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Effect of Sorbed or Adsorbed Water in Powdery Medicaments on Tablet Compressibility[1)]

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The recompression time dependencies of dynamic loss energy and of the maximum displacement of the upper punch on sorbed or hydrated and anhydrous three compounds of potato starch, dicalcium phosphate and glucose were studied. In every case of our experiments, a linear relationship was found to exist between dynamic loss energy and the maximum displacement of the upper punch. The gradient of the linear relationship expresses an amount of heat generation per unit viscous deformation (J/mm) in recompression and can be utilized as a parameter of solid medicament to evaluate its tablet compressibility. The values of those gradients were much influenced by the sorbed water in potato starch, but a little by the water of hydrated form in dicalcium phosphate and glucose.

Keywords——sorbed or adsorbed water; tablet compressibility; recompression; dynamic loss energy; maximum displacement; potato starch; dicalcium phosphate; glucose; hydrated and anhydrous

In the previous work,[3)] we analyzed the dynamic recompression process of powder and showed from the stress-strain curve of recompression process a new method of evaluating the amount of dynamic loss energy which stemmed from viscous behavior of the sample. In the present work, we found the facts that there is a linear relationship between dynamic loss energy (E_{loss}) and the maximum displacement of the upper punch (L_{max}), and that the gradients of these linear relationships could be utilized as a parameter to evaluate the degree of tablet compressibility of powdery material.

In general, the tablet compressibility depends upon many factors such as crystal habit, particle shape, size distribution, and water contained in the powder, among which the property and the amount of contained water have remarkable influence on the tablet compressibility. On the other hand, solid medicaments have various types of water; free water, sorbed water, and hydrated water.[4)] There is an empirical fact that in the mass production process of tablet, a certain amount of free water is essential to form good tablet. From the point of medicinal degradation, the water free condition at the tableting process is desirable, but keeping this condition, tendency of capping increases and electrostatic charge of particles makes it impossible to continue tableting. The water plays an important role in the bonding mechanism of particles.

For example, acetaminophene granules, containing two per cent of moisture, can be compressed satisfactorily without capping. This may be due to the squeezing out of water into the voids as pendular water, which may affect bonding and elastic recovery in the same way as the lubricants.[5)]

1) A part of this report was presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan at Sendai, Apr. 1974.
2) Location: *3190 Gofuku, Toyama, 930, Japan.*
3) I. Horikoshi, M. Morii, and N. Takeguchi, *Chem. Pharm. Bull.* (Tokyo), **22**, 327 (1974).
4) K. Higashi, "Chemistry of Proteins," Vol. 4. S. Akabori and S. Mizushima, Ed., Kyoritsu Pub. Co., Tokyo, 1965, p. 127.
5) L. Lachman, H.A. Lieberman, and L.L. Kaning, "The Theory and Practice of Industrial Pharmacy," Lea and Febiger, Philadelphia, U.S.A., 1970, p. 193.

In this investigation, we analyzed the influences of sorbed and hydrated water in the solid materials on the parameter described above in the recompression process. We used sorbed or hydrated and anhydrous compounds of potato starch, dicalcium phosphate, and glucose as sample powders, and compared the results with those of lactose and crystalline cellulose reported in the previous paper.[3] Some new information were obtained, which would be described in detail.

Experimental

Apparatus——The same apparatus described in the previous paper[3] was used. A single punch eccentric tablet press with a variable speeder and flat type punches, diameter of 16 mm, to which a strain gauge and a differential transformer were connected was also used, and signals corresponding to stress and strain were amplified and used as the inputs of X- and Y-axis on the synchroscope. The empty maximum depth of the die, the packing height, was 10 mm, and the shortest punch distance, when no sample was packed in, was set beforehand to 1.80 mm.

Procedure——Prior to the measurement, a small amount of magnesium stearate suspended in ether was sprayed on the surface of the die wall and punches, and the die wall and punches were dried sufficiently enough to reduce the die wall friction and also enough to reduce the adhesion of particles to the surface. After the sample (600 to 1000 mg) was put into the die by hand, it was compressed at the tableting velocity previously programmed, and recompressed once again at the same velocity. The amounts of samples were controlled to obtain constantly the maximum recompression pressure of 800 kg/cm^2. The hysteresis loop which appeared on the synchroscope in the recompression process was photographed. Since the value of X-axis has a dimension of force and that of the Y-axis has that of distance, the area surrounded by hysteresis loop expresses directly E_{loss} in the process of recompression. The recompression time, *i.e.*, recompression velocity, which was defined as the time to draw the whole hysteresis loop, was precisely measured by setting a time marker by which the light spots were projected on the line of hysteresis loop at the time interval of 0.005 sec.

Materials——The following J.P. VIII medicaments were used as the samples. The water content of potato starch were graded into eight degrees from 1.2 to 26.0%. Samples of 1.2, 3.4, and of 6.0% water content were prepared by dring J.P. VIII potato starch (16.2%) at 40° in vaccum of 10^{-3} Torr about 8, 2, and 1/2 hrs, respectively. Samples of 9.2 and 12.0% water content were also prepared by dring it (16.2%) at room temperature in a desiccator with P_2O_5 about 72 and 48 hrs. Samples of 22.5 and 26.0% were prepared by humidifing the potato starch (16.2%) in the glass tube at room temperature about 4 days and one week. The sample weights of potato starch were all kept 1000 mg. Anhydrous dicalcium phosphate was prepared by dring hydrated compound at 200° in vaccum of 3 Torr approximately for 3 hrs, and glucose monohydrate was prepared by recrystallizing anhydrous glucose from water. Dicalcium phosphate dihydrate, glucose monohydrate, and these anhydrous compounds, the sample weights of which were kept 860, 650, 740, and 600 mg, respectively, were used. After the experiment of recompression, the weight per cent of contained water was redetermined by a thermo balance (Kyoto Denshi, IM-02). The thermal character of contained water was checked by a differential scanning calorimeter (Perkin-Elmer, DSC-1B).

Results and Discussion

Viscous Behavior of Potato Starch in the Recompression Process

Fig. 1 shows the recompression time dependencies of E_{loss} and L_{max}, when water contents in potato starch were kept 1.2, 3.4, 6.0, 9.2, 12.0, 16.2, 22.5, and 26.0%, respectively. In the case that the range of water contents was from 1.2 to 6.0%, particles of potato starch did not adhear one another and tableting was impossible owing to the intrinsic elasticity of particles. In all the other cases where water contents were over 9%, tableting could be carried out satisfactorily. As there was no significant difference between the results for the water content of 22.5% and those for the water content of 26.0%, the datum of the former was omitted from Fig. 1.

As is shown in Fig. 1, E_{loss} increased as the recompression time decreased, while L_{max} decreased. Especially when the recompression time was shorter than 0.08 sec, remarkable changes appeared in each parameter. In the region, the gradients of E_{loss} and L_{max} increased or decreased steeply, and when water content was 26.0%, these gradients varied from 0.4 to 10.0 J/sec and from −0.09 to −3.8 mm/sec, respectively. These remarkable

changes suggested that from this point, 0.08 sec, the viscosity of the samples increased abruptly and good tablet formation became impossible, resulting in capping or lamination.

Furthermore, both values of E_{loss} and L_{max} could be devided into two regions; one was the case that the water content was less than 12.0% and the other was more than 16.0%. In the former region, the values of L_{max} decreased curvilinearly when water content increased, and in the latter region, the recompression time dependencies of E_{loss} and L_{max} were independent of water content, and the curves for 16.2, 22.5, and 26.0% were all overlapped to one another.

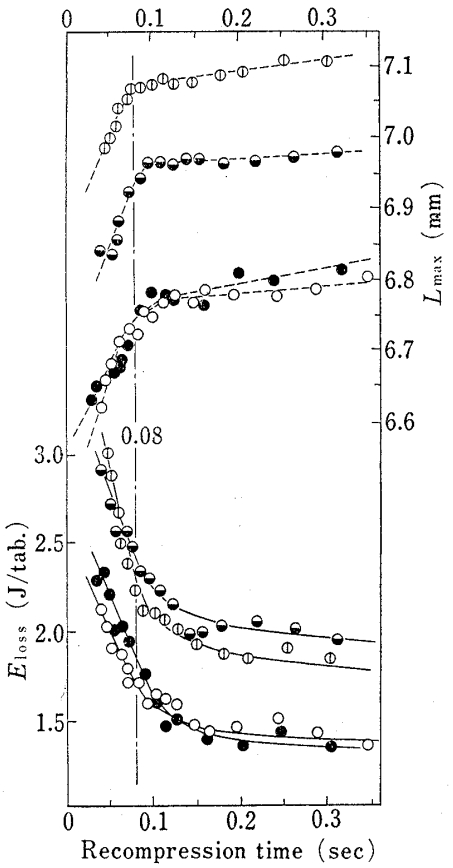

Fig. 1. Recompression Time Dependencies of Dynamic Loss Energy (E_{loss}) and Maximum Displacement of Upper Punch (L_{max}), when Water Content in Potato Starch were 9.2, 12.0, 16.2, and 26.0%, respectively, and the Tablet weight was 1000 mg

—◑—: 9.2% —◒—: 12.0%
—●—: 16.2% —○—: 26.0%

The physical characteristics of water contained in potato starch were studied in detail by one of the present authors (I. Horikoshi)[6] and especially dielectric behaviors of water in the process of adsorption isotherms were clarified. Their results showed that anhydrous potato starch was more hygroscopic than anhydrous silica gel at room temperature, and that the water contained in potato starch was a sort of sorbed water and when water content is under 12% the bond strength of sorbed water to the substrate is comparatively strong. It corresponds to the level of the first adsorption stage in the silica gel, in which the water molecules are sorbed on the surface of adsorbent in the state of monolayered system.[7] However, when the water content was over 16%, the bond strength of sorbed water to the powdery particles became remarkably loose forming multilayered adsorption system, which could be detected easily as the increase of dielectric loss. There is a clear boundary zone between

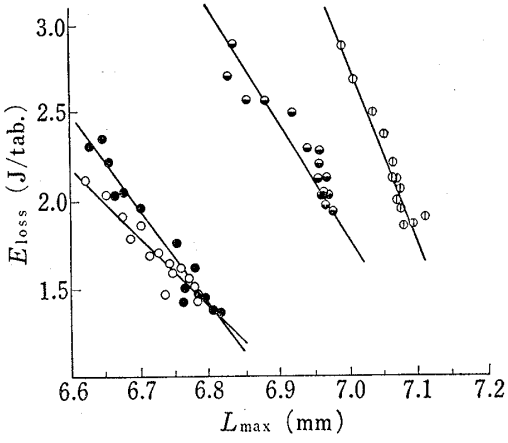

Fig. 2. Relationship between Dynamic Loss Energy (E_{loss}) and Maximum Displacement of Upper Punch (L_{max}), when Water Content in Potato Starch were 9.2, 12.0, 16.2, and 26.0%, respectively, and the Tablet Weight was 1000 mg

—◑—: 9.2% —◒—: 12.0%
—●—: 16.2% —○—: 26.0%

6) I. Horikoshi and I. Himuro, *Yakugaku Zasshi*, **86**, 319 (1966); *idem*, *ibid.*, **86**, 324 (1966).
7) S. Kurosaki, *J. Phys. Chem.*, **58**, 320 (1954).

12% and 16% of water content. This dielectric boundary zone described above corresponded well to the steep changes of E_{loss} in the recompression process.

When E_{loss} was plotted against L_{max}, a good linear relation was obtained between them in every case of various water contents, as shown in Fig. 2. The gradients of linear relations can be regarded as a parameter of medicaments to evaluate the tablet compressibility and to express an amount of heat generation per unit viscous deformation (J/mm) in the recompression.

As is shown in Fig. 2, the gradients of potato starch depend upon the water content within the range of 9.2 to 16.2%. The smaller the weight per cents of contained water are, the larger the gradients of curves are, and the good compaction becomes gradually more difficult. But when water content in potato starch was over 15%, the gradients of curves became less sensitive to the water content and converged to a constant value of 4.0 J/mm.

As a result, the water content 16%, which had about 6.0 J/mm, was found to be a lower limit to continue good tablet formation, when sample was composed of potato starch only.

Tablet Compressibility of the Other Medicaments

As to hydrated and anhydrous dicalcium phosphate and glucose, the recompression time dependencies of E_{loss} and L_{max} and also linear curves similar to the potato starch were obtained. In order to compare these data with those of the previous paper,[3] the values of the gradients were all illustrated in Fig. 3.

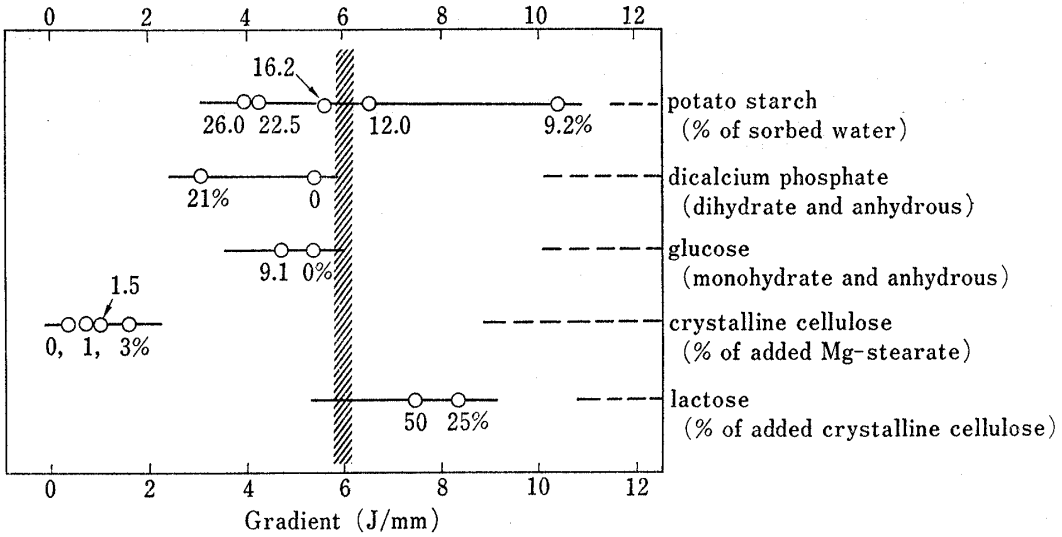

Fig. 3. Influences of Contained Water and of Added Materials on the Gradients of Linear Relationship between E_{loss} and L_{max}

Dicalcium Phosphate——This compound has about 21% of water of crystallization, which is easily dehydrated at 200°. Anhydrous compound is anhygroscopic and insoluble in water and alcohol, hence it is widely used as good excipients of compressed tablets in the pharmaceutical industry, when the medicinal ingredient of the tablet is unstable for moisture. Despite of the large amount, 21%, of water content, there was no remarkable difference between the gradients of hydrated and anhydrous dicalcium phosphate. The difference between hydrated and anhydrous dicalcium phosphate was only 2.0 J/mm which was small comparing to the difference, 6.5 J/mm, in potato starch when the water content was between 9.2% and 26.0%. The value of anhydrous one may be comparable to that of potato starch of 16.2% water content. The low values suggest that even when dicalcium phosphate is anhydrous, it is much available for compaction. These behaviors justify viscoelastically the fact that

anhydrous dicalcium phosphate has been used widely in the pharmaceutical industry as an excellent excipient of compressed tablets.

Glucose——As this compound has one mole of the water of crystallization and liberated it at comparatively low temperature of 67°, this water has been thought to be liberated spontaneously in the compression process,[8] and to be one of the factors to adhear particles and to harden the compressed tablet. However, in this experiment we could not find any effect of hydrated water to the viscous behavior. As is shown in Fig. 3, there is no difference between hydrated and anhydrous glucose, and their values are about 5.0 J/mm which are nearly equal to that of 16.2% water content in potato starch. Thus, in analogy with dicalcium phosphate, anhydrous and hydrated glucose have good tablet compressibility. It may be more reasonable to think that owing to the hygroscopicity of glucose the multilayered water molecules have been already adsorbed on the surface of glucose crystal, the amount of which is thought to be less than 0.5%, and this water has more influence upon the viscous behavior of glucose in the compression process than the water of crystallization.

Crystalline Cellulose——This compound has very small value of the gradient, 0.5 J/mm, and when the lubricant of magnesium stearate was added to it from 1.0 to 3.0%, a slight increase appeared in the value. This small value indicates that crystalline cellulose is the most excellent excipient used in this work .

Lactose——Good compaction was impossible, when the ingredient of tablet was composed of lactose only and even when 50.0% of crystalline celluose was added to it. The value of the gradient has a large value of 8.5 J/mm, which shows that the good compaction may be impossible.

From the facts described above, it may be concluded that we succeeded to obtain parametrical expression for the degree of tablet compressibility which has been empirically recognized by a skillful tabletter as one of the hidden techniques, and that the gradient of 6.0 J/mm is an upper boundary for good compaction.

8) H. Rumph, *Chem. Ingr-Tech.*, **30**, 144 (1958); E. Turba and H. Rumph, *ibid.*, **36**, 230 (1964).