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Impact of microcrystalline cellulose material attributes: A case study on continuous twin screw granulation

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ABSTRACT

The International Conference on Harmonisation (ICH) states in its Q8 'Pharmaceutical Development' guideline that the manufacturer of pharmaceuticals should have an enhanced knowledge of the product performance over a range of material attributes, manufacturing process options and process parameters. The present case study evaluates the effect of unspecified variability of raw material properties upon the quality attributes of granules; produced using a continuous from-powder-to-tablet wet granulation line (ConsiGma™ 25). The impact of different material attributes of six samples of microcrystalline cellulose (MCC) was investigated. During a blind study the different samples of MCC were used separately and the resulting granules were evaluated in order to identify the differences between the six samples. Variation in size distribution due to varying water binding capacity of the MCC samples was observed. The cause of this different water binding capacity was investigated and was caused by a different degree of crystallinity. Afterwards, an experimental design was conducted in order to evaluate the effect of both product and process variability upon the granule size distribution. This model was used in order to calculate the required process parameters to obtain a preset granule size distribution regardless of the type of MCC used. The difference in water binding capacity and its effect on granular properties was still present when combining the MCC grades with different binders.

1. Introduction

The Q9-guideline (2005) of the International Conference on Harmonisation (ICH) proposes a systematic approach for quality risk management. A risk management process consists of a risk assessment step, followed by risk control and risk review and can (should) be applied to all aspects of pharmaceutical quality. One of the important aspects in quality risk management, is the determination and evaluation of possible quality risks associated with variability of the properties of the starting materials. Moreover, in the PAT guidance for industry (FDA-Adminstration, 2004) the FDA states indeed that "*inherent, undetected variability of raw materials may be manifested in the final pharmaceutical product*". Processing difficulties can arise, which result in the failure of a product to meet specifications, even if the raw materials are conform to the pharmacopoeial specifications. Pharmaceutical manufacturing should be robust towards raw material variability. Therefore, the relationship between raw material variability, process and final product should be fundamentally understood. Microcrystalline cellulose (MCC) is a widely used excipient in the pharmaceutical industry. A schematic overview of the production of MCC (Avicel® PH) is given in Fig. 1. Highly purified cellulose (α-cellulose) is obtained from trees, then depolymerized by means

Abbreviations: DPMO, defects per million opportunities; FDA, Food and Drug Administration; *H*, Hausner ratio; HPC, hydroxypropylcellulose; HPMC, hydroxypropylmethylcellulose; ICH, International Conference on Harmonisation; MCC, microcrystalline cellulose; MLR, multiple linear regression; PAT, process analytical technology; PLS, partial least squares; PSD, particle size distribution; PVP, polyvinylpyrrolidone; SEM, scanning electron microscopy; WBC, water binding capacity; XRD, X-ray diffraction.

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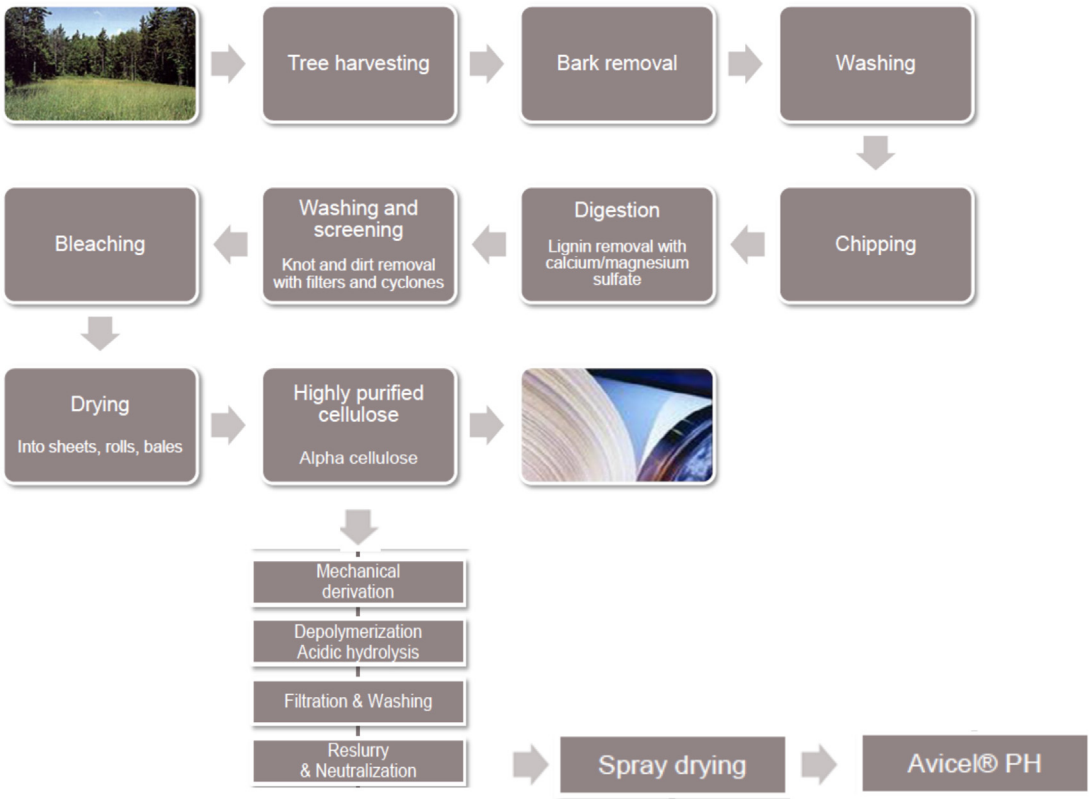

Fig. 1. Schematic overview of the production of Avicel® PH. Reproduced with permission from FMC Health and Nutrition.

of acid hydrolysis in order to remove the amorphous regions and achieve the desired degree of polymerization. MCC can be purchased from different suppliers in a large variation of grades, which typically differ in particle size or bulk density. In Table 1, a literature overview is provided, listing research studies in which the effect of the use of various MCC starting materials on the process and end product quality of pharmaceutical products was investigated.

Most studies reported in Table 1 were based on the use of different brands and/or grades of MCC, but there are very little analyses available on different samples of MCC of the same brand and grade. The observation of a variable processing behavior or different end product quality of pharmaceuticals arising from different grades or brands of MCC is expected (Almaya and Aburub, 2008; Alvarez et al., 2002; Dumarey et al., 2011; Haware et al., 2010; Heng and Koo, 2001; Herting and Kleinebudde, 2007; Inghelbrecht and Remon, 1998; Javadzadeh et al., 2009; Kleinebudde et al., 2000; Koo and Heng, 2001; Landin et al., 1992, 1993a,d; Law et al., 1997; Obae et al., 1999; Parker and Rowe, 1991; Parker et al., 1992; Patel and Podczeck, 1996; Pesonen and Paronen, 1986; Shlieout et al., 2002; Soh et al., 2008; Whiteman and Yarwood, 1988). Nevertheless, some authors reported significant batch-to-batch variation even when the same brand and grade were used (Albers et al., 2006; Doelker et al., 1987; Gamble et al., 2011; Liao et al., 2012; Shi et al., 2011; Staniforth et al., 1988; Williams et al., 1997). Landin et al. state that batch-to-batch variation of MCC is caused by the use of different wood pulps as starting materials for the production of MCC (Landin et al., 1993c). These different wood pulps cause a larger batch-to-batch difference than the used methodology for the MCC production itself. The use of various wood pulps results in a dissimilar degree of crystallinity when comparing batches (Landin et al., 1993b). It is important to determine the reasons for such variations in crystallinity index between MCC batches, which might be as high as 4%, thereby impacting the properties of the end products (Rowe et al., 1994).

The aim of this study was to elucidate the cause and effects of this variability of MCC upon processability and granule properties during continuous twin screw granulation. Earlier investigations showed that variability of MCC caused differences in processes which are characterized by a short interaction time between the powders and water (i.e., pellet size differences in extrusion–spheronization). During twin screw granulation, the residence time in the granulator barrel and the contact time between powder and granulation liquid is very short. Six different samples of Avicel® PH101 were delivered and could be considered as similar from a pharmacopoeial point of view. This paper reports about the thorough investigation of the raw material characterization of the different samples as well as the properties of the produced granules using these samples. Furthermore, the inherent cause of the observed MCC variability and resulting granule property differences is presented. In addition, solutions to manage these differences are suggested and evaluated. This paper reports the investigations in chronological order, starting with a blind study on the received samples. Afterwards, the effect of MCC variability upon granule properties has been elucidated and the root cause of the obtained differences has been investigated in depth. A comparison between the effect of raw material differences and the modification of process parameters was made, followed by an investigation on the effect of the presence of different binders for twin screw granulation of these MCC samples.

2. Materials and methods

2.1. Materials

The six samples of microcrystalline cellulose (MCC) Avicel® PH101 studied, were donated by FMC Health and Nutrition. For