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Studies on Hard Gelatin Capsules. I. Water Vapor Transfer between Capsules and Powders

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The adsorption and desorption of water vapor on capsules, microcrystalline cellulose, corn and potato starches were observed and the water vapor transfer between capsules and the powders in the closed container was examined.

Experimental equilibrium water contents and relative humidities after water vapor transfer and estimated values calculated from the sorption isotherms of these substances were in good agreement with each other.

Capsules are getting popular recently because of the convenience in medication. The hard capsules are made from gelatin and small amounts of opacifying agent and dyes. The water content of gelatin is usually about 15% and varies with the enviromental condition, and this is one of the weak points of capsules.

The transfer of water between capsules and contents and the diffusion of water vapor through the capsule wall may have harmful effect on the stability of contents. Very few work has been reported on the water transfer, while Strickland[2] noticed water transferred between crashed capsules and pentobarbital sodium powders.

The purpose of this work was to study the sorption of water vapor by hard gelatin capsules and by water insoluble macromolecules such as microcrystalline cellulose, corn and potato starches, and also to study the water vapor transfer between them.

Experimental

Materials——Two kinds of commercial hard gelatin capsules[3] of size 0, "Natural" or transparent and colorless and "Ivory opaque" were used. Microcrystalline cellulose or Avicel[4] used was pharmaceutical grade. Corn and potato starches used were J.P. grade.

Apparatus and Procedure——The water contents of capsules were determined after keeping at 60° for 10 hours under vacuum using Abdelhalden apparatus, and those of Avicel and starches were determined after keeping at 80° for 2 hours. The water contents were expressed in dry basis percentage through this study.

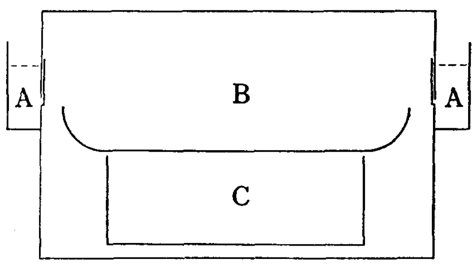

Fig. 1. Apparatus for the Determination of Water Transfer

A: seal
B: wire netted basket to place capsules on
C: glass dish for powders

The adsorption and desorption of water vapor were carried out in relative humidity chamber with saturated salt solutions at 25°. Thickness of the samples was 5—7 mm. In the case of capsules the cap and body were separated each other to promote the sorption to attain to equilibrium shortly. The samples were weighed sometimes to check the loss or gain in weight.

The determination of the water vapor transfer between capsules and powders was carried out in the 250 ml glass ware sealed with wax and paraffin mixture[5] as

1) Location: *Narihira 5-6-9, Sumida-ku, Tokyo*
2) W.A. Strickland, Jr. and M. Moss, *J. Pharm. Sci.*, **51**, 1002 (1962).
3) Park Davis.
4) Trade name, FMC Corp. American Viscose Devision.
5) JIS Z 0208–1953.

shown in Fig. 1. About 2 g of powder in a glass dish of 6 cm in diameter and 20 capsules in a wire-netted basket were placed in a closed container for 3 and 7 days at 25°.

Results and Discussion

Sorption Isotherm

To examine the hysteresis of the adsorption and desorption isotherm, the sample, which had been dried at 60° for 5 hours or moistened in a desiccator containing water at the bottom at 37° for 4 days, was kept standing in a relative humidity chamber. It took 3 to 5 days to bring the samples to constant weight for Avicel and starches, but 10 to 20 days for capsules especially in high and low humidities. Fig. 2 and Fig. 3 show the sorption isotherms obtained.

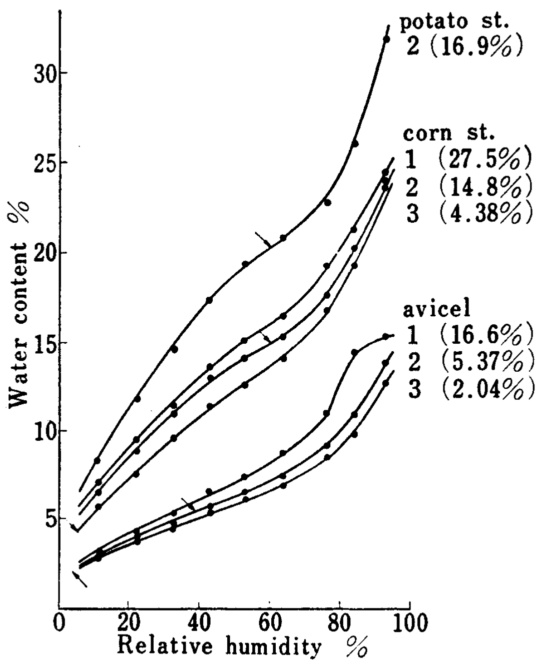

Fig. 2. Adsorption and Desorption Isotherms of Avicel, Corn and Potato Starches at 25°

1: samples absorbed water vapor at 37° for 4 days
2: samples non-treated
3: samples dried at 60° for 5 hours
↘ and ( ): initial water content %

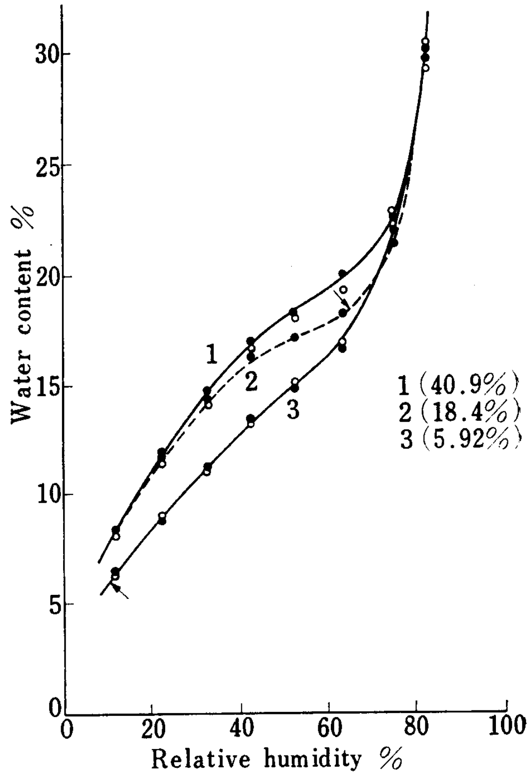

Fig. 3. Adsorption and Desorption Isotherms of Hard Gelatin Capsule at 25°

○: natural ●: ivory opaque

The shapes of the curves are all sigmoidal and show hysteresis. Many works have been reported on the water vapor adsorption of such substances and the adsorption has been interpreted on the basis of the polar or hydrophilic group of the molecule not only on the surface but also in the interior of the particle. But the hysteresis has been analyzed not so sufficiently as the case of water insoluble inorganic substances whose isotherms are also sigmoidal with hysteresis loops.

As the loops are comparatively large as seen in the Figures, this phenomenon can not be neglected on the estimation of water vapor sorption of the drug.

Water Vapor Transfer between Capsules and Powders

Fig. 4 is the water vapor sorption isotherms of the substances which were used in this water vapor transfer experiment. Water vapor transfer were examined between capsules and Avicel and corn starch. In the case of capsule and Avicel with water contents 18.44 and 2.41% respectively, for example, they were sealed in the container, and water vapor transferred from capsule to Avicel. The broken line ties the water contents after the transfer experiment for 7 days and apparent corresponding humidities show rather good agreement with each other.

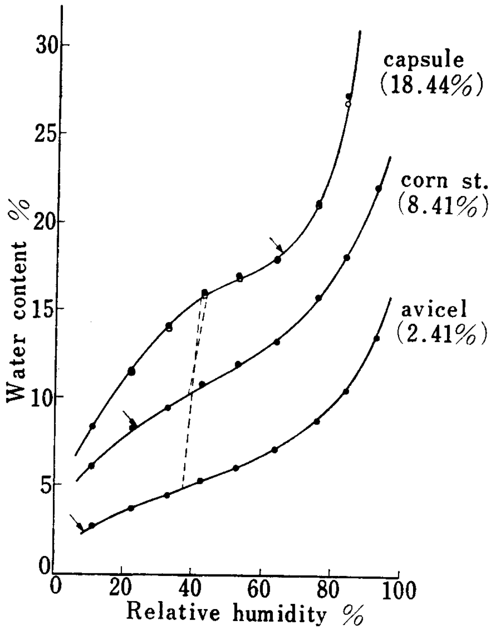

Fig. 4. Water Transfer between Capsules and Avicel or Corn Starch at 25°

----: experimental equilibrium state

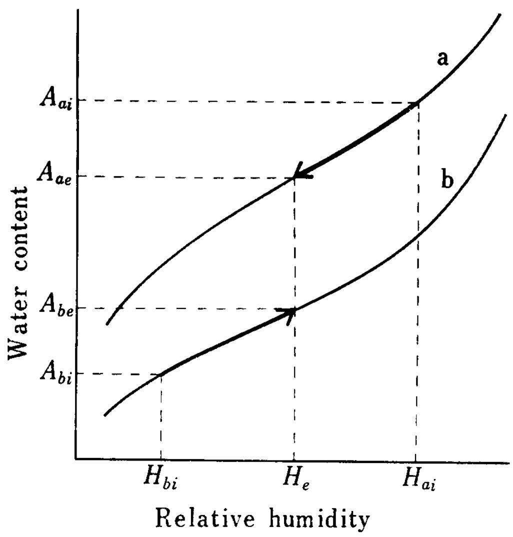

Fig. 5. Schematic Explanation for Water Vapor Transfer between Substance "a" and "b"

i and e indicate a initial and equilibrium state respectively

Table I shows the data obtained on the water vapor transfer between capsule and Avicel and corn starch.

Table I. Water Transfer at 25° in a Closed Container

	Initial wt. (g.)	Gain or loss after 3 days	Initial wt. (g.)	Gain or loss after 7 days
Avicel	2.0306 (2.41)	+0.0431 (4.58)	1.9704 (2.41)	+0.0438 (4.69)
Capsule, ivory op.	1.9639 (18.44)	−0.0421 (15.9)	1.9452 (18.44)	−0.0401 (16.0)
Corn starch	2.0267 (8.41)	+0.0383 (10.46)	2.0206 (8.41)	+0.0381 (10.46)
Capsule, ivory op.	1.9241 (18.44)	−0.0348 (16.3)	1.9824 (18.44)	−0.0360 (16.29)

( ): water content% in dry basis

The difference in the gain and loss of the sample weight may be due to the change of the atmospheric water vapor and the error in the measurement.

In available capsule preparations, powders or granules, whose equilibrium relative humidities are lower than those of capsules, are often used and then water vapor transfers from capsules to powders or granules. This kind of water transfer phenomena may take place, such as between a silica gel and a drug.

Now it is assumed that there are two substances "a" and "b" whose sorption isotherms are obtained already. The initial water contents are A_{ai} and A_{bi} in dry basis and the corresponding relative humidities are H_{ai} and H_{bi}, respectively. The weights of the samples are W_a and W_b, and these become $W_a/1+A_{ai}$ and $W_b/1+A_{bi}$ when expressed in dry basis.

If these two substances are put into a closed container, water vapor transfer from the one of the higher to the one of the lower relative humidity may take place until equilibrium is reached, as shown in Fig. 5. Assuming that the curve between initial and equilibrium humidities is straight line, the slopes of the line are given as follows.

$$S_a=\frac{A_{ai}-A_{ae}}{H_{ai}-H_e}, \qquad S_b=\frac{A_{be}-A_{bi}}{H_e-H_{bi}} \tag{1}$$

Neglecting the weight change of water vapor in the atmospheric air in the container, the weight loss of "*a*" must be equal to the gain of "*b*".

$$\frac{W_a}{1+A_{ai}}(A_{ai}-A_{ae})=\frac{W_b}{1+A_{bi}}(A_{be}-A_{bi}) \tag{2}$$

From (1) and (2)

$$\frac{W_a}{1+A_{ai}}S_a(H_{ai}-H_e)=\frac{W_b}{1+A_{bi}}S_b(H_e-H_{bi})$$

$$H_e=\left(\frac{W_aS_aH_{ai}}{1+A_{ai}}+\frac{W_bS_bH_{bi}}{1+A_{bi}}\right)\Big/\left(\frac{W_aS_a}{1+A_{ai}}+\frac{W_bS_b}{1+A_{bi}}\right)$$

$$=\frac{W_aS_aH_{ai}(1+A_{bi})+W_bS_bH_{bi}(1+A_{ai})}{W_aS_a(1+A_{bi})+W_bS_b(1+A_{ai})} \tag{3}$$

If the sample weight W is expressed in dry basis, equation (3) become more simple.

$$H_e=\frac{W_aS_aH_{ai}+W_bS_bH_{bi}}{W_aS_a+W_bS_b} \tag{4}$$

The weight W and the relative humidity H_i in the equation (3) and (4) are either known or can be determined experimentally. The slope of the curve is the function of the relative humidity, being estimated by assuming that the slope is constant in the region of the humidity of such as the present experiment. Equation (3) or (4) then gives an estimated value of relative humidity H_e. Introducing this estimated H_e to the equation (1), slopes are provided again. These values are put into the equation (3) or (4) again and then a more exact value of H_e is obtained.

In the experiment, calculated values of H_e were 41 and 44% for combination of Avicel–capsule and corn starch–capsule respectively, and these values were in good agreement with experimental values, as shown in Fig. 4.

Thus the equilibrium relative humidity and the water contents of the two component system in a closed container could be estimated from the weights of the components and the initial relative humidities and the slopes of the isotherms.

These calculation might be applied not only to two components but to more components system and the equilibrium relative humidities and the water contents might be estimated by the same process. On precooked packaged dehydrated food mixtures, Salwin[6] presented the data which showed the relatively good agreement between observed equilibrium water contents and calculated values from sorption isotherms.

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6) H. Salwin and V. Slawson, *Food Tech.*, **13**, 715 (1959).