Tableting

CL
- Cellulose
- Lactose

PK
- Polymer-coated microgranule

100 µm

Drug release (%)

Time (min)

CL 5.0 kN
CL 7.5 kN
CL 10 kN
PK 5.0 kN
PK 7.5 kN
PK 10 kN
Polymer-coated microgranules
Structural changes of polymer-coated microgranules and excipients on tableting investigated by microtomography using synchrotron X-ray radiation

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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.
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.

Keywords:

Multiple-unit tablets, polymer-coated microgranules, tableting, coating damage, computed microtomography, synchrotron X-ray radiation.
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; Bashiwoldu 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 (Becker 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 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 due to 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., 2014). However, details of the micro structures inside the tablet is 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 data from tiny samples in short measurement time (Uesugi et al., 2013; Landis et al., 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).

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.

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 250µm.

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±x.xx, 3.79±x.xx, 3.72±x.xx µm (n=5), and those of the tablets containing PK (PK tablets) were 4.00±x.xx, 3.76±x.xx, 3.69±x.xx µm (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 600×600×600 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 exposure time for each transmission image was set to 150 ms. The time required for the measurement of one sample was less than 5 min. Distance between the light receiving section of the area detector and the sample was 3 mm. Cross sectional images were calculated by the convolution back-projection method using the software CBP (Uesugi, 2004). Voxel size was 0.526×0.526×0.526 μm. The sets of the cross sectional images were analyzed using SLICE (Nakano et al., 2006), ImageJ 1.48v (Schneider et al., 2012), and Fiji (Schindelin et al., 2012). X-ray linear attenuation coefficient (LAC) values between 0 and 70.0 are shown in 8-bit grayscale, 0–255, in the slice images, with LAC values 70.0 and higher as white. LACs of drugs and excipients were calculated using the software MU_4 (Kato, 2014; Hubbell and Seltzer, 1996). Calculated LAC values of BRH, cellulose, lactose, sorbitol, and talc were 75.6, 12.4, 12.1, 11.9 and 90.7 cm⁻¹, respectively.

2.5. Particle properties of polymer-coated microgranules and excipients

2.5.1. Void-voxel ratio

To evaluate the porosity of the excipients, the void-voxel ratio (VVR) was calculated from the cross sectional images. VVR was defined as follows:

\[
VVR = \frac{\text{Number of void voxels of the excipient particle}}{\text{Total number of voxels of the excipient particle}} \times 100 \, (\%) \tag{1}
\]

A void voxel is defined here as a voxel with LACs of less than 0.3 cm⁻¹. Surface boundaries of the
excipient particles were determined from the modified object images prepared from their non-void regions. Images of the non-void regions were first dilated by 10 voxels and then eroding by 10 voxels using SLICE. Some surface boundaries in the modified object images were still irregularly discontinuous after this process, especially at the channels that were open to the surfaces of the excipients. Those were visually identified and modified manually so that the surfaces of the object images may be continuous and smooth.

2.5.2. Hardness of polymer-coated microgranules and excipients

The hardness of 50 polymer-coated microgranules and 10 excipient granules was measured using a particle hardness tester (GRANO, Okada Seiko Co., Ltd., Tokyo, Japan).

2.6. Tablet properties

2.6.1. Void-voxel ratio at the excipient region of the tablets

Three regions of approximately 400×400×50–100 voxels each were selected from the excipient regions in the cross sectional images of the tablet fragments. The VVR of each region was calculated by Eq. (1) as described in section 2.5.1. to evaluate the porosity of each tablet.

2.6.2. Hardness test

Three tablets were selected randomly and their hardness was measured by a hardness meter PC-30 (Okada Seiko Co., Ltd.) with a 300-N load cell with a precision of 1 N.

2.6.3. Disintegration test

The disintegration time of six tablets in 200 mM sodium acetate buffer (pH 4.0) was assessed using a disintegration tester (NT-1HM, Toyama Sangyo Co., Ltd., Osaka, Japan) according to
2.6.4. Penetration time test

The time for 10 µL of 200 mM sodium acetate buffer (pH 4.0) to be completely absorbed into a tablet after placing onto the tablet surface was measured.

2.6.5. Dissolution test

According to the paddle method of JP XVI, dissolution tests were conducted using 200 mM sodium acetate buffer (900 mL, pH 4.0) and a paddle speed of 50 rpm at 37.0 ± 0.5°C. Aliquots were removed at predetermined intervals, and the sample solutions were filtered through membrane filters with a pore size of 0.20 µm. Dissolved BHX concentrations were quantified by HPLC (Senthilraja et al., 2011). The column, wavelength for BHX detection and flow rate were ODS C18 (Tosoh Co., Ltd.), 245 nm, and 1.0 mL/min, respectively. The mobile phase consisted of acetonitrile, methanol, and 60 mM sodium potassium phosphate buffer (pH 4.2) with a volume ratio of 300:250:450.

3. Results and discussion

3.1. Structure of the excipient particles before tableting

The excipient CL particles consisted of fibrous materials with a thickness of approximately 4 µm and irregular grains with a diameter approximately 10–100 µm (Fig. 1a and b). The components of CL, cellulose and lactose, could not be distinguished by differences in contrast based on LAC values because they share a similar elemental composition of carbon, hydrogen, and oxygen. However, their morphologies suggested that the fibrous materials were cellulose and the irregular grains were lactose. The surface of each CL particle was mainly composed of lactose grains. The grains were closely packed on the surface with small pores with a maximum diameter of
approximately 10 µm between them. A large consecutive void space was present inside each CL particle, and the space was open to the surface through the pores between lactose grains. Fibrous cellulose inside the CL may contribute to the formation of the large void space. In contrast, the PK particles consisted of needle-shaped sorbitol crystals with a thickness of approximately 1 µm (Fig. 2a and b). Although void spaces were also found inside the PK particles, many were isolated and much smaller compared with those in the CL particles.

The VVR of both excipients was calculated from the three-dimensional models of five particles of each type. Figures 1 and 2 reveal that the VVR of CL, 35±1%, was higher than that of PK of 18±6%. The higher VVR of the CL particle indicated its lower particle density. Bulk density of CL, 370 g/L (Meggle Pharma Co., Ltd., 2014), is reported to be lower than that of PK, 450 g/L (Merck Co., Ltd., 2014). Since the particle diameters were comparable between PK and CL as shown in Supplemental Fig. S1, the lower bulk density of CL might be ascribable to its void-rich structure.

3.2. Structure of polymer-coated microgranules before tableting

Cross sectional and reconstructed surface images of a polymer-coated microgranule are presented in Fig. 3a and b, respectively. A BHX layer, which appears as a bright region because of its high LAC value of 75.5 cm\(^{-1}\), and a polymer coating containing Eudragit\textsuperscript{®} L30 D55, HPC-L and PEG were formed on the surface of the dense CP particle in the order sprayed. Each of these layers was approximately 4 µm thick. The polymer coating was tightly adhered to the BHX layer and no void space was found between them. L30 D55, HPC-L and PEG in the polymer coating could not be distinguished because their LACs were comparable. Regions with higher LAC values than the rest of the coating were scattered over the polymer coating. Because the LAC values of the coating components were approximately 70.0 cm\(^{-1}\) or higher, these regions are supposed to be talc, which was added only to the polymer solution as an anti-adherent agent (Yamada et al., 2014). In the case
of Smartseal®-coated microgranules prepared under the similar condition for this Eudragit-coated microgranules, the regions of high LAC values in the polymer coating had been identified to be not BHX but talc by the μCT analyses using two X-ray energies above and below the absorption edge of bromine (Noguchi et al., 2013). The thickness of some talc regions was comparable to that of the polymer coating.

3.3. Structural changes of the excipient particles and polymer-coated microgranules on tableting

Cross sectional images of CL tablet compressed at 5.0 and 10 kN are depicted in Fig. 4a and b, respectively. A decrease of void space was observed as the tableting force increased from 5.0 to 10 kN. The large void space inside the CL particles almost disappeared on tableting, probably because the fibrous cellulose inside CL was packed tightly together with lactose grains. However, the void spaces between compressed CL particles remained. This is because the surface of CL particles was mainly composed of lactose grains (Fig. 1b), which are hard and do not adhere well to each other in the absence of cellulose.

In contrast, PK tablets compressed at 5 and 10 kN (Fig. 4c and d, respectively) did not contain much void space. The compressed PK particles adhered to each other and the boundaries of the particles were difficult to resolve. This is because the PK particles consisted of fine needle-shaped crystals that were much smaller than the lactose and cellulose in CL particle and deformed smoothly even at low tableting force to fill the spaces between and inside the PK particles.

3.4. Interrelation between internal structures and physical properties of tablets

3.4.1. VVR and hardness of tablets

The VVRs of CL and PK tablets are shown in Fig. 5a. As the tableting force increased from 5.0 to 10 kN, the VVR decreased and tablet hardness increased almost linearly. In contrast, the VVRs of
PK tablets were approximately one fifth of those of the CL tablets, even at the lowest tableting force of 5.0 kN. This means that PK was more easily compressed on tableting than CL. The PK tablets showed higher hardness than the CL tablets (Fig. 5b). The binding area between compressed PK particles was larger than that of the compressed CL particles as shown in Fig. 4c and as also indicated by lower VVR values. This would lead to higher hardness of the PK tablets than the CL tablets. Although the VVRs of the PK tablets were almost the same at the three tableting forces used, the tablet hardness increased with tableting force. The void space in the PK tablets was much smaller than that of CL tablets, and the presence of void spaces smaller than the voxel size of the cross sectional images could not be fully evaluated with the VVR values. Such small void spaces might be dominant in the PK tablets. As the tableting force increased, the volume of the small void spaces was supposed to decrease accompanied by the increase of the binding area between sorbitol crystals, which resulted in the increase of the total binding force between sorbitol crystals. This could explain why the hardness of PK tablets increased with tableting force while the changes in VVR were small.

3.4.2. Penetration time and disintegration time of tablets

Buffer solution penetrated into the CL tablets within 5 s (Fig. 5c). A cross sectional image of a CL tablet showed that void spaces topologically connecting the outside and inside of the tablet remained even after compression at 10 kN (Fig. 6a). The solution could easily penetrate into the tablet through these void spaces. The penetration may be also facilitated by the high swellability of cellulose. For these reasons, the CL tablets disintegrated rapidly, within 30 s (Fig. 5d). This suggests that amount of disintegrant can be reduced when tablet formulation was designed using CL. In contrast, the penetration and disintegration times of the PK tablets were much longer, approximately 200 and 500 s, respectively, for tablets compressed at 5.0 kN (Fig. 5c and d). The slower penetration of solution and disintegration of the PK tablets can be explained by their structural features. PK
particles were tightly packed at the tablet surface as well as inside, and there was little void space to promote penetration of solution into the tablet (Fig. 6b).

3.5. Structure of the polymer-coated microgranules in tablets

Most of the polymer-coated microgranules surrounded by excipient particles showed little structural change upon tableting (Fig. 7). The excipient particles in these formulations seemed to cushion the tableting force efficiently in general. In contrast, the microgranules in contact with other microgranules were often severely deformed. This is ascribed to the higher hardness, approximately 800 mN/mm$^2$, of the polymer-coated microgranules, which is 1.5–2 times higher than that of the excipients used (Table 2). The high hardness of CP is consistent with its dense internal structure (Fig. 3a). As well as deformation, the polymer coating was damaged in the CL and PK tablets. When the polymer-coated microgranules were in contact with one another during tableting, shear force was generated along the surface of the microgranules, causing the polymer coating to separate from the core particles and finally tear, as observed in Fig. 7a (i), (ii) and 7b. In the CL tablets, deformation of the polymer-coated microgranules was also found near the region where only the lactose grains of CL were in contact with the polymer-coated microgranule (Fig. 7c). Although CL as a whole particle deformed easily, lactose grains may be hard enough to deform the polymer-coated microgranules and tear the polymer coating during tableting. Void space tended to remain around the compressed CL as mentioned above, and the polymer coating was found to separate from the CP and bulge out towards the space, as in Fig. 7a (iii). This suggests that the void space remaining in the tablets is a factor influencing the damage caused to the polymer coating upon tableting.

Results for the release of BHX from the polymer-coated microgranules and tablets are presented in Fig. 8. Drug release from the polymer-coated microgranules was considerably suppressed by the enteric polymer coating, although some leakage, 17% at 180 min, was observed.
The 10% polymer coating was possibly incomplete in some granules. Alternatively, some regions of the polymer coating were very thin in these formulations because of the presence of talc as mentioned in section 3.2 and the disintegration of talc might cause the formation of pores or regions with a very thin polymer coating during the dissolution test. These may have allowed the dissolution buffer to percolate into the microgranules, resulting in drug leakage.

Drug leakage from the polymer-coated microgranules was increased by tableting. Drug leakage at 180 min was 65% for the PK tablets and 45% for the CL tablets, which is 3.8 and 2.6 times higher than that of the polymer-coated microgranules before tableting, respectively. The drug would leak through the torn regions of polymer coating observed in Fig. 7. The results of the dissolution test also showed that the drug leakage from PK tablets at 180 min was higher by 1.4-fold than that from CL tablets, indicating that the polymer coating was more damaged in the PK tablets than in the CL tablets. This variation may be attributed to the difference in the internal structures of CL and PK. Because PK particles have smaller internal void spaces and higher bulk density than CL particles, fewer PK particles than CL were present when the same weight of excipient was used. As the smaller number of excipient particles were thought to surround polymer-coated microgranules less efficiently upon tableting, direct contact between polymer-coated microgranules occurred more frequently in the PK tablets, which resulted in more extensive breakage of the polymer coating and higher drug leakage. The total drug leakage from tablets did not depend on the tableting force in both CL and PK tablets, indicating that the most of the breakage of the polymer coating occurred at the lowest tableting force of 5.0 kN in these formulations. Because the tablets compressed at less than 5.0 kN were too fragile to handle, it is feasible to reduce not the tableting force but the number of direct contacts between polymer-coated microgranules in tablets to limit the breakage of the polymer coating. The information about the internal structure of these multiple-unit tablets suggests that it would be necessary to develop and use excipients consisting of fine materials to be highly plastic.
and, at the same time, possess a large volume of internal void space to have low bulk density. This should allow the manufacture of multiple-unit tablets with a high content of polymer-coated microgranules while keeping the polymer coating undamaged.

4. Conclusion

Synchrotron X-ray μCT was used to visualize the internal structures of multiple-unit tablets non-destructively, and reveal the structural changes of polymer-coated microgranules and excipients on tableting. The internal structural features of the tablets depended on the structure of the excipient, and these structural properties could readily explain the physical properties of the tablets. The mechanism of breakage of the polymer coating was also elucidated based on the visualized internal structures. The formulation design, understanding of pharmaceutical properties, and quality evaluation of tablets with high degrees of precision and efficiency are possible using the internal structural information provided non-destructively by synchrotron X-ray μCT.

Acknowledgment

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References


Figure captions

**Fig. 1.** 3D images of the CL particle reconstructed from the cross-sectional images. (a) Surface image. (b) Stereoview. Half of the particle is removed to show its internal structure. Images of capillaries have been removed. Contrast of all gray-scale images are enhanced for clarity.

**Fig. 2.** 3D images of the PK particle reconstructed from the cross-sectional images. (a) Surface image. (b) Stereoview showing its internal structure.

**Fig. 3.** (a) Cross sectional image and (b) surface image of a polymer-coated microgranule. Some of the talc regions are exposed on the surface.

**Fig. 4.** Cross sectional images of the center of tablets. The tableting forces and excipients are (a) 5.0 kN and CL, (b) 10 kN and CL, (c) 5.0 kN and PK, and (d) 10 kN and PK.

**Fig. 5.** Physical properties of CL (blue) and PK (red) tablets. (a) VVR, (b) hardness, (c) penetration time, and (d) disintegration time. Each value represents the average ± S.D of three to six measurements.

**Fig. 6.** Void spaces at the surface regions of the tablets. (a) Cross sectional image of the surfaces of CL tablet and (b) PK tablet. The images are perpendicular to the tablet surfaces in contact with the punch surface on tableting. The CL and PK tablets were compressed at 10 and 5.0 kN, respectively. (c) 3D image of the void spaces at the surfaces of CL tablet and (d) PK tablet. Surfaces of the void spaces in the tablets are shown with pale blue.
Fig. 7. Cross sectional images of (a), (c) CL and (b) PK tablets prepared with a tableting force of 5 kN. Damage to the polymer coating is indicated with circles.

Fig. 8. Dissolution profile of BHX from tablets. Symbols in blue and red show sampling points of CL and PK tablets, respectively. Tableting forces were 5.0 (diamonds), 7.5 (squares), and 10 kN (triangles). Green circles show the dissolution profile of polymer-coated microgranules before tableting.
**TABLES**

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

<table>
<thead>
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<th></th>
<th>Drug layering</th>
<th>Polymer coating</th>
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<tr>
<td>Air flow (L/min)</td>
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<td>Inlet air temperature (°C)</td>
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<tr>
<td>Spray rate (g/min)</td>
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<td>4</td>
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<tr>
<td>Spray air flow (L/min)</td>
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<td></td>
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<td>Rotation speed (rpm)</td>
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Table 2. Hardness of the polymer-coated microgranules and excipients. $n=50$ and 10 for the polymer-coated microgranules and excipient particles, respectively.

<table>
<thead>
<tr>
<th>Particle</th>
<th>Hardness (mN/mm²)</th>
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<tr>
<td>Polymer-coated microgranule</td>
<td>817 ± 225</td>
</tr>
<tr>
<td>CL</td>
<td>550 ± 133</td>
</tr>
<tr>
<td>PK</td>
<td>366 ± 125</td>
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</tbody>
</table>
Fig. 1.
Fig. 2.
Fig. 3.
Fig. 4
Fig. 5.
Fig. 6.
Fig. 7.
Fig. 8.
Fig. S1. Particle size distribution of excipient CL (blue diamonds) and PK (red squares).