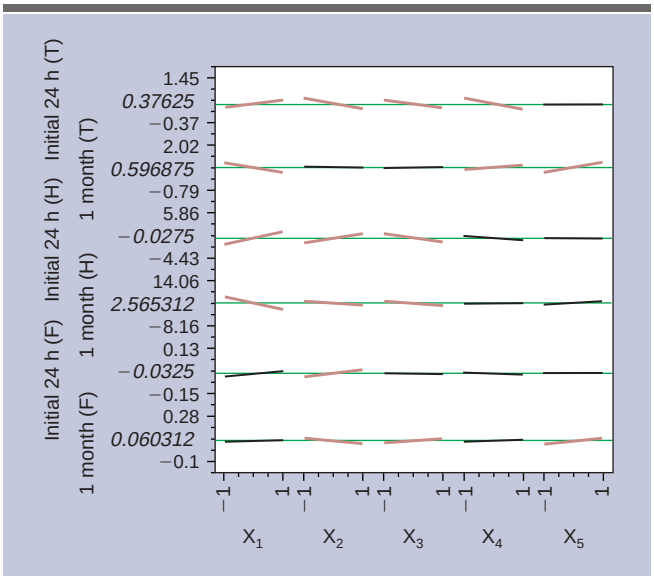

Figure 11: Effect plots for Avicel PH-102 (initial relaxation and storage stability).

The effects and p-values for the initial relaxation and physicomechanical stability data of Avicel PH-102 are summarized in Table XII, and the effect plots are shown in Figure 11 (the significant effects are highlighted). An increase in lubricant level (X_1) resulted in a more significant increase in tablet thickness and hardness in the first 24 h but a less significant increase in tablet thickness and hardness between 24 h and 1 month. An increase in lubrication time (X_2) resulted in a less significant increase in tablet thickness in 24 h and hardness and friability between 24 h and 1 month. However, an increase in lubrication

Table X: Initial relaxation and physicomechanical stability.

Fast Flo Lactose

				% Change in Thickness			% Change in Hardness			Change in Friability, %		
				Initial	1-Month Storage		Initial	1-Month Storage		Initial	1-Month Storage	
Lub%	LubT	Force	rpm	24 h	H_2	H_4	24 h	H_2	H_4	24 h	H_2	H_4
0.2	1 min	4.5 kN	30	0	+0.23	+1.43	+8.74	+24.11	−5.00	0	−0.09	+0.08
			60	+0.68	+0.07	−0.22	+3.96	+16.00	+25.52	−0.05	−0.06	+0.08
		9.0 kN	30	+0.08	0	+0.40	+5.78	+12.55	−17.68	+0.06	−0.06	+0.03
			60	+1.03	+0.16	+0.16	+1.05	+15.34	−17.67	+0.06	−0.06	+0.08
	3 min	4.5 kN	30	+0.08	+0.31	+0.08	+12.01	+20.21	+12.56	0	+0.06	+0.14
			60	−0.15	+0.08	+0.45	+17.46	−3.00	−0.30	0	+0.09	+0.18
		9.0 kN	30	−0.40	+0.40	+0.24	+15.05	+4.14	−29.45	0	+0.03	+0.17
			60	+0.40	−0.40	+0.24	+6.61	−43.30	−26.30	+0.06	+0.09	+0.09
1.0	1 min	4.5 kN	30	+0.23	+0.54	+0.76	+10.99	−25.24	−4.08	0	+0.27	+0.21
			60	+0.08	+0.61	+0.61	+6.94	+5.63	+4.76	−0.02	0	+0.24
		9.0 kN	30	−0.24	+0.24	+0.49	+12.36	+24.36	−5.01	+0.02	+0.01	+0.15
			60	−0.25	+0.33	+0.33	+4.50	+15.62	−14.97	0	+0.50	+0.18
	3 min	4.5 kN	30	+0.38	+0.23	+0.23	+29.21	−25.94	−16.09	0	+0.25	+0.18
			60	+0.54	+0.15	+0.23	+6.63	−9.77	−0.36	0	+0.26	+0.24
		9.0 kN	30	+0.08	+0.32	+0.49	+12.04	−46.17	−38.27	+0.06	+0.12	+0.11
			60	+0.16	+0.16	+0.40	−38.34	+33.21	+24.91	+0.11	0	0

Avicel PH-102

				% Change in Thickness			% Change in Hardness			Change in Friability, %		
				Initial	1-Month Storage		Initial	1-Month Storage		Initial	1-Month Storage	
Lub%	LubT	Force	rpm	24 h	H_2	H_4	24 h	H_2	H_4	24 h	H_2	H_4
0.2	1 min	4.5 kN	30	+1.44	+0.30	+0.75	−3.17	+4.15	+5.50	−0.09	+0.08	+0.11
			60	−0.37	+0.97	+2.02	0	+1.56	+0.52	−0.06	+0.06	+0.08
		9.0 kN	30	+0.08	+0.57	+0.98	+2.32	+8.95	+11.21	−0.05	0	+0.05
			60	0	+0.73	+1.29	−4.43	+7.19	+14.06	−0.02	+0.02	+0.03
	3 min	4.5 kN	30	+0.15	+0.53	+0.98	+0.50	+2.14	+3.13	−0.09	+0.09	+0.08
			60	+0.38	+0.08	+1.14	−1.49	+4.10	+5.00	−0.03	+0.05	+0.05
		9.0 kN	30	+0.41	+0.57	+0.90	−1.79	+1.24	+6.37	−0.02	+0.02	+0.03
			60	−0.32	+0.72	+1.52	−4.04	+3.81	+11.70	0	+0.04	+0.06
1.0	1 min	4.5 kN	30	+1.45	−0.79	+0.57	+2.14	+9.50	+2.90	+0.01	+0.05	+0.09
			60	+0.65	+0.29	+0.72	−2.48	+2.88	+6.61	−0.14	+0.11	+0.15
		9.0 kN	30	+0.82	−0.08	+0.57	−4.04	−2.74	−7.50	−0.12	+0.14	+0.15
			60	+0.56	+0.47	+0.55	+1.19	−3.53	−5.88	+0.04	−0.04	+0.28
	3 min	4.5 kN	30	+0.15	0	+0.82	+4.92	+3.00	+6.19	+0.13	−0.10	−0.09
			60	+0.23	+0.08	+0.45	+5.86	−3.69	+3.69	+0.04	−0.07	0
		9.0 kN	30	+0.24	+0.31	+0.63	+2.18	−8.16	−6.60	+0.03	+0.03	+0.11
			60	+0.15	+0.15	+0.31	+1.89	+0.37	−5.58	−0.15	+0.06	+0.21

Di-Tab

				% Change in Thickness			% Change in Hardness			Change in Friability, %		
				Initial	1-Month Storage		Initial	1-Month Storage		Initial	1-Month Storage	
Lub%	LubT	Force	rpm	24 h	H_2	H_4	24 h	H_2	H_4	24 h	H_2	H_4
1.0	1 min	4.5 kN	30	+0.07	0	−0.22	−4.46	+14.00	+12.00	+0.52	+0.20	+0.30
			60	0	+0.15	0	−5.60	+4.24	+7.63	+0.78	+0.13	+0.50
		9.0 kN	30	+0.54	+0.08	−0.23	+3.96	+22.15	+14.19	+0.27	0	+0.06
			60	−1.68	+1.24	−0.23	−20.14	+37.61	+25.21	+0.09	0	+0.18
	3 min	4.5 kN	30	−0.07	−0.65	−0.14	−6.86	+11.66	+13.50	+0.34	+0.06	+0.49
			60	−0.22	+0.15	+0.30	−2.31	+8.66	+3.94	+0.33	+0.28	+0.59
		9.0 kN	30	−0.30	+0.22	−0.07	+2.11	+15.38	+9.76	+0.19	−0.01	+0.09
			60	−0.08	+0.08	−0.08	−6.67	+21.77	+13.95	+0.10	+0.15	+0.15

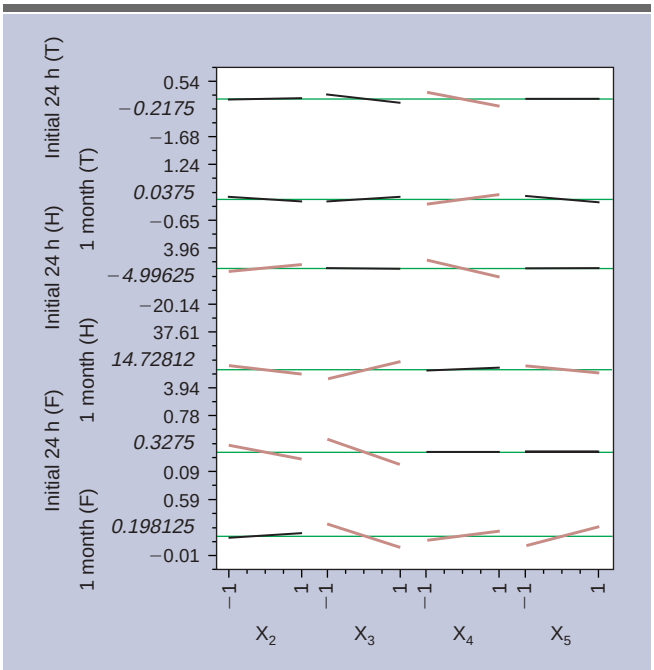

Figure 12: Effect plots for Di-Tab (initial relaxation and physicomechanical stability).

time enhanced the increase in tablet hardness and friability in 24 h. An increase in compression force (X_3) resulted in a less significant increase in tablet thickness in 24 h and tablet hardness in 24 h and between 24 h and 1 month, and a more significant increase in tablet friability between 24 h and 1 month. A higher compression speed (X_4) resulted in a less significant increase in tablet thickness in the first 24 h but enhanced the increase in tablet thickness between 24 h and 1 month. The accelerated storage condition ($X_5 : H_4$) enhanced the increase in tablet thickness and friability.

The effects and p-values for the initial relaxation and physicomechanical stability data of Di-Tab are summarized in Table XIII, and the effect plots are shown in Figure 12 (the significant effects are highlighted). An increase in lubricant time (X_2) reduced the initial decrease in hardness, reduced the increase in hardness from 24 h to 1 month, and reduced the initial increase in friability. An increase in compression force (X_3) resulted in a more significant increase in tablet hardness between 24 h and 1 month and a less significant increase in friability in the first hours and between 24 h and 1 month. An increase in compression speed (X_4) resulted in a more significant decrease in tablet thickness and hardness in the first 24 h and a more significant increase in tablet thickness and friability between 24 h and 1 month. The accelerated storage condition ($X_5 : H_4$) decreased tablet hardness and increased friability thereafter.

Conditions resulting in a more substantial initial relaxation. From the effect summaries in Tables XI–XIII, the conditions that resulted in more-significant initial changes in physicomechanical characteristics are summarized in Table XIV. For Fast Flo lactose, a more significant initial increase in tablet thickness is expected when the compression force is low or the compression speed is high. A more significant initial increase in tablet hardness is expected when the compression force or compression speed is low. And a more significant initial increase in tablet friability is expected when the blending time is long or the compression force is high.

For Avicel PH-102, a more significant initial increase in tablet thickness is expected when the lubricant level is high, lubrication time is short, compression force is low, or compression speed is low. A more significant initial decrease in tablet hardness is expected when the lubricant level is low, lubrication time is short, or compression force is high. A more significant initial decrease in tablet friability is expected when the lubrication time is short.

Table XI: Effect summary for initial relaxation and physicomechanical stability of Fast Flo lactose.

		Thickness		Hardness		Friability	
		Initial	1-Month	Initial	1-Month	Initial	1-Month
Factor	Effect	Relaxation	Stability	Relaxation	Stability	Relaxation	Stability
X_1	Effect	−0.09%	+0.16%	−3.29%	−4.07%	+0.01%	+0.12%
	p-value	0.2106	0.1727	0.3060	0.5481	0.5446	0.0088
X_2	Effect	−0.07%	−0.16%	+0.79%	−12.39%	+0.02%	+0.03%
	p-value	0.3731	0.1663	0.8019	0.0804	0.0248	0.4835
X_3	Effect	−0.12%	−0.11%	-9.61%	−7.98%	+0.06%	−0.04%
	p-value	0.1034	0.3098	0.0070	0.2465	<0.0001	0.2876
X_4	Effect	+0.29%	−0.19%	−12.17%	+8.77%	+0.00%	+0.02%
	p-value	0.0010	0.1016	0.0012	0.2048	0.7609	0.6955
X_5	Effect	–	+0.18%	–	−7.82%	–	+0.05%
	p-value	–	0.1171	–	0.2555	–	0.2492
Interaction Effects		X_1X_2 X_1X_3 X_1X_4 X_3X_4		X_1X_2 X_1X_3 X_1X_4 X_2X_3 X_2X_4 X_3X_4	X_1X_3 X_1X_4 X_3X_5	X_1X_2 X_2X_4 X_3X_4	X_1X_2 X_1X_5 X_2X_3

For Di-Tab, a more significant initial decrease in tablet thickness is expected when the compression speed is high. A more significant initial decrease in tablet hardness is expected when the lubricant time is short or compression speed is high. A more significant initial increase in tablet friability is expected when the lubrication time is short or compression force is low. When significant differences exist between the time-zero and 24-h values, it is important to understand these differences to design more effective in-process controls to achieve the desirable physicomechanical characteristics.

Conditions resulting in more-stable physicomechanical characteristics. From the effect summaries in Tables XI–XIII, the

Table XII: Effect summary for initial relaxation and physicomechanical stability of Avicel PH-102.

		Thickness		Hardness		Friability	
		Initial	1-Month	Initial	1-Month	Initial	1-Month
Factor	Effect	Relaxation	Stability	Relaxation	Stability	Relaxation	Stability
X_1	Effect	+0.31%	−0.56%	+2.97%	−6.20%	+0.03%	+0.01%
	p-value	0.0238	<0.0001	0.0038	<0.0001	0.3211	0.4170
X_2	Effect	−0.41%	−0.05%	+2.06%	−1.79%	+0.04%	−0.05%
	p-value	0.0049	0.6531	0.0320	0.1381	0.1009	0.0113
X_3	Effect	−0.27%	+0.08%	−1.63%	−2.02%	−0.01%	+0.03%
	p-value	0.0468	0.4275	0.0827	0.0980	0.7627	0.1226
X_4	Effect	−0.43%	+0.24%	−0.82%	+0.22%	−0.02%	+0.02%
	p-value	0.0031	0.0252	0.3641	0.8500	0.5476	0.3786
X_5	Effect	–	+0.58%	–	+1.28%	–	+0.05%
	p-value	–	<0.0001	–	0.2797	–	0.0072
Interaction		X_1X_2	X_2X_4	X_1X_2	X_1X_3	X_1X_3	X_1X_2
Effects		X_2X_4	X_3X_5	X_2X_3	X_1X_5	X_1X_4	X_1X_3
					X_3X_4	X_2X_3	X_1X_4
							X_1X_5
							X_2X_3
							X_3X_5
							X_4X_5

Table XIII: Effect summary for initial relaxation and physicomechanical stability of Di-Tab.

		Thickness		Hardness		Friability	
		Initial	1-Month	Initial	1-Month	Initial	1-Month
Factor	Effect	Relaxation	Stability	Relaxation	Stability	Relaxation	Stability
X_2	Effect	+0.10%	−0.12%	+3.13%	−4.80%	−0.18%	+0.05%
	p-value	0.7371	0.4999	0.0336	0.0261	0.0074	0.2675
X_3	Effect	−0.33%	+0.18%	−0.38%	+10.55%	−0.33%	−0.24%
	p-value	0.3008	0.3404	0.7402	0.0010	0.0004	0.0025
X_4	Effect	−0.56%	+0.33%	−7.37%	+1.30%	−0.01%	+0.10%
	p-value	0.1059	0.1096	0.0010	0.4375	0.9060	0.0705
X_5	Effect	–	−0.24%	–	−4.41%	–	+0.19%
	p-value	–	0.2097	–	0.0350	–	0.0064
Interaction		X_2X_4	X_2X_5	X_2X_3	X_2X_3	X_2X_3	X_3X_5
Effects		X_3X_4	X_3X_5	X_2X_4	X_3X_4	X_3X_4	
				X_3X_4	X_3X_4		

optimal conditions that generate tablets with the most-stable physicomechanical characteristics are summarized in Table XV. As shown in Table XV, the following conditions were found to be more likely to produce tablets with stable thickness, hardness, and friability:

- Fast Flo lactose: lower lubricant level, longer lubrication time, higher compression speed, and storage at 25 °C and 60% RH (H_2)
- Avicel PH-102: higher lubricant level, longer lubrication time, lower compression speed, and storage at 25 °C and 60% RH (H_2)
- Di-Tab: longer lubrication time and lower compression speed.

When the physicomechanical characteristics are critical for a pharmaceutical tablet, the information obtained from this study can be used to optimize the formulation and manufacturing process to achieve the most stable product.

Conclusion

When the physicomechanical characteristics are critical to the quality and efficacy of a pharmaceutical tablet, it is very important for a formulation scientist to optimize the physicomechanical characteristics and maximize the physicomechanical stability when developing tablet formulations. When Fast Flo lactose is used in a direct-compression tablet formulation, high hardness and low friability can be achieved by incorporating less lubricant, shorter lubrication time, higher compression force, and storage at room temperature (H_2). The lower lubricant level, longer lubrication time, higher compression speed, and H_2 storage condition improves the physicomechanical stability.

When Avicel PH-102 is used, high hardness and low friability can be achieved by using less lubricant, longer lubrication time, and lower compression speed. A higher lubricant level, longer lubrication time, lower compression speed, and H_2 storage conditions improve the physicomechanical stability. When Di-Tab is used, high hardness and low friability can be achieved by using longer lubrication time, higher compression force, lower compression speed, and storage at room temperature (H_2). A longer lubrication time and lower compression speed improve the physicomechanical stability. Overall, Avicel PH-102 seemed to have the most stable physicomechanical characteristics, Fast Flo lactose had the most significant initial hardening, and Di-Tab's initially high friability seemed to worsen substantially over time.

A formulation scientist should understand the physicomechanical characteristics of the major compressible excipients and the effects of formulation and processing variables on the physicomechanical stability to ensure an efficient formulation development.

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Table XIV: Conditions resulting in significant initial changes in physicomechanical characteristics.

	Fast Flo Lactose		
	Tablet Thickness 0–24 h (Resulting in a	Tablet Hardness 0–24 h (Resulting in a	Tablet Friability 0–24 h (Resulting in a
Factor	Significant Increase)	Significant Increase)	Significant Increase)
X_1 (0.2–1.0%)	–	–	–
X_2 (1–3 min)	–	–	3 min
X_3 (4.5–9.0 kN)	4.5 kN	4.5 kN	9.0 kN
X_4 (30–60 rpm)	60 rpm	30 rpm	–
	Avicel PH-102		
	Tablet Thickness 0–24 h (Resulting in a	Tablet Hardness 0–24 h (Resulting in a	Tablet Friability 0–24 h (Resulting in a
Factor	Significant Increase)	Significant Decrease)	Significant Decrease)
X_1 (0.2–1.0%)	1.0%	0.2%	–
X_2 (1–3 min)	1 min	1 min	1 min
X_3 (4.5–9.0 kN)	4.5 kN	9.0 kN	–
X_4 (30–60 rpm)	30 rpm	–	–
	Di-Tab		
	Tablet Thickness 0–24 h (Resulting in a	Tablet Hardness 0–24 h (Resulting in a	Tablet Friability 0–24 h (Resulting in a
Factor	Significant Decrease)	Significant Decrease)	Significant Increase)
X_2 (1–3 min)	–	1 min	1 min
X_3 (4.5-9.0 kN)	–	–	4.5 kN
X_4 (30–60 rpm)	60 rpm	60 rpm	–

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Table XV: Optimal conditions for the most stable physicomechanical characteristics.

	Fast Flo Lactose			
	Tablet Thickness	Tablet Hardness	Tablet Friability	
Factor	24 h–1 Month (To Reduce the Increase)	24 h–1 Month (To Reduce the Increase)	24 h–1 Month (To Reduce the Increase)	Optimal Levels
X_1 (0.2–1.0%)	0.2%	–	0.2%	0.2%
X_2 (1–3 min)	3 min	3 min	–	3 min
X_3 (4.5–9.0 kN)	–	–	–	–
X_4 (30–60 rpm)	60 rpm	–	–	60 rpm
X_5 (H_2–H_4)	H_2	–	–	H_2
	Avicel PH-102			
	Tablet Thickness	Tablet Hardness	Tablet Friability	
Factor	24 h–1 Month (To Reduce the Increase)	24 h–1 Month (To Reduce the Increase)	24 h–1 Month (To Reduce the Increase)	Optimal Levels
X_1 (0.2–1.0%)	1.0%	1.0%	–	1.0%
X_2 (1–3 min)	–	3 min	3 min	3 min
X_3 (4.5–9.0 kN)	–	9.0 kN	4.5 kN	–
X_4 (30–60 rpm)	30 rpm	–	–	30 rpm
X_5 (H_2–H_4)	H_2	–	H_2	H_2
	Di-Tab			
	Tablet Thickness	Tablet Hardness	Tablet Friability	
Factor	24 h–1 Month (To Reduce the Increase)	24 h–1 Month (To Reduce the Increase)	24 h–1 Month (To Reduce the Increase)	Optimal Levels
X_2 (1–3 min)	–	3 min	–	3 min
X_3 (4.5–9.0 kN)	–	4.5 kN	9.0 kN	–
X_4 (30–60 rpm)	30 rpm	–	30 rpm	30 rpm
X_5 (H_2–H_4)	–	H_4	H_2	–

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