Drug Development and Industrial Pharmacy, 25(10), 1137–1142 (1999)

COMMUNICATION

Preformulation: Effect of Moisture Content on Microcrystalline Cellulose (Avicel PH-302) and Its Consequences on Packing Performances

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ABSTRACT

This study evaluates the influence of moisture content on the packing performances of a new grade of microcrystalline cellulose (MCC) (Avicel PH-302) either by classical method or by an unconventional compression technique (constant volume reduction of powder bed). An increase in moisture content decreases the apparent density of the powder bed, resulting from interparticulate friction enhancement. This modification of apparent density seems to be the main effect caused by the presence of humidity, which explains the variations of compression properties, like an increase of powder plasticity generally observed in the experimental conditions.

INTRODUCTION

The physical and physicochemical characterization of the excipients during preformulation plays an important role in factors (manufacturability, stability, biopharmaceutical function, and correct use of medicine by patient) that affect the quality of a finished product. At the present time, there are few functionality-related tests required by the pharmacopoeias.

Microcrystalline cellulose (MCC) is a well-known, directly compressed excipient (1,2). Many works have been reported on different qualities of this powder, particularly concerning the usual types of Avicel PH-101 and PH-102 (3) and confirmed that the moisture content of MCC influences physicomechanical properties such as compaction and powder bed plasticity (4–6).

Our study concerned a new grade of MCC, Avicel PH-302, which has characteristics of high bulk density and

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longer disintegration time. But, this MCC is presented as hygroscopic; therefore, it seems important to investigate the behavior of this new Avicel grade at various environmental relative humidities during the preformulation stage.

The aim of this work was to investigate the powder functionality, packing behavior, and reaction during the compression cycle with an unconventional technique (constant powder volume reduction, but not constant punch pressure and tablet weight). In this case, the recording pressures depend on flow and plastic deformation of the powder in the die.

MATERIALS AND METHODS

Materials and Morphological Determinations

A single batch of MCC NF (Avicel PH-302, batch Q 549 C, FMC Corporation, Philadelphia, PA) was used in this study. The true density of Avicel PH-302 was determined using a helium pycnometer (Ultrapycnometer, Quantachrome) and the data obtained agreed with the literature.

Photomicrographs were taken with a scanning electron microscope (SEM Jeol 6400 F) to compare the morphology of different cellulose samples.

The particle size distribution was carried out by laser diffraction on particles in suspension in air (Coulter LS 130, Coultronics).

The estimate of specific surface area was calculated from the physisorption of krypton data by BET theory (Autosorb 1, Quantachrome).

Equilibrium Moisture and Storage

Before realizing an equilibrium of moisture content of Avicel PH-302, the study was previously performed to obtain a complete water adsorption isotherm and to fix the two relative humidity (RH) extremes (12% RH and 75% RH).

Equilibration of MCC at various humidity levels was accomplished by placing a thin layer of material (usually about 1 cm) into two desiccators, which had been pre-equilibrated with relative humidity adjusted by saturated salt solution at 12% ($LiCl_2$) and 75% (NaCl). The desiccators were kept at 25°C. Another sample was constituted by powder placed at known ambient laboratory atmosphere (30% RH).

After 8 days, the powders were removed, and the moisture content of each sample was checked either by the Karl Fischer reagent USP (Schott Gerate T80/20, TR85) (7) or by the loss-on-drying method according to the NF monograph on MCC (IR balance, Mettler PE 360).

Packing Characteristics

Bulk and Tapped Densities

Rheological properties of each sample of Avicel PH-302 (12%, 30%, and 75% RH) were assessed with a Stampfvolumenometer (STAV 2003). The bulk density was calculated from the volume of powder after turning over the cylinder, and the tapped density was obtained from the volume after 30,000 taps (quasi equilibrium).

Compression

Tablets, containing each moisture content of Avicel PH-302, were prepared in a single-punch tableting machine (Korsh EK0) fitted with 10-mm flat-faced punches. The height of the die was fixed at 10 mm, and the stroke of the upper punch was constant, so the powder volume reduction was constant. During compression, upper and lower punch pressures and punch displacements were recorded by a Gould Windograph 900. Corrections were made for elastic punch deformation. The maximal punch pressure required for reducing initial powder volume until a fixed final volume was compared for each sample.

For each moisture content of Avicel PH-302, a sample of 20 tablets was taken, produced at a compression speed of 20 tablets $\cdot$ min^{-1}.

The tablets were weighed to the nearest 0.1 mg; their thicknesses and their diameters were measured to the nearest 0.01 mm, and the packing fraction (*Pf* = bulk density/true density) of each tablet was calculated.

Heckel Analysis

The deformation mechanisms were investigated using the Heckel equation (8):

$$\ln(1/\eta) = KP + A \qquad (1)$$

where η is the porosity of the powder bed, and K is a material constant that is the slope of the straight-line portion of the plots. The reciprocal of K is the mean yield pressure P_y. A is the value of the intercept of the straight line and is a function of initial bulk density.

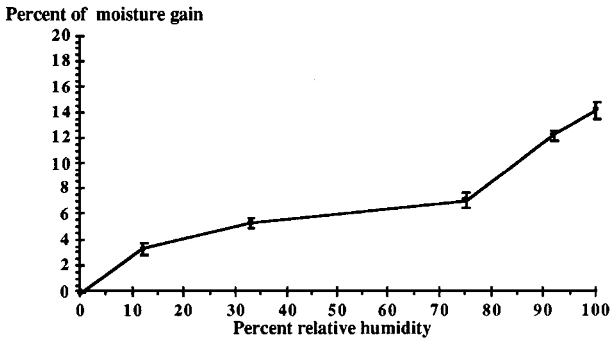

Figure 1. Equilibrium moisture content for microcrystalline cellulose Avicel PH-302.

RESULTS AND DISCUSSION

Equilibrium Moisture Content for Avicel PH-302

The equilibrium moisture content (EMC) values at each relative humidity tested are plotted in Fig. 1. The curve profile can be compared to the EMC curves of MCC, particularly Avicel PH-101. Avicel PH-302 is able to adsorb a maximum of 14% water, and according to these EMC results, the relative humidities of 12%, 30%, and 75% were chosen to examine the behavior of powder that contains different moisture quantities.

Determination of Moisture Content

European monograph specifications limit moisture content to not more than 6% (3 hr at 100 C–105°C). Table 1 presents the moisture content (mean of five determinations) for each sample immediately before compression. These results confirmed a significant increase of moisture content according to the relative humidity of storage conditions, that is, increases of 3.5%, 4.4%, and 7.5%, respectively, for Avicel placed at 12%, 30%, and 75% RH. A good correlation is found between the Karl Fischer method and the loss-on-drying method.

Table 1

Moisture Content of Each Sample of Avicel PH-302 at 12% RH, 30% RH, and 75% RH

	RH (%)		
	12	30	75
T_{KF} (%)	3.21 ± 0.64	4.35 ± 0.35	7.30 ± 0.50
T_{IR} (%)	3.80 ± 0.19	4.52 ± 0.40	7.72 ± 0.38

T_{KF} = moisture content (%) determined by the Karl Fischer method; T_{IR} = moisture content (%) determined by loss-on-drying method.

Morphological Properties

The particle size distribution is log normally distributed with a geometric mean diameter of 100 μm for the three samples of Avicel PH-302 (Fig. 2). The three curves are superimposable, showing that the presence of moisture, in the proportion of this work (12%, 30%, and 75% RH), does not modify the granulometrical distribution.

The specific surface area obtained is 0.51 $m^2\ g^{-1}$, and the true density of Avicel PH-302, calculated from a mean of five determinations, is 1.571 ± 0.001 $g \cdot cm^{-3}$, in accordance with FMC data.

No significant difference was found between cellulose samples at various humidities with SEM photomicrographs. The techniques carried out do not allow determination of the modifications of size, shape, and specific surface area of the powder stored at the three relative humidities.

Rheological and Mechanical Properties

Rheological Properties

Packing properties of the different samples of MCC are given in Table 2. These results suggest that the density is influenced by moisture content. The bulk density, as well as the tapped density, decreases with moisture content enhancement. All these observations are in close agreement with the decrease of tablet density when the cellulose moisture content increases as soon as the tablets are manufactured with a constant volume of powder.

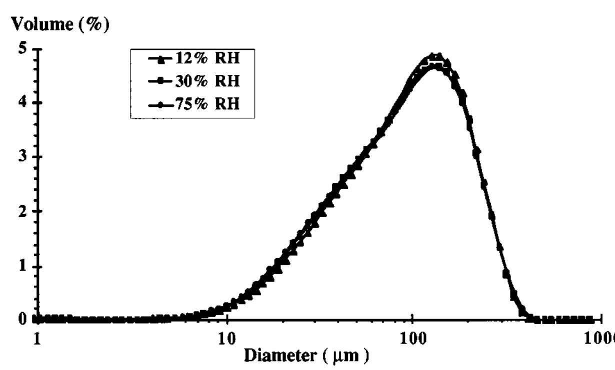

Figure 2. Particle size distribution of Avicel PH-302 at different moisture contents as determined by laser diffraction.

Table 2

Packing Properties of Avicel PH-302 at Various Relative Humidities

RH (%)	Bulk Density ($g \cdot cm^{-3}$)	Tapped Density ($g \cdot cm^{-3}$) After 30,000 Taps	Tablet Density ($g \cdot cm^{-3}$)
12	0.48 ± 0.010[a]	0.72 ± 0.011	1.122 ± 0.005
30	0.459 ± 0.001	0.66 ± 0.010	1.041 ± 0.008
75	0.431 ± 0.004	0.63 ± 0.011	0.939 ± 0.010

[a]95% confidence interval.

The bulk density ρ_b depends on two parameters: true density ρ_t of the material and particle arrangement, which define the total porosity ε, related by the following equation:

$$\rho_b = (1 - \varepsilon)\rho_t \quad (2)$$

First, a variation of apparent density therefore could simply result from a true density modification, but the experimental variations noted here, from 10% to 15%, are too large in comparison with the weak variation of moisture content. Second, as no intraparticulate porosity is observed concerning Avicel PH-302, the term ε in Eq. 2 could be simplified here to interparticulate porosity. It seems that the variation of bulk density could only be attributed to the interparticulate porosity modification ($\rho_t = 1.57\ g \cdot cm^{-3}$). Data from the laser diffraction particle sizer (Fig. 1) and observations from SEM (not presented here) show no difference of granularity according to the moisture content. So, only the particle arrangement of the same particle system could explain the porosity variation, resulting from differences of interparticulate friction (9,10). Then, when moisture content in the powder increases, bulk and tapped density decreases because of interparticulate friction enhancement.

Figure 3 shows tapping kinetics of the three cellulose samples until the volume powder reaches approximately quasi equilibrium. It could be noted that 30,000 taps were necessary just to obtain quasi equilibrium, which shows the extent of the friction process. Another experiment (Avicel PH-302 at 100% RH) was performed to confirm the first results. The four curves exhibit different rates of powder bed packing. This rate is reduced in the presence of moisture, underlining that water increases interparticular friction and restrains packing properties. The friction is so important that the compact state will never be reached.

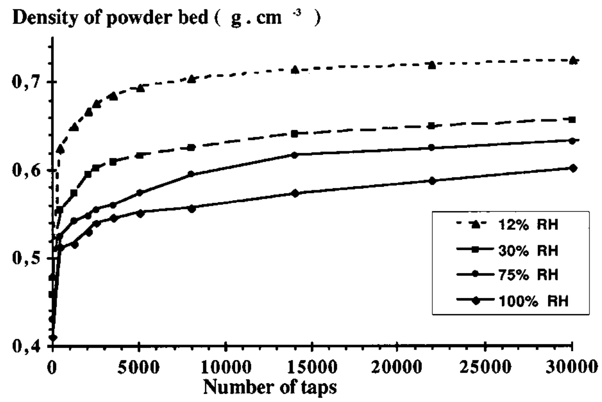

Figure 3. Kinetics of packing of Avicel PH-302 at various relative humidities.

Mechanical Properties

The tableting process depends on three steps: (*a*) the filling of the die controlled by the powder flow properties and the particle rearrangement (studied by bulk and tapped density; see previous section), (*b*) the volume reduction of the powder bed under an applied pressure (compressibility), and (*c*) the consolidation of the powder bed to obtain a compacted mass (cohesiveness). Table 3 describes the consolidation pressure and the characteristics of the tablets after a volume reduction of 60%. Because of the good compressibility of MCC, the pressure necessary to reduce the powder volume were very weak (only 12 MPa, for example, for Avicel at 12% RH).

After the powder is filled into the die and prior to the entrance of the upper punch into the die, the only forces that exist between the particles are those related to packing characteristics, density of particles, and total mass of material into the die. This explains that, when the volume powder reduction is constant (60%), the consolidation pressure results from the filling of the die. Therefore, for

Table 3

Compression Characteristics of Avicel PH-302 at Different Relative Humidities

RH (%)	Consolidation Pressure Maximum (MPa)	Tensile Strength (MPa)
12	48.8 ± 0.8	1.10 ± 0.10
30	29.8 ± 0.5	0.76 ± 0.07
75	12.2 ± 0.5	0.32 ± 0.03

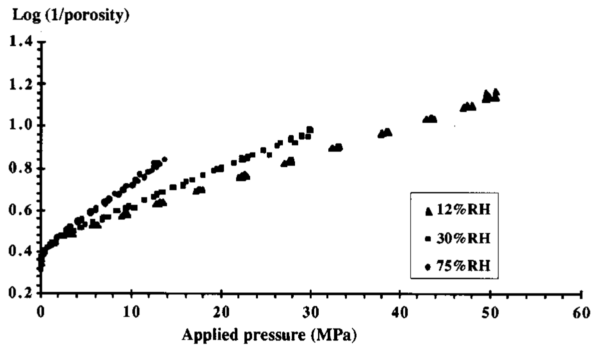

Figure 4. Heckel's representation for Avicel PH-302 samples at various moisture contents.

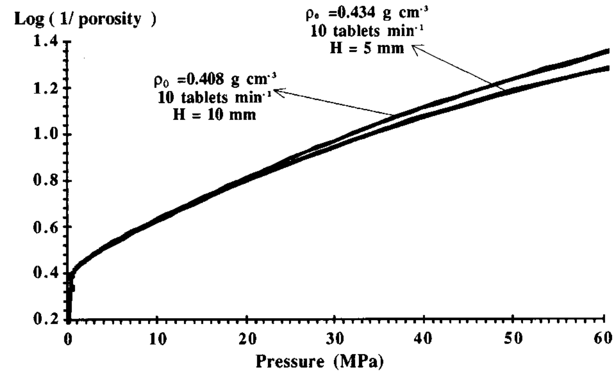

Figure 5. Heckel's representation for Avicel PH-302 at 30% RH (ρ_0 is the initial density of the powder bed, and *H* is the initial height of the die).

Avicel at 12% RH, the bulk density is higher than those of the two other samples (30% and 75% RH). So, more particles can fill the same volume die, and the resulting consolidation pressure must be higher for the same volume reduction. The consolidation pressure data agreed with this fact (48.8 MPa for 12% RH versus 12.2 MPa for 75% RH).

In many studies, the best-suited equation for discriminating the consolidation behavior of powder material has been proved to be that of Heckel (8). This equation investigates deformation mechanisms such as material plasticity.

Figure 4 exhibits an important straight line for the three curves, confirming the plastically deforming characteristics of MCC. In close agreement with many authors, the slope (Table 4) increases according to the moisture content (P_y decreases), which should mean that water plays a plasticizer role (6). But in this test, two parameters are concerned: the moisture content of Avicel PH-302 and the apparent density of powder in the die. The plasticity increase must be due directly to the presence of water or to the decrease of apparent density caused by moisture enhancement. However, another experiment realized with a powder at the same moisture content and with the same batch (about 4.4% water for Avicel at 30% RH) shows a similar increase of the Heckel's slope representation when only the initial density is modified artificially by the height of the die (board effect) (Fig. 5). Figure 5 shows that the slope of the curves increases (enhancement of plasticity) when the height of the die increases (ρ_0 from 0.434 g cm^{-3} [$H = 5$ mm] to 0.408 g cm^{-3} [$H = 10$ mm]).

In this study, it seems that water has an indirect effect on plasticity through its impact on the apparent density variations.

Table 4

Mean Yield Pressure (P_y) for Avicel PH-302 at Various Humidities

	RH (%)		
	12	30	75
P_y (MPa)	74 ± 1	56 ± 1	30 ± 1
Correlation coefficient for the straight line	1.000	0.999	0.996

CONCLUSION

Many authors confirm that the moisture content may have significant effects on the physicomechanical properties of MCC (5,11,12). This study demonstrates that moisture significantly affects the apparent density of a MCC (Avicel PH-302: A high water amount decreases the apparent density of the cellulose by the enhancement of interparticulate frictions.

When the compression is carried out with constant volume reduction of powder (but not with constant pressure), the recorder pressure must be considered as a true reaction of powder bed. In this work, its appears that the main effect of the presence of moisture is the apparent density modification. The compression property variations, which were attributed to the presence of humidity (like powder bed plasticity enhancement), are in fact the consequences of apparent density modifications.

The technological behavior of powders provides information on the interactions between water and raw materials, which can have a great effect on the quality of pharmaceutical products.

ACKNOWLEDGMENT

The authors are grateful to Vincent Jannin for his generous contribution to this study.

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