Refereed Proceedings

The 12th International Conference on Fluidization - New Horizons in Fluidization Engineering

Engineering Conferences International — *Year* 2007

Development of a New Measurement Method to Evaluate the Physical Properties of Granules for Dry Powder Inhalation Produced by New Spouted Bed Type Binderless Granulator

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DEVELOPMENT OF A NEW MEASUREMENT METHOD TO EVALUATE THE PHYSICAL PROPERTIES OF GRANULES FOR DRY POWDER INHALATION PRODUCED BY NEW SPOUTED BED TYPE BINDERLESS GRANULATOR

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ABSTRACT

The spouted bed type of binderless granulator is one of the most appropriate methods available for producing granules of dry powder inhalation (DPI) from cohesive fine powder. However the compressive strength of produced granule is too small to be measure by conventional method. In this work a new apparatus was developed to evaluate the strength of such a soft granule. Load and displacement curve of the granule were measured by new method of compressive strength measurement. To observe the compression process of the granule, photographs were taken with a microscopic camera. It was clarified that this measurement method was remarkably useful to evaluate the compressive strength of soft granule.

INTRODUCTION

Dry powder inhalation (DPI) is getting popular as it is effective for medical treatment of lungs by letting the fine powder reach the diseased part. However, granulation of DPI is required to make the handling fine powder (0.5 to 7 μm) easy. The granule of DPI prefers maintaining a minimum strength necessary for retaining the shape, Vidgrén, et al. (1). Property of granule obtained by using the spouted bed binderless granulator developed by Hatano, et al. (2-5), was

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appropriately small in mechanical strength, and enough for retaining the shape. In the experiment of re-dispersibility of the granule by using a cascade impactor, an extremely excellent performance was obtained. Conventionally, compressive strength has been generally used to evaluate strength of a granule obtained by granulation. However, Hatano, et al. (2-5) found that the compressive strength was weaker than the measurement accuracy of the conventional apparatus. In this study, to measure compressive strength of such a soft granule, a new apparatus was developed. Load and displacement of the compressing granule could be measured with a sufficient accuracy by using this apparatus, and the compression process of a granule was observed by photographs with a microscopic camera simultaneously. The measurement data of the compressive strength was compared with the conventional data, and the compressive strength for the evaluation of a soft granule for DPI was obtained.

Preparation of Granules by Spouted Bed Type of Binderless Granulator

Schematic diagram of apparatus of the granulator is shown in **Fig.1**. The spouted bed was composed of a cylinder and a tapered portion. The cylinder was made of transparent acrylic resin, and the tapered portion was made of brass. The gas distributor of 325 meshes of stainless steel was placed at the bottom of the tapered potion. A filter was set up on the top of bed to prevent fine powder from the entrainment of the bed. The experimental conditions are shown in **Table 1**. Three kinds of powders were used as raw materials. Each raw material was filled in the tapered portion. N_2 was adjusted to desired gas velocity and flowed from the bottom of the tapered portion into the bed. The SEM photograph of the obtained granule is shown in **Fig.2**. The diameter of raw materials and granules used for compressive strength measurement are shown in **Table 2**.

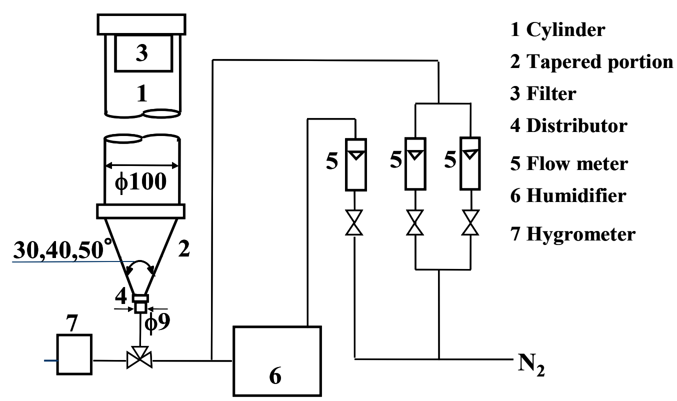

Fig.1 Schematic diagram of experimental apparatus

Table 1 Experimental conditions for granulation

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

Table 2 Diameter of raw materials and granules

Raw materials	Particle diameter D_{p50} (μm)	Granule diameter D_{g50} (μm)
Fused Alumina	0.3	88
Ethenzamide	2.56	410
Lactose	4.13	455

Conventional Apparatus of Compressive Strength Measurement

In general, particle hardness tester GRANO (OKADA SEIKO CO., LTD) was used for the measurement of compressive strength of a granule. Schematic diagram of GRANO is shown in **Fig.3**. Descent speed of tip to break a granule is 83 μm/s. The data of load and displacement can be loaded and analyzed on personal computer. The sample of granule is placed on the stage of GRANO, and then the compressive strength is measured under watching through attached microscope.

Fig.4 shows a typical pattern of the

Fig.2 SEM photograph of the obtained granule

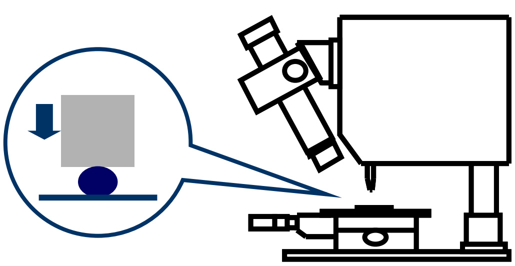

Fig.3 Schematic view of experimental apparatus for measurement of compressive strength of a granule

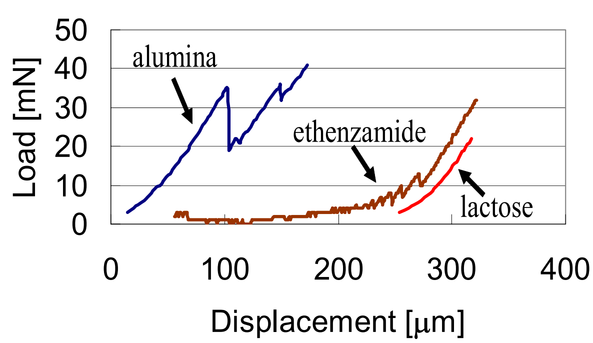

Fig.4 Typical pattern of the load- displace- ment curve using conventional apparatus

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load-displacement curve determined for a granule obtained from three kinds of raw materials by the conventional apparatus, GRANO. The result of fused alumina shows that a granule was broken with same clear peak pattern as the one reported in the past work by Hatano et al.(5). However, in the case of Ethenzamide and Lactose, clear peaks are not admitted. The apparatus recognizes the existence of a granule when the load surpasses 3mN at least for the present load cell. Accordingly, before the data sampling started the granule deformation or breakage mast have taken place. To evade this problem, higher sensitivity of load cell should be necessary, but, it is difficult to obtain data with sufficient accuracy due to the remarkable noise generation as far as structure of thin device is employed. This fact means that the apparatus for the measurement such a soft granule was not available in the past. Then, it is necessary to develop a new apparatus for strength measurement of such a soft granule as the dry powder inhalation.

New Apparatus for Measurement of Small Compressive Strength

Schematic view of new experimental apparatus for measurement of compressive strength of a soft granule is shown in **Fig.5**. The apparatus is composed of the sample stage where granule is fixed, the needle for compression attached in two blade springs and the laser displacement sensor. A microscopic camera is set up to observe and record the process from deformation until achieving at breakage of a granule. Movement speed of the sample stage during the measurement is 100 μm/s. Load-displacement curve (maximum load and displacement until break) can be displayed on the monitor of personal computer. After fixing a granule to the sample stage and aiming of the needle at a granule, measurement is started. When the needle is in contact with a granule, the blade spring compresses a granule while bending, and a short time later, a granule is broken. Strain of a granule can be calculated from the difference between the displacement

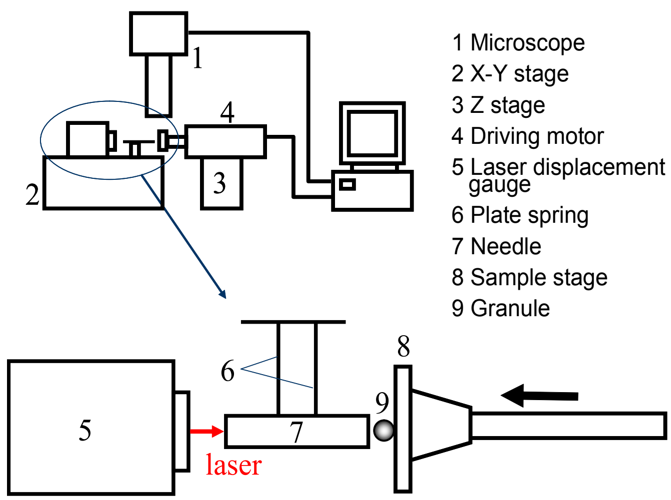

Fig.5 Schematic view of the new experimental apparatus for measurement of compressive strength

measured by laser displacement sensor and the moved distance of sample stage.

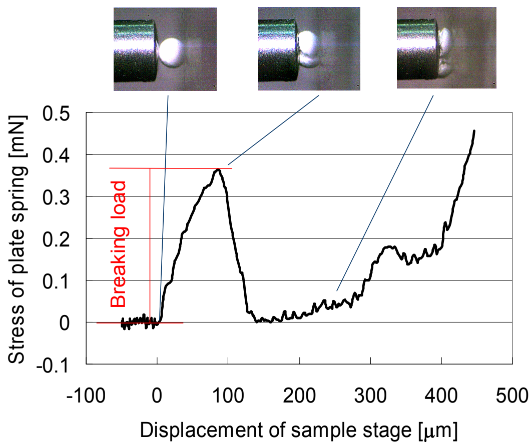

Fig.6 Typical pattern of the load-displacement curve of the measured compressive force of a granule of Lactose

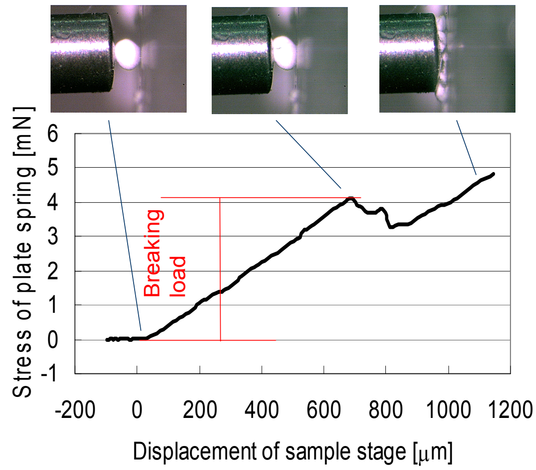

Fig.7 Typical pattern of the load-displacement curve of the measured compressive force of a granule of Ethenzamide

Evaluation of Compressive Force Measurement by New Experimental Apparatus

Figs.6 and 7 shows the typical pattern of the stress-displacement curve of the measured compressive force of three kinds of samples. These figures show the transition of the load against displacement. The result with Alumina that was able to be measured also by the conventional apparatus is shown in **Fig.8**. Clear peaks can be found from the data of Ethenzamide and Lactose carried out by the new apparatus, as shown in Fig.6 and 7, although the data by conventional apparatus can not be found these result as shown in Fig. 4, respectably. Especially, it can be confirmed that the granule of Lactose is broken by the extremely small load. These phenomena can be understood also from photographs of the microscopic camera. Displacement in the stress-displacement curves shown in Figs.6 to 8 is determined by the average of the amounts of the strain of a granule and the displacement of the blade spring. The relationship between the diameter of granule and the load was obtained as shown in **Fig.9**. Characteristic of granule strength can be compared from the gradient of a part of the start up. As shown in **Fig.10**, the gradient of a soft granule is small and the value of a hard granule is large.

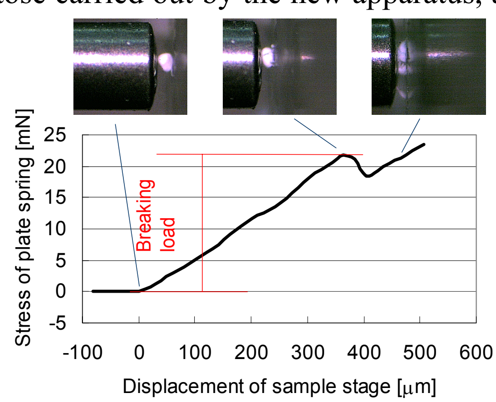

Fig.8 Typical pattern of the load-displacement curve of the measured compressive force of a granule of Alumina

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The load normalized by the maximum load resulting in breakage of granules is plotted against the strain in **Fig.11**.

The value of the vertical axis becomes unity when granule was broken. It can be understood that Alumina and Ethenzamide breaks for the strain about 20% of the diameter of a granule while Lactose breaks by about 10%. It is an interesting phenomenon that Lactose was breaks in small strength by small displacement.

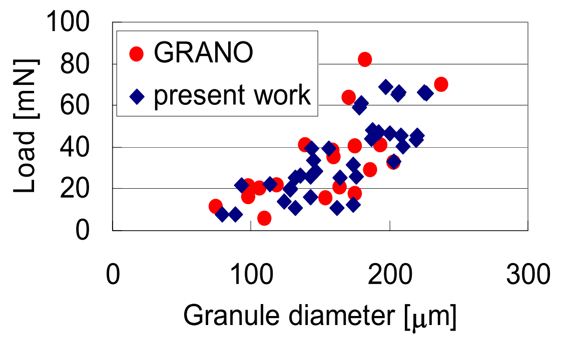

Fig.9 Comparison of compressive strength of a granule by conventional apparatus with that by present apparatus

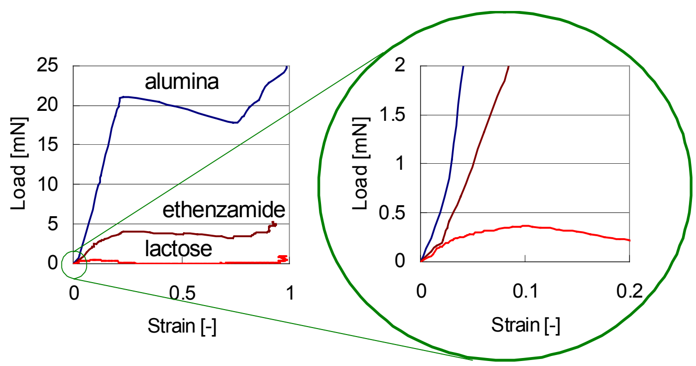

Fig.10 Load-strain curve and its part of the start up of the compressive force of a granule

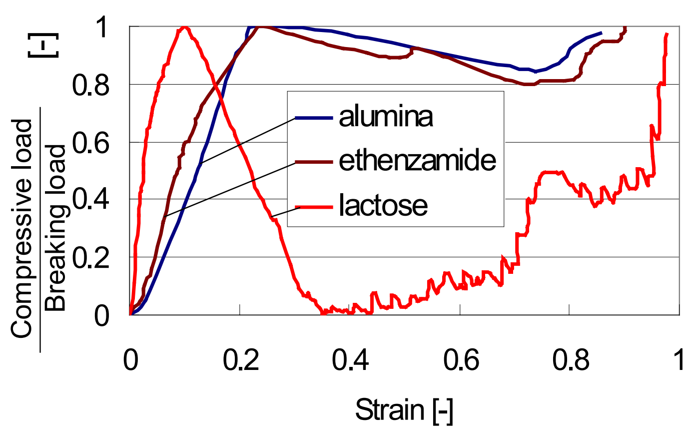

Fig.11 Comparison of the ratio of strain to diameter of a granule

Compressive Strength of a Granule

Compressive strength of a granule can be estimated from the Equation by Hiramatsu, (6), generally used in the pharmaceutical field in Japan.

$$\sigma = \frac{2.8P}{\pi D_p^{\ 2}} \qquad (1)$$

Here, σ [Pa] is compressive strength of a granule, P [N] is load when granule breaks and D_p [m] is diameter of a granule.

The correlation of compressive strength of a granule against the diameter of granule is compared among three kinds of samples in Fig.12. The granule strength of Ethenzamide and Lactose which could not be determined by a conventional apparatus are accordingly measured by proposal new apparatus. The granule strength of Lactose was the order of 1kPa, and Ethenzamide was 10kPa. These values were extremely small as compared with about 1000kPa in strength of Alumina.

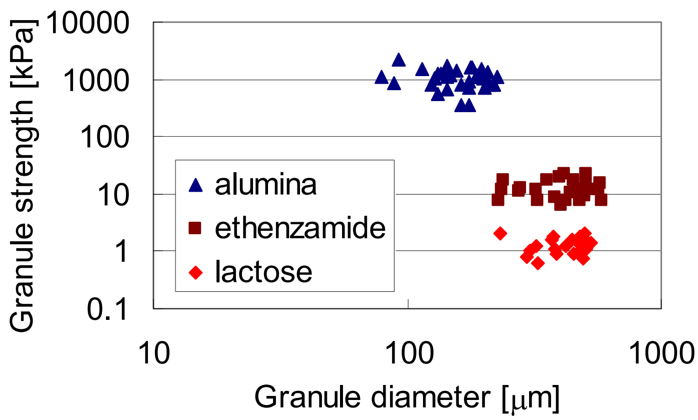

Fig.12 Comparison of compressive strength of each sample by present apparatus

CONCLUSION

It became possible to measure the compressive strength of a soft granule for dry powder inhalation by using the apparatus newly developed. It was found that Alumina and Ethenzamide breaks by about 20% strain of the diameter of a granule and Lactose breaks by about 10%. As for Lactose, the compressive strength was small furthermore the strain was smaller than Alumina and Ethenzamide by the ratio of strain to diameter of a granule. It was found that the value of the compressive strength was the order of 10kPa for Ethenzamide and 1kPa for Lactose. These values were extremely small as compared with Alumina.

ACKNOWLEDGEMENT

The authors wish to thank Dr.Hiroyuki Tsujimoto and Miss Kaori Hara (HOSOKAWA Powder Technology Research Institute) for supplying the medicine powders.

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