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Structural changes of polymer-coated microgranules and excipients on tableting investigated by microtomography using synchrotron X-ray radiation

Ryusuke Kajihara[a], Shuji Noguchi[a], Yasunori Iwao[a], Yoshio Suzuki[b], Yasuko Terada[b], Kentaro Uesugi[b], Shigeru Itai[a,*]

[a] Department of Pharmaceutical Engineering, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan
[b] Japan Synchrotron Radiation Research Institute, 1-1-1 Kouto, Sayo-gun, Hyogo 679-5198, Japan

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ABSTRACT

Multiple-unit tablets consisting of polymer-coated microgranules and excipients have a number of advantageous pharmaceutical properties. Polymer-coated microgranules are known to often lose their functionality because of damage to the polymer coating caused by tableting, and the mechanism of polymer coating damage as well as the structural changes of excipients upon tableting had been investigated but without in-situ visualization and quantitative analysis. To elucidate the mechanism of coating damage, the internal structures of multiple-unit tablets were investigated by X-ray computed microtomography using synchrotron X-rays. Cross sectional images of the tablets with sub-micron spatial resolution clearly revealed that void spaces remained around the compressed excipient particles in the tablets containing an excipient composed of cellulose and lactose (Cellactose® 80), whereas much smaller void spaces remained in the tablets containing an excipient made of sorbitol (Parteck® SI 150). The relationships between the void spaces and the physical properties of the tablets such as hardness and disintegration were investigated. Damage to the polymer coating in tablets was found mainly where polymer-coated microgranules were in direct contact with each other in both types of tablets, which could be attributed to the difference in hardness of excipient particles and the core of the polymer-coated microgranules.

1. Introduction

Among oral dosage formulations, multiple-unit formulations, such as tablets containing drug-loaded granules and excipients and capsules containing drug-loaded granules, have the advantages of small fluctuation of drug absorption and high reproducibility of drug release. Drug release from these formulations can be controlled by coating the drug-loaded granules with functional polymers. For instance, drugs can be released in specific organs when they are coated or kneaded with polymers with pH-dependent dissolution properties (Cuppok et al., 2011; Shiino et al., 2012). When drug-loaded granules are coated with a sustained-release polymer, the duration that the drug is in a patient is extended so the number of doses can be reduced (Lafuente et al., 2002), which would ease the patient burden and improve compliance. Multiple-unit tablets containing granules with both immediate- and sustained-release polymer coatings have been used to design formulations with various lag times of drug release (Li and Zhu, 2003).

Although multiple-unit tablets have various valuable functionalities arising from the polymer coating, this coating is often damaged by the high pressure of tableting, leading to a loss of functionality (Kucera et al., 2012; Okuda et al., 2014; Mehta et al., 2012; Bashaiwoldu et al., 2011; Dashevsky et al., 2004; Tunon et al., 2003). Two methods have been used to prevent damaging the coated granules. One is layering another polymer as a cushioning layer on the functional polymer-coated granules (Hosseini et al., 2013). The other method uses a cushioning excipient to protect the polymer-coated granules from the high tableting force (Beckert et al., 1996). These are practical powerful methods but are not always able to solve the problems associated with damage of the polymer coating during tableting.

Despite tableting being well known to damage the polymer coatings of the microgranules as described above, the damaged

Abbreviations: BHX, bromhexine hydrochloride; CL, Cellactose® 80; CP, Celphere® CP-102; μCT, computed microtomography; HPC-L, hydroxypropyl cellulose grade L; JP, Japanese pharmacopeia; LAC, linear attenuation coefficient; Mg-St, magnesium stearate; PEG, polyethylene glycol 6000; PK, Parteck® SI 150; SEM, scanning electron microscopy; TEC, triethyl citrate.

* Corresponding author. Tel.: +81 54 246 5614; fax: +81 54 264 5615.
E-mail address: s-itai@u-shizuoka-ken.ac.jp (S. Itai).

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polymer coating inside tablets has not been visualized non-destructively. The relationship between the structures of excipients and coated granules in tablets and tablet properties is also not fully resolved, probably because of the lack of their non-destructive structural information and in-situ quantitative analyses. X-ray computed tomography (CT) has been successfully used to analyze non-destructively the internal structures of various pharmaceutical materials including tablets (Farber et al., 2003; Busignies et al., 2006; Otsuka et al., 2012; Sano et al., 2013). However, details of the micro structures inside the tablet are still ambiguous, because the spatial resolution of their structural information was micro to millimeters due to the performance limitation of the CT instruments and X-ray generator. Recently, it became possible to visualize the three-dimensional internal structures of fine particles by using synchrotron X-ray computed microtomography (μCT) (Tsuchiyama et al., 2011). The advantages of synchrotron X-ray radiation is high brilliance and monochromatic characteristic, which make it possible to obtain highly precise CT images from tiny samples in short measurement time (Uesugi et al., 2012; Landis and Keane, 2010). We used μCT to investigate the internal structures of microgranular formulations with a diameter of sub-millimeter, and demonstrated its high potency for visualization with sub-micrometer spatial resolution (Noguchi et al., 2013). In this study, we use μCT method to visualize the internal structures of multiple-unit tablets containing polymer-coated microgranules to elucidate the structural changes of the microgranules and excipients on tableting, the mechanism of polymer coating breakage, and the relationship between the internal structures and physical properties of tablets.

2. Materials and methods

2.1. Materials

Cellactose® 80 (CL) was kindly provided by Meggle Japan Co., Ltd. (Tokyo, Japan), Parteck® SI 150 (PK) by Merck Ltd., Japan (Tokyo, Japan), Celphere® CP-102 (CP) by Asahi Kasei Co., Ltd. (Tokyo, Japan), and hydroxypropyl cellulose grade L (HPC-L) by Nippon Soda Co., Ltd., (Tokyo, Japan). The particle size distributions of CL and PK were determined according to the Japanese Pharmacopoeia (JP) XVI sieving method (Tsutsui Rikagaku Kikai Co., Ltd., Japan), and is shown in Supplemental Fig. S1. Median diameter of CL and PK were comparable values of 162 and 184 μm, respectively. Polyethylene glycol 6000 (PEG) and magnesium stearate (Mg-St) were purchased from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan), bromhexine hydrochloride (BHX) from Shiratori Pharmaceutical Co., Ltd. (Chiba, Japan), enteric polymer Eudragit® L30 D-55 from Röhm Degussa (Essen, Germany), triethyl citrate (TEC) from Morimura Brothers, Inc. (Tokyo, Japan), and talc from Matsumura Industrial Co., Ltd. (Tokyo, Japan). Epoxy-based bonding agent (High Speed Epo®) was purchased from Konishi Co., Ltd. (Osaka, Japan).

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2.2. Preparation of polymer-coated microgranules

HPC-L (14 g) and PEG (3.5 g) were dissolved in 40% ethanol–water solution (612.5 g) and then BHX (70 g) was dispersed in the solution. In order to pulverize BHX into fine powders of nano-order size, the dispersion was homogenized by a microfluidizer (M110-E/H, Powrex, Hyogo, Japan) operated at 175 MPa. This homogenized dispersion was layered onto CP (700 g) by side spraying in a tumbling fluidized-bed granulating-coating machine (MP-101, Powrex). Process parameters for BHX layering and Eudragit® L30 D55 coating are given in Table 1. The BHX-layered granules were dried for 10 min under an air flow of 28 °C, and then sieved through mesh size of 210 μm.

Table 1
Operating conditions of the fluidized-bed granulator during drug layering and polymer coating.

	Drug layering	Polymer coating
Air flow (L/min)	550	
Inlet air temperature (°C)	45–55	
Outlet air temperature (°C)	28	
Spray rate (g/min)	6	4
Spray air flow (L/min)	70	
Rotation speed (rpm)	400	

Talc (25 g) as an anti-adherent agent and TEC (5 g) as a plasticizer were added to water (203.3 g) and dispersed with a homogenizer (Kinematica® AG, Luzern, Switzerland) for 10 min. This dispersion was mixed with 30% Eudragit® L30 D55 aqueous dispersion (166.7 g). The mixture was sprayed onto sieved BHX-layered granules (500 g) using the tumbling fluidized-bed granulating-coating machine. The spray rate was 4 mL/min and other conditions were same as for BHX layering. After coating with Eudragit® L30 D55, an aqueous solution (100 g) containing 12% (w/w) D-mannitol and 1% (w/w) HPC-L was sprayed onto the polymer-coated microgranules under the same conditions used for polymer coating so that the granules might not adhere to each other. The resulting granules were dried for 10 min under an air flow of 28 °C, and then sieved through mesh size of 250 μm.

2.3. Preparation of multiple-unit tablets

Polymer-coated microgranules and excipient CL or PK were mixed in a weight ratio of 1:1 with a V-shaped rotating mixer (Microtype Transparent Mixer S-3, Tsutsui Rikagaku Kikai Co., Ltd., Tokyo, Japan) at a rotation rate of 35 rpm for 10 min. Subsequently, Mg-St (0.5% (w/w) of the total weight) was added as a lubricant and the mixture was stirred for a further 5 min at the same rotation rate. Tableting was performed using a single-punch tablet machine (TAB ALL N30-EX, Okada Seiko Co., Ltd., Tokyo, Japan) with a flat-faced punch with a diameter of 8 mm. The weight of each tablet was 250 mg and the tableting force was 5.0, 7.5 or 10 kN. The thicknesses of the tablets containing CL (CL tablets) compressed at 5.0, 7.5 and 10 kN were 3.98 ± 0.03, 3.79 ± 0.03, 3.72 ± 0.05 mm ($n = 5$), and those of the tablets containing PK (PK tablets) were 4.00 ± 0.02, 3.76 ± 0.03, 3.69 ± 0.03 mm ($n = 5$), respectively.

2.4. Synchrotron X-ray μCT measurement

For the μCT measurements of CL, PK, and polymer-coated microgranules, the samples were put into Lindemann glass capillaries with a diameter of 0.3 mm. For the μCT measurement of the tablets, fragments of approximately $600 \times 600 \times 600$ μm size were cut from the tablets prepared as in Section 2.3: one fragment from the central region inside the tablet and another one from the center of the upper surface of the tablet. Although the surface structures of the fragments may be affected by the cutting process, their core regions are thought to retain the original structures of the tablets. The fragments were attached to the tip of glass rods with epoxy-based bonding agent. The synchrotron X-ray μCT measurements of these granules and tablet fragments were performed at the SPring-8 BL37XU equipped with a μCT apparatus (Uesugi et al., 2012; Suzuki et al., 2011). An X-ray energy of 8 keV was used for the measurements. The samples were rotated continuously during the measurements, and 900 transmission images of parallel projection were recorded in 0.2° steps. The