2005年7月にGlasgowで行われた第7回化学工学世界会議において発表した論文に加筆したものです。

Particle design for dry powder inhalation by using spouted bed binderless granulation

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Abstract

Recently, a dry powder inhalation (DPI) has been attracted attention as a cure for bronchial asthma. The medicine was inhaled to bronchia by a patient's breathing through DPI equipment without using chlorofluocarbon. Therefore, the DPI was required good flowability and dispersiblility, and should be dispersed easily about 0.5 to 7 μm in aerodynamic particle diameter at the inhalation.

For making good quality DPI, the binderless granulation for cohesive fine powder in a spouted bed equipped taper was developed. In this granulation method, only adhesion force of raw powder was harnessed instead of using binder. Actual medicines were used for the granulation material in the granulation experiment. The produced granules in this method were almost spherical, and the diameters of granules were not affected by the granulation conditions, such as the fluidization gas velocity and taper angle of apparatus. However, it was found that the diameter of granule could be controlled by changing the initial packing condition of raw powder. The compressive strength of produced granules was too small to be measured with GRANO particle hardness tester, but the granules were hard enough for the handling. The dispersiblity of granule was also evaluated by the cascade impactor, then it turned out that the dispesion was satisfactory for DPI and the produced granules by this granulation method had good dispersion quality than that by the conventional granulation method.

KEYWORDS

Binderless granulation, Spouted bed, Cohesive fine powder, Dry powder inhalation (DPI)

INTRODUCTION

Inhaling via an inhaler is the method favored for the people suffering from bronchitic asthma or chronic obstructive pulmonary disease. Inhalers were classified by two types, metered dose inhaler (MDI) and dry powder inhaler (DPI). MDI is commonly used in Japan, because it is easy to carry and use. However, chlorofluorocarbon (CFC) or CFC's substitute is used as spray liquid for MDI and there is a movement for the abolition of inhaler from the point of destruction of ozone layer or global warming. Therefore, DPI attracts much attention as an alternative inhaler to MDI.

Fine powder (0.5 to 7 μm) is used for DPI, which can be taken up directly to the lung cells by inhaling drug. Since such fine powder had very strong adherability and poor flowability, the flowability of the powder needs to be improved by granulation. The granule needs to be broken into its initial particle size so that it can reach to the lung cells during inhalation.

The granule strength in the conventional binder type granulation was too strong to apply for DPI. In this study, a spouted bed binderless granulator was developed. This granulation needs no binder by harnessing particle's cohesive force. It was found that the obtained granule by this granulation method has low strength while retaining the shape (Hatano, et al. 1996). Thus, it was expected that new granulation method was applicable for DPI. Granulation experiment was carried out using powder drug as raw material which was indicated for curing practically, and application for DPI evaluated from granule size, strength, and dispersibility.

EXPERIMENTAL APPARATUS AND METHOD

Experimental apparatus and material

Schematic diagram of experimental apparatus is shown in **Fig.1**. The spouted bed was composed of the cylinder and tapered portion. The tapered portion was separable from the cylinder. The cylinder was made of clear acrylic plastic, and the tapered portion was made of brass. The inside diameter of bed and inlet was 100 mm and 9 mm respectively. The angle of taper was 40 degrees. The gas distributor was made of stainless steel of 325 meshes. The filter was set up on the top of bed in order to prevent fine powder from flying out of the bed. Gas flow rate was controlled by the flow meter.

Six sorts of organic powder including asthma pill were used as raw materials. They were different component. The physical properties of raw materials are shown in **Table 1**.

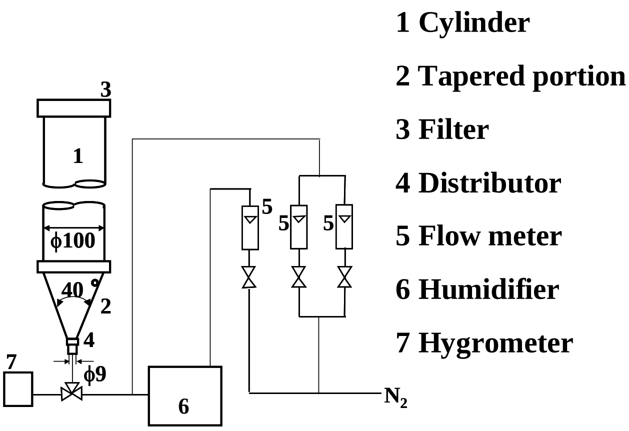


Fig.1 Spouted bed granulator

Table 1. The physical property of raw materials

Name	Aerodynamic diameter [μm]		Particle diameter [μm]	BET Specific surface [m^2/g]	Aerated / Packed bulk density [g/cm^3]	True density [kg/m^3]
	D_{50} [count]	D_{50} [mass]	D_{50}			
Lactose	-	-	4.13	9.99	150/180	1530
Drug A	2.22	1.64	2.56	-	-	-
Drug B	2.35	2.8	1.43	9.32	260/430	1600
Drug C	1.84	3.74	4.05	19.0	-	1290
Drug D	3.54	5.58	-	11.2	120/180	1360
Drug E	2.29	2.63	-	9.99	150/180	1150

Experimental conditions are shown in **Table 2**. Each raw material of 5.0 g was filled in the tapered portion. N_2 was adjusted to the desired gas velocity and flowed from the bottom of the tapered portion into the bed. Granulation was carried out for 20 minutes.

Table 2. Experimental conditions

Fluidized gas	N_2
Gas velocities at inlet [m/s]	2.5 to 5.0
Angle of taper [deg]	40
Operation time [min]	20
Amount of feed powders [g]	5.0

The measurement of granule size distribution and density of granule bed

The granule size distribution was measured by hand-operated sieving (JIS 8815). The granule obtained by granulation was measured three times to find out an effect of sieving operation to granule size. The result is shown in **Fig.2**. Three results corresponded well. Therefore, it was found that sieving operation was no effect on granule size. Considering the results mentioned above, the size distribution of granule was measured by hand-operated sieving.

The density of granule bed was measured by using a glass vessel. The volume of vessel was known, and inside diameter and depth was 1.5 cm and 2.0 cm respectively. The granule was fed about 1 cm from the top of the vessel. Overfilled granule was struck. Bulk density of granule bed was calculated by dividing weight of granule by volume of vessel.

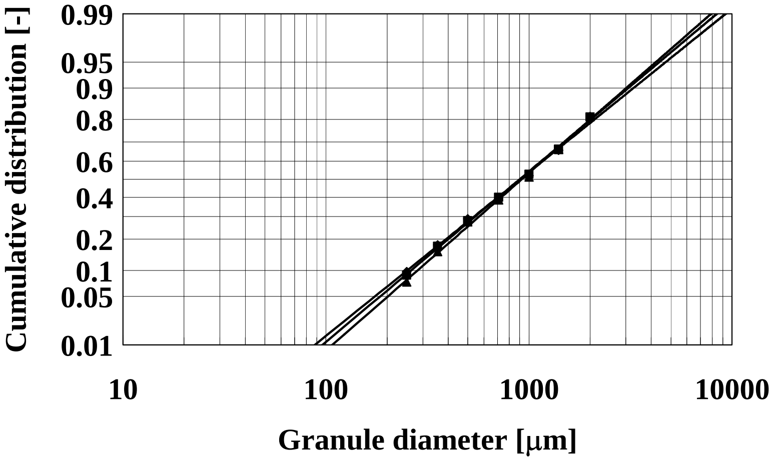


Fig.2 Effect of sieving operation on granule size

The measurement of granule strength

The granule strength was calculated by Equation 1,

$$S = \frac{2.8P}{\pi D^2} \qquad (1)$$

where S is granule strength [Pa], P is breaking load [N] and D is granule diameter [m]

The breaking load was measured by the particle strength tester. The diagram of tester is shown in **Fig.3**. The detection terminal came down constant speed as detecting the load. The tester started collecting data when the load reached 3×10^{-3} N. In this study, the point where the load reached 3×10^{-3} N was regarded as zero point. The granule diameter was defined as the distance from the zero point to the stage as shown in **Fig.4**.

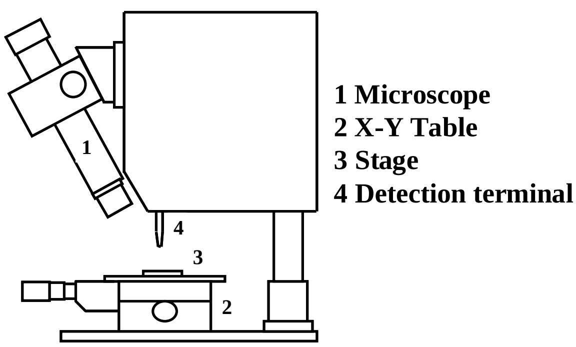


Fig.3 Particle hardness tester

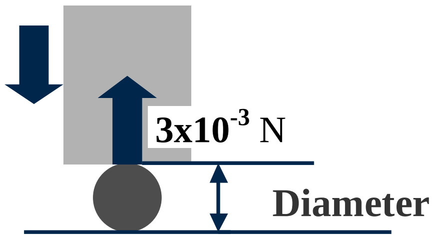


Fig.4. Detection of diameter

The measurement of dispersibility

To evaluate the application for DPI, dispersibility was measured by cascade impactor which is often used for evaluation of DPI. Schematic diagram of cascade impactor is shown in **Fig.5**. It equipped a device of DPI which was used to inhale the drug. It had eight stages. Each stage could sieve by different particle size. The granule was filled in a capsule which was let into the device. By pushing top of the device, capsule was holed by needles as shown in **Fig.6**. The granule was dispersed and released when the pump vacuumed up. The weight of the particle on each stage and the output from device were measured. And then fraction of particle dispersed below 7 μm was calculated. It was defined as the fraction of the particle getting to lung cells.

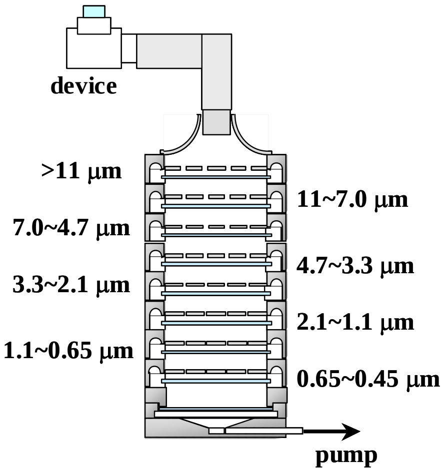


Fig.5. Cascade impactor

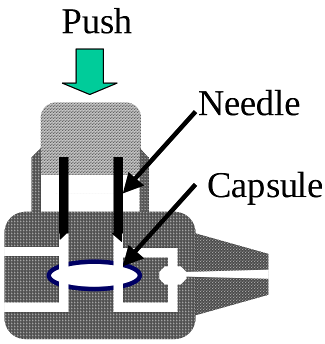
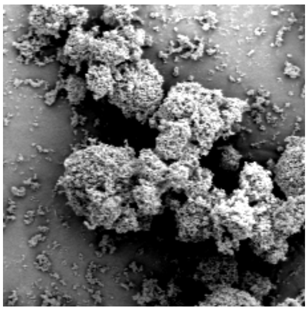


Fig.6. Device for DPI

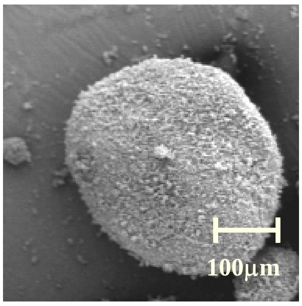
RESULTS AND DISCUSSION

The shape of granule

Shapes of granule were observed by SEM photographs. The photographs taken in a different magnification of raw material and granule were shown in **Fig.7(a,b,c,d)**. These photos were taken by 40 or 500-fold magnification.



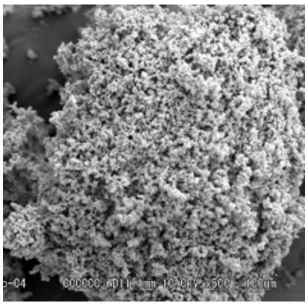
(a) Raw material (×40)



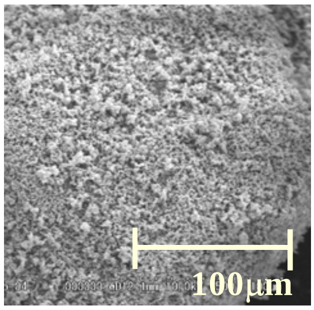
(b) Granule (×40)

Fig.7(a, b) SEM photos of raw material and granule

These photographs showed that the granule obtained in the spouted bed binderless granulation method were nearly sphere. Structure of the granule was observed that it was denser than the raw material.



(c) Raw material (×500)



(d) Granule (×500)

Fig.7(c, d) SEM photos of raw material and granule

The effect of gas velocity

The bulk density of granule bed was measured. It was obtained by granulation at gas velocity of 2.5 m/s or 5.0 m/s. As shown in **Fig.8**, the bulk density slightly increased at the high gas velocity. The difference of the bulk density came from the difference of the true density. However, the bulk density by each raw material showed the same tendency. According to the result, by increasing the gas velocity, compressive action became strong.

The yield was proportion of recovered granule to total filled raw material before granulation, defined as;

$$\text{Yield}[-] = \frac{\text{Recovered granule}[\text{g}]}{\text{Filled raw material}[\text{g}]} \qquad (2)$$

The decrease of yield was caused by the increase of gas velocity in the experiment using inorganic powder (Hatano, et al. 1996). In this study, organic powder was used as the raw materials. **Fig.9** shows that the yield was significantly reduced at the high gas velocity as with the result of inorganic powder. It was because fine powder, which had not been granulated, flied out of the system. It was also found that the yield increased with decreasing the initial particle size, because the adherability of small particle was stronger than that of large particle.

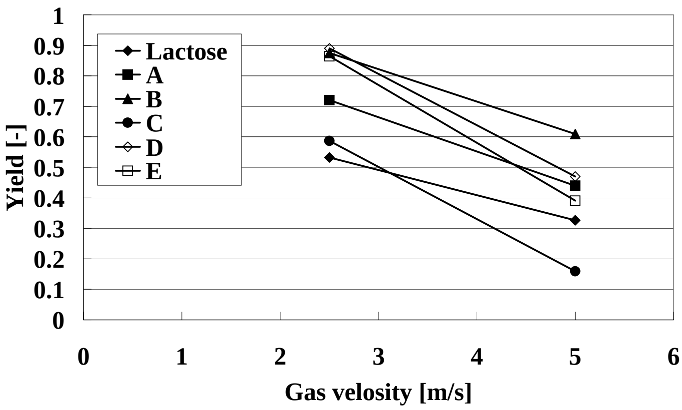


Fig.8 Effect of gas velocity on yield

The granule strength

Granule was screened by a sieve which sieve opening of 710, 500, 250 and 125 μm. Granule diameter was measured at each granule size range. Three crush patterns of granule (A-pattern, B-pattern and C-pattern) were appeared in the experiment using inorganic powder (Hatano, et al. 2004). A-pattern had clear load peaks. B-pattern also had a load peak, but the load value stayed constant after reached a peak. C-pattern had no load peak, hence its stress-strain curve was upward until the granule was completely collapsed. In this study, using organic powder, crush pattern appeared only C-pattern. It showed that very soft granule was obtained. The stress-strain curve of 500 to 710 μm granule is shown in **Fig.10**. It was curve of C-pattern. This figure showed that the value of granule diameter which detected by this tester was quite smaller than correct diameter. The result was caused by deformation of granule below $3x10^{-3}$N gf as shown in **Fig.11**.

Because the strength of very soft granule by this granulation method could not specify the point of crush, Hiramatsu equation could not be applied. Therefore, finding a new appraisal method was subject of future investigation.

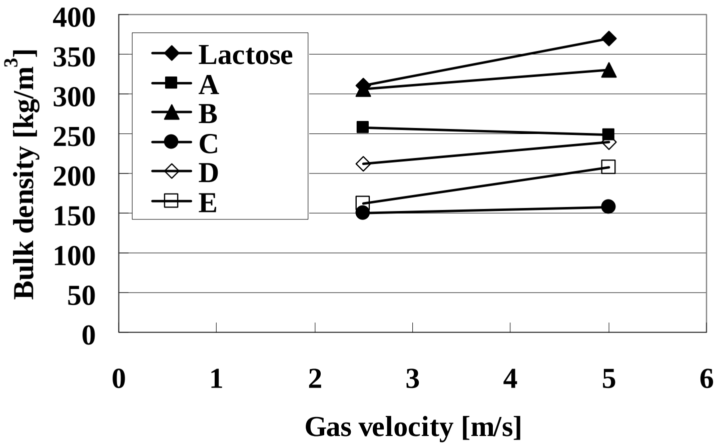


Fig.9 Effect of gas velocity on bulk density

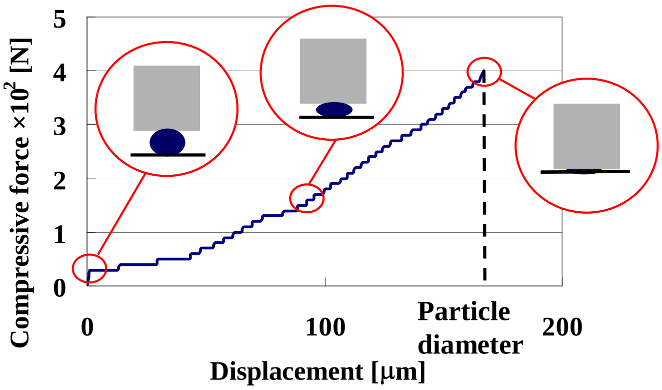


Fig.10 Typical pattern of the load-displacement curve of the measured compressive force of a single granule

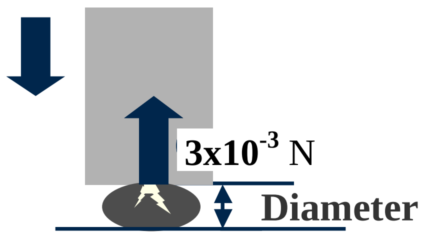


Fig.11. Detection of granule diameter in this study

The effect of filling way of raw material

The raw material passed through a sieve of 500 μm to adjust particle size of agglomerate. Big agglomerates over 500 μm were forcibly broken until they passed through the sieve. Granulation was carried out and the granule size distribution was measured. The granule size distribution was compared with the result of no sieving. The result of D is shown in **Fig.12** as the typical example. The result by each raw material showed the same tendency.

It showed that the granule by the raw material passed through a sieve had sharp distribution. Therefore, it was clear that the particle size of agglomerate in the raw material had much effect on the granule size distribution.

Therefore, the experiment by different sieve opening was carried out to find out effect of particle size of agglomerate in the raw material. Sieve opening of 250, 355, 500 and 710μm were used. As shown in **Fig.13**, the granule size was changed with sieve opening. And breadth of distribution was constant regardless sieve opening. It was found that granule size could be controlled by adjusting the size of agglomerate in the raw material.

The granule was observed by SEM photographs. SEM photographs of raw material, passed through by 250μm opening sieve, and granule is shown in **Fig.14(a,b,c)**.

The granule by the size -controlled raw material was observed that it was more spherical and denser than the granule shown in Fig.7.

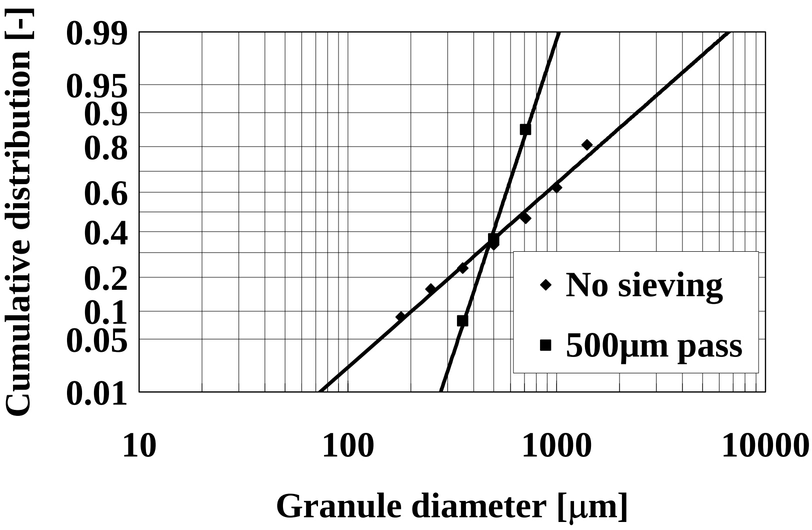


Fig.12. Effect of passing raw material through a sieve on granule size distribution

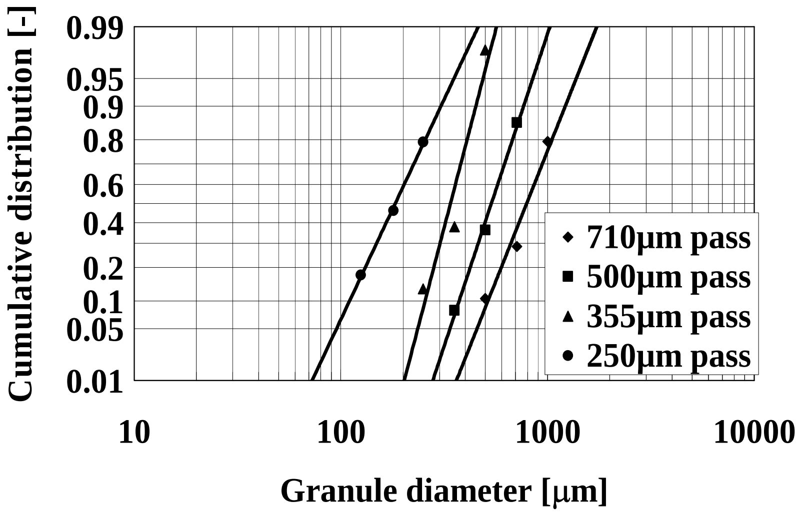
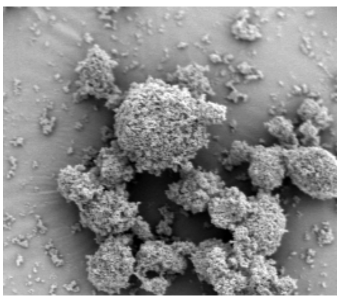
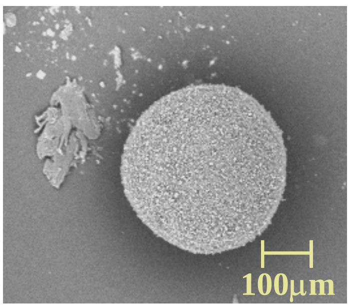


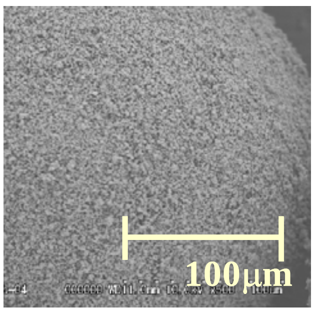
Fig.13. Effect of sieve opening passing raw material on granule size distribution



(a) Raw material (×40)



(b) Granule (×40)



(c) Granule (×500)

Fig.14. SEM photographs of raw material and granule

From these results, the mechanism of this granulation method seemed to make progress as follows. Agglomerate in raw material nucleate. Then the agglomerate was compressed by fluidization gas, and adhered particle on the surface. Repeating compression and adhesion encouraged growth up the granule.

Dispersibility

Dispersibility of granule is shown in **Table 3**, where OE was output efficiency from device and RE was respirable fraction (dispersed below 7 μm).

Fraction of getting to lung cells of DPI commercially available was about 20~40 %. It was found that the granules obtained by this granulation method had high dispersibility.

Table 3. Dispersibility of granule

Sample	Lactose	Drug A	Drug A	Drug A	Drug A	Drug A
OE [%]	82.4	99.0	73.8	89.9	62.2	62.3
RF [%]	36.0	40.5	33.1	66.0	34.7	42.1

CONCLUSIONS

The knowledge was obtained by this experiment as follows.

- Organic fine powder which initial particle size of 1 to 4 μm was granulated without binder by using the spouted bed granulator.
- Very soft granule was obtained by the spouted bed binderless granulator.
- The granule, obtained by this method, had higher dispersibility than the commercially available DPI in test by Cascade Impactor.
- Granule size could control by sieving the raw material to adjust the size of agglomerate.

These results showed that application for DPI by this spouted bed binderless granulation method was well possible.

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