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Studies on Anisotropy of Compressed Powders. III.[1] Effects of Different Granulation Methods on Anisotropy, Pore Size and Crushing Strength of Tablets

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The effects of different granulation methods on the anisotropy, the pore size and the crushing strength of tablets were studied. Calcium phosphate dibasic was granulated by three methods—(A) extruding granulation, (B) disintegrating granulation and (C) tumbling granulation. Five and 10% ethanol solutions of hydroxypropyl cellulose were used as binders. The degree of anisotropy of tablets was assessed in terms of the difference of the apparent compliance values between the compressive axial direction and the radial direction, which were obtained from the strain recovery at the ejection of tablets. The measurements of pore size in tablets were carried out with a mercury porosimeter.

For both concentrations of the binder, the degree of anisotropy was in the order tablets (C) (tumbling granulation)>tablets (B) (disintegrating granulation) >tablets (A) (extruding granulation). It is presumed that the structure, bulk density and strength of the granules are important factors. At the same porosity, the mean pore diameters of the tablets were in the order tablets (C) >tablets (B) >tablets (A). The crushing strengths of the tablets were in the order tablets (A) >tablets (B) >tablets (C) for both concentrations of the binder. The larger the degree of anisotropy was, the larger the strain recovery was. Thus, it is presumed that large pores are formed by large strain recovery in the tablets, and consequently the strength of the tablets becomes low.

Keywords——granulation; tablets; calcium phosphate dibasic; hydroxypropyl cellulose; anisotropy; strain recovery; compliance; pore size; mercury porosimetry; crushing strength

In the previous paper,[1] we reported that the anisotropy of compressed powders could be assessed by measurement of the elastic properties of the compacts, that the anisotropy of the tablets could also be assessed by measurement of the strain recovery at the tablet ejection, that the anisotropy of the tablets prepared from granules was smaller than that of tablets directly prepared from the original powders and that with decrease in anisotropy the capping tendency also decreased. In this study, tablets prepared from the granules made by different granulation methods were examined, and the effects of the granulation methods on the anisotropy, the pore diameter and the crushing strength of tablets were investigated. It is known that the pore diameter in a tablet affects its disintegration[2] and stability[3] properties. Selkirk and others[4] studied the difference of pore size between tablets prepared from powders and those from granules, but no work has been reported on the effects of different granulation methods on pore diameter, except for one comparison[5] of a slugging method and a wet granulation method, and no work has appeared on the relationship between anisotropy and the pores. We examined this relationship by comparing three kinds of wet granulation methods chosen from among the various granulation methods in general use in the drug manufacturing industry.

Experimental

Materials——Calcium phosphate dibasic (J.P.X, 100—200 mesh) was dried at 60°C for more than 8 h. Solutions of 5 and 10% hydroxypropyl cellulose (HPC-M, Nippon Soda Co., Ltd.) in ethanol were used as binders.

Granulation Methods——The following three kinds of granulation methods were used. In each case, 400 ml of the binder was added to 1 kg of calcium phosphate dibasic.

(1) Granules (A); extruding granulation.

Calcium phosphate dibasic was mixed with the binder in a Z-blade mixer and was forced through a 5 mm screen by means of a pelleter (EXD-60, Fuji Powdal Co., Ltd.). These granules were columnar in shape and strong.

(2) Granules (B); disintegrating granulation.

Calcium phosphate dibasic was mixed with the binder in a Z-blade mixer and this wet mixture was disintegrated in a power mill (P02-S, San'ei Seisakusho). These granules were irregular in shape and bulky.

(3) Granules (C); tumbling granulation.

Calcium phosphate disasic was granulated in a rotating coating pan (FM-2PA1, Freund Sangyo Co., Ltd.) by addition of the binder. These granules were ball-shaped.

For tableting, all the wet granules were dried at 60°C for more than 8 h, and then screened (16—60 mesh). Photographs of the granules are shown in Fig. 1. The bulk densities of the granules were measured with a bulk density tester (JIS K5101, Kuramochi Kagaku Co., Ltd.), and the results are shown in Table I.

Fig. 1. Scanning Electron Microscopic Photographs of Granules

Binder concentration=10%.

TABLE I. Bulk Densities of Granules

	Binder concentration (%)	Bulk density[a] (g/ml)
Granules (A)	5	0.495
	10	0.519
Granules (B)	5	0.441
	10	0.431
Granules (C)	5	0.465
	10	0.502

a) Average of three measurements.

Tableting——The tableting was carried out on a single punch tableting machine (KS-II, Nichiei Seiko Co., Ltd.) with a flat-faced punch (diameter=1.128 cm). The tableting speed was 6 tablets/min and the tablet weight was 0.65 g. A lubricant (magnesium stearate) was dispersed on the punch surface and on the die wall surface at each tableting. At the tableting, measurements of the punch pressure, the die wall pressure and the distance between the upper punch and the lower punch were carried out according to the methods that we reported previously.[6] The thicknesses and diameters of the tablets after ejection were measured by means of a dial gauge (Peacock). The punch pressure was set at about 500, 1000, or 1500 kg/cm^2. In this paper, we designate the tablets prepared from granules (A), granules (B) and granules (C) as tablets (A), tablets (B) and tablets (C), respectively.

Calculation of Apparent Compliance——The apparent compliance (elastic compliance) of the tablets was calculated by use of the following equations in the same way as described in our previous paper.[1]

$$\text{The apparent compliance in the compressive axial direction} = \frac{(L-l)/L}{(UP+LP)/2}$$

The apparent compliance in the radial direction $= \frac{(D-d)/D}{DP}$ Up, upper punch pressure; LP, lower punch pressure; DP, die wall pressure; L, D, thickness and diameter of the tablet immediately after ejection; l, d, thickness and diameter of the tablet at the maximum compression pressure in the die.

Porosity——The porosity of the tablets was calculated from the diameter and thickness of the tablet and the true density of the granules, which was calculated from the true volume of the granules determined with a comparison pycnometer (model 930, Toshiba-Beckman Co., Ltd.).

Measurement of Crushing Strength of Tablets——The stress at which the tablets were fractured in a tester of our own manufacture[7] during compression in the radial direction was regarded as the crushing strength of the tablets.

Pore Size Distribution of Tablets——The pore size distribution of the tablets was measured by means of a mercury intrusion porosimeter (motor-driven, 15000 psi, American Instrument Co., Ltd.) using a tablet divided into two. The contact angle between the mercury and the tablets was assumed to be 130°.

Results and Discussion

I. Granulation Methods and Anisotropy

The relationship between the apparent compliance in the radial direction and that in the axial direction for the tablets is illustrated in Fig. 2.

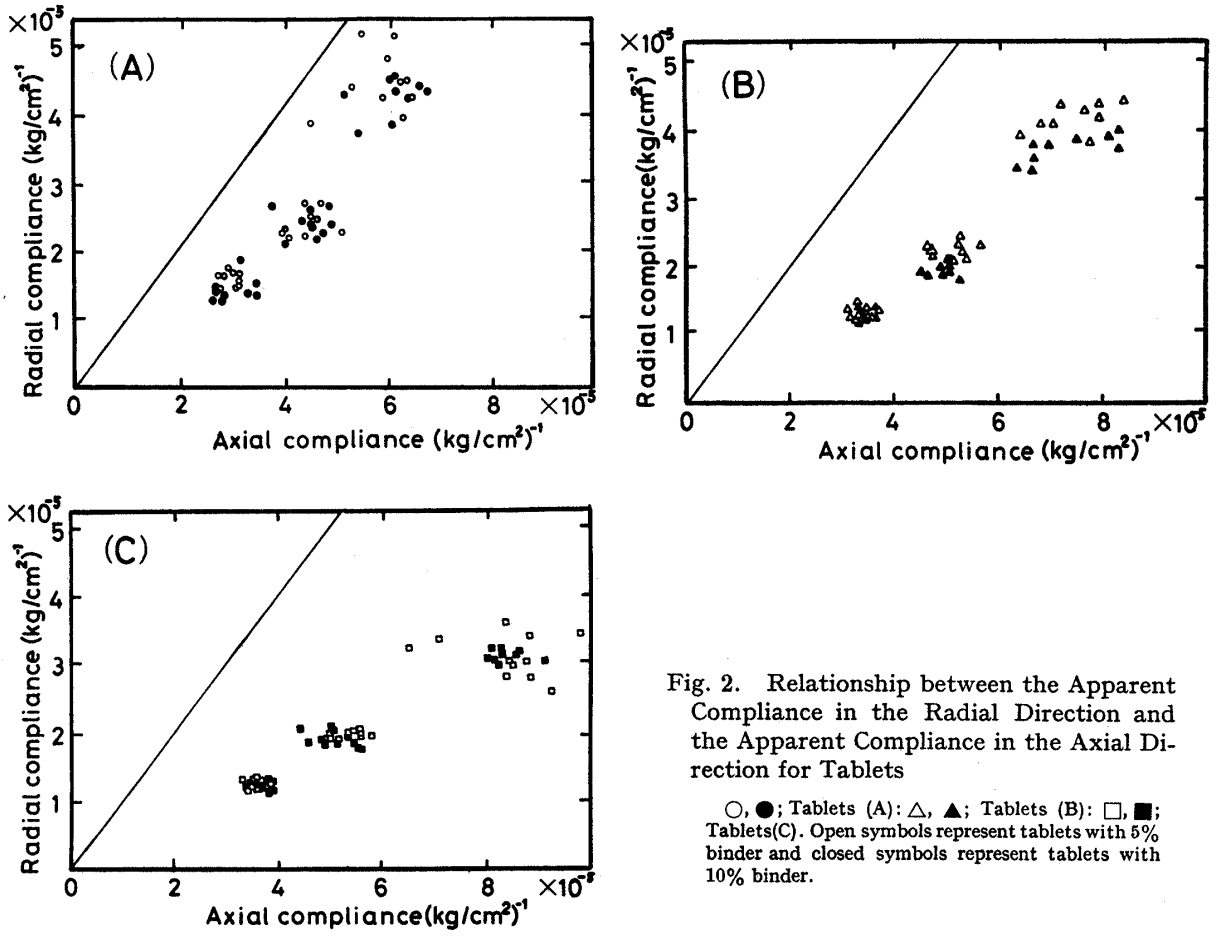

Fig. 2. Relationship between the Apparent Compliance in the Radial Direction and the Apparent Compliance in the Axial Direction for Tablets

○, ●; Tablets (A): △, ▲; Tablets (B): □, ■; Tablets(C). Open symbols represent tablets with 5% binder and closed symbols represent tablets with 10% binder.

When points are nearer to the straight line, the difference between the two compliance is smaller, and therefore the degree of anisotropy is smaller. For a given granulation method, the difference of anisotropy between tablets with the two binder concentrations was small. In order to evaluate the effects of the granulation methods on the anisotropy, the relationship between the ratio of the axial compliance to the radial compliance and the porosity of the

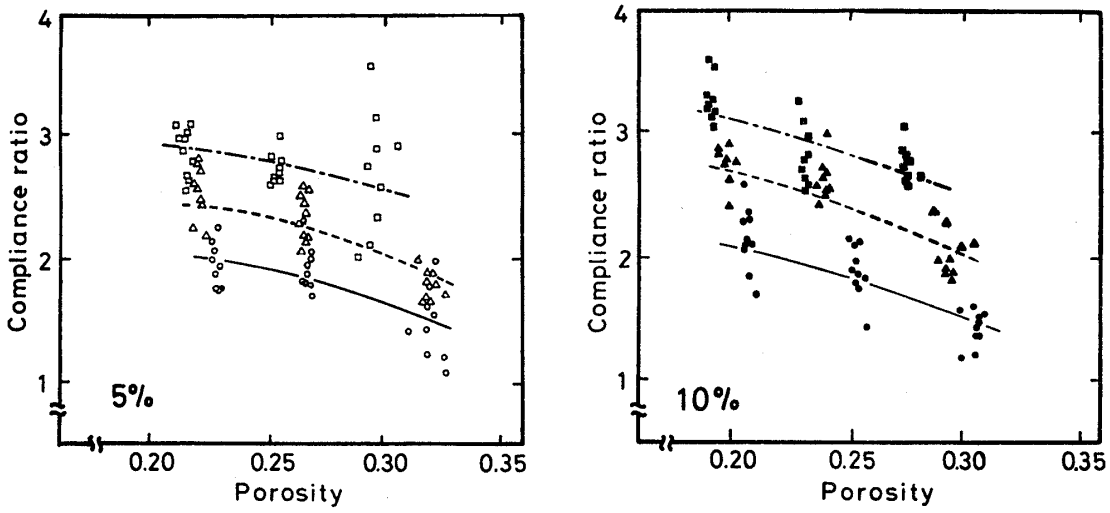

Fig. 3. Relationship between Compliance Ratio (Axial Compliance/Radial Compliance) and Porosity

—○—; tablets (A): ---△---; tablets (B): —□—; tablets (C).
—●—; ---▲---; —■—;

Open symbols represent tablets with 5% binder and closed symbols represent tablets with 10% binder.

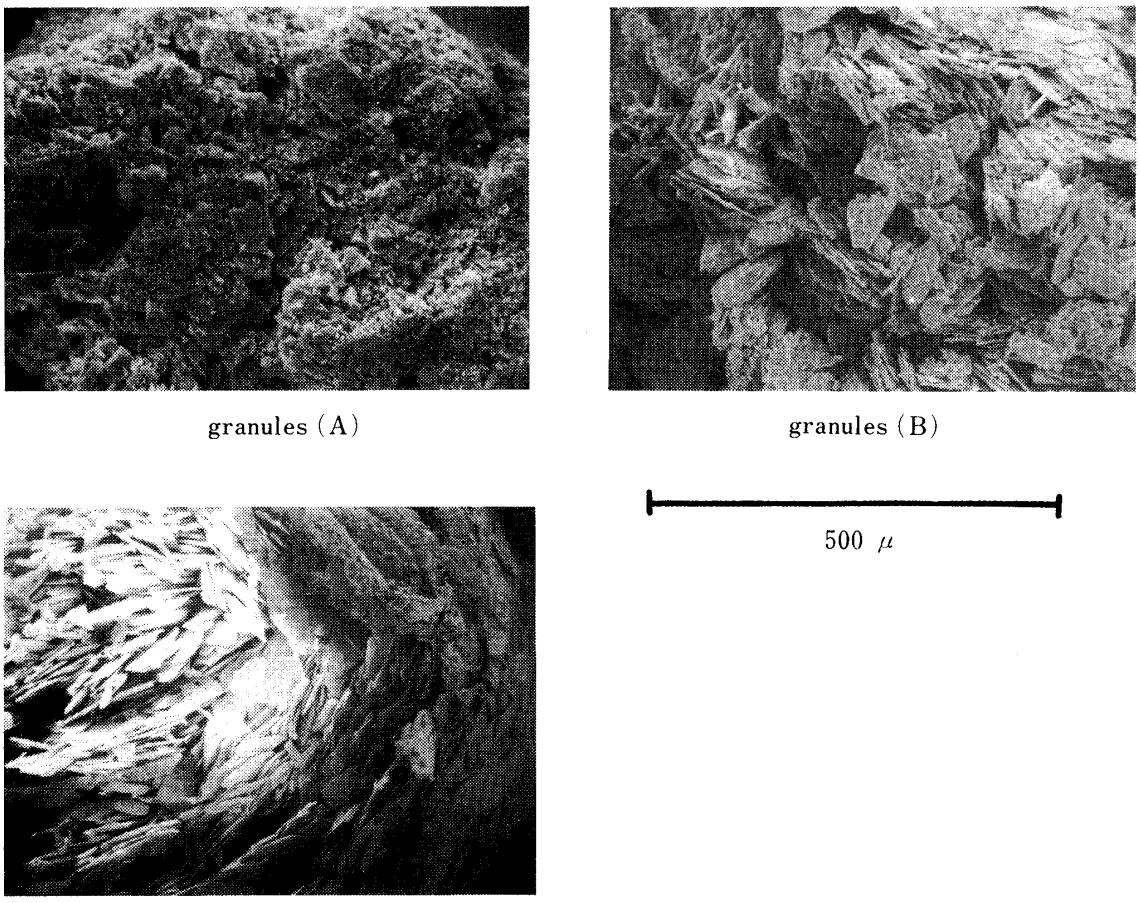

Fig. 4. Cross Sections of Granules

Binder concentration=10%.

tablets was plotted (Fig. 3).

It is considered that ratios nearer to 1 indicate smaller anisotropy. For both binder concentrations, the degree of anisotropy was in the order tablets(C)>tablets(B)>tablets(A). It can be considered that the difference in the degree of anisotropy (in terms of the elastic property) is due to the orientation of the particles and the structure of pores in the tablets, as we described before.[8] Thus, the degree of anisotropy in tablets (C) reflects the structure of granules(C). We therefore observed the cross sections of the granules under a scanning electron microscope (T-200, Japan Electron Optics Laboratory Co., Ltd.) (Fig. 4).

It was observed that calcium phosphate dibasic particles (flaky particles) were located in a coaxial arrangement in granules(C), whereas the particles were located at random in granules (A) and granules(B). The particles in granules(A) were slightly smaller than those in other granules because of crushing by the strong extrusion forces.

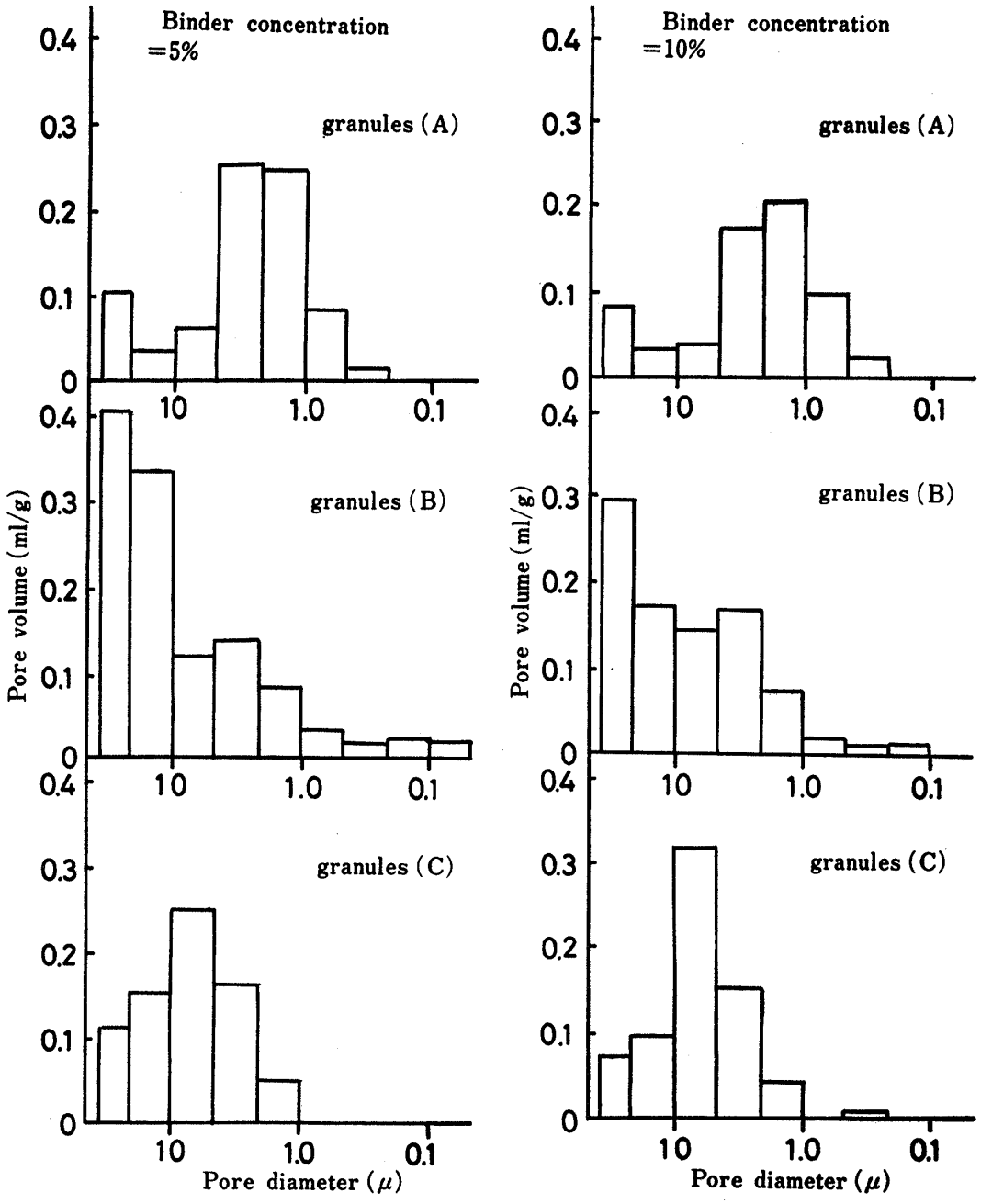

Fig. 5. Pore Distribution of Granules

It can be presumed that when granules(C), in which the particles are oriented, are compressed (in other words, when granules(C) are deformed and crushed by stress mainly in the axial direction applied by an upper punch and a lower punch), the particles and pores readily bcome strongly aligned. Granules(B) have irregular shapes, and are bulky (Table I, Fig. 5); when they are compressed the void spaces presumably become smaller, the particles move easily and orientation of the particles occurs. Granules(A) are strong and more closely packed than the others (Table I, Fig. 5), and are in a random arrangement. Thus, it can be presumed that when granules(A) are compressed the change in the void space is so small that movement of the particles is difficult, making orientation of the particles difficult, so that the degree of anisotropy is small. The fact that the particles in granules(A) are slightly smaller than the others may also contribute to the decrease of the anisotropy.[8] The relationship between the porosity of the tablets in the die at the maximum compression pressure at tableting and the compression pressure is illustrated in Fig. 6.

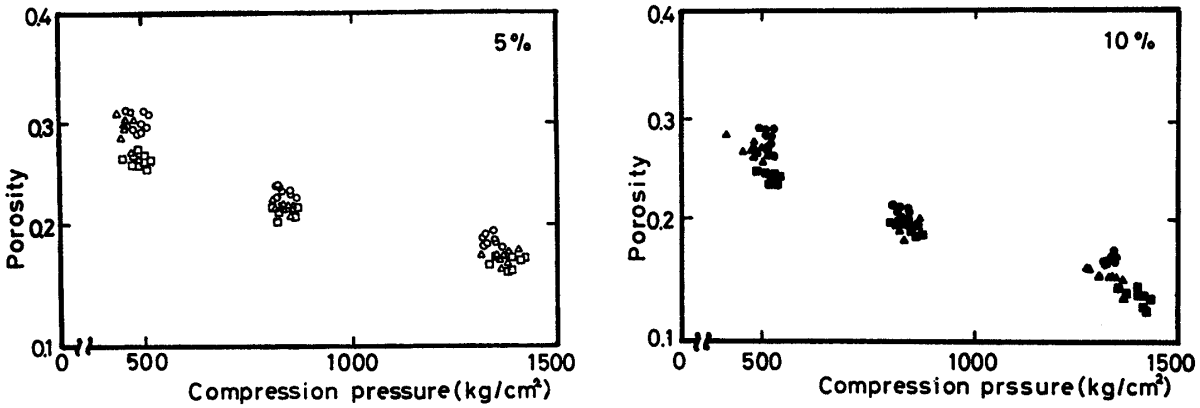

Fig. 6. Relationship between Porosity of Tablets in the Die at Maximum Compression Pressure During Tableting and Compression Pressure

Compression pressure is average of upper and lower punch pressures.
○, ●; tablets (A): △, ▲; tablets (B): □, ■; tablets (C).
Open symbols represent tablets with 5% binder and closed symbols represent tablets with 10% binder.

Tablets(A) have larger porosity than the others at a given pressure, and the difference is especially marked at lower pressures. This indicates that granules(A) resist compaction more strongly than the others.

Cross sections of the tablets are shown in Fig. 7.

No orientation of particles was apparent in tablets(A), while those in tablets(C) were highly oriented. Tablets with greater orientation have greater anisotropy, as indicated in our previous paper.[8]

II. Granulation Methods and Pore Size of Tablets

The pore diameter distribution of the tablets is shown in Fig. 8. With the increasing compression pressure, the pore diameter becomes smaller and the total pore volume also becomes smaller. Tablets(A) have larger total pore volume than the others, especially at lower compression pressure. This seems to be because of the resistance of granules (A) to compaction (Fig. 6). Little difference in the shapes of the pore distribution curves can be seen among the three kinds of tablets, though the variation of pore diameter in tablets(A) is slightly smaller than in the others. At the same compression pressure, the tablets with the higher binder concentration have a slightly smaller total pore volume, but there was little difference in the shapes of the pore distribution curves.

Shwartz[9] proposed the use of the log-normal distribution for expressing the characteristics

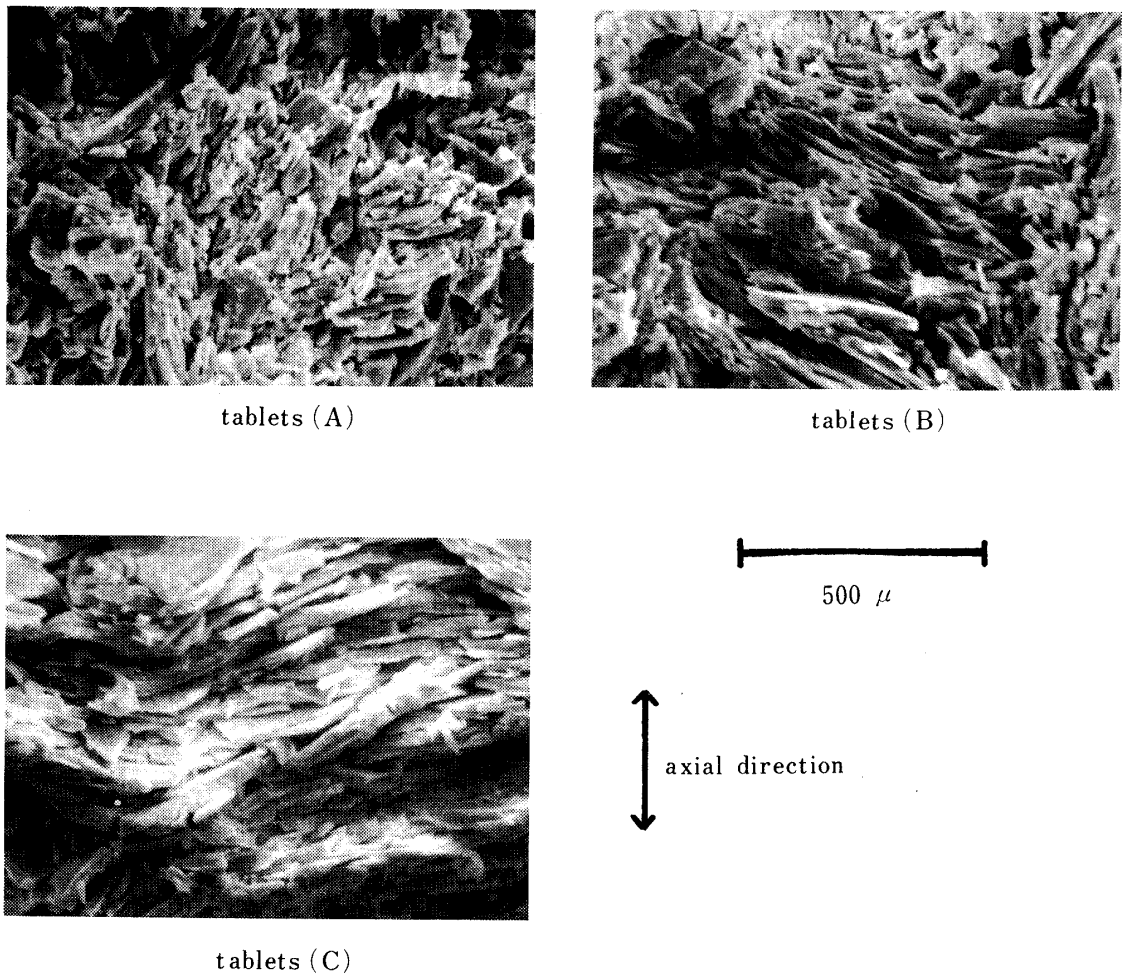

Fig. 7. Cross Sections of Tablets
Binder concentration=10%, upper punch pressure=1000kg/cm².

of the pore diameter distribution, and showed that, because plots of the pore diameter were nearly linear on log-normal probability paper, the variation of the distribution could be calculated easily by the graphical method. We also used his method, but the plots did not give good straight lines on the log-normal probability paper.

The relationship between the volume of the void calculated from the porosity and the total pore volume obtained from mercury porosimetry is illustrated in Fig. 9.

These volumes are almost equal. This shows that all the pores of the tablets have been filled with mercury at the end of the mercury intrusion experiments. Therefore, it is considered that so-called "closed pores" are essentially absent in the tablets.

Next, the relationship between the logarithm of the mean pore diameter and the porosity is shown in Fig. 10. The mean pore diameter is expressed as the pore diameter (median diameter) which corresponds to the point representing half the total pore volume in the plot of cummulative pore volume.

All the plots gave straight lines in our experiments. Even when the tablets are equal in porosity, the mean pore diameters differ depending on the granulation method. At both binder concentrations the mean pore diameters are in the order tablets(C)>tablets(B)> tablets(A). These results on the anisotropy and the pore size show that the tablets with a

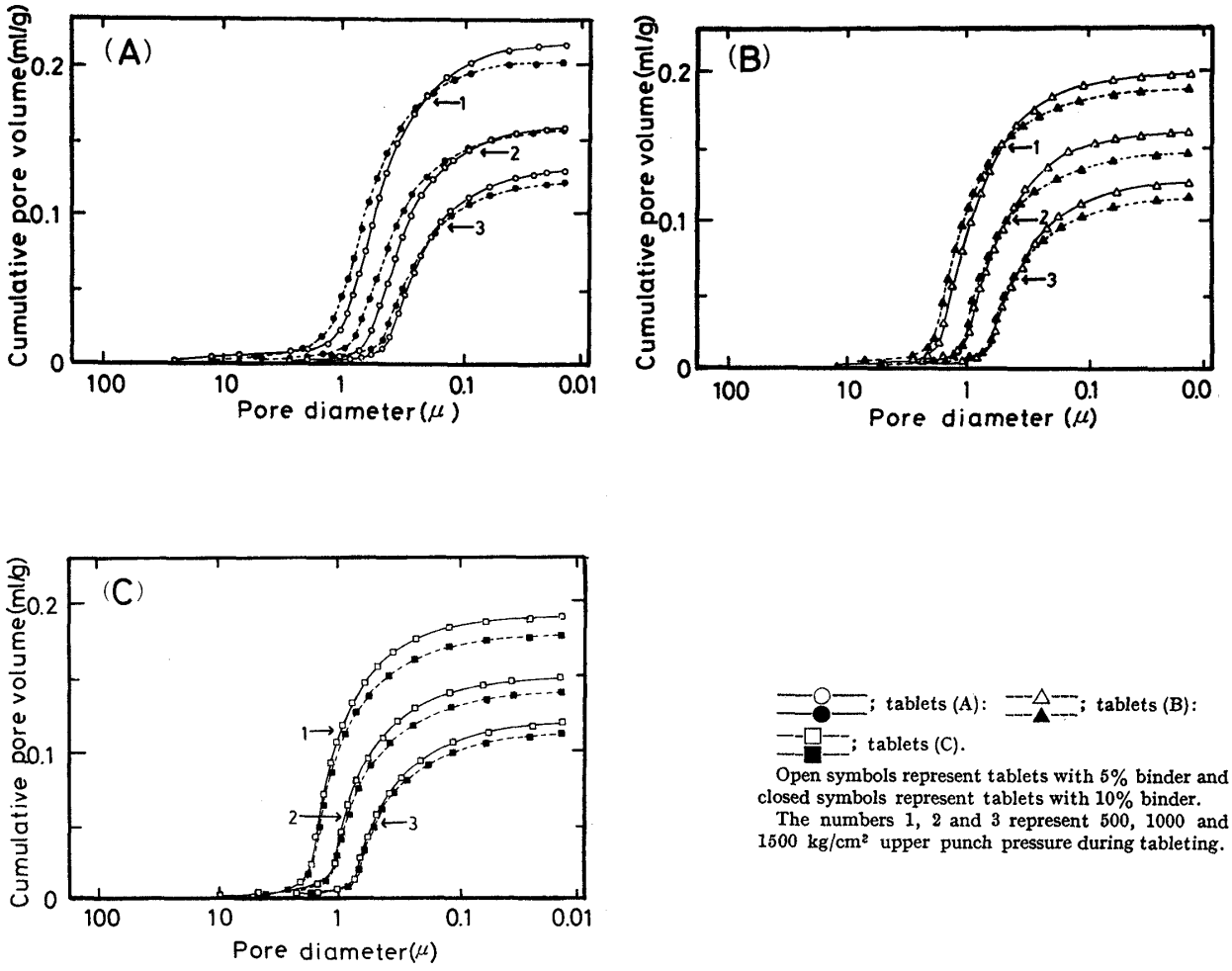

Fig. 8. Pore Distribution of Tablets

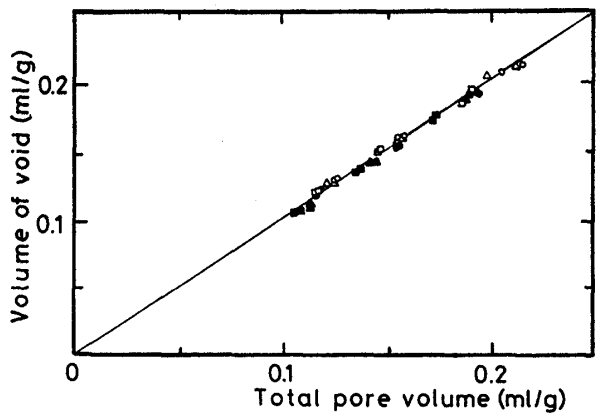

Fig. 9. Relationship between Void Volume and Total Pore Volume

○, ●; tablets (A): △, ▲; tablets (B): □, ■; tablets (C). Open symbols represent tablets with 5% binder and closed symbols represent tablets with 10% binder.

large degree of anisotropy have large pores. Fig. 11 shows that a large strain recovery occurs in the axial direction in the tablets with a large degree of anisotropy immediately after compression.

We showed previously[10] that lactose–starch tablets with a large proportion of starch had a large strain recovery. Nogami and others[11] reported that the pores in such tablets become larger because of the existence of the starch. In view of these reports and the results of the present experiment, it can be presumed that the large strain recovery produces large pores in the tablets.

III. Granulation Methods and Crushing Strength of Tablets

The relationship between the crushing strength of the tablets and their porosity is shown in Fig. 12.

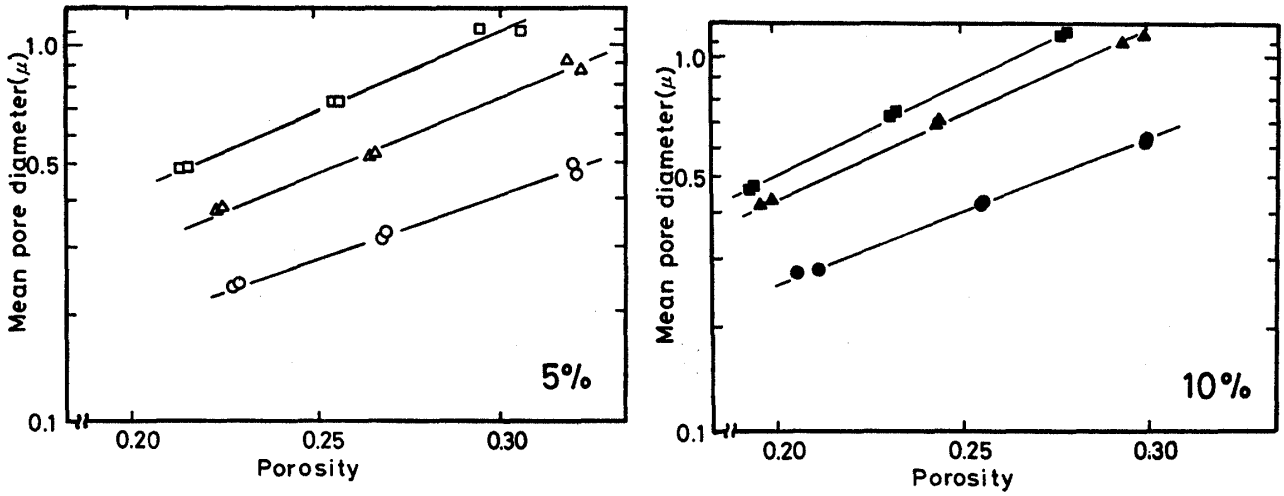

Fig. 10. Relationship between Mean Pore Diameter of Tablets and Porosity

○, ●; tablets (A): △, ▲; tablets (B): □, ■; tablets (C).
Open symbols represent tablets with 5% binder and closed symbols represent tablets with 10% binder.

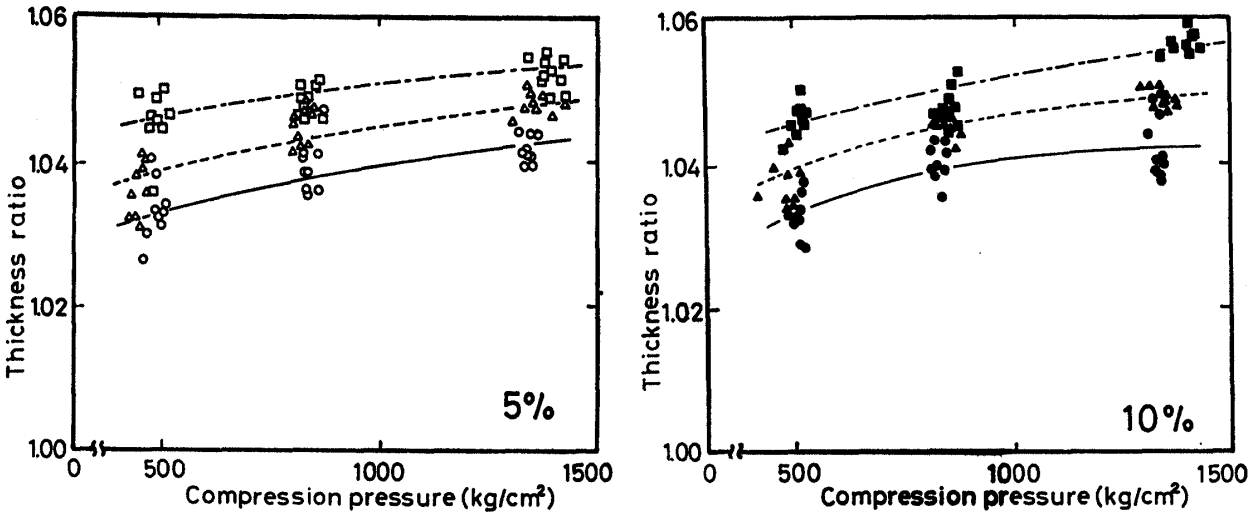

Fig. 11. Relationship between Thickness Ratio (the thickness of the tablet immediately after ejection/the thickness of the tablet in the die at maximum compression) and Compression Pressure

—○—; tablets (A): —△—; tablets (B): —□—; tablets (C).
—●— —▲— —■—
Open symbols represent tablets with 5% binder and closed symbols represent tablets with 10% binder.

For a given granulation method, the tablets with binder at a higher concentration have a larger crushing strength, because the inter-particle bonding force is increased by the binder. On the other hand, at both binder concentrations, distinct differences in the crushing strength were seen in tablets when the granulation methods were different. The crushing strength is in the order tablets(A)>tablets(B)>tablets(C) at the same porosity. We consider that this difference in the crushing strength is related to the size of pores in the tablets, because it is considered[12] that the fracture of a solid body occurs from the crack which is weakest in the solid body, and a solid body having larger cracks is weaker. Since pores are regarded as cracks in the present context, it can be presumed that the magnitude of the mean pore diameter of a tablet correlates with the crushing strength. Therefore the tablets with smaller pores should have larger crushing strength.

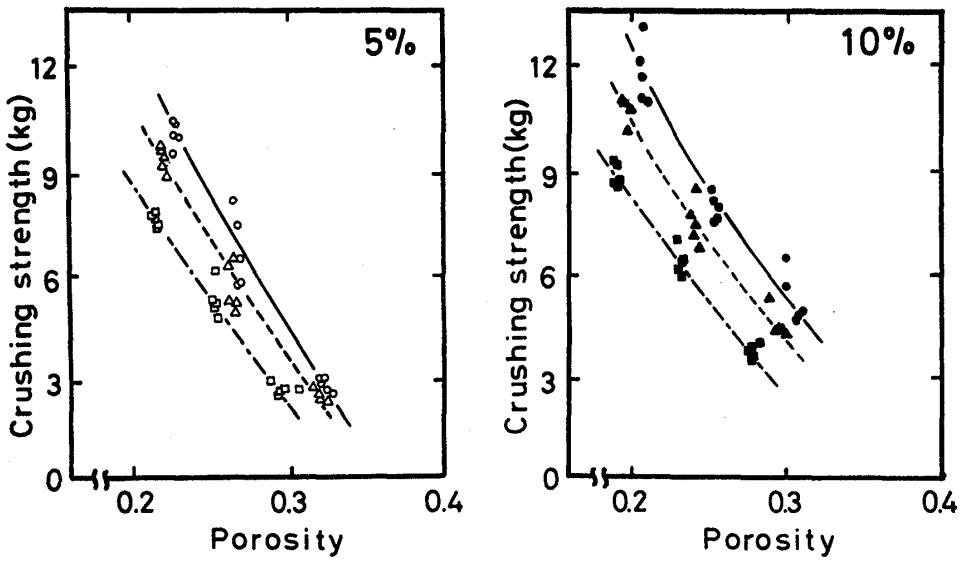

Fig. 12. Relationship between Crushing Strength of Tablets and Porosity

—○—; tablets (A): —△—; tablets (B): —□—; tablets (C).
Open symbols represent tablets with 5% binder and closed symbols represent tablets with 10% binder.

Conclusions

The degree of anisotropy, the pore size and the crushing strength of calcium phosphate dibasic tablets were influenced by the granulation method used.

1. Independently of the hydroxypropyl cellulose binder concentration, the degree of anisotropy and the pore size were both in the order tablets(C)>tablets(B)>tablets(A).

2. Independently of the binder concentration, the crushing strength of tablets was in the order tablets(A)>tablets(B)>tablets(C).

3. The degree of anisotropy, the pore size and the crushing strength of tablets were mutually correlated. A tablet with a larger degree of anisotropy had larger pores and a smaller crushing strength.

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