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Understanding the impact of microcrystalline cellulose physicochemical properties on tabletability

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ABSTRACT

The quality by design (QbD) initiative is promoting a better understanding of excipient performance and the identification of critical material attributes (CMAs). Despite microcrystalline cellulose (MCC) being one of the most popular direct compression binders, only a few studies attempted identifying its CMAs. These studies were based either on a limited number of samples or on MCC produced on a small scale and/or in conditions that deviate from those normally encountered in production. The present work utilizes multivariate analyses first to describe a large database of MCCs produced on a commercial scale, including an overview of their physicochemical properties, and secondly to correlate the most significant material attributes with tabletability. Particle size and moisture content are often considered as the most common if not the sole CMAs with regard to MCC performance in direct compression. The evaluation of more than 80 neat MCCs and the performance of selected samples in a model formulation revealed the importance of other potential critical attributes such as tapped density. Drug product developers and excipient suppliers should work together to identify these CMAs, which may not always be captured by the certificate of analysis.

1. Introduction

Microcrystalline cellulose (MCC) has been considered for the last fifty years as the diluent having the best binding properties and is recognized as one of the preferred direct compression (DC) binders (Bolhuis and Armstrong, 2006; Carlin, 2008; Patel et al., 2006; Saigal et al., 2009). The reasons for this preference include compactibility, tabletability, tradition, supply, handling, and physiological inertness (Bolhuis and Chowhan, 1996).

MCC is a purified, partially depolymerized cellulose prepared by treating with mineral acids alpha cellulose (type Iβ), obtained as a pulp from fibrous plant material, mostly from wood (Albers et al., 2006; Shlieout et al., 2002). The rate of hydrolysis slows to a certain level-off degree of polymerization (LODP). The LODP is a characteristic of a particular pulp and is typically found in the 200–300 range (Doelker, 1993).

MCC is commonly manufactured by spray drying the neutralized aqueous slurry resulting from the hydrolysis of cellulose. Most commercial grades are formed by varying and controlling the spray drying conditions in order to manipulate the degree of agglomeration (particle size distribution) and moisture content (loss on drying) (Reier, 2000). Other drying techniques may be used (Christiansen and Sardo, 2001), which may require additional screening steps post drying to control particle size distribution.

Several studies have compared microcrystalline cellulose from various sources, including different manufacturers and different sites (Albers et al., 2006; Doelker, 1993; Landín et al., 1993a,b,c; Williams et al., 1997). It was generally recognized that batch-to-batch variability from a sole manufacturing site was less important than differences observed between multiple sources. However, these conclusions were based only on single samples from two to three batches. Since MCC is manufactured by continuous production, a batch is defined as a certain period of time and could represent two days up to one week from a larger production campaign. It could therefore be argued that one sample (few hundred grams up to few kilograms) is not representative of the variability of a high volume continuously produced material.

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Table 1
Frequency table, number of MCC samples classified by manufacturing site (origin) and date of manufacture.

Origin	Month-Year							Total sample	Total %
	May-2011	Jul-2011	Aug-2011	Oct-2011	Jan-2012	Feb-2012	Mar-2012		
Cork	–	18	6	6	6	–	–	36	43
Newark	14	–	–	–	12	16	6	48	57
Total	14	18	6	6	18	16	6	84	100

Only a few studies have tried to correlate the manufacturing conditions of microcrystalline cellulose with its physicochemical properties and its performance in tableting applications (Dybowski, 1997; Shlieout et al., 2002; Wu et al., 2001a,b). This information could be highly valuable to control or even to optimize the performance of MCC. However, these MCC samples were prepared on a small scale and/or in conditions that deviate from those normally targeted in production. Any conclusion drawn at small scale might not correlate with large scale operating conditions.

There is an opportunity for a new and systematic study to gauge the variability encountered in a large manufacturing scale and to identify the physicochemical parameters of microcrystalline cellulose, i.e., its critical material attributes (CMAs), that may impact its tableting performance. The present study describes the evaluation of a substantial series of commercial samples, which allowed the implementation of proven multivariate analysis methods and the determination of statistically sound correlations (Haware et al., 2009; Kushner, 2013; Kushner et al., 2014; Souihi et al., 2013; Tho and Bauer-Brandl, 2011, 2012).

2. Material and methods

2.1. Material

In order to capture the variability of microcrystalline cellulose type 102 as manufactured by FMC Health and Nutrition, samples were randomly collected from two manufacturing plants, Cork, Ireland and Newark, DE, USA. This type of MCC has a median particle size of about 100 μm, a bulk density close to 0.3 g/cm^3, and is commonly used in direct compression. As summarized in Table 1, a total of 84 samples were obtained from 6 batches from each plant. Each batch was represented by at least 6 samples.

Ascorbic acid (Hebei Welcome Pharmaceutical Co., Ltd., China) and magnesium stearate (code 2257, Mallinckrodt Pharmaceuticals, USA) were also used to assess the impact of MCC on the tabletability of the model formulation described in Section 2.4.2.

2.2. MCC manufacture

MCC type 102 was produced under normal manufacturing conditions. The key steps of a typical manufacturing process are illustrated in Fig. 1.

After depolymerization with mineral acids, the soluble components of cellulose are washed out and the insoluble MCC is dried to obtain the well-known white, odorless, tasteless, direct compression binder (Guy, 2009). MCC was sampled immediately after the drying step and did not go through subsequent processing steps such as cyclones, screening and packaging.

2.3. MCC characterization

2.3.1. Moisture content

Moisture content, loss on drying (LOD), was determined with a halogen moisture analyzer (Mettler Toledo HR73, Switzerland) prior to any bulk density and tableting evaluation. In the case of tableting, moisture content was also measured once after the trial in order to calculate a mean value. The 'standard' drying program was selected. About 3 g (±10%) of MCC was exposed to 105 °C until the mean weight loss was less than 1 mg during 50 s.

2.3.2. Particle size

Particle size distribution was obtained by laser diffraction (Malvern Mastersizer 2000 equipped with the Sirocco Dry Powder Feeder, UK). One aliquot of about 2 g (a tablespoon) of MCC powder was fed to the measurement cell using a vibration feed rate of 75% and a dispersive air pressure of 3 bars. The refractive index was set to 1.45 and the desired obscuration was about 5%. Volume weighted particle size distributions were described by the 10, the 50 (median) and the 90 percentiles.

2.3.3. Bulk density

A Scott Volumeter (Paul N. Gardner Company, Inc., USA) was used to measure bulk density according to the method described in the MCC monograph and to the Method II of the General Chapter <616> (USP37-NF32, 2014a). The volumeter is composed of a funnel with a 10 mesh screen, a chute with glass baffles to minimize packing, and a 25 ml brass cup. MCC powder is poured through the assembly into the brass cup until powder overflows. The excess powder is then scored off with a spatula. The cup is tapped and moved to a two-decimal place balance (Mettler Toledo PM4800, Switzerland). Density is calculated based on sample weight and its known volume. The measurement is repeated three times in order to calculate a mean value.

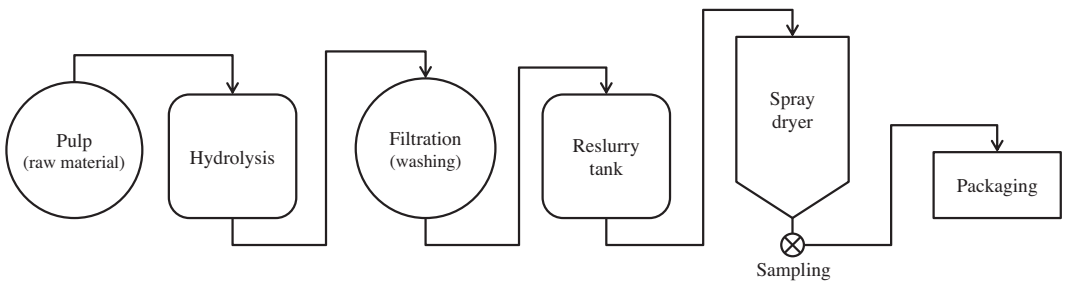

Fig. 1. Microcrystalline cellulose manufacturing overview.