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# Cohesion of Particulate Solids. VI.[1] Improvement of Apparatus and Application to Measurement of Cohesiveness at Various Levels of Humidity

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An electrical device was introduced in place of a torsion balance in the vertical tensile strength method, and all forces applied to the surface of the powder bed were recorded automatically. The complex peaks of tensile stresses recorded for irregular particles were consistent with the interparticulate interactions discussed in the preceding report in relation to cohesiveness. The tensile strength between particles at various humidities was measured and the influence of environmental humidity on the cohesiveness of pharmaceutical powder is discussed.

Hydrophilic and water-soluble powders showed an abrupt and large increase in cohesiveness with increasing humidity and a large amount of water was adsorbed in the vicinity of the critical relative humidity (R.H.). Hydrophilic and water-insoluble powders showed moderate changes of cohesiveness and amount of water adsorbed with increasing humidity. Some powders showed a progressive and exceptional increase of cohesiveness with increasing humidity due to swelling. A large amount of water was absorbed by such powders as starchs, silica gel, microcrystalline cellulose, and methylcellulose compared with other powders. Contact angle did not appear to be related to cohesiveness at various humidities. The slightly larger cohesiveness of hydrophobic powders than hydrophilic powders may have been a result of the irregular shapes of particles. The cohesiveness of particles became increasingly sensitive to humidity changes as the diameters of the particles was decreased, except in the case of water-insoluble powders.

**Keywords**——powder; pharmaceuticals; loose packing; cohesion; humidity; particle size; swelling; tensile strength; water vapor adsorption isotherm

In most pharmaceutical manufacturing processes such as pulverization, classification, mixing, storage, transport, *etc.*, powders are handled in a non-compressed state. Under these circumstances, it is necessary to know the cohesiveness of loose assemblages of particles and their characteristic behavior under various levels of humidity. Little work has been done on the influence of environmental humidity during storage or other processes on the cohesiveness of powders. Eaves *et al.*[2] reported an increase of tensile strength of hydrophilic powders due to moistening, using a horizontal split cell method. However, loosely packed powder beds or free-flowing powders cannot be studied by the split cell method. In the preceding report,[3] the influences of particle size and shape on cohesiveness were investigated by using the vertical tensile strength method. In the present work, the same method was used to study the influence of environmental humidity on the cohesiveness of loosely packed pharmaceutical powders, but the torsion balance was replaced with an electrical device.

## Experimental

**Apparatus**——The apparatus used is illustrated in Fig. 1. It consists of a scale pan (about 50 mg in weight) hung from a thin spring connected to a straingauge transducer with nylon thread, a bridge circuit, an amplifier, and a recorder. The principle is fundamentally the same as in the preceding report,[4] but some improvements were made as follows. First, a slightly convex disk, part of a relatively large spherical surface ($r=8$ cm) made of aluminium, was used as a scale pan instead of the flat disk. Secondly, to measure the tensile strength of powders at the surface of the powder bed, an electrical device was adopted instead of the torsion balance. These modifications, improved the sensitivity from 0.2 mg to about 0.01 mg.

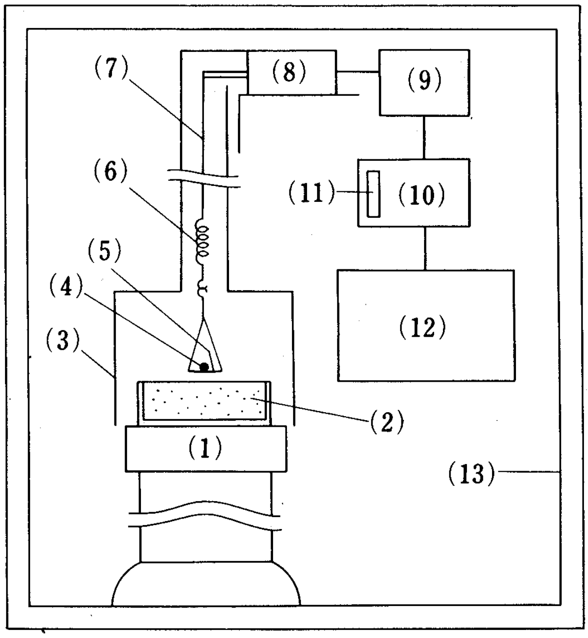

Fig. 1. Apparatus used for Measurement of Cohesiveness at Constant Temperature and Constant Humidity

(1), jack; (2), powder; (3), windbreak; (4), weight; (5), scale pan; (6), thin spring; (7), nylon thread; (8), strain-gauge transducer; (9), bridge circuit; (10), amplifier; (11), indicator; (12), recorder; (13), chamber of constant humidity and temperature.

**Procedure**——A thin layer of white petrolatum was spread on the bottom of the scale pan as a sticking agent. The scale pan was suspended from the rod of the transducer. A sample was placed on the jack and elevated slowly until it came into contact with the bottom of the scale pan. The load applied to the powder through the scale pan was controlled by raising or lowering of the sample, and at the same time it was monitored by reading the recorder deflection or using an amplifier coupled with an ammeter (Fig. 1). The magnitude of the load was selected so that the cohesiveness per weight was as large as possible, since it was considered[4] that single layer sticking produced the maximum value of cohesiveness per weight. Although suitable loads differed from sample to sample, loads from 20 mg to 200 mg were usually used. When the load required was larger than the weight of the scale pan itself, a sufficient weight was added to the scale pan. After the application of the required load for a period of approximately a second, the sample was lowered slowly till cleavage occurred between the surface layer adhering to the sticking agent and the underlying layer remaining in the cell. The force required, in other words, the sum of the tensile strength, $C_0$(dyn), and the weight of the sticking particles, $W$(mg), could be obtained by analysis of the loci of the tensile force (Fig. 2) using a calibration curve. The whole procedure was carried out in a humidity- and temperature-controlled chamber (TBS-10, Tabai Co., Ltd.), and measurement was repeated 30 times for each sample. The cohesiveness of the powders may be defined as $\alpha_c = C_0 / W$(dyn/mg). In contrast with the preceding paper,[3] cohesion force per contact point was not estimated in this study, since the shapes of particles differed so much among samples that the results would be extremely difficult to interpret. The humidity in the chamber was maintained constant in the range of relative humidity (R.H.) 40—90±5% at 25±1°C. A calibration curve between stress and deflection of the recorder was obtained in advance.

**Preparation of Samples**——Powders were classified into fractions using a set of standard sieves. The desired fractions were stored for a few days in a desiccator regulated to be R.H. 50% at 25±1°C using a saturated solution of a suitable salt, then they were moved into the humidity-controlled (also R.H. 50%) chamber. By passing the powders through a large-size sieve (18—50 mesh), loose powder heaps were made in the sample cells. The sieves and sample cells used were made of brass in order to facilitate the discharge of static electricity generated during sieving. The powder heaps in the cells were scraped off level with the cell rim using a sharp razor, taking care not to compact the powder beds. The prepared samples were stored again in a second desiccator regulated to the desired relative humidity, from 40 to 90%, for more than 24 h prior to use. When required, they were taken from the second desiccator and put in a chamber controlled to the same humidity level as the second dessicator.

**Materials**——Materials used and their physical properties are listed in Table I. They were all of J.P.IX or reagent grade. The contact angles of hydrophobic and comparatively hydrophobic powders were measured by Kossen's[5] method. For the other samples, Kossen's method was not applicable, since the contact angles were so small that the height of drops on disks (3.0 cm in diameter and 0.5—0.6 cm in thickness) could not be measured. In the present report, samples whose contact angles could not be measured for this reason were classified as hydrophilic, and the other samples were classified as hydrophobic. The mesh numbers used in particle size classification and the porosities of powders are listed in Table II.

## Results and Discussion

### Characteristics of the Improved Method and Shape of Stress Loci

In the preceding method,[4] the bottom of the scale pan and the surface of the sample had to be kept exactly horizontal and the adjustment was troublesome. The adoption of a convex scale pan overcomes this difficulty.

TABLE I. Characteristics and Classification of Samples used

| Samples | Specific gravity | Contact angle (degree) | Solubility (g/dl) at 25°C | Class |
|---|---|---|---|---|
| Methylcellulose | 1.59 | | 10 | Hydrophilic and soluble |
| Lactose | 1.66 | | 17 | |
| Sulpyrine | 1.55 | | 100 | |
| Sodium bicarbonate | 2.45 | | 11 | |
| Monosodium glutamate | 1.70 | | 10 | |
| Corn starch | 1.64 | | | Swelling |
| Potato starch | 1.58 | | | |
| Glass beads | 2.40 | | | Hydrophilic and insoluble |
| Glass powder | 2.39 | | | |
| Microcrystalline cellulose | 1.71 | | | |
| Silica gel | 6.20 | | | |
| $\alpha$-Alumina | 4.34 | | | |
| Benzoic acid | 1.33 | 80 | 0.27 | Hydrophobic and slightly soluble |
| Sulfamine | 1.51 | 53 | 0.75 | |
| Phenacetin | 1.23 | 77 | 0.067 | |
| Sulfisoxazole | 1.43 | 56 | 0.35 | |
| Aspirin | 1.38 | 58 | 0.25 | |

TABLE II. Porosity Values of Test Powders

| Samples | Mesh number of fractions | Porosity |
|---|---|---|
| Methylcellulose | 100/200 | 0.875 |
| Lactose | 100/200 | 0.507 |
| Sulpyrine | 100/200 | 0.642 |
| Sodium bicarbonate | 100/200 | 0.688 |
| Monosodium glutamate | 100/200 | 0.496 |
| Corn starch | <200 | 0.749 |
| Potato starch | <200 | 0.605 |
| Glass beads | 200/250 | 0.411 |
| Glass powder | 200/250 | 0.565 |
| Microcrystalline cellulose | 100/200 | 0.844 |
| | 200/250 | 0.846 |
| Silica gel | 200/250 | 0.923 |
| $\alpha$-Alumina | 200/250 | 0.563 |
| Benzoic acid | — | 0.803 |
| Sulfamine | 100/150 | 0.691 |
| Phenacetin | 48/80 | 0.418 |
| | 100/150 | 0.636 |
| | 150/200 | 0.694 |
| Sulfisoxazole | 48/80 | 0.445 |
| | 100/150 | 0.475 |
| | 200/250 | 0.643 |
| Aspirin | 28/100 | 0.456 |

The convex scale pan was compared with the flat one using 100/150 mesh fraction of phenacetin at R.H. 70%. The results obtained are listed in Table III. There was no statistically significant difference between the results obtained by the two methods.

The use of the electrical device to measure the cohesive force made the addition or removal of load to the samples very easy, since this operation could be done continuously, and further, the range of measurement could be easily adjusted.

TABLE III. Effect of Shape of the Bottom of the Scale Pan on the Measured Cohesiveness of Phenacetin (100/150 mesh) at R.H. 70%

| Shape of the bottom of scale pan | Mean cohesive force per weight (dyn/mg) | Coefficient of variation (%) |
|---|---|---|
| Flat disk | 4.1 | 25 |
| Slightly convex | 4.3 | 29 |

The recorded patterns of tensile stress loci may be classified into two types, A and B, as illustrated in Fig. 2. The difference between the two types could not be detected by the preceding method. Type A consisted of a single peak and was obtained for particles of regular shape and fine powders. In this type, the breaking between the surface layer and underlying layer occurred almost simultaneously. Type B consisted of complicated peaks and was obtained for particles of irregular shape and needle-like crystals such as methylcellulose (MC), sulpyrine, microcrystalline cellulose (M.C.C.), benzoic acid, sulfamine and phenacetin. These particles may become entangled with each other, and breaking will not occur simultaneously, as suggested in the preceding reports.[3,4] This qualitative difference of cohesion seemed to be reflected in the powder properties. It could be considered that the failure of the layers to break cleanly (or simultaneously) is a consequence of "stickiness" of the powder flow, and is thus analogous to viscosity in liquid flow, but further data are necessary before this can be fully discussed.

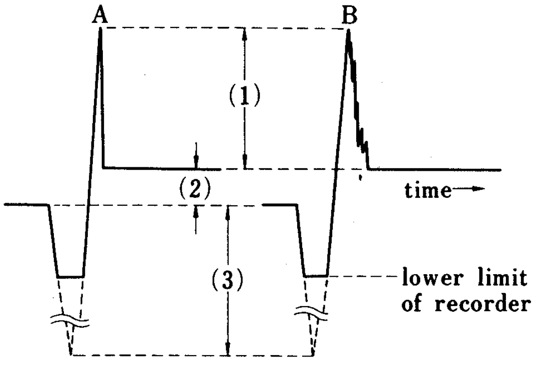

Fig. 2. Two Types of Recorded Signals and Meaning of Signal Height

(1), cohesive force; (2), weight of particles; (3), load applied to scale pan.

In this study, the cohesiveness varied considerably from sample to sample; there was 20 to 70% coefficient of variation. These values are almost the same as in the previous method.[1]

### Water-soluble and Hydrophilic Powders

Figure 3 shows the influence of humidity on the cohesiveness of water-soluble and hydrophilic powders, and Fig. 4 shows the water vapor adsorption isotherms for the same samples. Although the changes in cohesiveness and amount of water adsorbed were very small up to R.H. 80%, an abrupt increase in both cohesiveness and amount of water adsorbed was observed at R.H. 90%.

The mechanism of cohesion for soluble powders is more complex than that for insoluble powders, because both liquid and solid bridges between particles are formed with soluble powders. Thus, the slight increase of cohesiveness at below R.H. 90% may be due to liquid bridges (Fig. 3). From Fig. 4, it appears that R.H. 90% is above the critical relative humidity[6] for sulpyrine and monosodium glutamate or in its vicinity for lactose and sodium bicarbonate. Under these conditions, the dissolution of solids and crystallization of dissolved materials will occur simultaneously or alternately in view of the fluctuation of humidity (±5%) in the chamber, and solid bridges will be formed between particles. This phenomenon is known as caking, and the large tensile strength observed at R.H. 90% can be explained by this phenomenon.

MC, which is the only soluble polymer among the samples, showed a tendency for the cohesiveness to increase with increasing humidity quite similar to that for other soluble powders, although MC showed an adsorption isotherm similar to those of the water-insoluble polymers. The comparatively large cohesiveness of MC even at low humidity may be attribut-

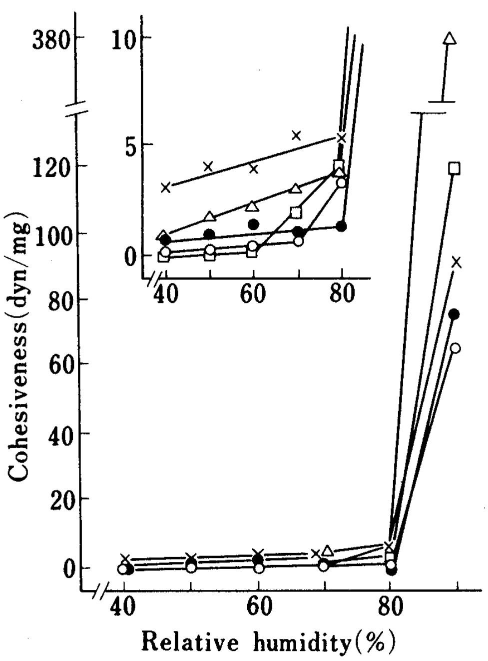

Fig. 3. Effect of Humidity on the Cohesiveness of Water-soluble and Hydrophilic Powders (Fraction of 100/200 mesh)

△, sulpyrine; □, sodium bicarbonate; ×, methylcellulose; ●, lactose; ○, monosodium glutamate.

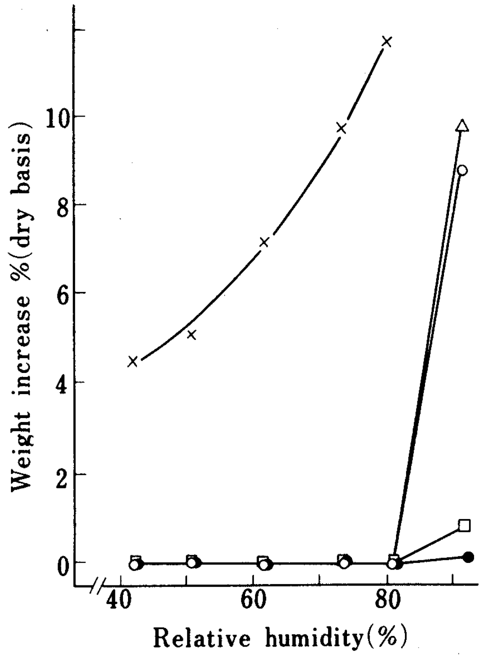

Fig. 4. Water Vapor Adsorption Isotherms for the Same Samples as in Fig. 3

△, sulpyrine; □, sodium bicarbonate; ×, methylcellulose; ●, lactose; ○, monosodium glutamate.

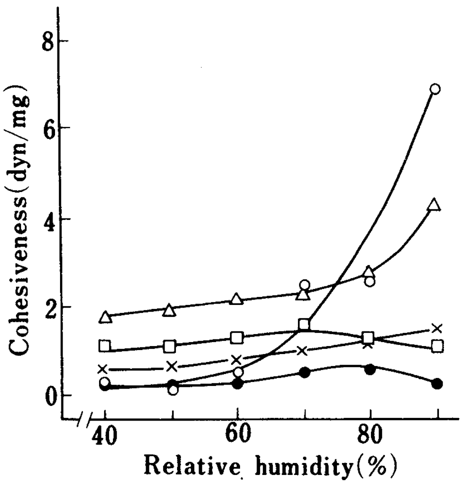

Fig. 5. Effect of Humidity on the Cohesiveness of Hydrophilic and Water-insoluble Powders (Fraction of 200/250 mesh)

○, α-alumina; △, microcrystalline cellulose; □, silica gel; ×, glass powder; ●, glass beads.

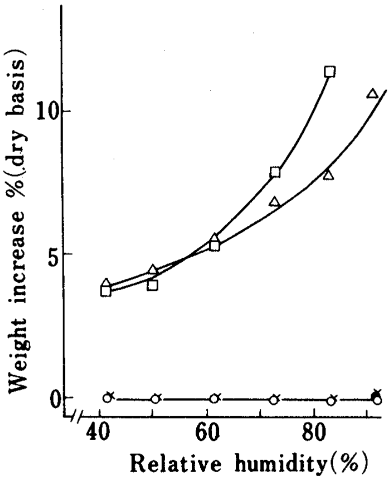

Fig. 6. Water Vapor Adsorption Isotherms for the Same Samples as in Fig. 5

○, α-alumina; △, microcrystalline cellulose; □, silica gel; ×, glass powder; ●, glass beads.

able to the interparticular interaction of irregular particles, since the pattern of tensile stress was of type B (Fig. 2).

## Insoluble and Hydrophilic Powders

In the case of insoluble and hydrophilic powders, a moderate increase of cohesiveness with increasing humidity was observed as shown in Fig. 5. This effect may be due to water bridges formed between the insoluble particles. There appear to be two types of curves of cohesive-

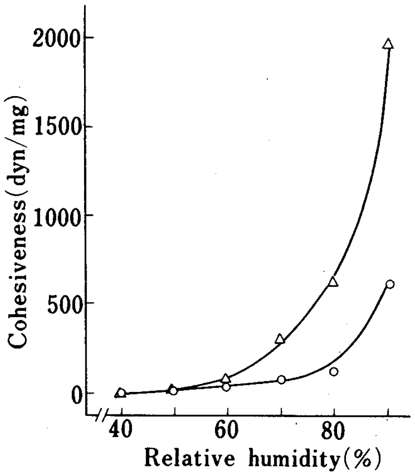

Fig. 7. Effect of Humidity on the Cohesiveness of Swellable Powders

△, potato starch <200 mesh; ○, corn starch <200 mesh.

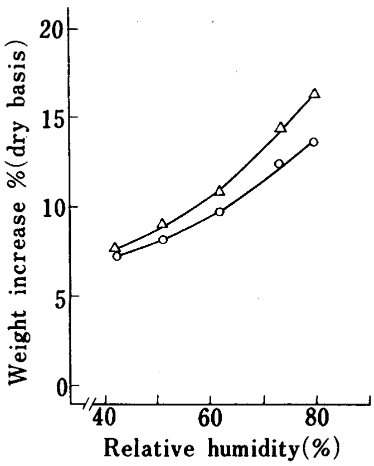

Fig. 8. Water Vapor Adsorption Isotherms for the Same Samples as in Fig. 7

△, potato starch; ○, corn starch.

ness against humidity. Silica gel and glass beads showed a slight maximum between R.H. 70 and 80%, whereas other powders showed a progressive increase of cohesiveness with increasing humidity. Nishino *et al.*[7] confirmed these maxima for glass beads using our method, compared the results with the theoretically evaluated value and attempted to explain the significant difference between them.

The water vapor adsorption isotherms for the same powders are shown in Fig. 6. The adsorption capacity of insoluble powders was very small except for M.C.C. and silica gel. M.C.C. and silica gel have adsorption isotherms similar to that of MC, as mentioned before (Fig. 4), and the amount of water adsorbed was large even at low humidity. It is known that silica gel has a porous structure and a large amount of water vapor was adsorbed in these micro-pores. On the other hand, Nakai *et al.*[8] revealed that M.C.C. was also porous to water vapor. It is clear that water vapor adsorbed and condensed in the micro-pores cannot form liquid bridges between particles. The small increase of cohesiveness with increasing humidity in spite of the large amount of water uptake may thus be explained. However, the large increase of cohesiveness of $\alpha$-alumina at R.H. 90% (Fig. 5) could not be elucidated in terms of the adsorption isotherm (Fig. 6).

## Insoluble and Swelling Powders

Potato starch and corn starch are hydrophilic, insoluble and swellable natural high polymers used as disintegrating agents for tablets. The influence of humidity on their cohesiveness is shown in Fig. 7, and the water vapor adsorption isotherms for the same samples are shown in Fig. 8. It is apparent from Fig. 8 that a large amount of water was absorbed by starchs such as silica gel, M.C.C., and MC. The curves of cohesiveness *vs.* humidity (Fig. 7) showed a progressive increase similar to that of the usual insoluble powders. However, the plots for the starchs showed greater slopes than for the usual insoluble powders. For instance, the cohesiveness varied from 2.5 dyn/mg at R.H. 40% to about 2000 dyn/mg at R.H. 90%. The mechanism of these remarkable and progressive increases of cohesiveness cannot be explained except in terms of the swelling of particles. Nakai *et al.*[9] measured the large swelling volume of starchs by following the absorption of water. The volume increase of starch particles due to swelling may cause an increase in the number of contact points, as well as in the contact pressure and contact area between starch particles in the powder bed. Subsequently, the powder bed would become consolidated.

It is doubtful whether liquid bridges are formed at the contact points between starch particles, since condensed water may be taken into the particles. However, even if they were formed, the contribution of this structure to the cohesiveness of starch powders seems to be negligible, especially at high humidity.

The difference of increment of cohesiveness between corn starch and potato starch can be explained in terms of the difference of volume increase due to swelling as reported by Nakai *et al.*[9]

### Slightly Water-soluble and Hydrophobic Powders

The influence of humidity on the cohesiveness of slightly water-soluble and hydrophobic powders is shown in Fig. 9. The water vapor adsorption isotherms for the same samples are shown in Fig. 10. Benzoic acid was tested without any preliminary classification, since the benzoic acid particles had a typical needle-like shape.

The curves of cohesiveness *vs.* humidity for slightly soluble and hydrophobic powders are similar to those for hydrophilic and insoluble powders except for the maxima that appeared in the case of silica gel and glass beads, and different from those for water-soluble powders. The difference in the slope of the ascending curve in Fig. 9 cannot be explained by a difference in ability to adsorb water vapor (Fig. 10) or in contact angle (Table I). Since the powder which showed larger cohesiveness at low humidity also showed larger cohesiveness at high humidity, this difference may be caused by other factors as discussed in the case of MC. In order to exhibit a large cohesiveness under low humidity, particles must be irregular in shape or they must exhibit plasticity (*e.g.* camphor and thymol), or they must develop static charge. However, plastic crystals were not used as samples here, and statick electricity was fully discharged.

A comparison of Fig. 9 with Fig. 5 suggests that, in spite of large particle size, the increase

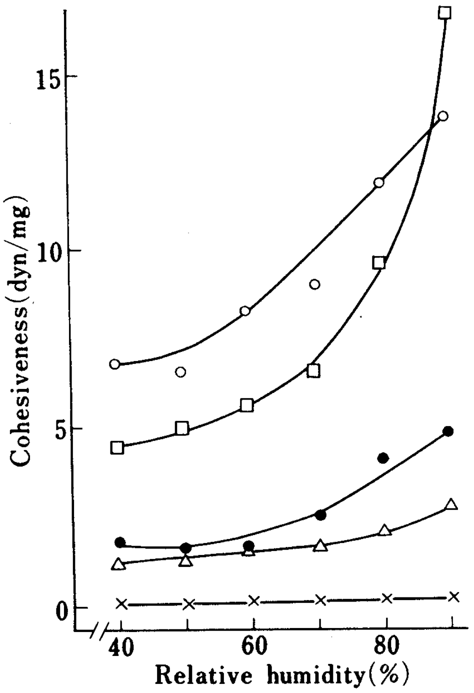

Fig. 9. Effect of Humidity on the Cohesiveness of Slightly Water-soluble and Hydrophobic Pharmaceutical Powders

□, sulfamine 100/150 mesh; ●, phenacetin 100/150 mesh; △, sulfisoxazole 100/150 mesh; ×, aspirin 28/100 mesh; ○, benzoic acid intact powder.

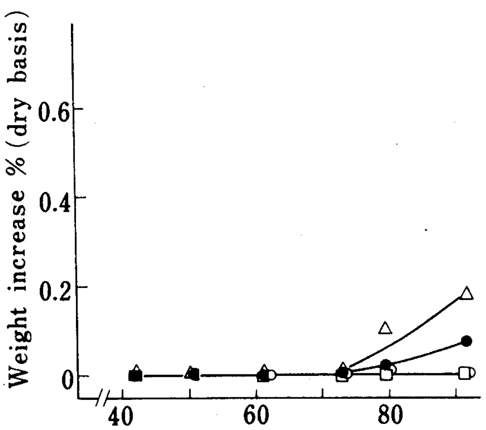

Fig. 10. Water Vapor Adsorption Isotherms for the Same Samples as in Fig. 9

□, sulfamine 100/150 mesh; ●, phenacetin 100/150 mesh; ×, aspirin 28/100 mesh; △, sulfisoxazole 100/150 mesh; ○, benzoic acid intact powder.

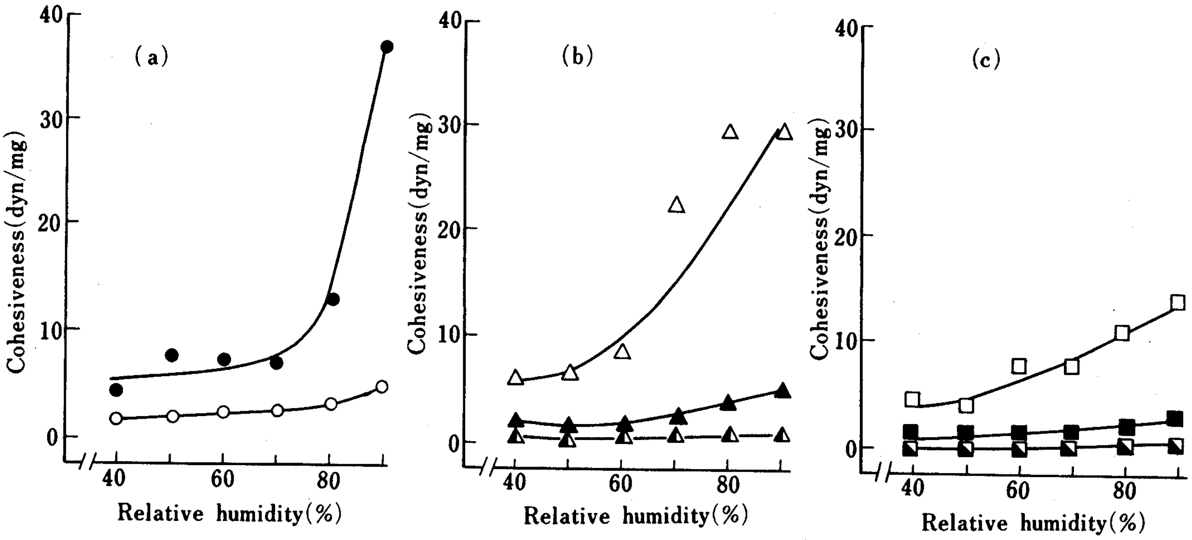

Fig. 11. Effect of Humidity and Particle Size on the Cohesiveness of Pharmaceutical Powders

(a) M.C.C. : ●, 200/250 mesh ; ○, 100/200 mesh.
(b) Phenacetin: △, 200/250 mesh ; ▲, 100/150 mesh ; ◭, 48/80 mesh.
(c) Sulfisoxazole: □, 150/200 mesh ; ■, 100/150 mesh ; ◩, 48/80 mesh.

in cohesiveness of hydrophobic powders was larger than that of hydrophilic powders. This may also arise from differences in the irregularity of particle shape.

In Fig. 9, aspirin (having large particle size compared with other samples) maintained a low level of cohesiveness, which was insensitive to the humidity. This suggested that the particle size is another principal factor influencing the sensitivity of cohesiveness to the humidity.

## Influence of Particle Size and Humidity

Three fractions of phenacetin and sulfisoxazole and two fractions of M.C.C. were used as samples. Although the influence of particle size on cohesiveness was evaluated in the preceding report,[4] the influences of both particle size and humidity have not been discussed jointly. The results obtained are illustrated in Fig. 11. Clearly, the cohesiveness of the large particles was insensitive to humidity, but as the particle diameter was decreased, the cohesiveness became sensitive to changes of humidity; the fractions of smaller than 200 mesh became particularly cohesive, except for the water insoluble powders (Fig. 5).

In recent years, most pharmaceutical powders have been pulverized as finely as possible in order to improve the bioavailability. However, it should be noted that the reduction of particle size is always accompanied by a large increase of cohesiveness, especially under conditions of high humidity, so that pulverization is actually undesirable from the standpoint of cohesiveness.

## Conclusion

The cohesiveness *vs.* humidity curves of the powders studied here were affected by several factors as discussed above, namely, solubility, particle shape, particle size and swellability of particles. However, the contact angle seemed not to be a major factor influencing the cohesiveness at any humidity. Since it is difficult to predict the cohesiveness of many powders under various levels of humidity, direct measurement may be essential, and the present report described an improved surface tensile strength method suitable for such measurement.

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