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Estimation of Stress Distribution in the Convex Type Tablet using Specific Enzyme Activity as a Parameter[1)]

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The concentration and the distribution of stress by compression with several different pressures in convex type tablets were studied, measuring specific enzyme activities of proteinase as a parameter. As for the parts where stress center, a new zone which gives worse damages to the enzyme activity was found that appeared about two third from the center of tablets in the longitudinal direction. And the new zone was related to structural breakings in the experiment of compression of large two dimensional model. It was estimated that Lamination is closely related to the recovery of elastic deformation at the new zone and that Capping is related to that at upper corners. The new zone was proposed by authors to be called the L zone for its close relation to the phenomenon of Lamination.

In the previous paper,[3)] the authors have reported that there exists a simple relationship between compression force and the specific enzyme activity,[4)] when powdery enzyme is compressed to thin tablet. In this paper, some observations are described on estimating stress distribution in the convex type tablet utilizing the partial inactivation of enzyme induced by pressure. Several workers have discussed on the stress distribution in the compressed material from the field of powder metallurgy.[5–10)]

In the field of pharmaceutical engineering, on the other hand, the most outstanding investigation about stress distribution was reported by D. Train[11)] in 1956 using the apparent density of sample and a manganine wire resistance gauge. These works above mentioned, however, are all on the behaviors of metallic or inorganic powdery substance when compressed with flat type punch, and not ones of organic medicinals with convex type punch by which the ratio of compression makes difference at the center and the corner zone in a tablet. Matsuno, *et al.* reported on the compression behavior of convex type tablet,[12)] using two dimentional model with 1.5% agar solution and observing it photoelastically. But it can not be considered to express the inner state of convex type tablet that has a density distribution by compression, because the sample was already molded to be a convex type model with homogeneous density before compression and there was no irreversible deformation during and after compression. If the specific enzyme activity is employed as a parameter, it is possible to measure the stress distribution in the convex type tablet of not scaled up model but of actual size. In this work, another experiment on the compression process convex type tablet

1) Presented at the 92nd Anual Meeting of the Pharmaceutical Society of Japan at Osaka, Apr. 1972.
2) Location: *3190 Gofuku, Toyama.*
3) M. Morii, A. Sano, N. Takeguchi, and I. Horikoshi, *Yakugaku Zasshi*, **93**, 300 (1973).
4) Specific enzyme activity means the per cent retention of enzyme activity.
5) M.Y. Bal'shin, *Vestinik Metalloprom.*, **18**, 124 (1938).
6) R.P. Seeling and J. Wulff, *Trans. Am. Inst. Mining Met. Engrs.*, **166**, 492 (1946).
7) R. Kamm, M. Steinberg, and J. Wulff, *Trans. Am. Inst. Mining Met. Engrs.*, **180**, 694 (1949).
8) M.E. Shanke and J. Wulff, *Trans. Am. Inst. Mining Met. Engrs.*, **185**, 561 (1949).
9) P. Duwez and L. Zwell, *Trans. Am. Inst. Mining Met. Engrs.*, **185**, 137 (1949).
10) C. Ballhausen, *Arch. Eisenhuttenw.*, **22**, 185 (1951).
11) D. Train, *J. Pharm. Pharmacol.*, **8**, 745 (1956).
12) M. Matsuno and H. Okano, *Yakugaku Kenkyu*, **29**, 45 (1957).

by large two dimensional model has also been carried out, and several informations were obtained by comparing those two experiments.

Experimental

Materials——1) Enzyme: Bacterial alkaline proteinase was supplied from Seishin Pharmaceutical Co., Ltd., as a highly purified specimen with an activity of 340000 $[UP]^{Cas.30FRA}_{\mu g\cdot tyr}/g$, extracted from Black Aspergillus. It has been proved in the previous paper[3] that this enzyme is less hygroscopic and the specific enzyme activity is not influenced by slight change of moisture content.

2) Particle Model: The vinyl straw pipe of diameter 4.4 mm and of length 20 mm, which had been made by cutting with leather knife was used as two dimensional particle model.

Apparatus and Procedure——1) Cell Assembly for Compression of Powdery Enzyme: An apparatus shown in Fig. 1 was devised and used. Cell consisted of a die, an upper and a bottom punches, a base plate and a bar that transmitted pressure to the upper punch. All segments were made of hardened steel. The diameter and the radius of curvature of the tablet made by this assembly were 16 mm and 12 mmϕ. A sample (2.0 g each) was poured into the die and compressed by an oil press machine (Rikenseiki, R-18) to give a maximal punch pressure of over 5000 kg/cm^2. The compression was done only by the motion of the upper punch, the velocity set to 500 kg/cm^2/sec, and the load was released immidiately after reaching the required pressure, the tablet of enzyme was taken from the die and used to determine the distribution of specific enzyme activity.

2) Cell Assembly for Compression of Two Dimensional Model: An apparatus, made of acrylic acid resin, illustrated in Fig. 2 was devised modifing Umeya's,[13] and used. It consisted of a container vessel (1), 20 mm in thickness and 150 mm in width, which corresponded to the diameter of the die, and two parts (2, 3) with 100 mm radius of curvature, which corresponded to the upper and the bottom punches. Vinyl straw pipes were filled in the equipment until they formed a packed structure, and revolving the volt on upper frame by hand the upper punch was moved downward and particles were compressed. By photographing momentarily the alternating state of compression that took place during the pressing period, the complicated features of particle breaking were directly observed.

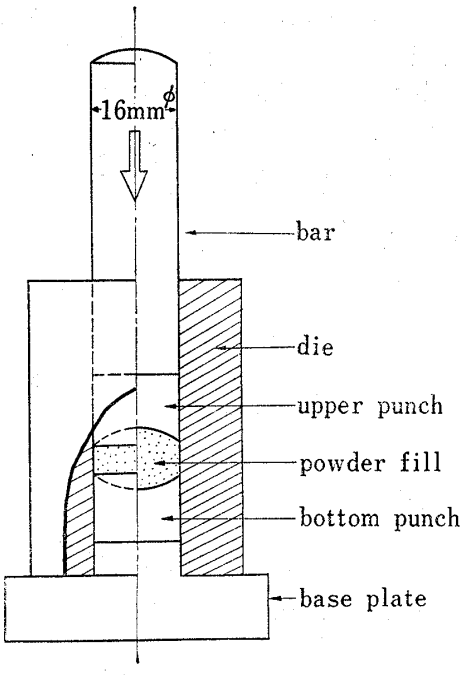

Fig. 1. The Die Assembly for the Compression of Powdery Enzyme

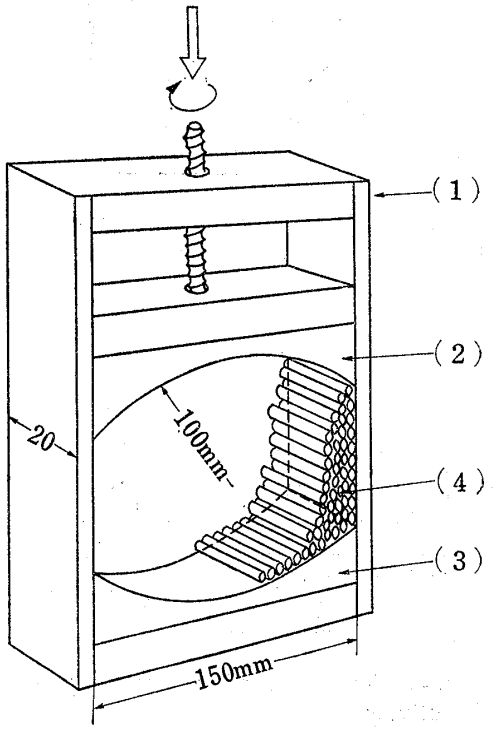

Fig. 2. The Apparatus for the Compression of Two-dimensional Model Powder System

(1): container vessel (2): upper punch
(3): bottom punch (4): vinyl straw pipes

13) K. Umeya, N. Kitamori, R. Hara, and T. Yoshida, *J. Soc. Materials Sci. Japan*, **18**, 489 (1969).

Measurement of Specific Enzyme Activity (S.E.A.)——Each convex type tablet of enzyme was cut in half along the compression axis, each of which section was divided into 29 parts as shown in Fig. 3, and from each part 2—4 mg sample were collected. This operation was continued on 3—5 tablets until the sample weight of each part became more than 20 mg. The activity of enzyme was colorimetrically measured by the Ogiwara and Anson's method which had been described in detail in the previous paper.[3]

Result and Discussion

(1) Distribution of S.E.A. by Compression

The method measuring directly the applied pressure at a selected point in a powder fill of actual size in the process of compression has not been devised, and only the indirect methods are in use such as estimating from the resistance change of a strain gauge which is located in a powder fill, from apparent density, or from the change of hardness. Although the method described in this paper, applying S.E.A., comes within the category of the indirect measurement, it is characteristic on the point that the observation of the inner behavior of not the scaled up model but the actual orally administering tablet is possible. In this experiment, no lubricant is added to the sample for the purpose of enlarging the irregularity of distribution of the value of S.E.A. The results are shown in Fig. 3, Fig. 4 and Fig. 5. These figures show the distribution of S.E.A. on a vertical sectional view of a convex type tablet when compressed respectively, to 495 kg/cm², 2500 kg/cm² and to 4900 kg/cm². The figures inserted in the left half of the diagrams present percentages of S.E.A. in each parts, averages of three times of experiment. The error is estimated to be about ±3% in this experiment. The curves drawn in the right half are contours of S.E.A. assumed from the values presented in the left half of the figure and from the color tone of the section of the powder fill. Since the enzyme used as the sample was a mixture of crystalline and amorphous powder, it was observed that the pressed sample became darker in color as higher pressure was applied.

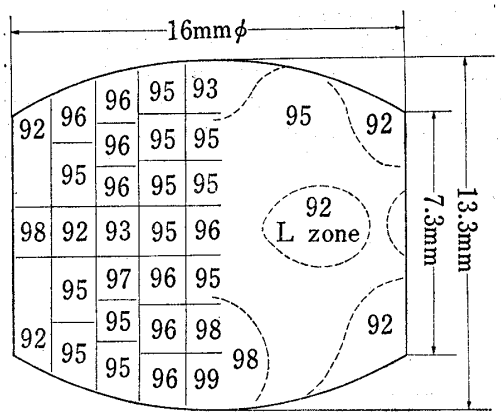

Fig. 3. Distribution of Specific Enzyme Activity
(pressure=495 kg/sq.cm,

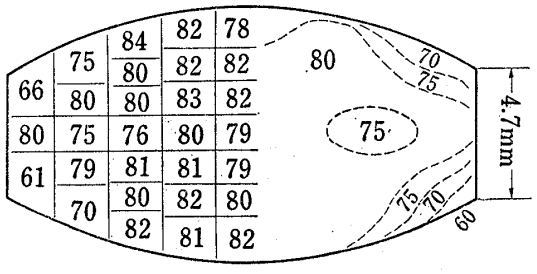

Fig. 4. Distribution of Specific Enzyme Activity
(pressure=2500 kg/sq.cm)

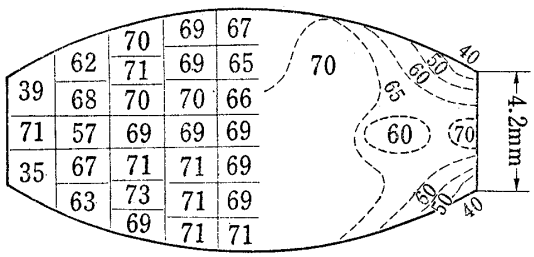

Fig. 5. Distribution of Specific Enzyme Activity
(pressure=4900 kg/sq. cm)

In the first stage of weak compression (pressure of about 0.5 tons/cm²), shown in Fig. 3, no great irregularity of distribution of S.E.A. was observed. If there ever were uneven distributions, there were four parts where S.E.A. went down to 92%; top center which contacts with the upper punch, top corners contacting with the upper punch and the die walls, bottom corners contacting the lower punch and the die walls, and a new zone (which will be

called L zone for convenience in this paper) which appeared near the die walls about two third from the center core of the pressing (see L zone in Fig. 3). In the greater part of other region, S.E.A. was about 95%, and the region which showed the least of it was bottom center, 98%.

In the second stage (pressure of about 2.5 tons/cm^2), shown in Fig. 4, the difference of the S.E.A. of each region became remarkable, and those of top corners and bottom corners went down to 60%. In the top center, it was not so conspicuous as compared with them in two zones of top corners and bottom corners. The bottom center zone in Fig. 3 which had comparatively high value of S.E.A. had almost disappeared. In L zone S.E.A. was 75%, and it went down much more than the value of the other region.

By the pressure about 5 tons/cm^2, third stage, S.E.A. at top corners and bottom corners reached at the level of 30%, which is shown in Fig. 5. In this experiment the value of bottom corners was usually smaller than that of top corners. It was also observed that in the middle side corners which contact with the die walls, zones of less S.E.A. was appearing. Such a complicated distribution of S.E.A. is thought to be the result of that the compression ratio at the center and at the surroundings of the pressing is different. In this case, compression ratio can be defined as the ratio of initial depth of die filled with the sample and punch distance during compression. When the compression ratio is one fifth at the center, it becomes smaller than one eighth in its surroundings. Accordingly it is at the surroundings that the poweder first reaches the closest packed structure, and then the powder moves to the direction of center core from surroundings when further compression is carried out. The movement is assumed to proceed mostly from top and bottom corners to L zone. It will be reasonable to consider that these powder movements, and particle destruction and deformation which give rise concomitantly to these movements, are the reason of decrease of S.E.A. at L zone.

As was reported in the previous paper,[3] when a powdery enzyme was compressed to thin flat tablet, its S.E.A. decreased to about 70% by 5 tons/cm^2 of pressure, and this value was minimum regardless of compression time, and even when the compression at the same pressure and towards the same direction was repeated, the change did not move forward. And when so called repeated compression at random direction, where the pressing was repowdered and recompressed, was done n times, the value of S.E.A. became equivalent to that of the first compression to the nth power and became finally zero value.

From the facts above mentioned, it might be better to consider that the appearance of the extremely low value of S.E.A. down to 57% in a convex type tablet was the result of the powder movement from surroundings to its center, which caused concomitantly deformation and destruction, than to consider the result of generating of high pressure upon certain zones. It is suitable to consider that these S.E.A. curves show the same tendency to those of pressure isobars.

(2) Comparison between Compression Behavior in the Two Dimensional Particle Model and S.E.A. Distribution

The vinyl straw pipe used as a particle model in this experiment has least frictional resistance and the closest packing state at the beginning of compression. It is impossible, consequently, to express the typical four regions of compression process[14] by this particle model, but the behavior of powder corresponding to the formation of L zone could be portrayed. One example of the results is shown in Fig. 6. By using the two dimensional model of vinyl pipe, no powder movement was observed after the closest packing had been completed, but that the deformation of particle model had taken place in the part where the stress had been concentrated. That is, the deformation took place at top corners and top center

14) The first stage is free-flowing region, the second, compaction region, the third, plastic deformation region and the last, pure deformation region.

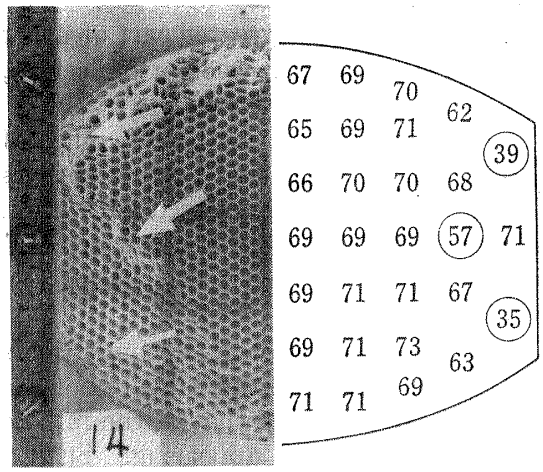

Fig. 6. Comparison between Compression Behavior in the Two Dimensional Particle Model and Distribution of Specific Enzyme Activity

first, then at bottom corners, and then it developed from top corners to downward obliquely, which was thought to correspond to remarkable drop of the value of S.E.A. in L zone. By further compression the deformation of particle model developed from circumference to center core, corresponding to the process of compression in Fig. 5. Although the deformation of particle model do not correspond directly with the movement of powder in the tablet of enzyme, it could be assumed that the direction the development of deformation advances is in close accord with the powder movement. This phenomenon might be a means of a proof of the existence of L zone. At the parts where appear much deformation or lower value of S.E.A., apparent density might be comparatively high, and strain might be stored up as elastic deformation. It is comprehensive to interpret that Capping and Lamination, which are often issues in the mass producing process of convex type tablet, take place when the elastic deformation recover respectively in the top corners and in L zone.

Acknowledgement We are pleased to acknowledg the considerable assistance of Mr. Y. Masakawa.