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Quantifying effects of moisture content on flow properties of microcrystalline cellulose using a ring shear tester

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In this work, we have quantified effects of moisture content, over the relative humidity (RH) range of 5–92% corresponding to 1.6–10.9% of water content, on flow properties of a grade of microcrystalline cellulose (Avicel PH102) using a ring shear cell. Several key powder flow parameters, including cohesion (τ_c), unconfined yield strength (f_c), powder bulk density ($\boldsymbol{\rho_b}$), flowability (ffc), and effective angle of internal friction (ϕ_e), were assessed. Powder flow properties deteriorated continuously with increasing RH, as shown by the higher f_c and τ_c as well as lower ffc, under all stress conditions. With increasing RH, $\boldsymbol{\rho_b}$ increased and then decreased with a maximum at 20% RH. The ϕ_e initially increased, from 41 to 43 degrees, and then remained approximately constant from 20% to 92% RH. The deterioration in powder flow properties is caused by surface modification by moisture, which enhances particle-particle interaction strength. The knowledge obtained in this study is useful to achieving consistent properties of this important tablet excipient and formulations containing it.

1. Introduction

Pharmaceutical powder properties can be impacted by many factors over a wide length scale, spanning from molecular structure, crystal packing structure, particulate properties (surface roughness, size and shape) [1–3], and structure of composite particles (e.g., coated particles) [4–8]. Changes in environmental relative humidity (RH) are expected to alter properties of pharmaceutical powders at several length scales. For examples, an anhydrous crystal may undergo hydration to become a hydrate when exposed to a certain RH [9] and a mechanically rigid glassy material may soften when taking up a high level of moisture [10]. As a result, pharmaceutically important properties, such as stability, tabletability, solubility, and manufacturability may be affected when a powder is exposed to an uncontrolled RH environment during storage or processing. Unintended changes in powder properties may impact the manufacturing process and quality of the finished drug products and, therefore, must be controlled to ensure the consistent manufacture of high quality tablet products.

Lot-to-lot variations in relevant properties of a key excipient or active pharmaceutical gradient (API) may cause problems in manufacturing. Unfortunately, powder properties important to manufacturing, such as powder flowability and tabletability, are usually not considered when releasing a batch of excipient or API for use in tablet manufacturing. Under unfortunate circumstances, this can cause manufacturing problems. Even if lot-to-lot variability is negligible, problems may still be encountered when the manufacturing environment has been changed, for example, when the manufacturing plant is moved to an area of different climate or if the product is manufactured during different seasons without appropriate RH control. This problem can be avoided if the potential impact of moisture on powder properties is understood and considered during the course of formulation and process design and optimization.

Of course, different materials have different sensitivity to a change in RH. For example, properties of a more hygroscopic material are likely more sensitive to RH changes. Therefore, a reliable assessment on the sensitivity of a formulation to RH can only be attained by either directly assessing the formulated powder or by considering the sensitivity of individual powders in the formulation. In term of tablet formulation, microcrystalline cellulose (MCC) is among the most frequently used excipients. Therefore, a detailed understanding of the sensitivity of its properties to RH is impactful and useful to the tablet formulation. In this context, we previously studied the dependence of MCC tabletability on RH [11]. However, flowability is equally important to tablet manufacturing. Insufficient powder flowability can lead to unacceptable tablet weight variations due to inconsistent powder filling as commonly observed during encapsulation, [12] poor content uniformity, and other inconsistent tablet properties. Therefore, this work was commenced to better understand effects of moisture content on flow properties of MCC. Because of its relatively high hygroscopicity, picking up more than 10% moisture at 90% RH, impact of RH on flow properties is more likely observed with this material.

Other than the important role of MCC in tablet formulation, the choice of MCC as a model powder was also based on two other reasons. First, contradicting effects of moisture on flow properties of MCC were

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reported. Based on compressibility index data, it was concluded that flow properties of Avicel PH101 were insensitive to water content below 5% of water but deteriorate at higher water contents [13]. In another study, using a device that monitors the consistency in forming avalanche by a powder in a rotating drum, it was concluded that flowability of two grades of MCC (Avicel PH102 and PH101) was continuously improved with increasing RH [14]. The contradicting conclusions from these studies may be partially due to the empirical nature of methods used for characterizing powder flow properties. To settle this matter with a new study, a more accurate and precise technique for flowability characterization is preferred. To this end, the ring shear cell test is ideal because it yields quantitative and precise flowability parameters with clear physical meanings. Second, Avicel PH102 has been suggested as a reference powder to assess adequacy of the flow properties of a formulation during high speed tableting by the way of comparison [15]. To attain reliable conclusions by this approach, it is imperative to understand how the flow properties of Avicel PH102 vary with RH.

2. Materials and methods

2.1. Materials

A single batch of microcrystalline cellulose (Avicel PH102, lot #P208819629, FMC Biopolymers, Philadelphia, PA) was used for the entire study.

2.2. Characterization of flow properties

Powder flow properties were assessed using a ring shear tester (RST-XS, Dietmar Schulze, Wolfenbüttel, Germany). Accuracy of the shear cell was verified using a limestone powder standard [16]. A sample of MCC, sprayed into a thin layer on a sheet of aluminum foil, was equilibrated at various relative humidities (RH) for at least 24 h. Samples and the shear cell were housed in a space isolated from laboratory conditions using plastic films. For RHs of 5%, 10%, 20%, 35%, and 52%, experiments were carried out when laboratory RH was stable. For 92% RH, the enclosed space was supplied with moist air by the means of a humidifier. The RH was monitored throughout the entire experiment with a hygrometer and the average and standard deviation were calculated and reported.

Shear cell data were collected at 1, 3, 6, and 9 kPa preshear normal stresses. For each preshear normal stress, maximum shear stresses at five shear normal stresses were used to construct a yield locus. The lowest normal stress was kept at 230 Pa while other points are equally distributed. Parameters assessed are the following: major principal stress (σ_1), unconfined yield strength (f_c), cohesion (τ_c), bulk density (ρ_b), powder density under stress ($\boldsymbol{\rho_s}$), and effective angle of internal friction (ϕ_e) [17].

Here, we defined the ratio of the major principal stress, σ_1, to the unconfined yield strength, f_c, as "flowability index (ffc)" [18]. In some of our earlier work, we termed this ratio "flow factor" [2,4,6,7,15,19–22] without realizing that this term had already been defined in the literature as: ff $= \sigma_1/\sigma_1'$, where σ_1' is the major principal stress required to support the arch. Here, ff is one of the parameters required for predicting the minimum hopper outlet dimensions from which a powder can flow out [23–25]. The terminology switch here is intended to minimize potential future confusion in the literature.

3. Results

Water content of Avicel PH102 at 5%, 10%, 20%, 35%, 52%, and 92% RH was 1.6%, 2.5%, 3.2%, 4.5%, 5.7%, and 10.9%, respectively. This can be obtained from the moisture sorption curve of this material [11]. Various flow parameters obtained in this work could be examined as a function of either RH or water content. However, we only plot these parameters against RH for practical reasons. Those plots can be easily converted to characterize the dependence of flow parameters on water content.

Fig. 1 shows yield loci of MCC at different RHs when the pre-shear normal stress is 3 kPa. With increasing RH, yield locus gradually moves up. This means that, under the same normal stress, MCC powder is more resistant to shear stress when equilibrated at a higher RH. The higher yield locus is translated to higher unconfined yield strength, f_c, obtained by the means of the Mohr's circle. Fig. 2 shows that, under all major principal stresses, σ_1, the f_c value rises continuously with increasing RH (or water content). This means that the powder becomes stronger when equilibrated at a higher RH. Therefore, it is more difficult to initiate flow of the powder at a higher RH.

Corresponding to the increasing trend of fc with RH at a fixed σ_1, ffc, decreases continuously with increasing RH under all stress conditions (Fig. 3). For example, ffc is 7.89 at 5% RH but only 3.83 at 92% RH under the 1kPa preshear normal stress (corresponding to σ_1 of 2.1 kPa). This suggests that flowability of MCC deteriorates with increasing RH (or water content). The rate of decrease is high below 20% RH but is more gradual above 20% RH.

Interestingly, the dependence of powder cohesion, τ_c, on RH (Fig. 4) closely resembles that of fc (Fig. 2). This suggests that the two parameters, fc and τ_c, are closely related. Although the quantitative relationship between the two parameters remains to be identified, the qualitative resemblance is not surprising. The parameters fc and τ_c describe the powder strength and the cohesion, respectively. It is not surprising that a more cohesive powder has a higher strength.

The $\boldsymbol{\rho_b}$ of MCC powder initially increases up to ~20% RH and then decreases (Fig. 5a). This trend is similar to that of the true density ($\boldsymbol{\rho_t}$) – RH profile of MCC [26]. The similarity in the two profiles suggests that the true density change is likely a dominant factor in the observed change in $\boldsymbol{\rho_b}$. If particle packing is identical at all RHs, $\boldsymbol{\rho_b}$ profile would be identical to that of the $\boldsymbol{\rho_t}$ profile. However, the relative decrease in $\boldsymbol{\rho_b}$ above 20% RH is more than that of $\boldsymbol{\rho_t}$ where relative reduction in true density and $\boldsymbol{\rho_b}$ are ~3% and ~12%, respectively, between 20% RH and 92% RH. This indicates that, other than the contributions from $\boldsymbol{\rho_t}$, powder packing efficiency is also involved. At higher RHs, the poor flowability and higher cohesion is associated with less efficient packing of the powder (e.g., easier formation of air pockets), which contributes to the further decrease in powder $\boldsymbol{\rho_b}$. Bulk density of a finer grade of MCC was observed to decrease continuously with increasing water content in a previous study [13]. The different trends of the two powders may be related to their different flowability, where the finer MCC (Avicel PH101) is more cohesive and flows more poorly [1]. Consequently, for Avicel PH101, the contributions by lower packing efficiency at a higher RH are much greater than those by $\boldsymbol{\rho_t}$. Therefore, the overall trend appears as a continuous decline because the contribution by changes in $\boldsymbol{\rho_t}$ is small relative to changes in powder bulk volume.

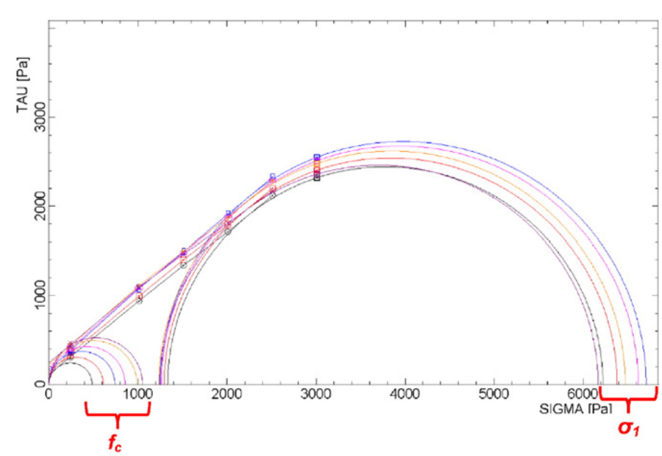

Fig. 1. Yield loci of MCC equilibrated at different RHs. Points are obtained at the pre-shear normal stress of 3 kPa. The unconfined yield strength ($\boldsymbol{f_c}$) and major principal stress ($\boldsymbol{\sigma_1}$) for each powder are obtained from the Mohr's circles drawn for each corresponding yield locus.