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Mechanism of the formation of hollow spherical granules using a high shear granulator

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ABSTRACT

Recently, we have developed a novel granulation technology to manufacture hollow spherical granules (HSGs) for controlled-release formulations; however, the mechanism of the granulation is still unclear. The aim of this study is to determine the mechanism of the formation of the HSGs using a high shear granulator. Samples of granulated material were collected at various times during granulation and were investigated using scanning electron microscope and X-ray computed tomography. It was observed that the granulation proceeded by drug layering to the polymer, followed by formation of a hollow in the granule. In addition, it was also found that generation of a crack in the adhered drug layer and air flow into the granules might be involved in forming the hollow in the structure. Observation of the granulation of formulations with different types of drugs and polymers indicated that negative pressure in the granules occurred and the granules caved in when the hollow was formed. The hollow-forming speed and the shell density of the hollow granules depended on the particular drug and polymer. Taken together, the granulation mechanism of HSGs was determined and this information will be valuable for HSGs technology development.

1. Introduction

Controlled-release (CR) solid dosage formulations are frequently used to change the drug absorption profile from gastrointestinal fluid. There are two types of CR technology: single unit and multiple unit (Abdul et al., 2010). The multiple unit type has several advantages over the single unit type in terms of improved bioavailability and reduced local drug concentration, as well as reduced side effects (Clarke et al., 1995). The representative multiple unit type are fluidized bed coated particles and extrusion-spheronized particles. The particles prepared by fluidized bed coating technology have good CR properties and suitable physicochemical properties for the tableting process. On the other hand, the fluidized bed coating process is time-consuming, especially in the case of preparing formulations with a high drug content or high polymer loading (Teunou and Poncelet, 2002). Extrusion-spheronization is a popular CR technology for preparing high drug content formulations (Kondo et al., 2015). However, the spheronized granules have a large particle size that sometime causes content uniformity problems in tableting process (Wagner et al., 1999). Hence, the invention of a manufacturing technology to prepare high drug content CR granules with good physicochemical properties preferable for tableting is desirable. We have recently developed a manufacturing technology named "OPUSGRAN®" for preparing CR granules as described previously (Asada et al., 2017). This technology can manufacture hollow spherical granules (HSGs) in a simple manner, just by spraying a solvent onto a powder of the drug and polymer during high-shear granulation. Granules prepared by this technology can obtain a high drug content of over 90%. The granules also have good physicochemical properties preferable for tableting and good CR properties.

To date, there have been two reports of such hollow-structured granules manufactured by high-shear granulation (Kulinowski et al., 2016; Hapgood and Khanmohammadi, 2009). However, hollow was formed in a drying process after high-shear granulation, and the obtained granules did not have the uniform shape and size. In fluidized bed granulation, hollow granules have also been reported (Ansari and Stepanek, 2006); the hollow was formed in granulation process, however, the granules showed a relatively broad particle size distribution, unstructured and porous structure. The differences in granule

Abbreviations: HSGs, hollow spherical granules; CR, controlled-released; PSD, particle size distribution; SEM, scanning electron microscope; X-ray CT, X-ray computed tomography

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properties between our granulation and other granulations must be the way to form hollow in the granules. As the most important factor in forming the spherical hollow, air must be generated or blown into the hollow space of the granules. In fluidized bed granulation, air might flow into the hollow space through the porous cavities. On the other hand, since our HSGs have a heavy shell and there is no cavity in the shell, the hollow-forming mechanism of the HSGs remains to be solved.

The aim of the present study is to determine the mechanism of the hollow formation in the HSGs by our manufacturing technology. We prepared granules using a high-shear granulator, collected the granules at specified times, and observed the hollow-forming process of the HSGs by scanning electron microscope (SEM) and computed tomography (CT) using synchrotron X-ray radiation.

2. Methods

2.1. Materials

Ammonio methacrylate copolymer (Eudragit® RSPO) was purchased from Evonik Degussa Japan Co., Ltd. (Tokyo, Japan). Fractioned Eudragit® RSPO (149–210 μm) was prepared by sieving the commercial materials. Hydroxypropylcellulose (HPC-SL) was purchased from Nippon Soda. Co., Ltd. (Tokyo, Japan). Fractionated HPC-SL was prepared by sieving the commercial material (149–210 μm). Bromhexine and phenytoin were purchased from Sumitomo Dainippon Pharma Co., Ltd. (Osaka, Japan).

2.2. Preparation of granules

The powders listed in Table 1 were blended in a polyethylene bag for 5 min and fed into a high-shear granulator (MECHANOMILL, model: MM-20N, batch size: 100 g, Okada Seiko Co., Ltd., Tokyo, Japan). MECHANOMILL has cylindrical column vessel (110 mm radius and 100 mm height), 108 mm diameter agitating straight blade and no chopper. An angle of the blade is 35 degrees. The solvent was sprayed onto the powders with the 3 g/min solvent speed and 0.11 MPa spray air pressure. During the spraying, the powders were mixed by the agitator rotated at 600 min^{-1}. The added amounts of the solvent were 24 g, 24 g and 21 g in HSG-1, HSG-2 and HSG-3 granulation, respectively. To determine the granulation process precisely, granules were collected at indicated time on the granulation. The solvent-wet granules of the collected samples and the final products were subsequently dried using a shelf dryer (42 °C, over 24 h) and sieved (149–350 μm) to give the HSGs. The mass % yield of granules (149–350 μm sieve fraction) compared to whole batch is over 90% in all batches. The total granulation time and residual solvent content was about 10 min and 1.0% in all batches.

2.3. Characterization

2.3.1. Surface and cross-sectional images of HSGs

Surface and cross-sectional images of the HSGs were observed by SEM using a TM3030 MINISCOPE scanning electron microscope (Hitachi, Tokyo, Japan). All of the samples were sputter coated with an Au alloy using an ion sputtering system (E1030, Hitachi, Tokyo, Japan) before being observed by SEM. Cross-section of the granules was made by cutting the granule with a surgical knife.

Table 1
Formulation of the granules.

	HSG-1	HSG-2	HSG-3
Bromhexine hydrochloride (g)	80	–	80
Phenytoin (g)	–	80	–
Eudragit RSPO (149–210 μm) (g)	20	20	–
HPC-SL (149–210 μm) (g)	–	–	20
Total (g)	100	100	100

2.3.2. Inner structure of HSGs

The inner structure of the HSGs was non-destructively observed using synchrotron X-ray CT measurement system. The synchrotron X-ray CT measurement of the granules was performed at SPring-8 BL37XU equipped with μCT instrument as essentially same as described by Noguchi et al. (2013). X-ray linear attenuation coefficients between 0 and 70 are shown in grayscale with 70 as white.

2.3.3. Particle size distribution (PSD)

Each sample was dispersed in purified water and the PSD of the suspended samples was measured by a laser diffraction particle size analyzer (Mastersizer2000, Spectris Co., Ltd., Tokyo, Japan).

2.3.4. Sphericity

The granules were imaged using a Microscope digital camera (DP10, Olympus Corporation, Tokyo, Japan). The sphericity was measured with image analysis measurement (WinROOF, MITANI corporation, Tokyo, Japan) ($n = 30$). The sphericity was defined by their roundness (P_t/P_r), where P_t is the theoretical perimeter length of a perfectly spherical granule having the same area as the particle under analysis, and P_r is the actual perimeter length of the particle.

3. Result

3.1. Evaluation of the morphological characteristics of HSG-1 granules during granulation

To determine the granulation process precisely, SEM and X-ray CT analyses were conducted with granules that had been collected at the indicated times on the granulation. The results of the SEM observations of the HSG-1 samples are shown in Fig. 1, and the particle size distribution and sphericity of the HSG-1 samples are shown in Table 2. From these data, it was confirmed that the particle size, sphericity, and surface smoothness of the HSG-1 granules increases in a time-dependent manner as the granulation proceeds. The SEM observations of the cross sections of HSG-1 samples are shown in Fig. 1. After a granulation time of 2 min, there are dark gray and light gray areas in the surface of the cross section. Judging from the position, the outer light gray area might indicate a mainly drug-containing area and the inner dark gray area might indicate a polymer-containing area. At 4 min, the thickness of the shell consisting of the light gray area increased and a small hollow was seen in the dark gray area. At 6 min, the shell thickness had increased and the hollow in the dark gray area had expanded. At 7 min, the hollow in the dark gray area had completely expanded; however, not all the drug particles appeared to be completely adhered to the granules. At 8 min, all the drug particles were completely adhered to the granules and a slight increase in the shell thickness was observed.

3.2. Evaluation of the morphological transition of HSG-1 granules using X-ray CT

The results of the X-ray CT observations of the HSG-1 samples are shown in Fig. 2. As mentioned previously (Noguchi et al., 2013), the bromine in the structure of bromhexine hydrochloride can be clearly distinguished from carbons in X-ray CT analysis. As observed in the SEM images, there are following two areas; a dark gray area which represents the existence of mainly polymer and a light gray area which represents the existence of mainly drug, in the X-ray images of the granules. At 2 min, drug particles began to adhere to the polymer particles. At 4 min, the thickness of the light gray layer had increased and a part of the dark gray area had caved in. The hollow was not observed in the X-ray CT analysis at 4 min in contrast to the SEM images. This difference might be because of sample variations among