Effect of Moisture on Physical Characteristics of Tablets Prepared from Direct Compression Excipients

S. A. SANGEKAR▲, M. SARLI, and P. R. SHETH

Abstract □ Twenty-four formulations of placebo tablets, made from eight excipients for direct compression and three disintegrants, were evaluated under various conditions of relative humidity. The data were evaluated statistically so that the formulations could be given a relative ranking on the basis of maximum hardness, minimum change of disintegration time, minimum moisture uptake, and minimum change in volume. The three preferred direct compression formulations in order of overall performance were: (*a*) dibasic calcium phosphate dihydrate–starch USP, (*b*) lactose hydrous beadlets–direct compression starch, and (*c*) lactose anhydrous DTG–starch USP. Mannitol appears to be the best sugar for direct compression chewable tablet formulations.

Keyphrases □ Tablet formulations—effect of moisture on direct compression excipients □ Moisture effect—direct compression tablet excipients □ Direct compression tableting—effect of moisture on excipients □ Excipients, direct compression—effect of moisture on tablet formulations

A recent trend in pharmaceutical technology is to use excipients (1–9) that permit making tablets by direct compression. Lactose (10), dibasic calcium phosphate (11), and microcrystalline cellulose (12) are the most commonly used excipients. The direct compression technique often affords the distinct advantages of lower costs and improved product stability compared to tablets prepared by slugging or wet granulation. However, tablets prepared by direct compression using lactose and microcrystalline cellulose were observed to swell considerably when subjected to storage at high relative humidities for even short periods of time. This phenomenon was observed in these laboratories during packaging studies conducted at 37° and 85% relative humidity. Similar observations were reported by several groups of investigators (13, 14).

The present study was undertaken to evaluate tablets made from available direct compression excipients

Table I—Tableting Ingredients[a]

Direct Compression Excipients (*E*)	Binder (*B*)	Disintegrant (*D*)
Dibasic calcium phosphate NF (dihydrate, unmilled) (E_1)[b]	Microcrystalline cellulose NF (*B*)[i]	Starch direct compression (D_1)[j]
Monobasic calcium phosphate monohydrate (E_2)[b]		Starch USP (D_2)[k]
Lactose USP (anhydrous), DTG (E_3)[c]		Alginic acid (D_3)[l]
Lactose hydrous beadlets (E_4)[d]		
Mannitol USP (granular) (E_5)[e]		
Sorbitol USP (crystalline tablet type) (E_6)[f]		
Dextrose (anhydrous), (E_7)[g]		
Sucrose (direct compression), (E_8)[h]		

[a] Magnesium stearate at a level of 0.5% was used as a lubricant in all compositions. [b] Stauffer Chemical Co., New York, N. Y. [c] Sheffield Chemical Division of National Dairy Products, Union, N. J. [d] Foremost Dairies, Inc., San Francisco, Calif. [e] Atlas Chemical Industries, Inc., Wilmington, Del. [f] Pfizer Inc., New York, N. Y. [g] Celutab, Penick & Ford, Ltd., Cedar Rapids, Iowa. [h] Amerfond, American Sugar Co., New York, N. Y. [i] Avicel PH101, FMC Corp., Marcus Hook, Pa. [j] STA-Rx 1500, Colorcon Co., West Point, Pa. [k] Anheuser-Busch, Inc., St. Louis, Mo. [l] Edward Mendell, Inc., Yonkers, N. Y.

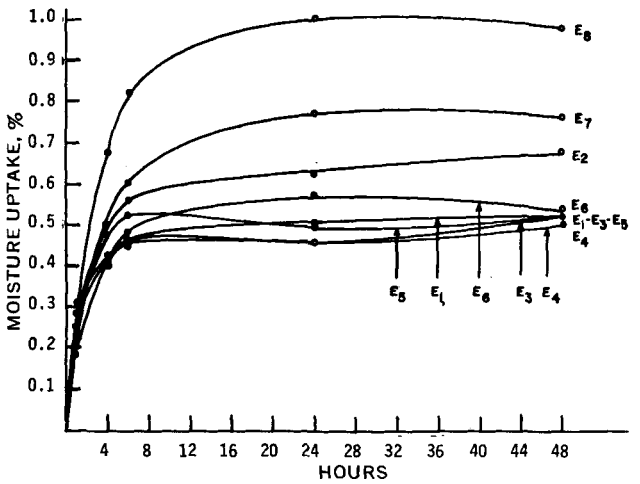

Figure 1—*Percent moisture uptake at different time intervals by direct compression tablets prepared with different excipients* (E_1–E_8), *a common binder* (B), *and a common disintegrant* (D_3) *at 43% relative humidity (25°). Key:* E_1, *dibasic calcium phosphate NF (dihydrate, unmilled);* E_2, *monobasic calcium phosphate monohydrate;* E_3, *lactose USP (anhydrous), DTG;* E_4, *lactose hydrous beadlets;* E_5, *mannitol USP (granular);* E_6, *sorbitol USP (crystalline tablet type);* E_7, *dextrose (anhydrous);* E_8, *sucrose;* B, *microcrystalline cellulose; and* D_3, *alginic acid.*

Table II—Percent Composition of Various Tablets

Component	Percent
Excipient (E_1–E_8)	79.5
Binder (*B*)	10.0
Disintegrant (D_1–D_3)	10.0
Magnesium stearate	0.5

Table III—Percent Increase in Weight, Percent Increase in Volume, Hardness (Strong-Cobb-Arner Units), and Disintegration (Seconds) at Room Temperature and after 48 hr. at Four Humidity Levels

Formulation EBD	Room Temperature				43% Relative Humidity at 25°				65% Relative Humidity at 25°				75% Relative Humidity at 25°				100% Relative Humidity at 25°			
	M^a	V^b	H^c	D^d	M	V	H	D	M	V	H	D	M	V	H	D	M	V	H	D
E_1BD_1	—	—	9.9	60	0.52	0	8.5	15	1.09	2.16	6.3	15	1.89	5.31	5.2	15	3.89	13.3	3.2	28
E_1BD_2	—	—	11.9	60	0.44	0	10.8	7	0.98	1.67	7.6	7	1.35	3.91	6.6	7	3.40	12.5	3.9	16
E_1BD_3	—	—	10.2	60	0.52	0	9.0	31	1.13	2.18	6.1	32	1.55	4.74	4.9	33	5.13	17.6	2.3	40
E_2BD_1	—	—	15.6	330	0.39	0	12.7	580	1.42	3.64	10.3	420	2.11	6.45	9.0	267	8.24	27.3	4.9	180
E_2BD_2	—	—	14.1	180	0.52	0	13.3	186	1.53	4.45	8.7	155	2.25	6.71	7.2	120	8.96	23.5	4.2	80
E_2BD_3	—	—	13.5	300	0.68	0	10.8	510	1.86	4.60	7.5	285	2.66	8.36	6.9	260	10.4	23.1	3.5	180
E_3BD_1	—	—	12.7	330	0.36	0	13.5	445	0.88	0	8.6	445	1.32	2.75	10.6	465	5.13	15.0	8.7	325
E_3BD_2	—	—	14.0	420	0.48	0	12.2	330	1.00	0	11.2	335	1.43	2.42	10.8	345	4.99	15.0	7.9	295
E_3BD_3	—	—	12.4	480	0.52	0	11.3	495	1.17	2.02	9.2	518	1.63	3.49	8.7	495	5.81	19.4	7.6	270
E_4BD_1	—	—	14.2	60	0.28	0	11.9	40	0.83	2.54	8.3	40	1.17	4.97	6.0	40	3.33	17.5	3.8	35
E_4BD_2	—	—	12.8	60	0.44	0	10.2	23	0.94	3.86	7.0	23	1.27	5.74	5.6	23	3.71	19.2	3.4	23
E_4BD_3	—	—	11.6	60	0.50	0	9.5	35	1.11	5.13	6.1	39	1.54	7.45	5.7	39	4.60	17.6	3.0	30
E_5BD_2	—	—	9.9	60	0.43	0	7.6	10	1.04	4.83	4.9	10	1.34	12.4	3.6	10	5.75	39.5	1.7	10
E_5BD_3	—	—	13.0	60	0.52	1.90	10.0	45	1.20	7.40	7.1	63	1.61	9.78	4.5	45	11.1	21.9	2.8	20
E_6BD_1	—	—	15.3	300	0.16	1.67	16.4	315	1.75	9.44	10.9	315	5.29	31.8	7.4	390	22.0	44.4	4.8	315
E_6BD_2	—	—	14.7	300	0.34	2.03	12.2	300	1.81	10.4	8.1	300	5.98	37.3	6.4	300	20.9	66.5	4.2	335
E_6BD_3	—	—	12.7	360	0.54	2.20	9.3	325	2.30	12.4	6.7	325	6.89	38.9	5.6	315	12.7	62.5	3.5	310
E_7BD_1	—	—	13.3	300	0.43	0	10.4	300	1.46	6.17	5.5	300	2.20	13.0	4.1	300	8.17	—[e]	1.8	300
E_7BD_2	—	—	15.6	240	0.58	0	11.4	235	1.59	5.54	6.2	210	2.28	10.6	4.0	230	9.59	—[e]	1.8	135
E_7BD_3	—	—	11.9	210	0.76	0	9.5	125	1.81	6.44	4.6	175	2.67	11.7	2.7	45	8.98	66.6	1.4	45
E_8BD_1	—	—	14.9	330	0.65	0	10.2	345	1.68	12.4	5.9	345	3.00	19.4	4.7	360	12.1	—[e]	1.8	360
E_8BD_2	—	—	15.1	300	0.81	3.54	7.2	315	1.86	14.3	2.3	410	3.06	22.2	1.2	445	13.0	—[e]	0.2	595
E_8BD_3	—	—	15.0	300	0.97	2.66	8.8	395	2.22	12.4	4.7	395	3.71	19.1	3.6	380	15.1	32.8	1.5	175

[a] M = percent increase in weight. [b] V = percent increase in volume of the tablet. [c] H = hardness in Strong-Cobb-Arner units. [d] D = disintegration time in seconds. [e] Unable to take an accurate measurement because the tablets were too soft to handle. For statistical evaluation, extrapolated values were used.

which were subjected to high relative humidity storage conditions. The following parameters were studied: (*a*) volume, (*b*) moisture uptake, (*c*) hardness, and (*d*) disintegration time. Data from these measurements were analyzed statistically to obtain a relative ranking of the formulations.

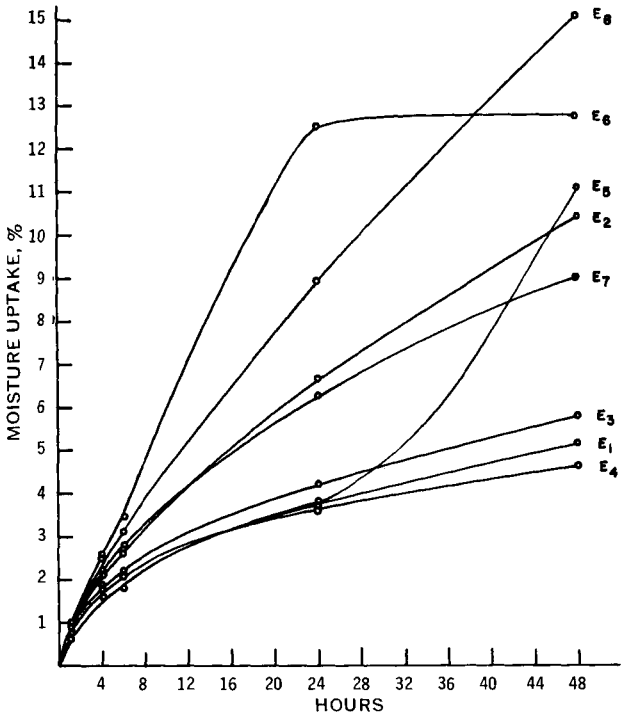

Figure 2—*Percent moisture uptake at different time intervals by direct compression tablets prepared with different excipients* (E_1–E_8), *a common binder* (B), *and a common disintegrant* (D_3) *at 100% relative humidity (25°). Key:* E_1, *dibasic calcium phosphate NF (dihydrate, unmilled);* E_2, *monobasic calcium phosphate monohydrate;* E_3, *lactose USP (anhydrous), DTG;* E_4, *lactose hydrous beadlets;* E_5, *mannitol USP (granular);* E_6, *sorbitol USP (crystalline tablet type);* E_7, *dextrose (anhydrous);* E_8, *sucrose;* B, *microcrystalline cellulose; and* D_3, *alginic acid.*

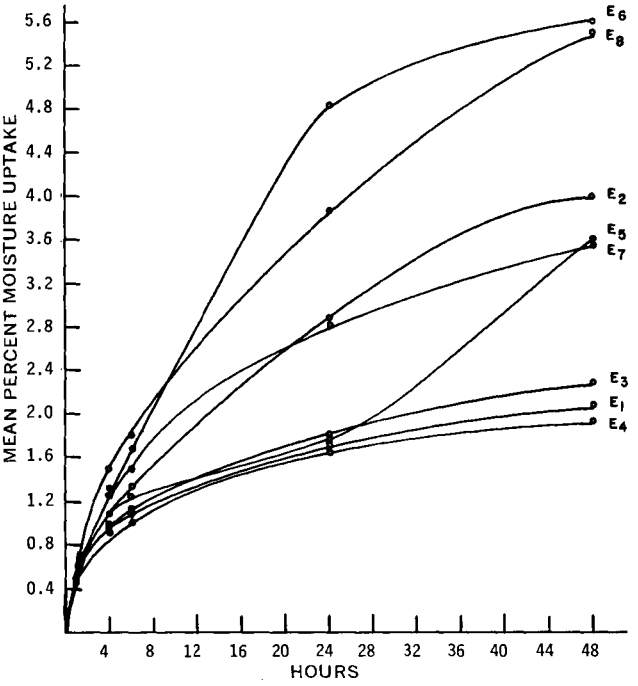

Figure 3—*Mean percent moisture uptake at different time intervals across the four humidity levels (43, 65, 75, and 100% relative humidity at 25°) by direct compression tablets prepared with different excipients* (E_1–E_8), *a common binder* (B), *and a common disintegrant* (D_3). *Key:* E_1, *dibasic calcium phosphate NF (dihydrate, unmilled);* E_2, *monobasic calcium phosphate monohydrate;* E_3, *lactose USP (anhydrous), DTG;* E_4, *lactose hydrous beadlets;* E_5, *mannitol USP (granular);* E_6, *sorbitol USP (crystalline tablet type);* E_7, *dextrose (anhydrous);* E_8, *sucrose;* B, *microcrystalline cellulose; and* D_3, *alginic acid.*

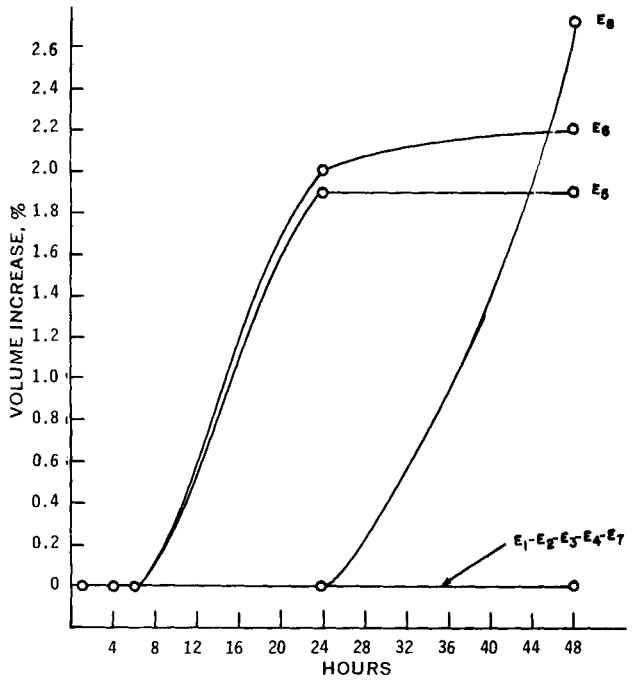

Figure 4—*Percent increase in volume at different time intervals of direct compression tablets prepared with different excipients* (E_1–E_8), *a common binder* (B), *and a common disintegrant* (D_3) *at 43% relative humidity (25°). Key:* E_1, *dibasic calcium phosphate NF (dihydrate, unmilled);* E_2, *monobasic calcium phosphate monohydrate;* E_3, *lactose USP (anhydrous), DTG;* E_4, *lactose hydrous beadlets;* E_5, *mannitol USP (granular);* E_6, *sorbitol USP (crystalline tablet type);* E_7, *dextrose (anhydrous);* E_8, *sucrose;* B, *microcrystalline cellulose; and* D_3, *alginic acid.*

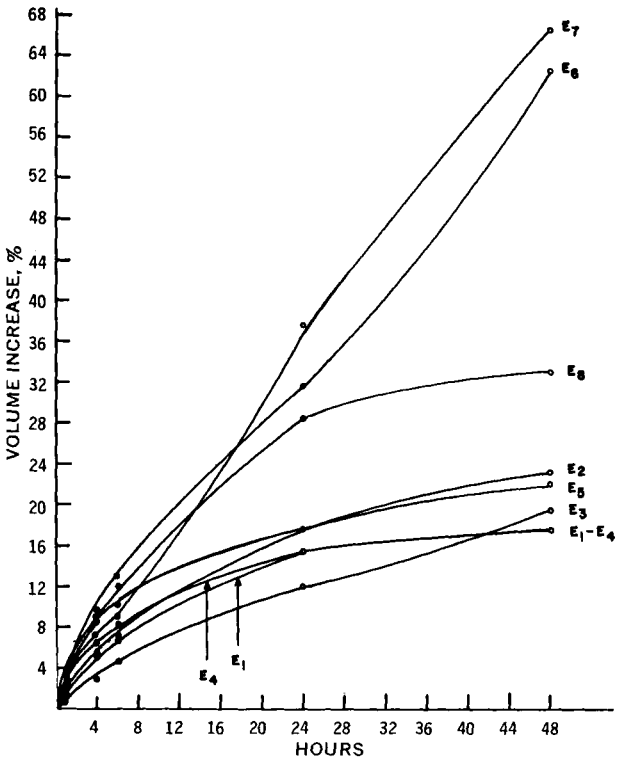

Figure 5—*Percent increase in volume at different time intervals of direct compression tablets prepared with different excipients* (E_1–E_8), *a common binder* (B), *and a common disintegrant* (D_3) *at 100% relative humidity (25°). Key:* E_1, *dibasic calcium phosphate NF (dihydrate, unmilled);* E_2, *monobasic calcium phosphate monohydrate;* E_3, *lactose USP (anhydrous), DTG;* E_4, *lactose hydrous beadlets;* E_5, *mannitol USP (granular);* E_6, *sorbitol USP (crystalline tablet type);* E_7, *dextrose (anhydrous);* E_8, *sucrose;* B, *microcrystalline cellulose; and* D_3, *alginic acid.*

EXPERIMENTAL

Placebo tablets were prepared from the ingredients shown in Table I. A full factorial experimental design involving eight excipients, three disintegrants, and a common binder was carried out as follows:

E = excipient	*B* = binder	*D* = disintegrant
E_1BD_1	E_1BD_2	E_1BD_3
E_2BD_1	E_2BD_2	E_2BD_3
E_3BD_1	E_3BD_2	E_3BD_3
E_4BD_1	E_4BD_2	E_4BD_3
.	.	.
.	.	.
.	.	.
E_8BD_1	E_8BD_2	E_8BD_3

Table IV—Tablet[a] Size Changes and Solubility of Direct Compression Excipients

Excipient	Solubility[b]	Percent Volume Increase in Tablet Size[c]
Dextrose	100	68
Sorbitol	83	63
Sucrose	200	33
Lactose	20	18
Mannitol	18	22
Dibasic calcium phosphate, dihydrate	0	18
Monobasic calcium phosphate, monohydrate	2	23

[a] Tablets contained alginic acid and microcrystalline cellulose. [b] Solubility expressed as g./100 ml. [c] Tablets were stored for 48 hr. at 100% relative humidity.

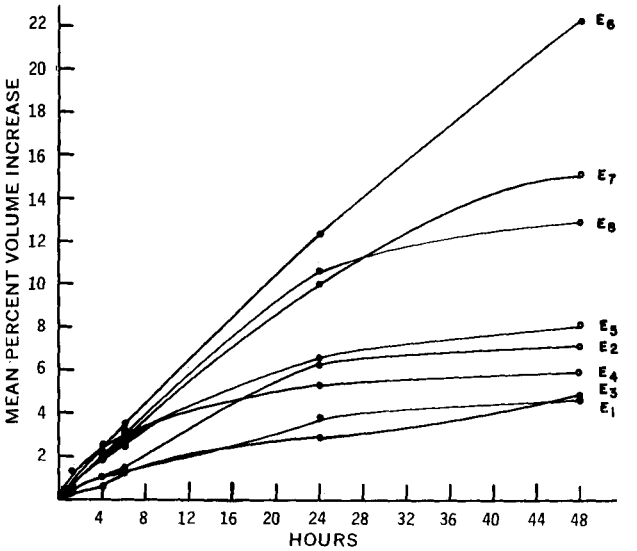

Figure 6—*Mean percent increase in volume at different time intervals across the four humidity levels (43, 65, 75, and 100% relative humidity at 25°) of direct compression tablets prepared with different excipients* (E_1–E_8), *a common binder* (B), *and a common disintegrant* (D_3). *Key:* E_1, *dibasic calcium phosphate NF (dihydrate, unmilled);* E_2, *monobasic calcium phosphate monohydrate;* E_3, *lactose USP (anhydrous), DTG;* E_4, *lactose hydrous beadlets;* E_5, *mannitol USP (granular);* E_6, *sorbitol USP (crystalline tablet type);* E_7, *dextrose (anhydrous);* E_8, *sucrose;* B, *microcrystalline cellulose; and* D_3, *alginic acid.*

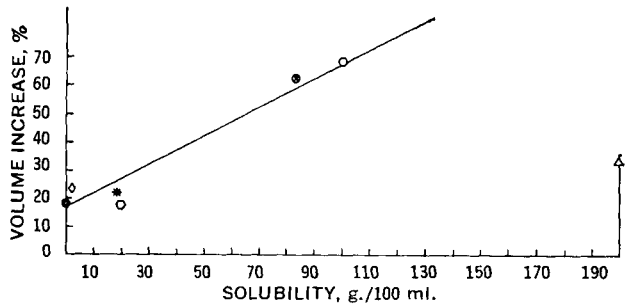

Figure 7—*Plot of solubility and percent increase in volume of tablets containing various excipients after 48 hr. at 100% relative humidity (25°). Key: ○, dextrose; ⊗, sorbitol; △, sucrose; ○, lactose; *, mannitol; ⊙, dibasic calcium phosphate dihydrate (unmilled); and ◇, monobasic calcium phosphate monohydrate.*

The composition of the tablets compressed is shown in Table II.

Formulation—The various tablet compositions outlined in Table II were made as follows. Quantities of the materials sufficient to make 5000 tablets were sieved through a 40-mesh screen to break up agglomerates and then mixed in a twin-shell blender for 15 min. The blends were compressed on a single-punch F press, using a 0.94-cm. (0.375-in.) diameter flat-faced punch at 70 r.p.m. The tablet press was adjusted so that the thickness and the hardness of the various tablet compositions were approximately the same. The tableting of these formulations was performed in a room controlled at 10% relative humidity.

With all of the formulations, except E_5BD_1 (mannitol–microcrystalline cellulose–direct compression starch), tablets of excellent quality were obtained; these then were subjected to various tests and evaluated statistically for the relative ranking. Formulation E_5BD_1 could not be compressed due to lubrication problems.

Test Methods—Tablets in groups of four in open dishes were stored at 25° in 43, 65, 75, and 100% relative humidity chambers. The initial readings on the samples were tested as the controls for the studies. The following tests were performed.

Moisture Uptake—Sets of four tablets were weighed initially and after storage at the four relative humidity levels for 1, 4, 6, 24, 48, and 96 hr.; moisture pickup was expressed as percent weight gain.

Hardness—Hardness was determined by a Strong-Cobb-Arner hardness tester and expressed in Strong-Cobb-Arner units (S.C.U.) The hardness was measured initially and after storage for various times and relative humidities; each tablet of every set of four was measured individually.

Disintegration Time—Disintegration time was determined in water at 37° using the USP apparatus without disks; this value was measured in seconds.

Volume Change—The thickness and diameter of all tablets were measured in millimeters. The change in volume was calculated after exposure to moisture.

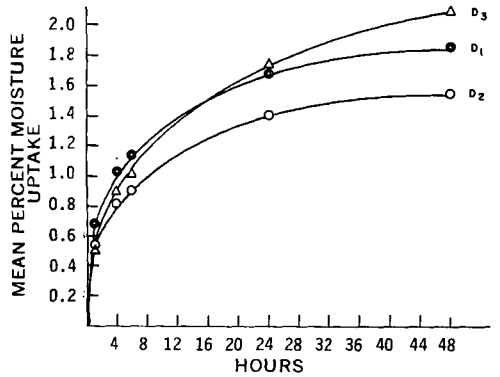

Figure 8—*Mean percent moisture uptake at different time intervals across the four humidity levels (43, 65, 75, and 100% relative humidity at 25°) by direct compression tablets containing dibasic calcium phosphate NF (dihydrate, unmilled) (E1), microcrystalline cellulose (B), and different disintegrants (D1–D3). Key: D1, direct compression starch; D2, starch USP; and D3, alginic acid.*

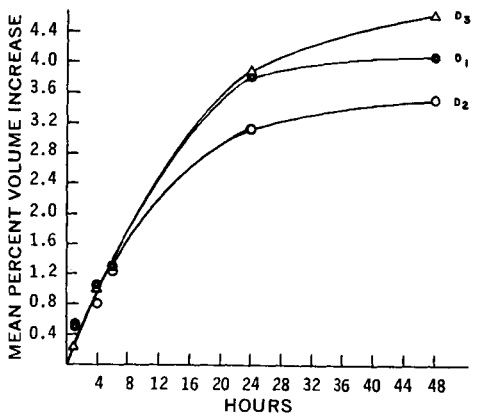

Figure 9—*Mean percent increase in volume at different time intervals across the four humidity levels (43, 65, 75, and 100% relative humidity at 25°) of direct compression tablets containing dibasic calcium phosphate NF (dihydrate, unmilled) (E1), microcrystalline cellulose (B), and different disintegrants (D1–D3). Key: D1, direct compression starch; D2, starch USP; and D3, alginic acid.*

RESULTS AND DISCUSSION

Maximum moisture uptake and increase in volume were found for almost all formulations at all relative humidity levels within 48 hr., except for the sucrose and mannitol compositions (Fig. 2) that continued picking up moisture beyond 48 hr. at 100% relative humidity. However, it was decided to analyze the data only up to 48 hr., because beyond this time some tablets became too soft to handle. Table III lists the changes that occurred after 48 hr. for the various formulations at the four relative humidity levels used.

The results on weight gain (Figs. 1–3) and percent increase in volume (Figs. 4–6) were plotted against time in hours at different humidity levels. Figures 1 and 2 show the percent moisture uptake of tablets containing different direct compression excipients and a common disintegrant (alginic acid) after exposure to 43 and 100% relative humidity. At 43% relative humidity, equilibrium is reached within 12 hr.; however, at 100% relative humidity, it required about 48 hr. to reach equilibrium except in the cases of mannitol (E_5) and sucrose (E_8).

All of the formulations picked up more than 4% moisture at 100% relative humidity within 48 hr. This can be an important consideration when extremely moisture-sensitive active ingredients are to be incorporated into a direct compression formula. Figure 3 shows the mean percent moisture uptake pattern. Dibasic calcium

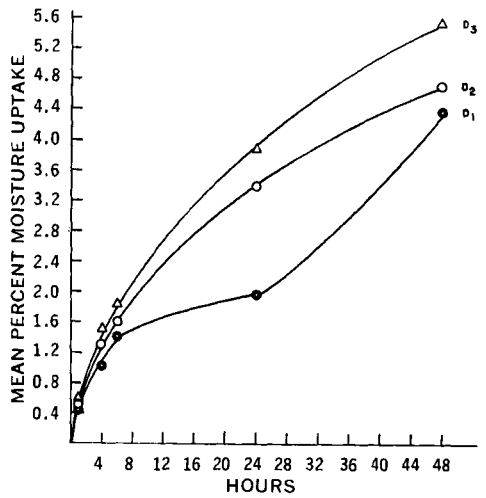

Figure 10—*Mean percent moisture uptake at different time intervals across the four humidity levels (43, 65, 75, and 100% relative humidity at 25°) by direct compression tablets containing sucrose (E8), microcrystalline cellulose (B), and different disintegrants (D1–D3). Key: D1, direct compression starch; D2, starch USP; and D3, alginic acid.*

Table V—Summary Effects Averaged over the Results at the Four Levels of Relative Humidity (43, 65, 75, and 100%)

Excipient	48-hr. Disintegration Time, sec. Disintegrant D_1	D_2	D_3	48-hr. Hardness, S.C.U. Disintegrant D_1	D_2	D_3	48-hr. Change in Weight Percent, Moisture Uptake Disintegrant D_1	D_2	D_3	48-hr. Change in Volume Percent Disintegrant D_1	D_2	D_3
E_1	22	10	36	4.9	5.3	3.3	1.4	1.2	1.5	4	3	4
E_2	230	103	189	6.1	4.7	4.0	1.8	2.0	2.4	6	6	7
E_3	326	315	346	8.7	8.9	7.9	1.2	1.4	1.5	4	3	5
E_4	34	19	32	5.9	4.6	4.5	1.0	1.2	1.4	5	5	6
E_5	—[a]	13	35	—[a]	3.0	4.4	—[a]	1.4	1.8	—[a]	9	8
E_6	386	374	311	6.4	4.6	3.8	2.4	3.0	3.2	19	20	21
E_7	315	188	27	1.8	1.5	1.6	1.8	2.1	2.4	15	14	14
E_8	444	430	307	2.9	1.3	1.8	2.5	2.8	3.3	12	12	13

[a] Due to the lubrication problems, formulation could not be compressed.

Table VI—Relative Rankings of the Formulations Based on Results Averaged over the Four Relative Humidity Levels (43, 65, 75, and 100%)

Excipient E	48-hr. Disintegration Time, sec. Disintegrant D_1	D_2	D_3	48-hr. Hardness, S.C.U. Disintegrant D_1	D_2	D_3	48-hr. Change in Weight Percent, Moisture Uptake Disintegrant D_1	D_2	D_3	48-hr. Change in Volume Percent Disintegrant D_1	D_2	D_3
E_1	4	1	9	8	7	16	8	3	9	4	2	5
E_2	13	10	12	5	9	14	11	14	18	11	10	12
E_3	18	16	19	2	1	3	4	5	10	3	1	6
E_4	7	3	6	6	10	12	1	2	7	7	8	9
E_5	—	2	8	—	17	13	—	6	12	—	14	13
E_6	21	20	15	4	11	15	16	21	22	21	22	23
E_7	17	11	5	20	22	21	13	15	17	20	18	19
E_8	23	22	14	18	23	19	19	20	23	16	15	17

phosphate (E_1), lactose anhydrous DTG (E_3), and lactose beadlets (E_4) absorbed the minimum amount of moisture, while sorbitol (E_6) and sucrose (E_8) absorbed the maximum. Mannitol (E_5), dextrose (E_7), and monocalcium phosphate (E_2) were found to be intermediate.

Figures 4 and 5 compare the volume increase of the tablet formulations at 43 and 100% relative humidity. Figure 6 shows the mean percent volume increase over the four humidity levels. A volume increase of more than 5% is noticeable visually. The mean volume increase or swelling of more than 5% was observed for monocalcium phosphate (E_2), mannitol (E_5), sorbitol (E_6), dextrose (E_7), and sucrose (E_8) across the four humidity levels (Fig. 6). All formulations showed a considerable volume increase at 100% relative humidity exposure. It is remarkable that sorbitol and dextrose showed more than a 60% increase in volume within 48 hr. at 100% relative humidity. These data definitely indicate that one should judiciously select the direct compression excipients so as to keep the swelling at a minimum when exposed to humid conditions.

The solubility (15) of seven different excipients and the increase in volume of all the tablets prepared with these excipients upon exposure to 100% relative humidity for 48 hr. are shown in Table IV.

A plot of the data from Table IV yields a straight line except for the tablets containing sucrose (Fig. 7). The intercept also indicates that even for insoluble substances, some volume increase should be expected due to the binders and disintegrants in the tablet formulations. This may serve as a useful guide in developing new raw materials for direct compression.

To show graphically the effect of different disintegrants, two direct compression excipients were used. Dibasic calcium phosphate, which showed relatively low moisture uptake, and sucrose, which

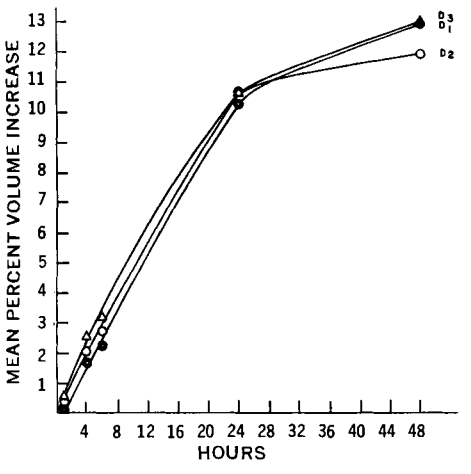

Figure 11—*Mean percent increase in volume at different time intervals across the four humidity levels (43, 65, 75, and 100% relative humidity at 25°) of direct compression tablets containing sucrose* (E_8), *microcrystalline cellulose* (B), *and different disintegrants* (D_1–D_3). *Key:* D_1, *direct compression starch;* D_2, *starch USP; and* D_3, *alginic acid.*

Table VII—Sum of Relative Ranking

Excipient E	Disintegrant D_1	D_2	D_3
1	24	13	39
2	40	43	56
3	27	23	38
4	21	23	34
5	—	39	46
6	62	74	75
7	70	66	62
8	76	80	73

Table VIII—Relative Ranking

Excipient E	Disintegrant D_1	D_2	D_3
E_1	5	1	9.5
E_2	11	12	14
E_3	6	3.5	8
E_4	2	3.5	7
E_5	—	9.5	13
E_6	15.5	20	21
E_7	18	17	15.5
E_8	22	23	19

Table IX—Relative Ranking of 23 Formulations

Formulation	Excipient	Disintegrant	Relative Ranking
E_1BD_2	Dibasic calcium phosphate, dihydrate	Starch USP	1
E_4BD_1	Lactose hydrous beadlets	Direct compression starch	2
E_3BD_2	Lactose anhydrous DTG	Starch USP	3.5
E_4BD_2	Lactose hydrous beadlets	Starch USP	3.5
E_1BD_1	Dibasic calcium phosphate, dihydrate	Direct compression starch	5
E_3BD_1	Lactose anhydrous DTG	Direct compression starch	6
E_4BD_3	Lactose hydrous beadlets	Alginic acid	7
E_3BD_3	Lactose anhydrous DTG	Alginic acid	8
E_1BD_3	Dibasic calcium phosphate, dihydrate	Alginic acid	9.5
E_5BD_2	Mannitol, granular	Starch USP	9.5
E_2BD_1	Monobasic calcium phosphate, monohydrate	Direct compression starch	11
E_2BD_2	Monobasic calcium phosphate, monohydrate	Starch USP	12
E_5BD_3	Mannitol I, granular	Alginic acid	13
E_2BD_3	Monobasic calcium phosphate, monohydrate	Alginic acid	14
E_6BD_1	Sorbitol crystalline tablet type	Direct compression starch	15.5
E_7BD_3	Dextrose	Alginic acid	15.5
E_7BD_2	Dextrose	Starch USP	17
E_7BD_1	Dextrose	Direct compression starch	18
E_8BD_3	Sucrose	Alginic acid	19
E_6BD_2	Sorbitol crystalline tablet type	Starch USP	20
E_6BD_3	Sorbitol crystalline tablet type	Alginic acid	21
E_8BD_1	Sucrose	Direct compression starch	22
E_8BD_2	Sucrose	Starch USP	23

showed a high moisture uptake, were selected. Figures 8–11 compare moisture uptake and the increase in volume for dibasic calcium phosphate and sucrose tablets, with three different disintegrants. In all cases, it was observed that tablets with alginic acid, irrespective of the excipients, showed relatively maximum moisture uptake and increase in volume, while no definite conclusions could be derived for starch USP or direct compression starch. Sucrose tablets containing alginic acid (Fig. 10) showed an initially rapid moisture uptake which leveled off after 8 hr. and then continued to pick up additional moisture after 24 hr.

The resulting data were analyzed statistically to develop a comprehensive ranking of the 23 different formulations. The latest available 48-hr. mean values (for moisture, volume, disintegration, and hardness data) were averaged across the four humidity levels (Table V). For relative ranking of the formulations, the following criteria were used. Tablets should show maximum hardness, minimum amount of disintegration time, minimum moisture uptake, and minimum increase in volume. On this basis, each characteristic was relatively ranked as displayed in Table VI. Table VII gives the sum of the relative ranking. Table VIII shows the relative overall ranking across the characteristics. The decoded formulations are shown in Table IX.

Based on the overall performances of compositions containing microcrystalline cellulose as a binder, the three best excipient–disintegrant combinations were: (*a*) dibasic calcium phosphate dihydrate (unmilled)–starch USP, (*b*) lactose hydrous beadlets–direct compression starch, and (*c*) lactose anhydrous DTG–starch USP.

Among the direct compression sugars examined, mannitol showed the least moisture pickup and change in volume.

CONCLUSIONS

1. Data obtained from direct compression tablets prepared from eight excipients and three disintegrants (with microcrystalline cellulose as a common binder) indicate that all tablets swell from 12 to 65% when exposed to 100% relative humidity conditions for 48 hr.
2. The three best direct compression formulations were: (*a*) diabasic calcium phosphate dihydrate (unmilled)–starch USP, (*b*) lactose hydrous beadlets–direct compression starch, and (*c*) lactose anhydrous DTG–starch USP.
3. A comparison of the sugars available for direct compression chewable tablets indicated that mannitol tablets showed the minimum swelling and moisture pickup.
4. There is some rank order correlation between solubility and swelling characteristics of direct compression excipients.
5. In addition to chemical stability, a careful evaluation of the physical parameters of tablets should be made before selecting inert excipients for direct compression. The data indicate that some excipients pick up moisture avidly, resulting in an increase in tablet volume.

REFERENCES

(1) R. N. Duvall, K. T. Koshy, and R. E. Dashiell, *J. Pharm. Sci.*, **54,** 1196(1965).

(2) G. Milosovich, *Drug Cosmet. Ind.*, **92,** 557(1963).

(3) W. C. Gunsel and L. Lachman, *J. Pharm. Sci.*, **52,** 178(1963).

(4) C. D. Fox, M. D. Richman, G. E. Reier, and R. F. Shangraw, *Drug Cosmet. Ind.*, **92,** 161(1963).

(5) K. S. Manudhane, C. E. Hynniman, and R. F. Shangraw, *Pharm. Acta Helv.*, **43,** 257(1968).

(6) G. E. Reier and R. F. Shangraw, *J. Pharm. Sci.*, **55,** 510 (1966).

(7) K. C. Kwan and G. Milosovich, *ibid.*, **55,** 340(1966).

(8) G. M. Enezian, *Prod. Probl. Pharm.*, **23,** 185(1968).

(9) K. S. Manudhane, A. M. Contractor, H. Y. Kim, and R. F. Shangraw, *J. Pharm. Sci.*, **58,** 616(1969).

(10) N. H. Batuyios, *ibid.*, **55,** 727(1966).

(11) P. R. Sheth and J. H. Wiley, U. S. pat. 3,134,719 (1964).

(12) G. E. Reier, Ph.D. dissertation, University of Maryland, Baltimore, Md., 1964.

(13) S. Lee, H. G. DeKay, and G. S. Banker, *J. Pharm. Sci.*, **54,** 1153(1965).

(14) M. A. Shah and R. G. Wilson, *ibid.*, **57,** 181(1968).

(15) "The Merck Index," 8th ed., Merck & Co. Inc., Rahway, N. J., 1968.

ACKNOWLEDGMENTS AND ADDRESSES

Received May 12, 1971, from the *Product Development Department, Hoffmann-La Roche Inc., Nutley, NJ 07110*

Accepted for publication February 16, 1972.

The statistical analyses done by T. M. Lewinson are gratefully acknowledged.

▲ To whom inquires should be directed.