Some Effects of Humidity and Heat on the Tableting Properties of Microcrystalline Cellulose Formulations I

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Microcrystalline cellulose was exposed to the atmosphere of the tableting room. It was found that this exposed material did not tablet as well as material taken from the original, sealed container. Heating of the exposed material improved its tableting characteristics as was shown by increases in the weight and hardness of the tablets produced. Lubrication of the exposed material served to increase tablet weight, but this was accompanied by a decrease in the hardness of the tablets. The combination of heat and lubrication also gave heavier tablets, but again at a sacrifice in hardness.

MICROCRYSTALLINE CELLULOSE is a comparatively new material for use in the manufacture of pharmaceutical tablets. Its significance to the pharmaceutical industry is indicated by its recent inclusion in the "National Formulary" (1) as a pharmaceutic aid (tablet diluent). Several groups of investigators have reported on research work involving this new material. Among them, Lee *et al.* (2) studied the effect of water vapor pressure on the moisture sorption and stability characteristics of microcrystalline cellulose based tablets. Reier and Shangraw (3) found that microcrystalline cellulose-containing tablets swelled, gained in weight, and lost in hardness when exposed to humid conditions. The effect was shown to be a reversible phenomenon.

During preliminary work, it was observed that microcrystalline cellulose which had been exposed to the normal atmospheric conditions of the tableting room did not perform as well in tableting as did material of the same batch which was drawn from the original, closed container. The problem seemed to lie in the flow of material from the feed hopper of the tableting press. Several methods were suggested for improving the performance of the exposed material and experiments were carried out to test the effects of heat and/or lubricant upon the exposed microcrystalline cellulose. The results of two of these experiments are reported here.

MATERIALS AND EQUIPMENT

The microcrystalline cellulose,[1] as supplied was packed in a polyethylene bag contained in a standard cylindrical fiber drum. The magnesium stearate[2] was of USP quality.

All tablets were compressed on a single-punch Stokes model B tablet machine, using $^3/_8$ in. standard concave punches and die. The die fill adjustment and upper punch movement were set so they would remain essentially constant throughout any one part of the investigation. The tablets were compressed at the rate of 70 tablets per minute. Tablet weights were measured with an analytical balance. Tablet hardness was determined using a Pfizer hardness tester. The USP disintegration test, using distilled water, and the Roche Friabilator were used to test disintegration and friability, respectively. Where it was necessary to heat the microcrystalline cellulose, a bacteriological incubator was used in which the temperature could be held to $\pm 2°$.

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[1] Marketed as Avicel by FMC Corp., New York, N. Y.

[2] Distributed by R. F. Reyson Chemicals Co., New York, N. Y.

EXPERIMENTAL

A—Nonlubricated Microcrystalline Cellulose—In one part of the experimental work, microcrystalline cellulose was removed from the original container and exposed to the uncontrolled atmosphere of the tableting room for a 3-week period. During this time the temperature ranged from 10–28°, at a relative humidity of 50–80%. An amount of exposed material sufficient for a 60-min. tableting run was divided into three portions. One of these was placed in an oven at 37° for 16 hr., while the other two were held under ambient room conditions. The tableting press was adjusted, and all three batches were then run consecutively, starting with a room temperature batch, continuing with the heated batch, and then finishing the run with the second batch of material at room temperature. This design served two purposes: (*a*) by running the room temperature microcrystalline cellulose before and after the heated batch, it could be shown that the press settings would remain essentially constant throughout the entire run; and (*b*) it was possible to compare the tableting properties of the heated and unheated portions of the exposed material. The tablets were collected in a predetermined pattern so as to avoid any variation due to the start-up of the press or shifts from one material to another in the course of the tableting run. The results obtained are shown in Table I.

There was but a slight variation in tablet weight or in tablet hardness between tablets made from the same portion and no significant difference between the two batches of room temperature material compressed before and after the heated batch. This indicates that the press settings remained constant, and the powder flowed at uniform rates during these two parts of the experiment. There was, however, a marked and statistically significant difference between the exposed unheated, and the exposed heated, portions of the material. Heating the exposed microcrystalline cellulose caused it to fill the die cavity to a greater extent and thus to produce a heavier, harder tablet. This was accomplished without a sacrifice in the disintegration characteristics of the tablets and with what appeared to be a slight improvement in tablet friability.

B—Lubricated Microcrystalline Cellulose—In another part of the work, microcrystalline cellulose was exposed for a 3-week period and again divided

TABLE I—EFFECT OF MICROCRYSTALLINE CELLULOSE ON TABLETS

Property	Microcrystalline Cellulose—Room Temp., Compressed Before Heated Portion	Microcrystalline Cellulose—Heated 16 hr. at 37°
Av. tablet wt. (100 tablets)	220.8 mg.	240.8 mg.
S. D. in av. tablet wt.	1.7 mg.	1.3 mg.
Av. tablet hardness (20 tablets)	10.6 lb.	14.5 lb.
S. D. in av. tablet hardness	0.6 lb.	0.6 lb.
Disintegration time (USP test)	Practically instantaneous	Practically instantaneous
Friability (Roche Friabilator)	0.15% loss in wt.	0.11% loss in wt.

into three parts. One part was held as an untreated control. The other two parts were lubricated with magnesium stearate at a concentration of 1% by weight. One of these lubricated portions was then heated in an oven at 37° for 16 hr., while the other was held under room conditions. The press was set, and the three portions were processed in sequence through the tableting machine. The results obtained are shown in Table II. The data on the tablets produced from the plain, unlubricated microcrystalline cellulose show that the tablets of part *B* were lighter than those of part *A*, *i.e.*, a different press setting, as well as having been treated at a different temperature level. The results of the two parts of the experiment are not to be compared against each other. Considering part *B*, alone, it is evident that the addition of magnesium stearate gave a marked and significant improvement in average tablet weight, and that an even further and again statistically significant improvement was obtained by heating the lubricated material for 16 hr. at 37° prior to tableting. However, these significant increases in the average weights of the tablets produced were accompanied by important decreases in tablet hardness and friability. In addition it was observed that the lubricated microcrystalline cellulose seemed to give tablets with imperfect surfaces, and ones which would presumably be too soft for most commercial purposes. Further studies would be required before a definite decision could be reached on this point.

TABLE II—EFFECT OF MAGNESIUM STEARATE ON MICROCRYSTALLINE CELLULOSE TABLETS

Property	Microcrystalline Cellulose—Plain (No Lubricant), Held at Room Temp.	Microcrystalline Cellulose—1% Magnesium Stearate, Held at Room Temp.	Microcrystalline Cellulose—1% Magnesium Stearate, Heated at 37°
Av. tablet wt. (100 tablets)	196.6 mg.	249.8 mg.	257.3 mg.
S. D. in av. tablet wt.	1.7 mg.	1.7 mg.	1.3 mg.
Av. tablet hardness (20 tablets)	9.6 lb.	6.1 lb.	6.2 lb.
S. D. in av. tablet hardness	0.7 lb.	1.2 lb.	1.4 lb.
Disintegration time (USP test method)	Practically instantaneous	Practically instantaneous	Practically instantaneous
Friability (Roche Friabilator)	0.18% loss in wt.	0.92% loss in wt.	0.87% loss in wt.

SUMMARY

Microcrystalline cellulose was used in direct compression tableting studies. It was observed that the tableting characteristics of the material changed with time during exposure to the atmosphere of the tableting room. Three procedures were suggested as possible ways to improve the performance of the exposed material. These were: (*a*) to heat the exposed material, (*b*) to add magnesium stearate as a lubricant, and (*c*) to combine the effects of heat and lubrication.

An analysis of variance, using the F ratio, was applied to the data from each of the experimental runs. It was found that heating the exposed microcrystalline cellulose prior to its direct compression gave a statistically significant ($P < 0.01$) increase in both the weight and hardness of the finished tablets. The use of magnesium stearate as a lubricant also increased the tablet weight significantly ($P < 0.01$), but there was an undesirable decrease in the hardness of the finished tablets. The combined use of heat and lubricant gave an increase in average tablet weight over that obtained with lubricant alone, but the hardness of the tablets was still at a low and unsatisfactory level. Futher studies are being conducted on the effects of exposure upon the tableting characteristics of microcrystalline cellulose. More should be known about the underlying reasons for the changes that have been observed.

REFERENCES

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Keyphrases

Microcrystalline cellulose tablets
Moisture effect
Heat effect
Magnesium stearate lubricant effect
Tablet hardness
Tablet friability