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85. **Hiroshi Fujiwara, Jun Toda, and Mitsuo Kato**: Studies on Pore Structure of Granules by Mercury Porosimetry.*[1]

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In studies of granules used as a material of the oral pharmaceutical preparations, much interest about their porosity or pore-size distribution has been observed recently. The granules are porous materials, and their porosity, pore-size or pore structure influences their qualities. It has been reported,[1] for instance, that the porosity of granules has an effect on the mechanical strength of the granules. So it is important to determine the porosity or pore-size distribution of the granules. The purpose of this work is to establish the relationship between the pore-size distribution of granules and their physical properties. In this paper, determination of the pore-size distribution of the granules was studied by mercury porosimetry.

Matsumaru[2] determined the pore-size distribution of aluminum-silicate tablets by a water vapor adsorption method. Furthermore, mercury porosimetry has been frequently employed for the pore-size determination of various porous materials, such as active carbon, silica gel, clay, etc.[3]

However, the granules in the pharmaceutical preparations have a relatively large pore diameter and there have been few reports on the pore-size determination of such granules.

In the present study, the pore-size determination of sucrose and lactose granules was elucidated, and investigation was made on the pore structure of the granules from these results.

Experimental

Materials——Sucrose: Commercial sucrose powder (particle size, below 100 μ). Three fractions (250~100, 100~45 and below 45 μ) were obtained by grinding in a ball mill and sieving by the JIS sieves.

Lactose: 1st Grade (Wako Pure Chem. Ind., Ltd.), (particle size, below 100 μ).

Preparation of Granules——Powder was kneaded with water, and then the wet mass was granulated by passing through a 20 mesh sieve. The wet sucrose granules thus obtained were dried at room temperature under reduced pressure, lactose granules being dried at 95° under atmospheric pressure.

The granules between 42 and 20 meshes in size were used for investigation.

Preparation of Granules Coated with Paraffin——After the air kept in the pores of the granules was removed in vacuum, the granules were immersed in the liquidized paraffin and dried at room temperature.

The solid volume was determined by the Beckman Air Comparison Pycnometer and the true density was calculated from the data. True densities of sucrose and lactose powders were 1.588 and 1.566, respectively. These values were used for determination of solid volume throughout this study.

Determination of the Pore Volume of Granules——The pore volume of granules is the difference between apparent volume and solid volume of granules. The apparent volume of granules was determined by the mercury porosimeter of Strickland, *et al.*[4] with minor modifications. For the determination, 2~7 g. of granules was used. Procedure was similar to that described by Strickland, *et al.*[4]

Under a given pressure, mercury will enter into the pores which have diameters larger than that indicated

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1) E. Awata, Y. Ikegami: Yakugaku Zasshi, **82**, 555 (1962).
2) H. Matsumaru: *Ibid.*, **79**, 198 (1959).
3) A. Tsuruizumi: J. Chem. Soc. Japan, **79**, 142 (1958). A. J. Juhola, E. O. Wiig: J. Am. Chem. Soc., **71**, 2069, 2078 (1949).
4) W. A. Strickland, Jr., L. W. Busse, T. Higuchi: J. Am. Pharm. Assoc., **45**, 482 (1956).

by the following equation.[5)]

$$D=-4S\cdot\cos\theta/P$$

where D (cm.) is pore diameter, S (dyne/cm.) surface tension of mercury (480 dyne/cm.), θ contact angle of mercury with solids (180°), and P (dyne/cm^2) pressure.

From the above equation, relationship between pore diameter and pore volume of a porous material can be obtained by measuring the apparent volumes at various pressures. The change of temperature was within $\pm 1°$ during measurement, and the volume change of mercury itself caused by the pressure raising was negligible.

Results and Discussions

Intergranular Pores and Intragranular Pores

Pore volume can be calculated from the apparent volume and the solid volume, and the apparent volume of granules is concerned with only the intragranular pores, but it is supposed that both the intergranular and intragranular pores are included in the apparent volume obtained in this measurement.

In order to examine the effect of the intergranular pore volume on the determined apparent volume, the apparent volume of the paraffin-coated sucrose granules was determined (Fig. 1). As shown in Fig. 1, the result indicates that the porosity of granules is below 1%, and it is clear that the intergranular pore volume is insignificant. The volume of the paraffin coated on granules was equal to the pore volume of uncoated granules (23% as porosity).

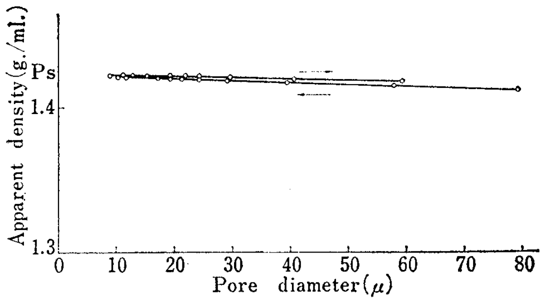

Fig. 1. Relationship between Pore Diameter and Apparent Density of Sucrose Granules Coated with Paraffin

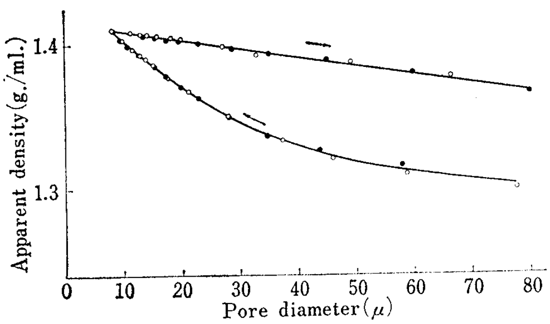

Fig. 2. Effect of Amount of Granules on Apparent Density

Weights of granules
● 2.343g
○ 6.492g

Moreover, if the apparent volume of granules depends on the intergranular pore volume, it is expected that the apparent density becomes greater, as the amount of granules used for determination decreases, since the number of contact points of granules becomes less and the intergranular pore volume smaller. The apparent density, however, was independent of the amount of granules as seen in Fig. 2.

This result indicates that only the intragranular pore volume is included in and the intergranular is excluded from the apparent volume.

Hysteresis in Mercury Porosimetry and Analysis of Pore Structure

As seen in Fig. 2, there is hysteresis between pressure-raising curve and pressure-reducing curve. The same phenomena were observed by some authors in mercury porosimetry. Ritter and Drake[6)] attributed hysteresis to the so-called ink-bottle shaped pores, and Caro and Freeman[7)] to open cylindrical pores in addition to them.

5) E. W. Washburn: Proc. Natl. Acad. Sci., **7**, 115 (1921).

As hysteresis was observed in the experiments, this phenomenon was investigated. The following possibilities can be considered as the causes of hysteresis; 1) destruction of both granules themselves and pore construction in granules during measurement, 2) time-lag required for the establishment of equilibrium state and 3) the shape of pore structure in granules.

The former two possibilities can be excluded, for no change in the granular-size was observed at the end of measurement and the end point of the pressure-re-raising curve falls on the starting point of the pressure-reducing curve in each hysteresis loop (Figs. 5 and 6). Therefore, only the shape of pore structure should be regarded as the cause of hysteresis. Consequently, studies on hysteresis are of advantage to investigating pore structure and properties of granules.

Now, the shapes of pore structure can be classified into three types according to their behaviors in mercury porosimetry. The typical models of these shapes are illustrated in Fig. 3.

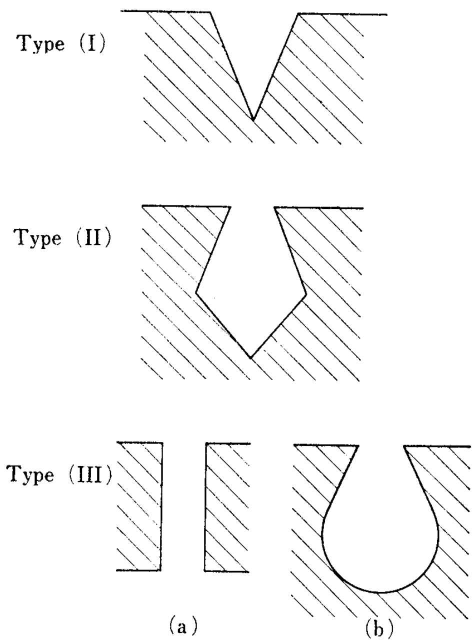

Fig. 3. Model Types of Pore Structure

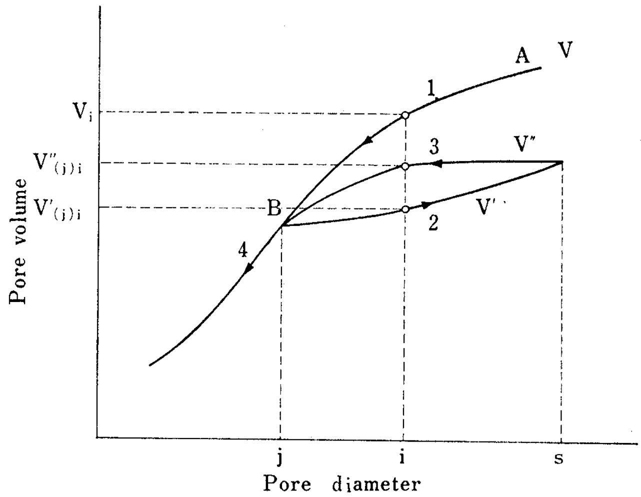

Fig. 4. Schematic Diagram of Scanning Curve

The pores of Type I do not cause hysteresis. In the pores of Type II, the volume of the mercury penetrating on raising pressure will not be equal to the mercury volume flowing out from the pores when the pressure is released. In the pores of Type III(a), the mercury once introduced into the pores does never flow out, since the intra-granular mercury forms continuous phase with outer-granular mercury. And the pores of Type III(b) are ideal case, in which the concave surface of pore structure coincides with the convex surface of mercury head introduced into the pore; so the mercury will completely fill the pore at the pressure corresponding to the pore-diameter of entrance, gas-mercury interfaces disappear and this mercury will never flow out. To investigate the distribution of each of these types of pores, scanning curves were drawn.

Fig. 4 shows the schematic diagram of the scanning curve. This curve starts

6) H. L. Ritter, L. C. Drake : Ind. Eng. Chem., **17**, 782 (1945).
7) J. H. Caro, H. P. Freeman : J. Agr. Food Chem., **9**, 182 (1961).

from A and pressure is raised along curve V till the pressure corresponding to the pore diameter j is obtained (point B). Then the pressure is released along curve V′ till the pressure corresponding to the pore diameter s is obtained, and then pressure is again raised along curve V″. This curve crosses with curve V at B. V_i is the pore volume at the pore diameter i on the pressure-raising curve, $V'_{(j)i}$ the pore volume at the pore diameter i on the pressure-reducing curve from j, and $V''_{(j)i}$ the pore volume at the pore diameter i on the pressure-re-raising curve from s starting from the pressure-reducing from j.

Thus, the following equations can be obtained :

$$V_i = (\mathrm{I})_{e<i} + (\mathrm{II})_{e<i} + (\mathrm{III})_{e<i} \quad (1)$$

$$V'_{(j)i} = (\mathrm{I})_{e<i} + (\mathrm{II})_{e<j} + (\mathrm{II})_{\substack{j\leq e<i \\ b<i}} + (\mathrm{III})_{e<j} \quad (2)$$

$$V''_{(j)i} = (\mathrm{I})_{e<i} + (\mathrm{II})_{e<j} + (\mathrm{II})_{\substack{j\leq e<i \\ b<s}} + (\mathrm{III})_{e<j} \quad (3)$$

where (I), (II) and (III) are the pore volumes of Type I, Type II and Type III, respectively, and suffix e indicates the pore diameter and b the internal maximum diameter in Type II, respectively.

As equations (1), (2) and (3) represent the cumulative curves, the total pore-size distribution can be calculated by differentiating equation (1). From equation (3), the pore-size distribution of sum of Type I and Type II is calculated. Consequently, the pore-size distribution of Type III is obtained by substracting the distribution of sum of Types I and II from that of total pores.

Furthermore, from equations (2) and (3), equation (4) is induced :

$$V''_{(j)i} - V'_{(j)i} = (\mathrm{II})_{\substack{j\leq e<i \\ i<b<s}} \quad (4)$$

Equation (4) represents only the pores of Type II. The pore-size distribution of Type II can be calculated in the case of i≒j. Accordingly, in each hysteresis loop of scanning curve, the distribution of Type II pores can be calculated where i≒j, and over the whole range of pore diameter, this distribution is obtainable by connecting the distributions of each hysteresis loop.

From the above consideration, the consecutive scanning curves shown in Figs. 5a and 6a were obtained. From these results, each distribution of the three types of pores is calculated (Figs. 5b and 6b).

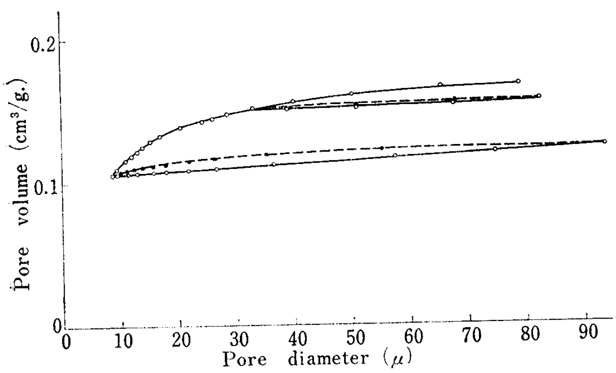

Fig. 5a. Scanning Curve of Sucrose Granules of Type A

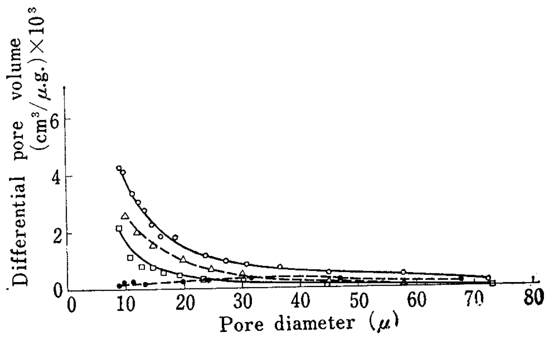

Fig. 5b. Pore Size Distribution Curve of Sucrose Granules of Type A.

—○— Total pore
⋯●⋯ Pore of type (I)
—□— Pore of type (II)
⋯△⋯ Pore of type (III)

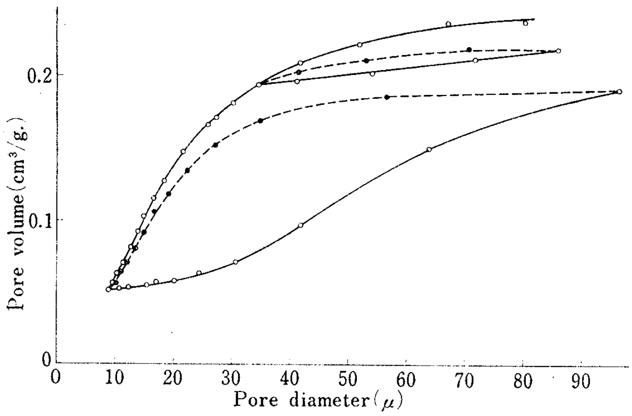

Fig. 6a. Scanning Curve of Sucrose Granules of Type B.

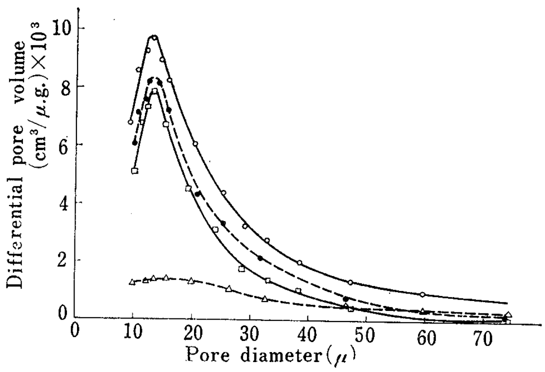

Fig. 6b. Pore Size Distribution Curve of Sucrose Granules of Type B

—○— Total pore
⋯●⋯ Pore of types (I) and (II)
—□— Pore of type (II)
⋯△⋯ Pore of type (III)

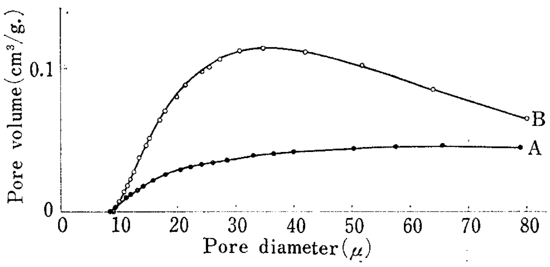

Fig. 7. Difference Curves of Sucrose Granules

Fig. 7 plots the difference values obtained by subtracting the pore volume on the pressure-reducing curve from that of the pressure-raising at any pore diameter against pore diameter. These curves are defined as difference curves and classified into two types, that is, one type having a maximum, and the other no maximum. The author denotes the former as B-type and the latter A-type.

In the A-type, the pore volume of Type III is the most abundant in the range of measurement, whereas, in the B-type, that of Type II is predominant. As the difference curve indicates the difference between equations (1) and (2), it is obvious that in the granules of the B-type, the pores of Type II take a relatively large part of the total pores, and from the difference curves the pore structure can be assumed roughly.

Effect of Amount of Water Added in Granulation

In the wet granulation method, it is expected that the amount of the water added for granulation has an effect on pore-size and pore structure of granules. To investigate the effect of the amount of the water added in granulation, the following experiment was carried out on sucrose granules, and the results are shown in Fig. 8. When 5 ml. of water is added to 100 g. of powder, the distribution curve of pore diameter has a maximum at 12μ, and it is expected that the maximum will shift to smaller diameter, when the amount of water becomes larger.

Fig. 9 also shows the effect of water on lactose granules, and a similar tendency is observed.

In both cases, the granules prepared with the less amount of water have the difference curves of B-type and vice versa. In these granules, as only water was used for granulation, it is supposed that the binding mechanism is due to the solid bridge, which once dissolved in water, is educed and deposited on drying. Therefore, when less amount of water is added and the amount of educed solid decreases, the pore diameter becomes larger, and the pore structure formed by accumulation of powders still remains intact for the most part in granules and the pores of Type II are made.

Lactose granules have a property of B-type even 20 ml. of water is added to 100 g. of powders. This can be explained by the fact that the solubility of lactose in water is less than that of sucrose.

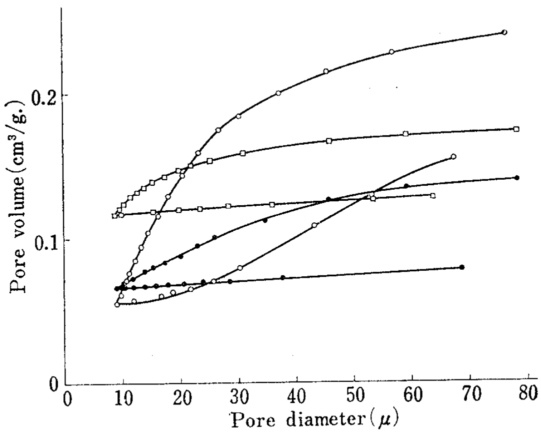

Fig. 8a. Effect of Amounts of Water Added in Granulation on Pore Volume of Sucrose Granules

Amount of water
—○— 5 ml./100g.
……□…… 7 ml./100g.
—●— 9 ml./100g.

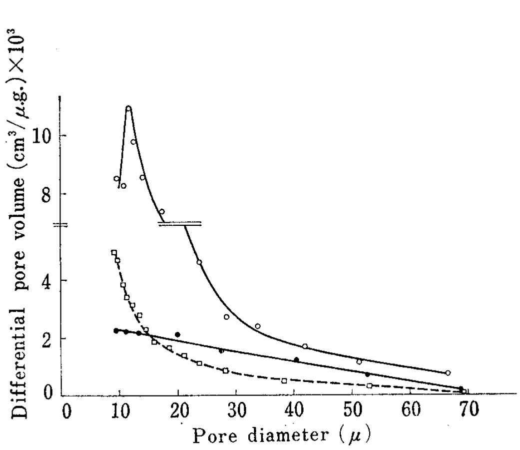

Fig. 8b. Effect of Amounts of Water Added in Granulation on Pore Size Distribution of Sucrose Granules

Amount of water
—○— 5 ml./100g.
……□…… 7 ml./100g.
—●— 9 ml./100g.

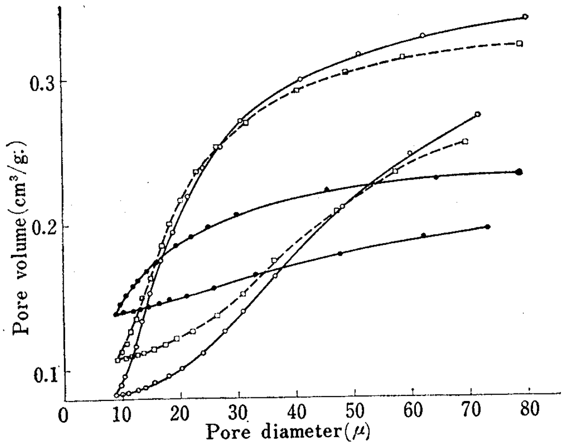

Fig. 9a. Effect of Amounts of Water Added in Granulation on Pore Volume of Lactose Granules

Amount of water
—○— 15ml./100g.
……□…… 17ml./100g.
—●— 21ml./100g.

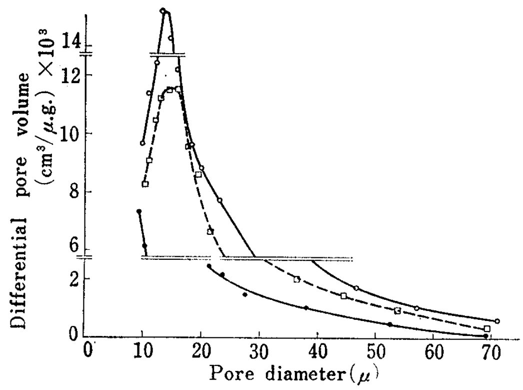

Fig. 9b. Effect of Amounts of Water Added in Granulation on Pore Size Distribution of Lactose Granules

Amount of water
—○— 15ml./100g.
……□…… 17ml./100g.
—●— 21ml./100g.

Effect of Particle-Size of Powders

It is reported[8] that the particle-size of powders has an influence upon the properties of granules, such as mechanical strength. So the sucrose granules were prepared from powders of various particle-sizes to investigate the effect of the particle-size of powder on the pore-size distribution of granules. As seen in Fig. 10, the granules prepared from powders of 100~250 μ have a very small pore volume. A similar result was observed in the commercial cube sugar and its apparent volume is closely equal to true solid volume. The granules prepared from powders of large particle-sizes have a large pore diameter and hence the pore volume can not be determined unless a lower pressure is applied to.

The pore-size distribution curve of granules prepared from powders of 45~100 μ has a maximum at about 35 μ of pore diameter, and it is supposed that the granules

8) E. Awata, Y. Ikegami: Yakugaku Zasshi, **82**, 555 (1962).

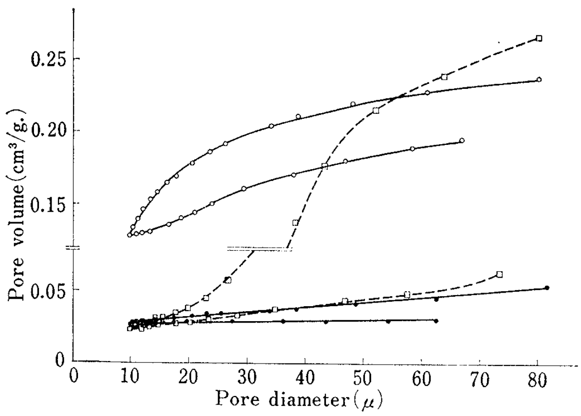

Fig. 10a. Effect of Particle Sizes of Powder on Pore Volume of Sucrose Granules

Particle size
—○— 45μ<
……□…… 45～100μ
—●— 100μ>

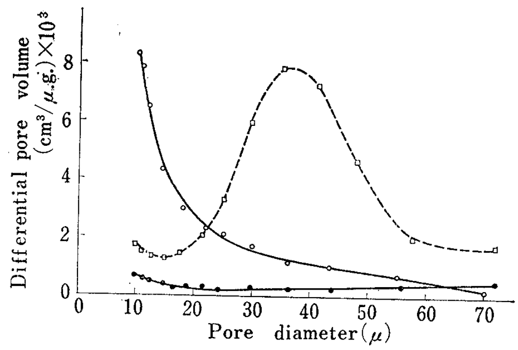

Fig. 10b. Effect of Particle Sizes of Powder on Pore Size Distribution of Sucrose Granules

Particle size
—○— 45μ<
……□…… 45～100μ
—●— 100μ>

prepared from powders of smaller than 45 μ have a maximum at a pore diameter smaller than 8 μ.

From the results, it is concluded that, in the wet granulation method, when less amount of water is added, the pore diameters in granules become larger, and that when more amount of water is added, they become smaller. And also the pore structure in granules can be estimated by mercury porosimetry.

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Summary

1. The pore-size distribution and the pore structure of sucrose and lactose granules were determined by mercury porosimetry. The detailed informations on the pore structure could be obtained by scanning curves, and the property of pore structure could be estimated by the difference curve roughly.

2. The granules prepared by a wet granulation method have the greater pore-size when less amount of water is added, and vice versa.

3. The granules prepared with powder of greater particle-sizes have the greater pore-sizes.

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