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Cavities spatial distribution confined by microcrystalline cellulose particles determines tablet disintegration patterns

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ABSTRACT

Cavities and the architectures inside tablet play a decisive role for the permeation of water within tablet to initiate disintegration phenomenon. The present study aims to establish inner structure characterization methodology based on synchrotron radiation X-ray microcomputed tomography (SR-μCT) for microcrystalline cellulose (MCC) tablets and to correlate the cavities and 'their attributes to tablet disintegration phenomenon. The three-dimensional (3D) morphological architecture and quantitative data of single particles for 12 specifications of MCC, and respective MCC tablets' cavities structure were obtained through advanced SR-μCT studies. The image processing techniques were established to study the morphology of voids and porosity in an axial and radial direction based on the highly resolved 3D structure of tablets. The in-situ visualization of morphological disintegration behavior indicates that there were two patterns of disintegrations, which can be cataloged as laminating type (LT) and splitting type (ST) disintegrations. The principal component analysis (PCA) was used for multivariate data analysis to get the meaningful correlation among disintegration behaviors, cavities morphology, single particles attributes, and the cavities spatial arrangement within the tablets. These findings have deepened insights into inner structures of tablets and single particle structural attributes to tablet disintegration, reflecting the mechanism of disintegration mode, and the significance of pharmaceutical structure evaluated via SR-μCT.

1. Introduction

Disintegration is an initial and foremost important step in the tablets, whose rate and process are dependent upon the disintegrant types and tableting processes. Conventionally, the regulatory process and the testing requirements for disintegration are outlined in the pharmacopeia giving strong emphasis on the rate of disintegration of dosage form but fail to explain the underlying mechanistic behavioral information about the causes [1]. The fundamental understanding between inter-dependency of microstructure and disintegration phenomenon along with their quantification is essential for the development and innovation of effective tablet formulation [2–4]. Studies have been proceeded till date to characterize the morphological attributes of different pharmaceutical excipients using scanning electron microscope (SEM), Raman spectroscopy, and magnetic resonance imaging (MRI). SEM and Raman spectroscopy usually depict structural information about the surface and inner region just below the surface of the granules, whilst MRI can reveal the internal structure of dosage form without destruction but has disadvantage of low spatial resolution [5].

Abbreviation: API, Active Pharmaceutical Ingredient; ANOVA, Analysis of Variance; AS, Area of Surface; BR, Box Ratio; C-L, Central-Lower; C-M, Central-Middle; C-U, Central-Upper; D, Diameter; DE, Depth; FR, Feret ratio; FX, Maximum Feret Diameter; FN, Minimum Feret Diameter; HI, Height; keV, Kilo electron Volt; LT, Laminating Type; μCT, Micro-Computed Tomography; M-L, Middle-Lower; M-M, Middle-Middle; M-U, Middle-Upper; MRI, Magnetic Resonance Imaging; MCC, Microcrystalline Cellulose; O-L, Outer-Lower; O-M, Outer-Middle; O-U, Outer-Upper; PC, Principal Component; PCA, Principal Component Analysis; PITRE, Phase-sensitive X-ray Image processing and Tomography REconstruction; PO, Porosity; ROI, Region of Interest; SEM, Scanning Electron Microscope; SIMCA, Soft Independent Modelling of Class Analogies; SR-μCT, Synchrotron Radiation X-ray Microcomputed Tomography; SSRF, Shanghai Synchrotron Radiation Facility; ST, Splitting Type; VO, Volume; WI, Width; 2D, Two Dimensional; 3D, Three Dimensional.

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Although all the methods can give more or less information about the morphological characteristics of the excipients but fail to give a quantitative data or attributes relevant to the disintegration phenomenon.

Synchrotron X-ray microcomputed tomography (SR-μCT) is an advanced technology and efficient tool which can directly reveal the internal structures and dynamic characteristics of pharmaceutical excipient non-invasively via tomographic images. High flux intensity synchrotron radiation X-ray with good X-ray coherence produces high-quality images that are not possible by the commercially available μCT X-ray machine even though resolution are comparable. As a qualitative and quantitative tool, it allows us to section samples virtually in any direction with sub-micrometer resolution in their natural state to obtain quantitative data. Three dimensional (3D) particle's structure of pharmaceutical excipient along with quantitative data have potential for providing a fundamental understanding of the matters' properties [6–8]. The irregular architecture of tablets can be characterized by its fractal dimension, which can be correlated with disintegration phenomenon in drug delivery systems [9,10].

The investigation of the coating layer from tablets was done by μCT in order to determine the porosity via volume images [11]. Porosity of the granules were evaluated via μCT, in the dynamic structure of the granules when it was placed in the dissolution medium. The effective diffusion coefficient of the API through the granule structure were studied, showing quantitative structure-property in relation with dissolution [12]. The application of μCT is commonly used to determine porosity of the sample in various other fields such as in the medical field [13–15], geology [16,17], and food science [18].

The structure at the micron scale determines a significant range of critical quality of a dosage form. Studies have been performed till date confirming that the microstructure and crystallinity of the pharmaceutical excipient determine the drug release kinetics [9,19–21]. Disintegration phenomenon which is accomplished by the liquid penetration through the cavities confined via excipient's microstructural attributes, and formulating procedure in the tablets is the initial step during the drug release. When plotting disintegration force versus liquid contact time, there was a pattern following saturated kinetics dependent on the liquid penetration into voids of the tablets [22]. Generally, pore size, porosity, and tortuosity in the tablet determine the rate and extent of water penetration into the tablets facilitating the disintegration performance [23].

Disintegrants are hydrophilic moieties that swells after absorption of water for the initiation of the disintegration phenomenon in the tablets [24]. Microcrystalline cellulose (MCC) and various superdisintegrants like cross-carmellose sodium, sodium starch glycolate, cross-povidone are usually used in the amount between 2% to 5% by weight in the tablet formulation for enhancing disintegrating attributes of the tablets upon contact with the gastrointestinal fluid [25].

Successful direct compression of a tablet is solely dependent upon the pharmaceutical excipients, which are used during formulation. MCC is one of the valuable tableting agent in the pharmaceutical formulation for having an attribute of superdisintegrant [26]. The appropriate distribution of MCC between and within granules may optimize both dissolution and compactibility without compromising overall tablet composition [27]. MCC is highly hygroscopic in nature which enhances liquid transport by accelerating both diffusion and capillary action [28]. The cavities formed within the tablet during formulation play a decisive role for liquid permeation in commencing disintegration. Currently, single particle structures of MCC type 102 from different companies were studied using synchrotron X-ray radiation computed tomography (SR-μCT) which clearly distinguished that the MCCs from different suppliers have morphological diversity when assessed at the individual particle level, and that affect in the variation of powder properties and tableting performance [29]. Hence, the microstructure of the excipients along with cavities' spatial distributions in tablets play a judicious role for the effective performance of the tablets disintegration [25,30].

Single particle attributes and inner microstructure architecture of the tablets play a decisive role on the dynamic attributes of the tablets affecting drug release kinetics [31]. Therefore, this report established an inner structure characterization methodology for MCC single particles and its respective tablets. Different specifications of MCC single particles and cavities confined within the tablets were analyzed via SR-μCT. Quantitative 3D attributes of the single particles and cavities confined by it in the tablets were calculated. Furthermore, it was also correlated with newly identified disintegration patterns, namely, splitting type disintegration pattern and laminating type disintegration pattern via statistical model.

2. Materials and methods

2.1. Materials

MCC samples were obtained from 5 manufacturers such as, Anhui Shanghe (China), JRS PHARMA GmbH & Co., KG. (Germany), Blanver Farmoquimica Ltd. (Brazil), FMC Co., Ltd. (United States of America), Mingtai Chemical Co., Ltd. (Taiwan, China). Samples were named as A102, B102, C102, D102, E102, F200, G200, H302, I302, J12, K12, and L112 respectively. Copovidone (PVP/VA, Plasdone S630) were provided by Shanghai Chineway Pharmaceutical Tech Co., Ltd. (China). All other chemicals and solvents were of analytical grade and used without further purification.

2.2. Preparation of the MCC tablets

About 100 mg of MCC was weighed and compressed in the tablet presser (ZPS8; Tianjiu Machinery factory, Shanghai, China) by using round 6 mm flat-faced punches. The thickness of the tablets was maintained at 3 mm and the speed of the rotating punching machine was maintained at 8 rpm with constant pressure. The friability test, hardness test, and tensile strength test of the prepared tablets were also investigated (Supplementary data).

2.3. Disintegration in static medium

A digital video camera (Microsoft LifeCam Studio™) was used to record the disintegration process when the tablet was placed into a 140 × 20 mm petri dish filled with about 200 mL purified water at room temperature. Twelve specifications of samples were investigated in the static medium, in both horizontal and vertical position. The experiment was triplicated in order to get concurrent results [32].

2.4. Conventional disintegration time test in dynamic medium

Disintegration test was carried out using a disintegration tester (LB-2D, Huanghai Medicine & Drug Testing Instruments co., Ltd., China) containing 900 mL of pre-warmed water at 37.0 ± 0.5 °C. The tablets were immersed in the pre-warmed water in the disintegrating machine's cylinder, and experiments were carried out and timed until tablets were fully disintegrated (no visible residue of the tablet remain on the screen of the test apparatus or adhere to the lower surface of the discs). The tests were performed for 6 tablets of each 12 different specifications of MCC types.

2.5. Tablet measurement by SR-μCT

For MCC tablets, SR-μCT tomographic images were acquired from the beamline BL13W1 at Shanghai Synchrotron Radiation Facility (SSRF). The samples were scanned through synchrotron radiation X-ray at 15.0 keV. The size of the X-ray window was maintained at 45 mm × 5 mm for the exposure of X-ray to the sample. Double-crystal monochromator with Si (111) and Si (311) crystals was used to monochromatize the X-rays. Synchrotron radiation was made to