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Technical Articles

Microcrystalline Cellulose in Tableting

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The development of microcrystalline cellulose has made available to the pharmaceutical industry an extremely valuable tableting agent. It was found that tablets of plain microcrystalline cellulose will tend to soften and swell when exposed to humid conditions, but the effect is reversed upon the removal of increased humidities. Elevated temperatures have no effect on these tablets. Microcrystalline cellulose tablets will disintegrate very slowly in solvents of a relatively low polarity. It is postulated that tablets of this material are a special form of cellulose fibril in which the individual crystallites are held together largely by hydrogen bonding. Tablet disintegration is merely the breaking of the intercrystallite bonds by the disintegrating medium. No significant separation of components was found during the compression of a microcrystalline cellulose-containing formulation. The release of amphetamine sulfate and sodium phenobarbital from tablets containing microcrystalline cellulose is excellent. Determinations after 10 weeks at various environments indicate that no release problems exist. When the cellulosic compound was used as a dry binder–disintegrator in the direct compression of formulations of ephedrine hydrochloride, quinine sulfate, and a low melting steroid, tablets of outstanding quality were produced.

THE SUCCESSFUL application of direct compression as a tableting procedure is dependent upon the development of suitable materials which in themselves are both highly fluid and cohesive. Spray-dried lactose exhibits these characteristics and has enjoyed considerable success as a tableting agent in direct compression. However, it has the disadvantage of browning under certain conditions (1–3) and there is a limiting hardness to tablets produced from spray-dried lactose which, if exceeded, results in capping. This pressure sensitivity occurs at lower tablet hardnesses than usually encountered with granulations of conventional lactose.

Received January 13, 1966, from the School of Pharmacy, University of Maryland, Baltimore.
Accepted for publication February 11, 1966.
Abstracted from a thesis submitted by George E. Reier to the Graduate School, University of Maryland, in partial fulfillment of Doctor of Philosophy degree requirements.
Presented to the Scientific Section, A.PH.A., New York meeting, August 1964.
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Another material which possesses the required properties for direct compression is microcrystalline cellulose.[1] This material is not a derivative of the parent compound, nor is it merely purified cellulose (4, 5).

A preliminary report pointed up the ability of microcrystalline cellulose to form extremely hard tablets that are not friable and yet possess unusually short disintegration times (6). The preparation and stability of glyceryl trinitrate tablets produced by direct compression of the drug in a microcrystalline cellulose matrix have been described (7). A comparison of the effect of water vapor pressure on the moisture sorption and stability characteristics of aspirin and ascorbic acid tablets containing various fillers including microcrystalline cellulose has been published (8). Microcrystalline cellulose has been included in

[1] Marketed as Avicel by the American Viscose Corp., Marcus Hook, Pa.

TABLE I.—THE EFFECT OF ENVIRONMENT ON WEIGHT AND HARDNESS OF PLAIN MICROCRYSTALLINE CELLULOSE TABLETS COMPRESSED TO A CONSTANT THICKNESS

Batch	Initial Wt., Gm.	Initial Hardness, S.C. units	Initial Thickness, in.	After 1 Wk. Wt., Gm.	After 1 Wk. Hardness, S.C. units	After 1 Wk. Thickness, in.
			75% Relative Humidity			
1	0.149	13.1	0.1011	0.156	6.4	0.1094
2	0.144	11.5	0.0986	0.152	6.3	0.1067
3	0.132	8.3	0.0985	0.139	5.2	0.1058
4	0.128	7.6	0.0973	0.135	5.0	0.1045
5	0.123	5.7	0.1001	0.129	4.3	0.1072
6	0.114	4.3	0.1015	0.119	3.4	0.1074
7	0.108	3.6	0.1007	0.113	2.6	0.1059
			60° Temperature			
8	0.150	13.1	0.1020	0.146	11.6	0.1020
9	0.144	11.0	0.1013	0.141	10.5	0.1014
10	0.132	9.3	0.0990	0.129	7.2	0.0992
11	0.130	6.9	0.1021	0.127	6.3	0.1023
12	0.124	5.9	0.1020	0.121	5.4	0.1021
13	0.115	4.9	0.0973	0.113	5.1	0.0973
14	0.107	3.9	0.1005	0.105	4.1	0.1004

studies of disintegrants in direct compression systems (9, 10).

There can be no doubt that microcrystalline cellulose is a unique material and a more detailed study of the following appeared warranted: (*a*) the effect of elevated temperature and humidity on plain microcrystalline cellulose tablets; (*b*) the disintegration time in media of varying polarities of plain microcrystalline cellulose tablets; (*c*) the extent of hopper segregation occurring during tableting; (*d*) the extent of irreversible adsorption of drugs of different ionic character onto microcrystalline cellulose; and (*e*) the further investigation of microcrystalline cellulose as a dry binder.

EXPERIMENTAL

Throughout the investigation, tablets were evaluated with respect to weight, hardness, disintegration time, and friability. All hardnesses were measured by means of a hand operated Strong Cobb hardness tester. Disintegration times were determined by means of the U.S.P. disintegration apparatus, utilizing distilled water at 25° as the immersion fluid.

TABLE II.—THE EFFECT OF PROGRESSIVE CHANGES IN CONDITIONS ON WEIGHT AND HARDNESS OF PLAIN MICROCRYSTALLINE CELLULOSE TABLETS

Time, Days	Conditions, R. H. and Temp.	Wt., Gm.	Hardness (S.C. units)[a]
0	...	0.145	11.7
2	75% R. H.	0.153	7.2
4	60° C.	0.141	10.7
6	Ambient conditions[b]	0.146	11.6
8	60° C.	0.143	12.3
10	75% R. H.	0.151	8.0
12	Ambient conditions[b]	0.147	11.5

[a] Strong Cobb units. [b] Ambient conditions are approximately 25° and 40% relative humidity.

Effects of Temperature and Humidity.—A study of variations in hardness and weight caused by environment was conducted on tablets compressed to a constant thickness by means of a hand operated single punch Erweka tablet machine using $^{5}/_{16}$-in. dies and flat-faced punches. In order to vary hardness while keeping thickness constant, it was necessary to change the die fill and, consequently, the average tablet weight between batches. The tablets were stored at a high relative humidity (75%) or high temperature (60°) for 1 week and changes in weight, hardness, and thickness noted. These results can be seen in Table I. Tablets were also cycled through temperature and humidity changes. These results are summarized in Table II.

Influence of the Polarity of the Disintegration Medium on Tablet Disintegration.—Flat-faced $^{5}/_{16}$-in. plain microcrystalline cellulose tablets having an average weight of 0.15 Gm. and hardness of 6 were produced on a hand operated press. The effect of the polarity of the disintegration medium on the disintegration of these tablets was studied by determining the time for disintegration in media of different dielectric constants. One tube from the U.S.P. basket rack assembly was suspended in a 250-ml. graduated beaker containing the disintegration medium at room temperature. The tube was raised and lowered according to U.S.P. specifications but disks were not used. Table III shows the results of this study.

Determination of Component Separation During Compression.—A formula containing 30% red spray-dried lactose was chosen since it was thought that spherically shaped particles in such an amount could easily "settle through" the microcrystalline cellulose when the powder blend was subjected to vibration. The colored material was utilized so that the degree of separation could be estimated by extraction of the dye from the tablet. Amphetamine sulfate was also included in a concentration such that each tablet of the mixture would contain

TABLE III.—THE DISINTEGRATION TIME OF PLAIN MICROCRYSTALLINE CELLULOSE TABLETS IN MEDIA OF VARYING POLARITY

Solvent[a]	Disintegration Time, sec.	Dielectric Constant,[b] 25°
Water	20	78.5
25% Glycerin	30	...
50% Glycerin	57	...
75% Glycerin	232	...
Glycerin U.S.P.	>300[c]	42.5
25% Alcohol	38	...
50% Alcohol	65	...
75% Alcohol	180	...
Alcohol U.S.P.	>300	24.3
Acetone N.F.	>300	20.7
25% Isopropyl alcohol	75	...
50% Isopropyl alcohol	300	...
75% Isopropyl alcohol	>300[d]	...
Isopropyl alcohol N.F.	>300[e]	18.3

[a] Percentage strengths refer to aqueous solutions (v/v). [b] Reported in "Handbook of Chemistry and Physics," 39th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1957, pp. 2331–2335. [c] Tablet softened, lateral cracks observed but no flaking off. [d] Some flaking occurred, tablet soft but not disintegrated. [e] A few small pieces flaked off.

5 mg. No lubricant was necessary in the compression of the formulation. The total composition was:

Amphetamine sulfate.....	75 Gm. (1.7%)
Red spray-dried lactose.....1350 Gm.	(30.0%)
Microcrystalline cellulose...3075 Gm.	(68.3%)

Tablets were produced on a Colton model 216 rotary press fitted with $^{7}/_{16}$-in. standard concave punches. Die fill and pressure were adjusted at the beginning of the run to produce tablets of about 300 mg. in weight and 6–7 Strong Cobb units in hardness. Three different machine speeds were used during the course of the study: 600, 860, and 1120 tablets/min.

Tablet samples were taken at intervals that varied with the speed of the machine. These tablets were assayed by a spectrophotographic method which allowed for the separate determination of amphetamine sulfate and red spray-dried lactose. The means of the assay results for each sample were calculated, and the per cent deviations of the sample means from the over-all mean are shown in Table IV. The disintegration times of all tablet samples were less than 30 sec. while friability ran from 0.1–0.25% weight lost.

Amphetamine Sulfate and Sodium Phenobarbital Release from Tablets of Microcrystalline Cellulose.—Since the acidity or basicity of the therapeutic agent must be taken into account, an ionic drug from each category was included in this study. The tablets were placed at three storage stations. The determination of drug release was carried out by placing the tablets, previously weighed, into 1-oz. dry square bottles and adding 25 ml. of distilled water prewarmed to 37°. The bottle and contents were placed in a 37° water bath and rotated end-over-end at 20 r.p.m. At the end of the desired time, the mixture was quickly filtered, and a sample collected for further dilution and spectrophotometric assay. The tablets were compressed using flat-faced $^{13}/_{32}$-in. tooling and the mg. per tablet formulas were as follows:

Amphetamine sulfate	15.0	...
Sodium phenobarbital	...	15.0
Spray-dried lactose	75.0	75.0
Microcrystalline cellulose	158.8	157.5
Magnesium stearate	1.2	2.5

The results of this experiment are shown in Tables V and VI.

Microcrystalline Cellulose as a Dry Binder–Disintegrator.—Ephedrine hydrochloride and quinine sulfate have long posed problems in regard to disintegration and until recently were allowed to possess unusually long disintegration times (11). For this reason, these materials were chosen for use in further evaluating the binding and disintegration properties of microcrystalline cellulose in direct compression.

An androstane-type steroid (under clinical investigation by the National Institutes of Health) was also included in this part of the work. The steroid melts at 60° and liquefies under pressure, thus microcrystalline cellulose was utilized as an adsorbent as well as a dry binder–disintegrator in order that tablets of a uniform surface appearance might be produced by direct compression.

In all cases it was necessary to slug the powder blend. The slugs were passed through a No. 16 screen and additional lubricant added before recompression on a rotary tablet machine. The mg. per tablet formulas were as follows:

Ephedrine Tablet	
Ephedrine hydrochloride.....	30.0
Spray-dried lactose.....	37.5
Microcrystalline cellulose.....	112.5
Calcium sulfate.....	187.5
Magnesium stearate.....	7.5

TABLE IV.—DETERMINATION OF COMPONENT SEPARATION DURING COMPRESSION

Sample	—% Deviation from Over-All Mean— Amphetamine Sulfate	Red Spray-Dried Lactose
1[a]	−3.48	+6.92
2	−3.48	−0.61
3	+0.79	−0.27
4	−0.43	−0.27
5	−1.53	+0.38
6	−0.86	+0.03
7	−1.89	+1.60
8	−1.71	+0.38
9	−0.43	−2.18
10	−0.79	+0.44
11	−0.61	+0.72
12	+0.79	+2.52
13[b]	+1.83	−0.85
14	+0.49	−2.08
15	−0.31	−0.99
16	+3.24	−1.09
17	−0.67	+1.02
18	+1.41	+0.17
19[c]	+1.89	−2.28
20	+2.50	−2.28
21	+2.19	−0.38
22	+2.20	−0.85

[a] Samples 1–12, machine speed of 600 tablets/min. [b] Samples 13–18, machine speed of 1120 tablets/min. [c] Samples 19–22, machine speed of 860 tablets/min.

TABLE V.—EFFECT OF 10-WEEK STORAGE ON CHARACTERISTICS OF DIRECTLY COMPRESSED AMPHETAMINE SULFATE–MICROCRYSTALLINE CELLULOSE TABLETS

Storage Conditions	Hardness, S. C. units[a]	Disintegration Time, sec.	% Drug Release, 3 min.	% Drug Release, 30 min.
Control before storage	10.1	39	98.8	...
Ambient conditions[b]	10.0	54	99.3	...
75% R. H.	4.7	42	95.5	102.8
60°	9.1	36	103.0	...

[a] Strong Cobb units. [b] Ambient conditions approximately 25° and 40% relative humidity.

TABLE VI.—EFFECT OF 10-WEEK STORAGE ON CHARACTERISTICS OF DIRECTLY COMPRESSED SODIUM PHENOBARBITAL–MICROCRYSTALLINE CELLULOSE TABLETS

Storage Conditions	Hardness, S.C. units[a]	Disintegration Time, sec.	% Drug Release, 3 min.	% Drug Release, 30 min.
Control before storage	8.2	31	100.1	...
Ambient conditions[b]	8.5	68	89.3	101.9
75% R. H.	5.1	42	96.9	99.2
60°	7.3	36	97.0	101.6

[a] Strong Cobb units. [b] Ambient conditions approximately 25° and 40% relative humidity.

Quinine Tablet	
Quinine sulfate	300.0
Spray-dried lactose	60.0
Microcrystalline cellulose	200.0
Calcium sulfate	28.0
Magnesium stearate	18.0

Steroid Tablet	
Androstane-type steroid	250.0
Spray-dried lactose	62.5
Microcrystalline cellulose	300.0
Magnesium stearate	12.5

Attempted recompression of the steroid product resulted in considerable "picking." However, freezing of the granulation by placing it in a container with dry ice for a short period of time immediately prior to compression eliminated this difficulty. The success of this procedure would suggest that further studies should be conducted on the effect of low temperatures on compaction. The characteristics of the tablets produced in this study are shown in Table VII.

DISCUSSION

Mechanism of Compaction and Disintegration.—As may be seen from Table I, plain microcrystalline cellulose tablets after storage at 75% relative humidity for 1 week exhibit an increase in weight and a decrease in hardness. The latter result is consistent with that noted in an earlier report (6). In addition, tablet thickness appears to increase. The mean thicknesses of the group before and after exposure to increased humidity were tested by means of Student t test (12). While the changes in thickness appear quite large, they are not statistically significant at the 95% confidence level. This lack of significance can be attributed to the relatively high variance found in the group. However, the consistent increase in thickness for the batches studied certainly is indicative of a swelling effect. Similar tablets stored at 60° for 1 week exhibit a uniform weight loss but no change in thickness. A slight decrease in hardness may be noted, but it was not large enough to even consider a test for significance.

The changes in plain microcrystalline cellulose tablets brought about by storage in various environmental conditions are not permanent as evidenced by the data in Table II. Loss of hardness of microcrystalline cellulose tablets at increased humidities may be explained by the adsorption of water onto the surfaces of the cellulose crystals. The adsorbed water molecules interrupt the bonding between particles thus causing a softening of the tablet and a tendency to swell. When humid conditions are removed, the equilibrium moisture content is lowered in the tablet, and it resumes its original hardness and thickness. At elevated temperatures, there is a slight weight loss due to the driving off of water, but this appears to have no appreciable effect on hardness.

As the mechanism of disintegration of microcrystalline cellulose tablets has been attributed to hydrogen bonding and its interruption (6), a study of disintegration times in media of variable polarities should and did give interesting results. Table III shows the variation of tablet disintegration time with the dielectric constant of the disintegrating medium. The dielectric constant is a measure of a solvent's polarity or ability to form dipoles and is,

TABLE VII.—PROPERTIES OF MICROCRYSTALLINE CELLULOSE-CONTAINING TABLETS

	Active Ingredient		
	Ephedrine Hydrochloride	Quinine Sulfate	Androstane-Type Steroid
Wt., Gm.	0.374	0.621	0.625
Punch, in.	13/32[a]	13/32[a]	7/16[a]
Wt. variation, %	1.18	1.55	...
Hardness, S.C. units	8.4	14.6	23.5
Disintegration time, sec.[b]	104	59	12
Friability, % wt. lost	0.37	0.10	...

[a] Standard concave. [b] With disks.

consequently, a measure of a compound's ability to hydrogen bond, since this phenomenon is a particular kind of dipole–dipole interaction. As the dielectric constant decreases, the medium becomes less able to hydrogen bond with the individual crystals of cellulose. The result is that the crystals remain bonded to each other and tablet disintegration does not occur.

Because of the extreme ease of compression of microcrystalline cellulose into hard tablets, apparently very little elastic deformation occurs within the microcrystals during tablet formation (13). In fact, it is even doubtful that significant amounts of plastic slip and crystal fusion take place. Undoubtedly, a much more important factor contributing to the compaction of this material is hydrogen bonding. A microcrystalline cellulose tablet may be visualized as a special form of cellulose fibril in which the crystals are compacted close enough together so that hydrogen bonding between them can occur.

Problems in Tableting.—Due to the small particle size of microcrystalline cellulose as well as its fluidity, hesitancy to assume a charge, and lack of aggregation, blending with other substances does not appear to offer difficulty. While one might expect these mixtures to separate when subjected to vibration, the results in Table IV do not so indicate even though the formulation studied was designed to point up segregation. The initial high reading for spray-dried lactose in the first sample can be ascribed to a small quantity of the higher density lactose separating from the mixture during the period of free fall when the hopper was loaded. The effect rapidly disappeared and deviation from the average appears relatively random until the end of the experiment where some increase in drug concentration did occur. However, none of the variations found can be considered serious.

Because of the large surface area of microcrystalline cellulose and its adsorptive capacity (5), tablets composed largely of this material might not exhibit complete release of the therapeutic agent contained therein. The data in Tables V and VI show the effects of various environmental conditions on the release of amphetamine sulfate and sodium phenobarbital from tablets containing microcrystalline cellulose and spray-dried lactose as the fillers. Immediately following manufacture, full drug release was achieved within 3 min. After 10 weeks storage at 75% relative humidity and room temperature, the release of the amphetamine sulfate product was slightly decreased. However, the full amount of drug was available after 30 min. No slowing of release was found at the other storage stations.

In the case of the sodium phenobarbital tablets, the same slight decrease in drug release was found in those tablets stored at 75% relative humidity and room temperature as well as at 60° and ambient humidity. Those tablets stored under ambient conditions showed a considerably greater reduction in the amount of drug released within 3 min. However, all sodium phenobarbital tablets exhibited complete drug release at the end of 30 min. thus indicating no drug–binder interaction.

While the usefulness of microcrystalline cellulose as a dry binder-disintegrator has previously been reported (6), the results in Table VII serve to emphasize the uniqueness of the material when used in such a manner. The properties of the ephedrine hydrochloride and quinine sulfate products illustrate the outstanding tablet quality routinely available through the use of microcrystalline cellulose as a dry binder–disintegrator. It would certainly appear that microcrystalline cellulose should be given serious consideration by tablet formulators as a dry binder, particularly in direct compression.

SUMMARY AND CONCLUSIONS

1. It was found that increased humidities caused a softening and a tendency to swell of plain microcrystalline cellulose tablets. Neither tablet change is permanent since they disappear upon removal of the humid conditions. Elevated temperatures do not affect tablets of this material.

2. The disintegration time of such tablets is markedly influenced by the polarity of the disintegrating medium. From the environment and disintegration observations, it was postulated that a plain microcrystalline cellulose tablet is a special form of cellulose fibril which is held together largely by hydrogen bonding.

3. Hopper segregation was studied. The results of the experiment indicate that no significant separation need be anticipated.

4. Amphetamine sulfate and sodium phenobarbital tablets prepared utilizing a blending of spray-dried lactose and microcrystalline cellulose as a filler exhibited no problems in respect to dissolution of active ingredients.

5. The characteristics of tablets produced with microcrystalline cellulose as a dry binder–disintegrator were outstanding.

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