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PII: S0378-5173(15)30193-9
DOI: http://dx.doi.org/doi:10.1016/j.ijpharm.2015.08.097
Reference: IJP 15180

To appear in: *International Journal of Pharmaceutics*

Received date: 28-7-2015
Revised date: 18-8-2015
Accepted date: 28-8-2015

Please cite this article as: Kajihara, Ryusuke, Noguchi, Shuji, Iwao, Yasunori, Yasuda, Yuki, Segawa, Megumi, Itai, Shigeru, Structural investigation of spherical hollow excipient Mannit Q by X-ray microtomography.International Journal of Pharmaceutics http://dx.doi.org/10.1016/j.ijpharm.2015.08.097

Structural investigation of spherical hollow excipient Mannit QbyX-ray microtomography

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Graphical abstract

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Abstract

The structure of Mannit Q particles, an excipient made by spray-drying a D-mannitol solution, and Mannit Q tablets were investigated by synchrotron X-ray microtomography. The Mannit Q particles had a spherical shape with a hollow core. The shells of the particles consisted of fine needle-shaped crystals, andcolumnar crystals were present in the hollows. These structural features suggested the following formation mechanism for the hollow particles:during the spray-drying process, the solvent rapidly evaporated from the droplet surface, resulting in the formation of shells made of fine needle-shaped crystals.Solvent remaining inside the shells then evaporated slowly and larger columnar crystals grew as the hollowsformed. Although most of the Mannit Q particles were crushed on tableting, some of the particles retained their hollow structures, probably because the columnar crystals inside the hollows functioned as props. This demonstrated that the tabletswith porous void spaces may bereadilymanufactured using Mannit Q.

Abbreviations: μCT, computed microtomography; SEM, scanning electron microscopy

Keyword: Excipient particle, mannitol, tablet, computed microtomography,synchrotron X-ray radiation.

D-Mannitol has been widelyused as a pharmaceutical excipientbecause of its low reactivity and low hygroscopicity. Recently, D-mannitol has beenespecially used for preparing oral disintegrating tablets, because its sweetness can mask the bitterness of drugs. However, excipients made of D-mannitol crystals oftenshow relatively low flowability and low tablet-formability.Mannit Q manufactured by the spray-drying of a mannitol solution was developedto overcome those weaknesses(Segawa et al., 2012). Mannit Qparticles have been revealed to be spherical and hollow by conventional X-ray computed microtomography (μCT). Theshells of the hollow particlesconsist of fine needle-shapedβ-form mannitol crystals of submicrometer thickness. Although Mannit Q shows higher flowability and compressibilitythanD-mannitol crystal powdersowing to thesestructural characteristics,the detailed structureof inside the particles is stillambiguousowing to the limited spatial resolution of the conventional nondestructive X-ray μCT method.The change in structureof the hollow particles on tableting is also unknown. In this study, Mannit Q particles were studied before and after tabletingusing asynchrotron X-ray μCT method with submicrometer spatial resolution (Uesugi et al., 2012; Noguchi et al., 2013), to elucidatein detail the structures of Mannit Q particles and their structural changes on tableting.

Mannit Q (median particle size 37 μm) was obtained from Mitsubishi Shoji Foodtech (Shizuoka, Japan). The Mannit Q was dried at 40°C overnight before use and was sieved into three fractions,< 37 μm (fraction A), 37–53μm (fraction B),and 53–74μm (fraction C). The weight ratio of the three fractions was36:30:34. Each fraction was mixed with 0.5% (w/w) magnesium stearate as a lubricant using a V-shaped rotating mixer (Microtype Transparent Mixer S-3, Tsutsui Rikagaku Kikai Co., Ltd., Tokyo, Japan) at 35 rpm for 5 min. Tableting was conducted using a single-punch tablet machine (TAB ALL N30-EX, Okada Seiko Co., Ltd., Tokyo, Japan) with a flat-faced punch of 8 mm in diameter. Compression forces of 5.0, 7.5, and

10 kN were used. The weight of each tablet was 250 mg. The hardnesses of five randomly-selected tabletswere measured with a PC-30 hardness meter (Okada Seiko Co., Ltd., Japan).The disintegration times of six tablets in distilled waterwere measuredat 37.0°Cusing a disintegration tester (NT-1HM, Toyama Sangyo Co., Ltd., Osaka, Japan) according to Japanese Pharmacopoeia XVI.Synchrotron X-ray μCT measurements of Mannit Q particles and tablet fragments were conducted at BL37XU of SPring-8 (Hyogo, Japan), which wasequipped with a μCT apparatus (Uesugi et al., 2012; Suzuki et al., 2011). Mannit Q particles were put into a Lindemann glass capillary with a diameter of 0.3 mm. Cubic fragments of approximately 500–600 μm in length were cut out from the center of Mannit Q tablets and were adhered to the tip of glass rods with cyanoacrylate-based bonding agent (Kajihara et al., 2015). The conditions for theμCT measurements of these samples wereset as usually employed for μCT measurementsof fine granular pharmaceutical samples(Noguchi et al., 2013).Briefly, the X-ray energy was set at 8 keV,900 parallel projection transmission images were recorded in 0.2° stepswith continuous rotation at 25°C, and the exposure time for each transmission image was 150 ms. Cross-sectional images with a voxel size of 0.506×0.506×0.506 μm^3were calculated using the *CBP*software package (Uesugi, 2004). Image analyses were performed using *SLICE* (Nakano et al., 2006) and*ImageJ*(Schneider et al., 2012).The roundness of the Mannit Q particles (n = 3–4) was calculated from their cross-sectional images by μCT analyses by using*ImageJ*. The void–voxel ratio (VVR) defined below was calculated from the cross-sectional imagesto evaluate the porosity of the Mannit Q particles and tablet fragments:

$$\mathrm{VVR} = \frac{\text{Number of void voxels in the sample}}{\text{Total number of voxels of the sample}} \times 100\ (\%)$$

wherevoid voxel was defined as a voxel with a linear absorption coefficient of less than 0.3 cm^{-1}.The surface structure of the Mannit Q particleswas observed by scanning electron microscopy (SEM;TM3030,Hitachi High Technologies, Tokyo, Japan). The particleswere

placed on adhesive tape and were sputter-coated with gold prior to SEM imaging.

The cross-sectional images of the Mannit Q particles byμCT analyses confirmed that they hada highly spherical shape with a hollowcore (Fig. 1a). The roundness of Mannit Q particles of fractions A, B, and C were0.982±0.01, 0.963 ±0.03, and 0.952±0.05, respectively. The shell thicknesses of the particles were 2–6 μm. Small pores of 1–2 μmin diameter were found in the shells and were also observed in the surface SEM images (Fig. 1b). The VVR values of Mannit Q particles of fractions A, B, and C were 39.1 ±4.6%, 40.1 ±5.8%, and 44.6 ± 4.4%, respectively. Theseresults indicatedthat the particles were highly spherical and had large void spaces inside the shell independent of the particle diameter. The cross-sectional imagesalso revealed that columnar mannitol crystals of 2–5 μm thicknesshad grown insidethe hollows (Fig. 1c).The number of Mannit Q particles in which columnar mannitol crystals were present was countedby inspecting the cross sectional images visually, and the ratio is shown as a function of particle diameter in Fig. 2. The ratio increased as the particle diameter increased, and all particles with a diameter larger than 50 μm containedcolumnar crystals.

These structural features of Mannit Q suggested the mechanism of how the spherical hollow particles formed during the spray-drying process (Fig. 3).During the process, the mannitol solution forms spherical dropletsas it is sprayed from the nozzle.The solution would evaporate so rapidly from the surfacethat fine needle-shapedmannitol crystalswould precipitate immediately and form spherical shells.Vapor from solution trapped inside the spherical shellswould slowly come out through the pores of the shells. The evaporation of the solution inside the shell would be so slow that much larger mannitol crystals could grow inside the shell, resulting in the formation of a hollow structure containing columnar crystals.Becauseit would takea longer time for the solution inside the shells of larger droplets to evaporate, such columnar crystals would have even more chance to grow. This could explain why most of the larger

106 particles contained columnar crystal in their hollows, as shown in Fig. 2.D-Mannitol formed
107 β-form crystals in the spray-drying process of Mannit Q, in spite that excipients often precipitate
108 as amorphous in spray drying (Chidavaenzi et al., 2001). In the crystal structure of β-form, each
109 hydroxyl moiety of D-mannitol molecule formed two hydrogen-bonds and total 12
110 hydrogen-bonds per one D-mannitol molecule were formed (Botezand Stephens, 2003). The
111 tight hydrogen-bond network might promote the rapid nucleation and growth of not the
112 amorphous but the crystals at the surfaces of the sprayed droplets as well as the in the hollows
113 of Mannit Q. β-Form crystal structure also indicated that the hydroxyl moieties of D-mannitol
114 molecules would be exposed on the surface of the crystals. The exposed hydroxyl moieties
115 would form hydrogen bonds with those of other crystals, which might contribute to the tight
116 adhesion between needle-shaped crystals and the formation of the hard shells.
117 The cross-sectional images of tablet fragmentsand the physical properties of the tablets are
118 shown in Fig. 4.Surprisingly, some of the particles in the tabletsretained theirhollow structures
119 even at the highest compression force of 10 kN, indicating that spherical hollows were
120 distributed sporadically in theMannit Q tablets. Columnar crystals were found in almost all the
121 hollows remaining in the tablet fragments. The hollow structures in the tablets were retained
122 probably because the columnar crystals in the hollows functioned as props of the hard shells
123 against the compression force. Most of the Mannit Q particles in the tablets were crushed by the
124 compression force.Closepacking of the fine needle-shaped crystals increased the binding area
125 and therefore binding force between them, and contributed to enhancing the tablet hardness.
126 Indeed, VVRdecreased, hardness increased, and disintegration time elongated as compression
127 force increased,regardless of the Mannit Q fractions used. However, the increase in hardness
128 with compression force was most prominent in tablets made of fraction A. The ratio of fine
129 particles of Mannit Q less than 10 μm diameterin fraction A would be higher than those in

fractions B and C. These fine particles would have filled the space between larger particles on tableting and thereby aid the formation of the close packing especially at higher tableting compressing force.

In conclusion, synchrotron X-ray μCT analyses revealed thatMannit Q is formed ofspherical particles with hollows containingcolumnarmannitol crystals. The unique hollow structure was partly retained even in tablets prepared at high compression force. Our results demonstrate that tablets with porous void spaces, which might enhancetheliquid penetration into the tablets, may bereadily manufactured using Mannit Q as the main excipientor possibly as an additive.

Conflict of interest

YY and MS are employees of Mitsubishi Shoji Foodtech. The other authors have no potential conflict of interest to declare.

Acknowledgments

The synchrotron radiation experiments at BL37XU were performed with the approval of the Japan Synchrotron Radiation Research Institute (JASRI; Proposal Nos. 2014B1120 and2013A1187). This work was partly supported by JSPS KAKENHI (Grant Nos. 26460224, 26460039 and26460226).

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177

Figure captions

Fig. 1. (a) Cross-sectional image of Mannit Q particles byμCT analyses. X-ray linear attenuation coefficients (LACs) between 0 and 70 are shown in grayscale with 70 as white.The calculated LAC of β-form mannitol crystal is 11.1 cm^{-1}.The sample capillary has been removedfrom the image for clarity. (b) SEM image of Mannit Q surface. (c) Three-dimensional stereoview images of Mannit Q particle reconstructed from the cross-sectional images byμCT analyses.Half of the particle is removed to show itsinternal structure.

Fig. 2. Ratio of Mannit Q particles possessing columnar crystals in their hollows(*n*=8–40).

Fig. 3. Possible scheme for the formation of Mannit Q particles by spray-drying.

Fig. 4. (a) Cross-sectional images of tablet fragments. Bars at the lower right of each image are scales indicating 50 μm length. (b) Hardness, disintegration time, and VVR of the tablets.

Figure(s)

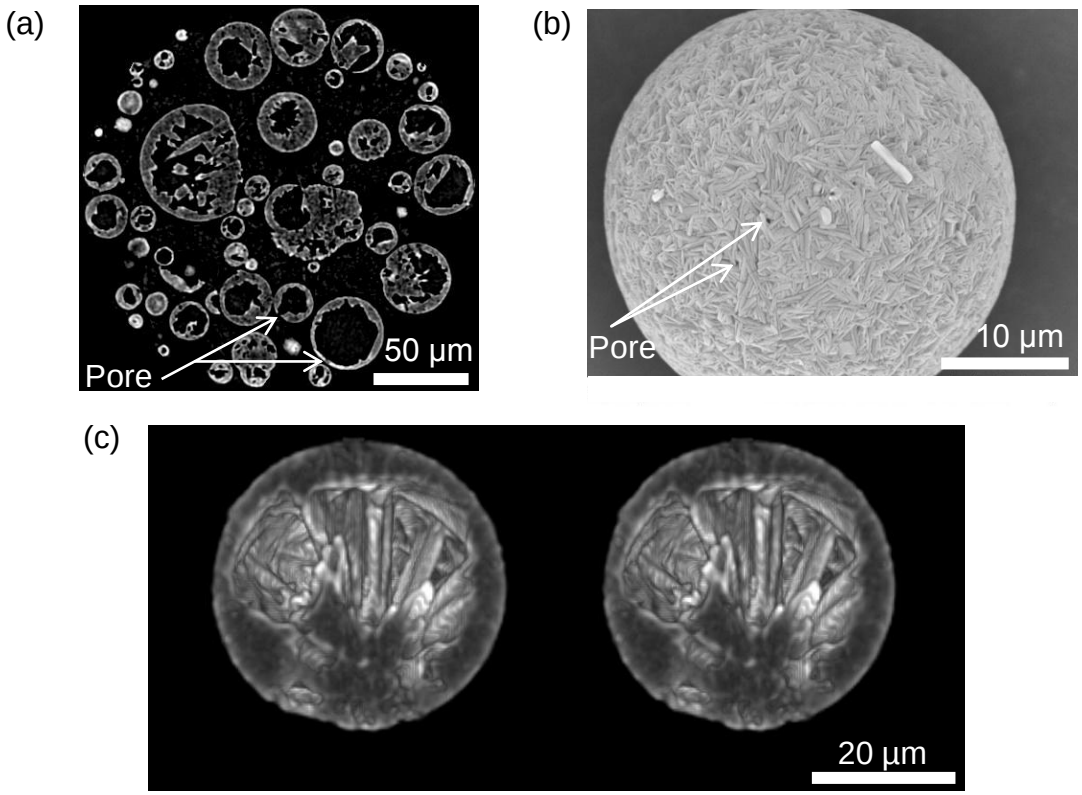

Fig.1

((c) is a stereo figure, so the distance between centers of two images should be 60±3 mm)

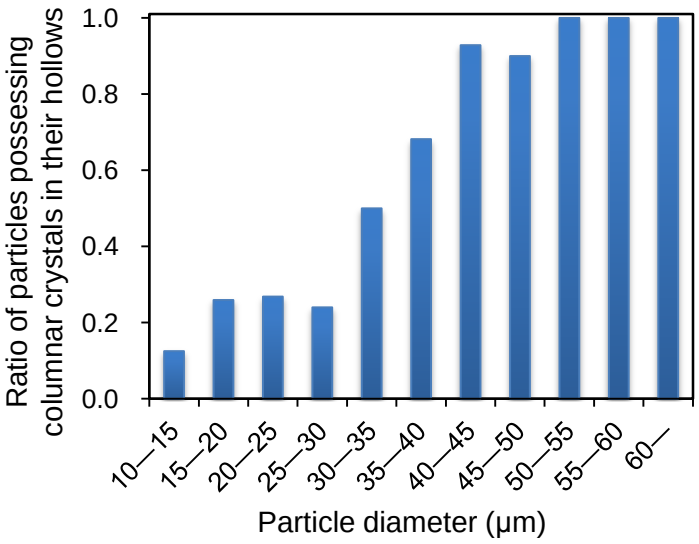
Ratio of particles possessing columnar crystals in their hollows
1.0
0.8
0.6
0.4
0.2
0.0
10—15
15—20
20—25
25—30
30—35
35—40
40—45
45—50
50—55
55—60
60—
Particle diameter (μm)

Fig.2

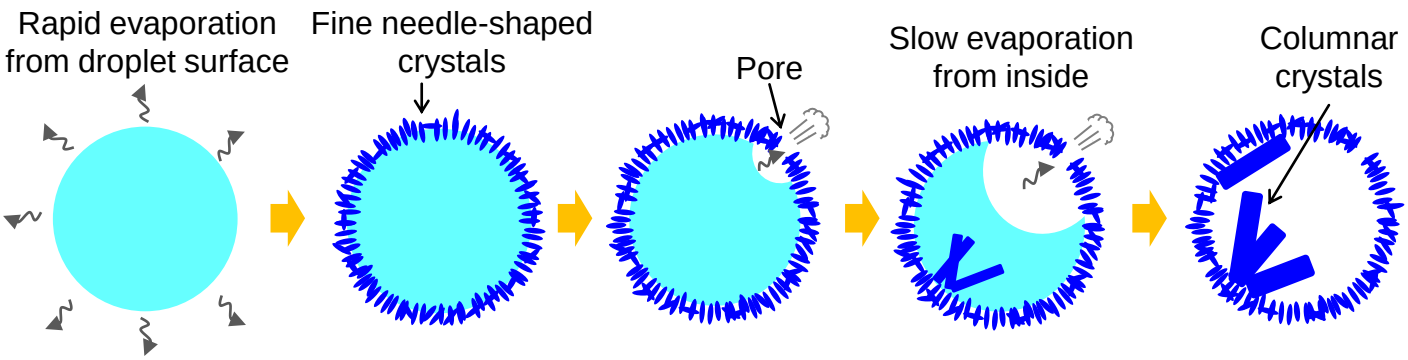
Rapid evaporation
from droplet surface
Fine needle-shaped
crystals
Pore
Slow evaporation
from inside
Columnar
crystals

Fig. 3

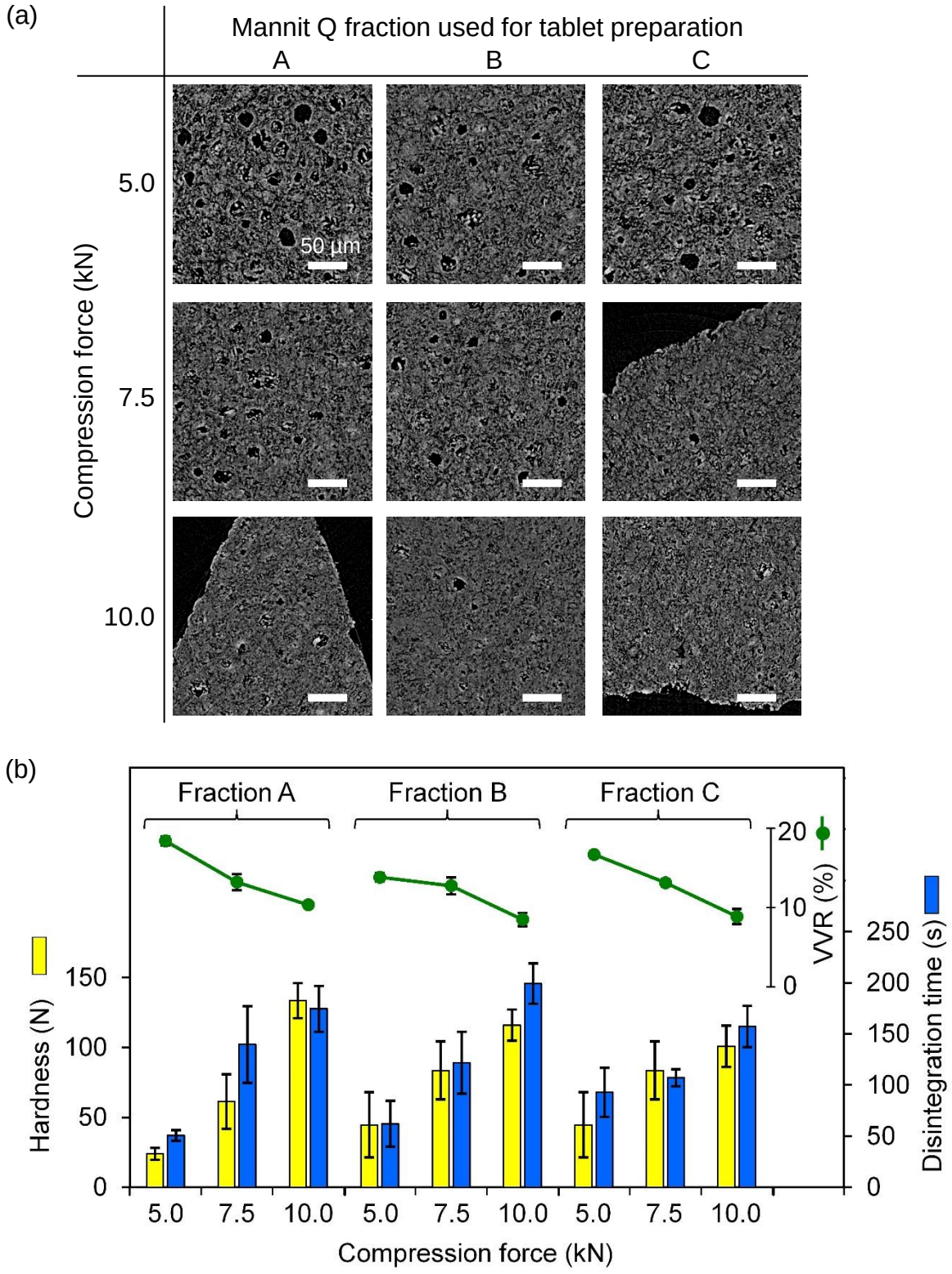
(a)
Mannit Q fraction used for tablet preparation
A
B
C
Compression force (kN)
5.0
7.5
10.0
50 µm
(b)
Fraction A
Fraction B
Fraction C
Hardness (N)
VVR (%)
Disintegration time (s)
Compression force (kN)

Fig. 4