The Effect of Moisture on the Mechanical and Powder Flow Properties of Microcrystalline Cellulose

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**Purpose.** This study determined the effects of moisture on the mechanical and powder flow properties of microcrystalline cellulose. **Methods.** A variety of mechanical properties were determined as a function of solid fraction at moisture levels ranging from 0 to 12.2% and included: compaction pressure required to form a compact, dynamic indentation hardness, quasi-static indentation hardness, tensile strength, best case and worst case Bonding Index, Brittle Fracture Index, Strain Index, Compressibility Index and shear cell index. **Results.** Significant changes were observed as the moisture level of microcrystalline cellulose increased. The compaction pressure required to produce a compact at a solid fraction of 0.6 decreased with increasing moisture content. The permanent deformation pressure and tensile strength of compacts were observed to be relatively independent of moisture content below about 5% moisture and then decrease as the moisture content increased further. The "best case" Bonding Index was also observed to be independent of moisture content below 5% and then increase with increasing moisture. The Brittle Fracture Index and "worst case" Bonding Index, however, did not appear to be affected by changes in moisture content. Powder flow was shown to decrease with increasing moisture content. **Conclusions.** These mechanical property data are consistent with the hypothesis that water acts as a plasticizer and influences the mechanical properties of microcrystalline cellulose. At moisture levels above about 5%, the material exhibits significant changes consistent with a transition from the glassy state to the rubbery state.

**KEY WORDS:** microcrystalline cellulose; moisture; mechanical properties; flow; tabletting indices; compression; hardness; tensile strength; brittleness.

**INTRODUCTION**

Microcrystalline cellulose is a common tabletting excipient used in the pharmaceutical industry. It consists of purified, partially depolymerized cellulose prepared by treating α-cellulose with mineral acids. It exists as a partially amorphous material with microcrystalline regions and serves a number of functions in solid dosage formulations. The moisture content of a typical lot of microcrystalline cellulose is about 3 to 4% while USP monograph specifications limit moisture content to not more than 5%. A number of studies have, in fact, confirmed that the moisture content of microcrystalline cellulose influences such physico-mechanical properties as compaction properties (1), tensile strength (1,2) and viscoelastic properties (3).

Upon hydration, it has been proposed that the amorphous regions of the material absorb water (4) and that the total amount of sorbed water is proportional to the fraction of amorphous material present in the solid and independent of the surface area (5). Recent work with PVP and other polymeric materials containing amorphous regions suggests that moisture affects the solid properties by acting as a plasticizer as it is absorbed into the amorphous regions, lowering the glass transition temperature ($T_g$) of the material (4). This change in $T_g$ would be expected to affect the molecular mobility of the solid and produce significant changes in its viscoelastic and mechanical properties. The effects of hydration have, in fact, been seen to change the viscoelastic properties of this excipient over the range of relevant moisture levels (3). These changes would also be expected to have an influence on the mechanical, flow, and tabletting properties of the solid. The purpose of this study was to determine the effects of moisture on the mechanical and powder flow properties of microcrystalline cellulose.

**MATERIALS AND METHODS**

**Materials**

A single lot of microcrystalline cellulose NF—medium powder (Avicel PH101, Lot 6043, FMC Corporation, Philadelphia, PA) was used in this study. The material was screened prior to use to eliminate any large agglomerates which might be present. The particle size distribution was determined by sonic sifter to be log normally distributed with a geometric mean diameter of 50 μm and a geometric standard deviation of 1.9.

**Hydration and Storage**

Equilibration of microcrystalline cellulose at various moisture levels was accomplished by placing a thin layer (usually less than 1 cm) of the material into a shallow dish and placing the uncovered dish in a constant humidity atmosphere. Material was periodically mixed to facilitate homogeneity of moisture sorption. Humidity was controlled by one of several methods including: (1) glass chambers containing saturated salt solutions, (2) controlled humidity room, or (3) controlled humidity chamber (ETS Model 512 Automatic Humidity Controller, Cole-Parmer Air Cadet Pressure/Vacuum Pump). Dry microcrystalline cellulose (i.e. 0% moisture) was obtained by drying microcrystalline cellulose for 3 hours at 105°C. The moisture level of the material was determined by loss on drying at regular intervals until a constant level of moisture was achieved. Once equilibration had been reached, the material was double bagged in polyethylene and promptly tested. Exposure of the bagged material outside the constant humidity atmosphere was minimized so that the equilibrium moisture level of the microcrystalline cellulose would be maintained. The moisture content is reported on a % (w/w) basis.

**Moisture Determination**

The moisture level of the microcrystalline cellulose was
determined by loss on drying at 105°C as described in USP (6).

True Density Determination

The true density of dried microcrystalline cellulose was determined using a helium-air pycnometer (Micromeritics Model 1305 Multivolume Helium-Air Pycnometer).

Moisture Sorption

The moisture sorption characteristics of microcrystalline cellulose were examined using an automated, controlled atmosphere microbalance. About 10 mg of material was used. The sample was equilibrated on the balance at a low relative humidity (1–2%) until a stable weight was obtained (nominally 1 hour). The moisture uptake was then measured in a sequence of sorption steps, and the moisture loss was subsequently measured in a sequence of desorption steps.

Compact Formation

A specially designed triaxial tablet press (7) was used to prepare compacts of pure microcrystalline cellulose which were free of macroscopic defects such as cracks, laminations, etc. Briefly, 19 mm square compacts were formed by adding an appropriate amount of material to the specially designed split die (7,8,9). The material was compressed and the punch pressure maintained by computer control for 1 minute. By computer control, decompression was then initiated and both the punch and die-wall pressures were released simultaneously in a linear fashion over a 1.5 minute period. Computer control permitted the punch and die-wall pressures to be maintained approximately equal during a majority of the decompression process. This process minimizes the internal stresses within the compact during decompression. Compacts prepared in this way have been shown to be essentially free of macroscopic defects which could influence mechanical property characterization (8,10). By varying the amount of material added to the die, the solid fraction of the compact was varied between approximately 0.5 and 0.7. Compact solid fraction was calculated: (1) by assuming the tablet was homogeneous, (2) by measuring the dimensions of the square compact formed immediately upon removal from the die and (3) on the basis of the weight of microcrystalline cellulose present in each compact by subtracting the weight of the moisture present.

Dynamic Indentation Hardness

A pendulum impact arrangement was used to determine the dynamic hardness of compacts (8,11,12). A pendulum arrangement was formed by suspending a 2.54 cm diameter stainless steel ball from a thin wire 92 cm in length. The stainless steel ball was released from a height corresponding to an angle of 30° and was allowed to strike a compact of microcrystalline cellulose which was held firmly in place on all sides but the front. The diameter of the indentation was subsequently determined using a surface analyzer (9) and the energy consumed in the formation of the indentation was calculated from the rebound height of the stainless steel ball. The dynamic hardness (worst case hardness) was then calculated as previously described (11).

Quasi-static Indentation Hardness

A specially designed multi-function tablet tester (13,14) was used to determine compact hardness under “quasi-static” conditions (15). Briefly, a 2.54 cm diameter stainless steel ball was pressed into a compact of microcrystalline cellulose at a velocity of 0.025 mm/sec a total distance of 0.25 mm and held in place for 15 minutes. During the test, the force applied to the indenter was monitored by computer. On removal of the indenter, the diameter of the indentation was determined as described above and the quasi-static hardness (best-case hardness) of the compact was calculated according to the following equation:

$$H_b = \frac{F_t}{\pi r^2}$$ (1)

where $F_t$ is the indentor force at completion of the test and $r$ is the chordal radius of the indentation.

Tensile Strength

The tensile strength of square compacts was determined using the multi-function tablet tester described above. The tensile strength of solid compacts was determined by transverse compression (8). Because variations in the viscoelasticity of the different samples can influence the tensile strength, the rate at which stress was applied to the square compacts was varied such that the time constant (1/e) was maintained in the range of 3 to 5 seconds (15). Plots 0.4 times the width of the square compacts were used to determine the force necessary to cause the tablet to fail in tension. To determine the brittleness of microcrystalline cellulose, the tensile strength of compacts with a hole in the center of the tablet (to serve as a stress concentrator) was also determined and the Brittle Fracture Index calculated (10).

Bonding Indices

Several indices of tabletting performance have been developed by Hiestand and coworkers (8,9,10,11,16). These indices provide relative measures of properties which are considered important and which reflect the performance of materials during processing. These include the Bonding Index, Strain Index and the Brittle Fracture Index (8,10). These indices of tabletting performance are useful tools in understanding and interpreting the events and processes which are occurring during material compaction. A high Bonding Index, for example, indicates that, relatively speaking, a significant portion of the compact strength (a maximum at the maximum compaction pressure) has survived decompression. Conversely, a low Bonding Index indicates that less of the strength remains. The term Bonding Index, then, is a good description since it, in effect, characterizes the tendency of the material to remain a strong compact after it has been decompressed. Tablets made of materials with poor bonding characteristics may be quite friable. Compacts made of materials with a good Bonding Index may, conversely, make strong tablets.

Hiestand has further refined the concept of Bonding Index to include both a worst case and a best case Bonding Index (8). The Bonding Index is determined under different