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Classification of microcrystalline celluloses via structures of individual particles measured by synchrotron radiation X-ray micro-computed tomography

Longwei Fang[a,b,1], Xianzhen Yin[b,d,1], Li Wu[b], Yaping He[b,c], Yuanzhi He[b], Wei Qin[b], Fanyue Meng[b], Peter York[d], Xu Xu[a,**], Jiwen Zhang[a,b,c,*]

[a] School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201418, China
[b] Center for Drug Delivery System, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China
[c] University of Chinese Academy of Sciences, Beijing 100049, China
[d] Institute of Pharmaceutical Innovation, University of Bradford, Bradford, West Yorkshire BD7 1DP, United Kingdom

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ABSTRACT

Microcrystalline cellulose (MCC) is one of the most important excipients due to its outstanding binding and tableting properties. Owing to the absence of high resolution characterization techniques at the single particle scale, 3D (three dimension) microstructure of MCC and its effects on formulation performance remain unexamined. The aim of this work was to establish a methodology for single particles of MCC type 102 based on synchrotron radiation X-ray micro computed tomography (SR-μCT), principal component analysis (PCA) and partial least square discriminant analysis (PLSDA). Scanning electron microscopy, SR-μCT, powders properties together with tensile strength (TS), disintegration time (DT), Kawakita plots and force/displacement profiles of tablets were measured. PCA-PLSDA was applied to evaluate the structural classification of MCC particles on the basis of 2D and 3D SR-μCT derived images. The studied MCCs were found to differ in the TS, DT, Kawakita plot and force/displacement, while box ratio and Feret ratio had major influence on the principal components, but the angle of repose, bulk and tapped density did not exhibit significantly. These findings verified that different samples of MCCs from alternative suppliers have morphological diversity when assessed at the individual particle level, which could result into variation in powder properties and tableting performance.

1. Introduction

Unit operations of particulate systems need to be optimized before processing powders and granules into dosage forms such as tablets or capsules (Stoklosa et al., 2012). It is obvious that each particle contributes to the overall pharmaceutical behavior of the powder, but is difficult to correlate the bulk behavior of powder to single particle analysis. Evaluation of powder behavior is often empirical and the decision-making processes are experience-based, generally ignoring the actual impact of single particles (Meier et al., 2008). Therefore, development of a method to characterize single particle structure is of interest and would provide a basis for the qualitative and quantitative evaluation for understanding the powder behavior in 3D structural architectures.

Since different excipient attributes may be required in alternative formulations and individual manufacturing processes, it is of interest to identify the critical material attributes of the excipient for a particular application, and if necessary, to specify the appropriate specifications and suppliers (Carlin and Moreton, 2010). To ensure the excipient performance consistency in formulation, the physico-chemical properties, composition, manufacturing method and the supplier of the excipients should be fully investigated. Conventional evaluation techniques to investigate the excipients include scanning electron microscopy (SEM), X-ray powder diffraction, infrared spectroscopy, near infrared reflectance spectroscopy (Wang et al., 2015), and X-ray scattering (Meitz et al., 2014; Myśliwiec et al., 2016; Sun et al., 2016). Although all these methods provide some general

* Corresponding author at: Center for Drug Delivery System, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 501 Haike Road, Shanghai, 201203, China.
** Corresponding author at: School of Chemical and Environmental Engineering, Shanghai Institute of Technology, 100 Haiquan Road, Shanghai, 201418, China.
E-mail addresses: xuxu3426@sina.com (X. Xu), jwzhang@simm.ac.cn (J. Zhang).
[1] These authors contributed equally to this work.

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information related to structure, they fail to provide the quantitative information on structural architecture of single particles for detailed analysis.

Synchrotron radiation X-ray micro-computed tomography (SR-μCT), an advanced technique for the investigation of three dimensional (3D) internal structures, has been shown to provide major advantages in quantitative evaluation of the solid multi-particles drug delivery systems (Guo et al., 2016). SR-μCT has been used non-destructively to investigate the mixing and segregation of granules in 3D in combination with a statistical method based on single particle structure characterization (Liu et al., 2013). After structure reconstruction, irregular architecture of particulate materials can be quantitatively characterized (Yin et al., 2013). SR-μCT has also been applied to define the drug release behavior of taste masked single pellets (Guo et al., 2016; Yang et al., 2014) and fine granules prepared by melt granulation with irregular shapes (Noguchi et al., 2013).

Mathematical tools such as principal component analysis (PCA) help in data mining and modeling complex correlations (Haware et al., 2014; Moore et al., 2009). The potentiality provided by such multivariate data analysis techniques has been utilized in areas such as metabolomics, meteorology, environmental studies and process automation. However, it is rare to use PCA for the characterization of pharmaceutical excipients (Lin et al., 2015; Geurts et al., 2016; Westerhuis et al., 2008). Another model, partial least square discriminant analysis (PLSDA), has also been applied to address multi-variant challenges (Geurts et al., 2016; Wang et al., 2015).

Microcrystalline cellulose (MCC) is a depolymerized, non-fibrous form of crystalline cellulose powders, composed of porous particles (Gryczke et al., 2011), used in a range of formulations, particularly for direct compression tableting (Kalita et al., 2013; Otsuka et al., 2013; Panda et al., 2015). Owing to outstanding properties, MCCs have become one of the most widely used tableting excipients since their discovery in 1955 by Battista and Smith (Suzuki and Nakagami, 1999) and first commercialized with the major attributes of good powder flowability and tabletability (Gamble et al., 2011; Thoorens et al., 2014).

Identifying and understanding the preferred MCCs type and their pivotal properties from the structural perspective is an important but challenging task for which conventionally, MCCs are primarily classified by particle size, surface area and bulk density into sub-types, e.g., 101, 102 and 200 (Awa et al., 2015). These aggregates, accounting for a large volume/mass fraction but a low number fraction, affect the flowability of the powders with drug and tablet formulations (Hentzschel et al., 2012; Mustafa and Chaw, 2016; Ofori-Kwakye et al., 2015). For example, MCC type 102 with a median particle size of 100 μm presents acceptable flow properties for successful high speed tableting (Thoorens et al., 2014). However, these descriptive classifications are based on powder properties without particle's structural evaluation. The collective assembly of individual particles determines the optimal processability in the pharmaceutical unit (Stoklosa et al., 2012). As for particulate system influencing processing behavior, powder evaluation is an elementary and challenging part of the product development work (Crouter and Briens, 2014; Hirschberg et al., 2016; Leturia et al., 2014). The challenge of classifying excipient powders based upon comprehensive structural analysis of individual particles is addressed in this research.

In this paper, MCC samples of type 102 were selected for structural classification. Fifteen structural parameters of single particle were obtained by advanced SR-μCT studies and analyzed by multivariate analysis using PCA and PLSDA to correlate the structural attributes of MCC particles with formulation performance of powder properties and compaction, such as angle of repose, bulk density, tapped density, degree of compression, tablet tensile strength, disintegration time and tablet mechanical compaction behavior including Kawakita plot and tablet mechanical test.

2. Materials and methods

2.1. Materials

MCCs were obtained from several multi-national companies, such as Asahi Kasei Chemicals Corporation (Japan), JRS Pharma GmbH & Co., KG. (Germany), Blanver Farmoquimica Ltd. (Brazil), FMC Co., Ltd. (the United States), Mingtai Chemical Co., Ltd. (China) and so on. Five samples of MCC type 102 were named as sample A to sample E from five primary manufacturers. Vinyl pyrrolidone and vinyl acetate copolymer (PVP/VA, Plasdone® S630) were provided by Shanghai Chineway Pharmaceutical Tech Co., Ltd (China). All other chemicals and solvents were of analytical grades and used without further purification.

2.2. Individual particles measurement by SR-μCT

MCC type 102 samples were sieved through 60∼100 mesh size (250∼150 μm). PVP/VA was sieved through 200 mesh size (75 μm) as fine powder diluent and mixed with MCC particles in the ratio of 1:1 (w/w), shaken thoroughly to minimize inter-particle adhesion and cohesion. Then the MCC mixtures (MCC 102: PVP/VA, 1:1) were fixed into a pipettor. SR-μCT tomographic images were acquired with beam line BL13W1 at Shanghai Synchrotron Radiation Facility. Samples were scanned by synchrotron radiation X-ray at 13.0 KeV. The size of the beam was approximately 45 mm (horizontal) ×5 mm (vertical) and a double-crystal monochromator, with Si (111) and Si (311) crystals, was used to monochromatize the X-rays. After penetration through the sample, the X-rays were first converted to visible light by a cleaved Lu_2SiO_5: Ce single crystal scintillator (10 μm thickness). Data were acquired with the sample placed 34 m downstream of the synchrotron source. Projections were magnified by diffraction-limited microscope optics and digitized by high-resolution with an efficient pixel size of 0.65 μm (ORCA Flash 4.0 Scientific CMOS, Hamamatsu K.K., Shizuoka Pref., Japan, physical pixel size: 6.5 μm). The exposure time was 2 s and the distance from detector to sample was set at 5 cm. For each acquisition, 1440 projection images were captured with an angular step size of 0.125° for 180°. Flat-field and dark-field images were also collected during each acquisition procedure in order to correct the electronic noise and variations in the X-ray source brightness. To enhance the quality of reconstructed slices, PTRE software (http://www.exelisvis.com/language/en-us/productsservices/idl.aspx) was used for phase contrast extraction. The 3D rendered data were analyzed with the commercially available software Amira (version 6.01, FEI, the United States), Image Pro Plus 6.0 software (version 6.0, Media Cybernetics, the United States) and Image Pro Analyzer 3D (version 7.0, Media Cybernetics, Inc., Bethesda, MD, the United States) to obtain quantitative data, including the surface area (SA), width (WI), height (HI), depth (DE), box ratio (BR), diameter (D), sphericity (SP), radius (max) (RX), radius (min) (RN), radius ratio (RR), Feret (max) (FX), Feret (min) (FN), Feret ratio (FR), volume (VO) and porosity (PO). The detailed descriptions of the 3D structural parameters are shown in the Supporting information (SI).

2.3. Morphological characterization by scanning electron microscope

Morphological characterization of MCC was carried out by scanning electron microscopy (SEM, S-3400N, Hitachi). The specimens were immobilized on a metal stub with double-sided