Design of Dry Powder Inhalation by a Novel Supercritical Freeze Granulation

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Abstract

In the particulate design for dry powder inhalation (DPI), drug particles are required to have a good flowability in handling and dispersibility when delivering the drug to lung in order to treat effectively the pulmonary and systemic diseases. In this study, a simple preparation process of drug particles for DPI has been developed by using a novel supercritical carbon dioxide freeze granulation based on rapid expansion of supercritical solutions (RESS process). When a drug dissolved into supercritical carbon dioxide is sprayed through a nozzle into atomosphere, frozen carbon dioxide lumps are generated owing to the rapid temperature drop (i.e., Joule-Thomson effect), resulting in the formation of agglomerate of fine drug particles. The effect of the operating parameters such as temperature and pressure on granule properties was investigated.

1. Introduction

In the pharmaceutical industry, inhalation is a targeting to lungs, which is now extensively used in asthma therapy [1]. It is also expected that inhalation can be used as a self-medication, in which medical doctors or nurses are not required [2]. Dry powder inhalation (DPI) is one of the most promising types of inhalation due to its advantages, such as good portability and less environmental load. In this system, drug particles can be delivered through the inspiratory flow of the patient. The size of drug particles should be designed in the range of 0.3 - 8 μm of aerodynamic diameter in order to deliver the drug effectively to the targeting region such as bronchi or alveoli [3, 4]. However, it is very difficult to handle such fine drug particle due to its strong cohesive force, and also it causes adhesion in capsule or inhaler. Therefore, it is very important to prepare the drug particles having a good flowability and dispersibility for DPI.

So far, preparation processes of the drug particle for DPI have been proposed such as pressure swing granulation [5] and nano composite granulation [6]. However, these processes are relatively complicated, thus it is required to develop more simplified one.

Recently, a rapid expansion of supercritical solutions using supercritical fluid (RESS process) has gathered special interest since fine drug particle can be easily produced. This process has the following mechanism [7- 10]; material dissolved into supercritical fluid (SCF) is sprayed through a nozzle into

atmosphere with rapidly expansion of its volume and decreasing the density, followed by a rapid drop of the solubility. Finally, it leads to generate micronized drug particles. Since the precipitation time is incredibly short, the size distribution becomes narrow [11, 12]. When CO_2 is used as the SCF, dry ice can be easily produced due to the rapid drop of temperature of the SCF (i.e., Joule- Thomson effect) at higher flow rate. This dry ice agglomerates the precipitated fine drug particles.

In this study, a novel and simple particulate process for DPI has been proposed by the supercritical freeze granulation (FG-SCF) utilizing produced dry ice in RESS process. In this process, drug particles can be simultaneously micronized and granulated. Also, it is expected that obtained granules have soft and suitable strength, since dry ice quickly sublimates from granules at room temperature and pressure [13]. The effect of the operating parameters on granule properties such as granule size distribution and dispersibility was investigated, and the mechanism of the granulation was discussed.

2. Experimental

Experimental set-up

A schematic diagram of the experimental apparatus of FG-SCF is shown in Fig. 1. This process consists of SC-CO_2 quantitative supply system, vessel (770 ml), spray nozzle (ID: 4.0 mm) and particle collector. The flow rate of liquefied CO_2 was measured by using a flowmeter, and then the liquefied CO_2 was supplied to pre-heater using a high pressure pump (NP-AX-15, Nihon seimitsu kagaku Co., Ltd). CO_2 reached at supercritical state at a given temperature and pressure, and SC-CO_2 was continuously sprayed through the nozzle under the constant temperature and pressure. CO_2 could be easily removed from a granule due to the subliming of dry ice by the hot air (420K).

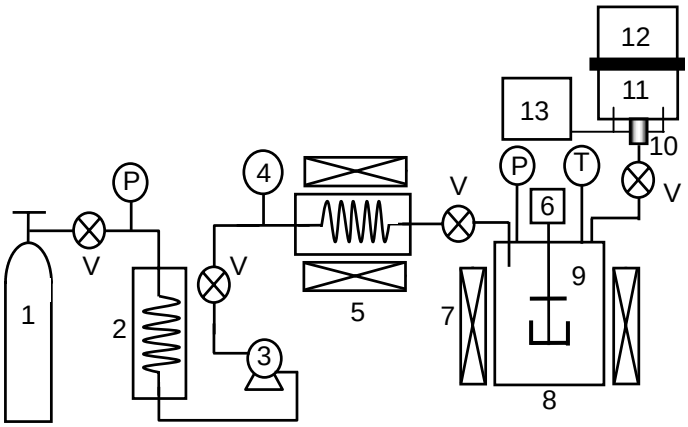


Figure 1. Schematic diagram of experimental set-up. (1) CO_2 cylinder, (2) Cooler, (3) Pump, (4) Flowmeter, (5) Pre-heater, (6) Motor, (7) Heater, (8) Vessel, (9) Paddle, (10) Nozzle, (11) Vessel, (12) Particle collecter, (13) Hot air generator, P : Pressure gauge, V : Valve, T : Thermometer.

Experimental procedure and operating parameters

Theophylline ($C_7H_8N_4O_2$, D_{50}: 75.3 μm, ρ: 0.426 g/cm^3) [11], which is well used as asthma therapy, was used as model drug. D-mannitol ($C_6H_{14}O_6$, D_{50}: 33.1 μm, ρ: 0.467 g/cm^3) [14] was also used as an excipient. The charged mass of theophylline was 5.0 g, and the weight content, *C,* of D-mannitol was 0- 50 wt%. The liquefied CO_2 became supercritical state at a certain temperature (T = 323- 383 K) and pressure (P = 8- 15 MPa), and theophylline was dissolved in SC-CO_2 by agitating for 20 minutes. The liquefied CO_2 was continuously supplied using the pump in order to keep constant pressure and temperature in the vessel. The SC-CO_2, with dissolved theophylline was sprayed, and then the produced granules were collected.

Evaluation method

The granule size (Ferret number diameter) and the degree of circularity were measured by the image analyzer (Luzex-FS, Nireco Co., Ltd.). The degree of circularity, ϕ, was calculated by the following equation:

$$\phi = 4\pi A / L^2 \quad (1)$$

where, *A, L* show projected area and boundary length of projected image, respectively. The discharge rate was defined as the granule flowability. The discharge rate, *V*, was also calculated by the following equation:

$$V = m / t \quad (2)$$

where, *m*, *t* show the mass of granules in a funnel and the discharging time, respectively. The funnel is made of polyethylene (bore: 45 mm, foot ID: 5.5 mm, foot length: 45 mm). The bulk density, ρ, was measured by using 10 ml messzylinder. The dispersibility of granules was evaluated by a cascade impactor (AN-200, Tokyo Dylec Co., Ltd.) shown in Fig. 2. First, 20 mg of granules were filled into a hydroxy-methylcellulose capsule (Qualicaps Co.,Ltd.), and then charged into a inhaler (Jethaler, Hitachi Co., Ltd.). The device was connected with the cascade impactor via a throat. The granules were inhaled for 5 seconds on the constant pumping rate of 472 ml/s. The cascade impactor has structure that the screens of small pore diameter are upheaped in ascending order. Dispersed drug particles are collected on each stage depending on the particle size. The collected theophylline particles on each stage were dissolved into ethanol, and the absorbance of that was measured by using UV spectral photometer (UV-160, Shimazu Co., Ltd) at a wavelength 270 nm. Drug deposition ratio was evaluated by the mass fraction of fine particle (FPF: 0.3- 8 μm), which corresponds to the stages 2- 5.

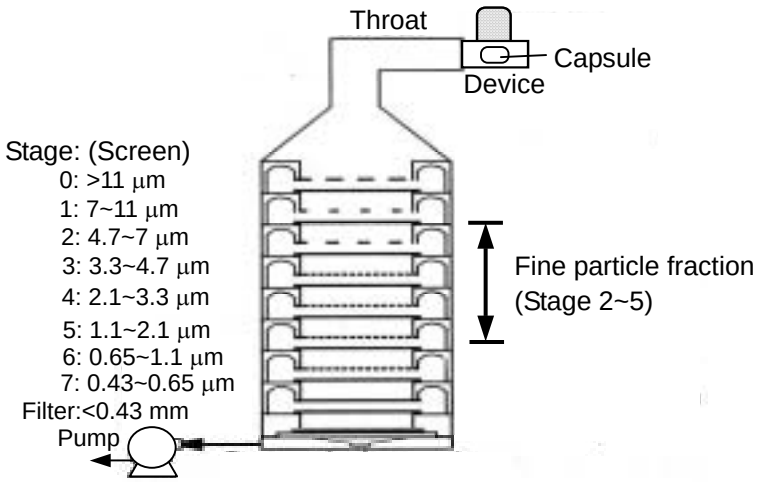
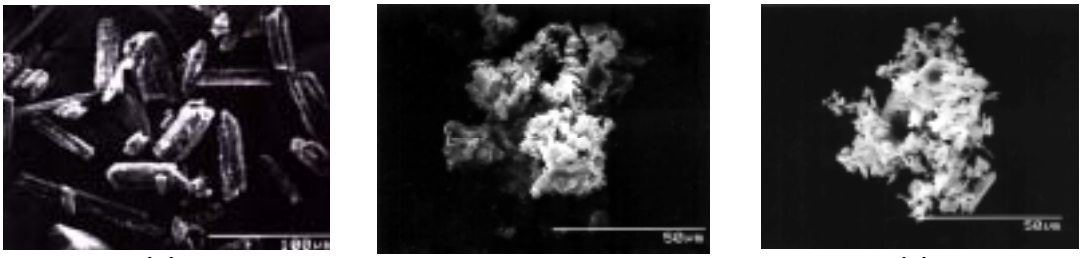


Figure 2. Schematic diagram of cascade impactor.

3. Results and discussion

Effect of operating parameters on granules properties

Figure 3 shows the SEM images of granules and original theophylline particles. Original particles were needle-like shaped, and the obtained granules by FG-SCF composed of micronized particles with large voids.



(a) (b) (c)

Figure 3. SEM photographs of granules. (a) Original, (b) FG-SCF (10 MPa, 343 K), (c) FG-SCF (10 MPa, 343 K) with D-mannitol.

The effects of temperature, *T,* and pressure, *P,* of SC-CO_2 on granule properties are shown in Figs. 4 and 5. Generally, lower *T* and higher *P* results in a lower temperature of SC-CO_2 after spraying [13]. Therefore, the granule size increased and the size distribution became narrow under the lower *T* and higher *P*, because the dry ices were more easily generated, and they led to agglomerate micronized drug particles. In evaluation of the flowability, original theophylline particles couldn't discharge from a funnel because of the high cohesive force. However, the flowability of granules was significantly improved by increasing of particle size as shown in Fig. 5. In addition, the bulk density decreased and the void increased under the conditions that the dry ice could be easily produced. It is considered that this structure effectively contributes to increase dispersibility of granules in inhalation.

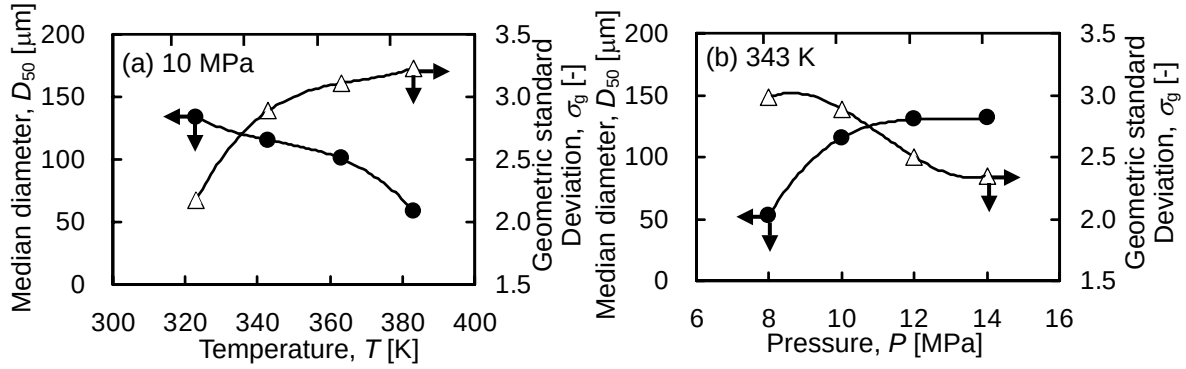


Figure 4. The effect of temperature and pressure on median diameter and geometric standard deviation (without excipient). (a) P =10 MPa, (b)T =343 K.

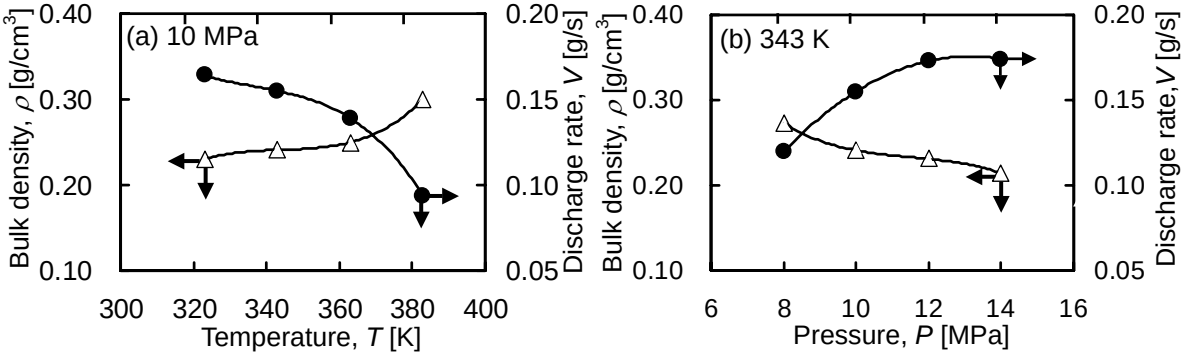


Figure 5. The effect of temperature and pressure on bulk density and discharge rate (without excipient) (a) P =10 MPa, (b)T =343 K.

Figure 6 shows the effect of D-mannitol on the granule properties. In the higher C, the flowability increased, because the granule shape became spherical, and the cohesive force decreased with an increase in the content of D-mannitol.

As a result, the mechanism of the FG-SCF is analyzed; original drug particles are micronized by the spraying of SC-CO_2, which are agglomerated by the simultaneously generated dry ice.

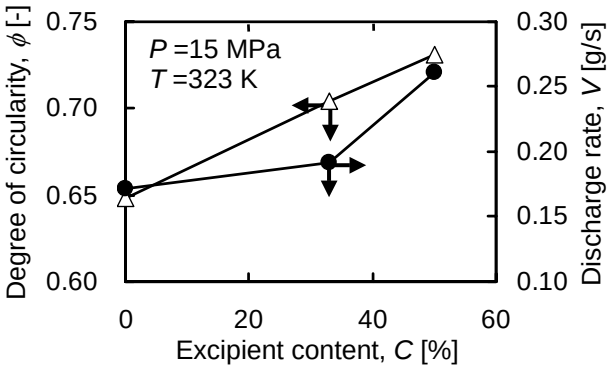


Figure 6. Change in degree of circularity and discharge rate with excipient content (P =15 MPa, T =323 K).

Dispersibility of granules

The effects of operating parameters on the dispersibility of granules in inhalation were shown in Fig. 7. The higher deposition ratio of granule within the FPF (stage 2- 5) was obtained under the conditions of lower *T* and higher *P* of SC-CO_2, because the granules could be easily dispersed under those conditions due to their larger internal void. It is noteworthy that the deposition ratio of the granules prepared by the FG-SCF within FPF was more than twice that of the granules obtained by the conventional methods, such as a binderless granulation [15]. With an increase in the *C*, the higher deposition ratio within FPF was observed, because the mass of residual granules in capsule and device decreased as shown in Fig. 7(c). It was concluded that the adhesion of drug particles onto inside wall of the device affected on the deposition ratio within the FPF.

The dispersibility of granules was also evaluated after the treatment of anti-electrostatic coating (positive ionic surfactant) onto the inside wall of the device (Fig. 8). The deposition ratio within the FPF significantly increased after the treatment, while large amount of granules still remained in the device without the treatment. These results indicated that the prevention of electrostatic charge contributed very much to the improvement of the granule dispersibility.

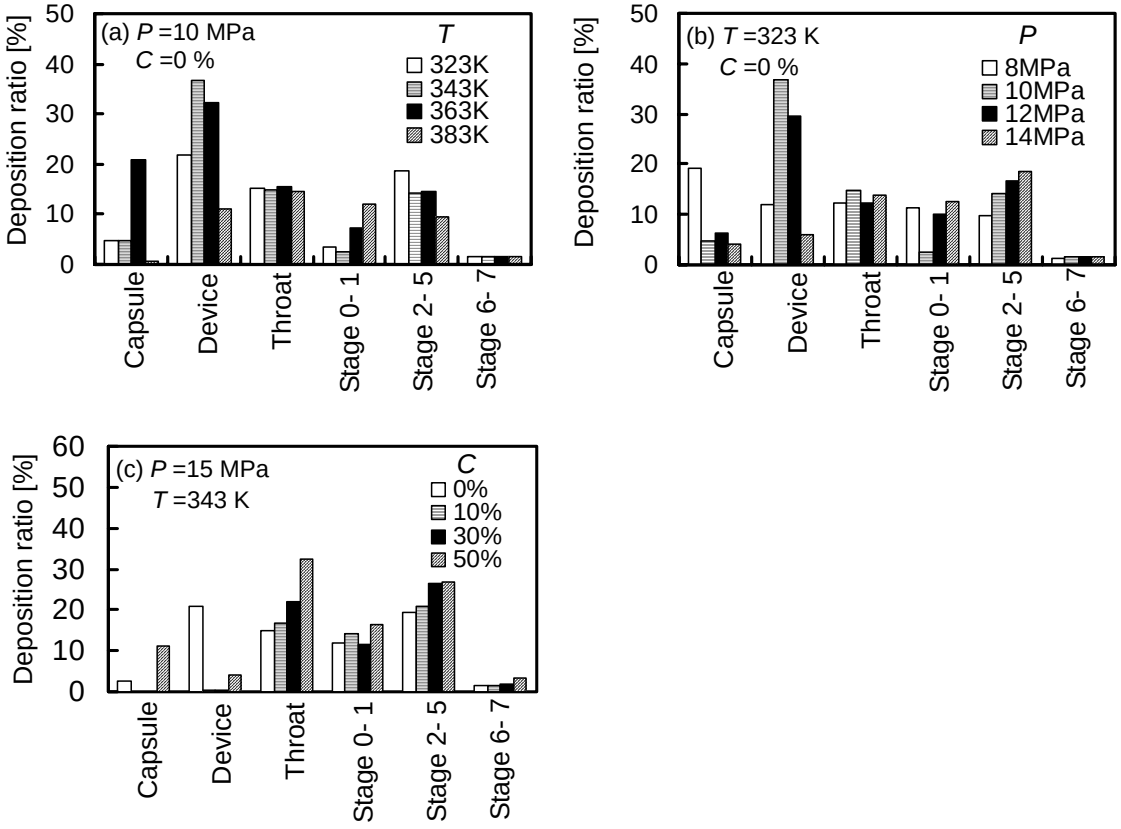


Figure 7. The effect of operating parameters on deposition ratio.
(a) *P* =15 MPa, *C* =0 %, (b) *T* =343 K, *C*=0 %, (c) *P* =15 MPa, *T* =343 K.

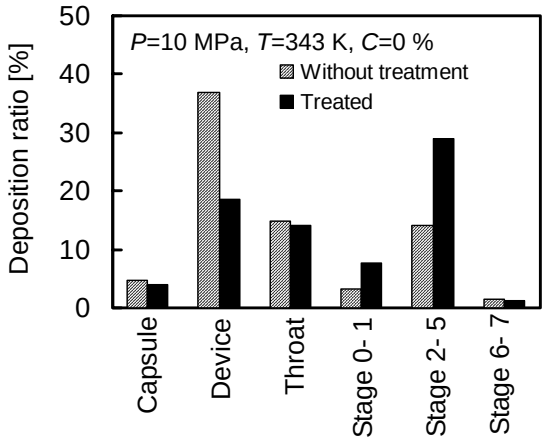


Figure 8. The effect of electrostatic treatment on deposition ratio.

4. Conclusions

In this study, a novel and simple production process of drug particles for DPI was developed by using supercritical freeze granulation (FG-SF). Conclusions are summarized as follows:

1) The granules prepared under the lower T and higher P of SC-CO_2, in which dry ices were easily generated, showed a good flowability with large granule size and suitable strength. The large void contributed to the higher dispersibility within the FPF.

2) The flowability and dispersibility of granules with containing the excipient were improved due to the spherical shape and the decreased cohesive force with an increase in the C. In addition, it is also found that the control of electrification of the device was very important for the better improvement of the dispersibility.

3) The mechanism of the FG-SCF was discussed. This granulation method can be well used to particulate design for DPI.

5. Notation

C: Mass content of excipient in granules	[wt%]
P: Pressure of SC-CO_2	[MPa]
T: Temperature of SC-CO_2	[K]
D_{50}: Median diameter	[μm]
σ_g: Geometric standard deviation	[-]
ρ: Bulk density	[g/cm^3]
ϕ: Degree of circularity	[-]
A: Projected area	[m^2]
L: Boundary length of projected image	[m]
V: Discharge rate	[g/s]
m: Mass of filled granules	[g]
t: Discharging time	[s]

6. References

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