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Studies on Whisker Growth on the Tablet Surface. III.[1] Mechanism of Whisker Growth on Aspirin Tablet and Its Effect on the Mechanical Strength of the Tablet[2]

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In view of a recent report which suggested that the crystallinity of crystalline medicines such as aspirin and phenacetin gradually decreased during storage with an adsorbent such as activated carbon at room temperature, tablets containing aspirin and activated carbon were prepared, and the changes of mechanical strength (*e.g.* hardness and friability) during storage were examined. It was found that whiskers developed on the tablet surface. With increasing storage time, the weight of the tablets and their hardness decreased whereas the friability, the porosity and the mean pore diameter increased. When the storage containers containing tablets with growing whiskers were opened, an odor of acetic acid was noticed, and its intensity apparently increased proportionally to the amount of whiskers. The melting point of these whiskers coincided with that of salicylic acid.

From these results it is presumed that the above changes in the weight, hardness, friability, porosity and mean pore diameter of the tablets occurred because aspirin in the tablets was hydrolyzed to acetic acid and salicylic acid (the latter forming non-proper whiskers on the tablets), and that activated carbon accelerated the hydrolysis.

Keywords——aspirin; activated carbon; tablet; hardness; friability; porosity; pore diameter; salicylic acid; whisker; hydrolysis

Many studies on whiskers have been carried out, but most of them have dealt with inorganic substances,[3] and there have been only a few reports on organic substances.[4] The authors and co-workers have already reported whisker growth on the tablet surface of ethenzamide and caffeine anhydride in the field of organic medicines.[1,5] We carried out the present experiments in view of the report of Konno and Kinuno,[6] who suggested that the crystallinity of crystalline medicines, such as aspirin and phenacetin, gradually decreases during storage with an adsorbent such as activated carbon at room temperature, and whisker growth occurs. Our experiments started with an examination of the mechanical strength (*e.g.* hardness and friability) of tablets containing aspirin, activated carbon and microcrystalline cellulose.

Experimental

Material——Aspirin (A in Figs.) was purchased from Maruishi Pharmaceutical Co., Tokyo and was of pharmacopoeial grade (JP X). Microcrystalline cellulose (M in Figs.) was obtained from Asahi Kasei Kogyo Co., Tokyo, and Molecular sieves 5A from Nishio Industry Co., Tokyo. Activated carbon (C in Figs.), salicylic acid and all other reagents were of reagent grade and were obtained from Wako Pure Chemical Industries, Ltd., Osaka.

Tableting——Aspirin was ground, and sieved. The fractions between 32—60, 100—150 and 200—400 mesh were collected. Activated carbon was used as received and microcrystalline cellulose which had been passed through a 200 mesh sieve was used. Aspirin, activated carbon and microcrystalline cellulose were mixed in three different mixing ratios; 15 : 15 : 70, 15 : 0 : 85 and 30 : 0 : 70. Each mixture was tableted at a compression pressure of 1000 kg/cm^2 into tablets of 400 mg each by the direct compression method, using a tableting machine (Nichiei Seiko Co., Tokyo, Type

UPF-6) with a single flat punch of 1 cm^2 cross section equipped with a strain guage.

Storage of the Tablets——Storage at Various Temperatures: The tablets were kept in glass containers of 20, 30 or 50 ml immediately after tableting, and stored in constant temperature ovens at room temperature, 40, 50 or 60 °C. Storage under Various Relative Humidities: Immediately after tableting, the tablets were kept in glass containers of different humidities, and stored at 60 °C. Five different relative humidities at 60 °C were provided by using the following materials; 0%-molecular sieves 5A, 25.3%-sodium iodide, 49.9%-sodium bromide, 74.9%-sodium chloride, 80.9%-potassium chloride.

Measurement of Mechanical Strength and Physical Properties of Tablets——Hardness: The mean ± standard deviation of the hardness was obtained from 10 tablets by using a hardness meter.[7] Friability: The friability was obtained by the method of Funakoshi *et al.*[8] using 20 tablets. Tablet Weight: The mean ± standard deviation of the tablet weight was obtained from 10 tablets. Porosity: The mean ± standard deviation of the porosity was obtained by using the weight, thickness and diameter of 10 tablets, and the density of the powder mixture. Mean pore diameter; the mean pore diameter of the tablet was measured from the penetration curve by the method described in the previous paper.[9] The measuring apparatus was a porosimeter (AMINCO, motor-driven, 1053 kg/cm^2). The hardness, friability, tablet weight and mean pore diameter were measured after removal of the whiskers.

Quantitative Analysis of Aspirin in the Upper Part of the Tablet——Part of the surface of the upper punch side of each tablet at four different temperatures was scraped off after removal of the whiskers, ground, and analyzed with a differential scanning calorimetry (DSC, Seiko Electronics Industries Ltd., type SSC/560). The heat of fusion for aspirin in each ground sample was obtained, and compared with that of the initial tablet.

Quantitative Analysis of Whiskers on the Tablet——As described in the previous paper,[1] the volume of whiskers on the surface of the upper punch side of the tablet was measured with an optical microscope (Nikon, type SMZ-10), and then, the weight was calculated on the basis of the density of the whiskers.

Results and Discussion

Changes in Physical Properties and Whisker Growth on the Tablet Surface during the Storage

The time course of hardness of the tablets at four different temperatures is shown in Fig. 1. Whether the tablets contained activated carbon or not, the hardness decreased, and the higher the temperature, the greater the degree of decrease. However, the time courses of decrease were different. In the case of tablets containing activated carbon, the decrease was large in the first week from the start of storage, and thereafter no further change occurred. As for the tablets containing no activated carbon, the decrease was minimal in the first week, and subsequently became large.

The time course of the friability of the tablets is shown in Fig. 2. With the tablets containing no activated carbon, the friability increased very slightly during storage, while with the tablets containing activated carbon, the increase was large and fast, and the higher the temperature, the greater and faster the increase.

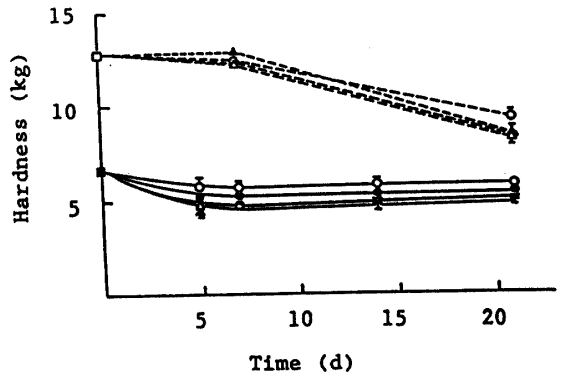

Fig. 1. Time Course of Hardness of the Tablets

□, initial tablet (A : M = 30 : 70); ■, initial tablet (A : C : M = 15 : 15 : 70); ----, A : M = 30 : 70; ——, A : C : M = 15 : 15 : 70; ○, room temp.; ●, 40 °C; △, 50 °C; ▲, 60 °C. Each point represents the mean ± S.D. for ten tablets.

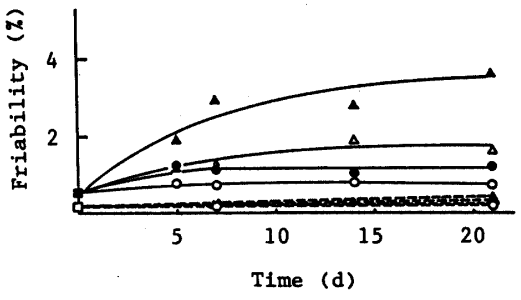

Fig. 2. Time Course of Friability of the Tablets

□, initial tablet (A : M = 30 : 70); ■, initial tablet (A : C : M = 15 : 15 : 70); ----, A : M = 30 : 70; ——, A : C : M = 15 : 15 : 70; ○, room temp., ●, 40 °C; △, 50 °C; ▲, 60 °C.

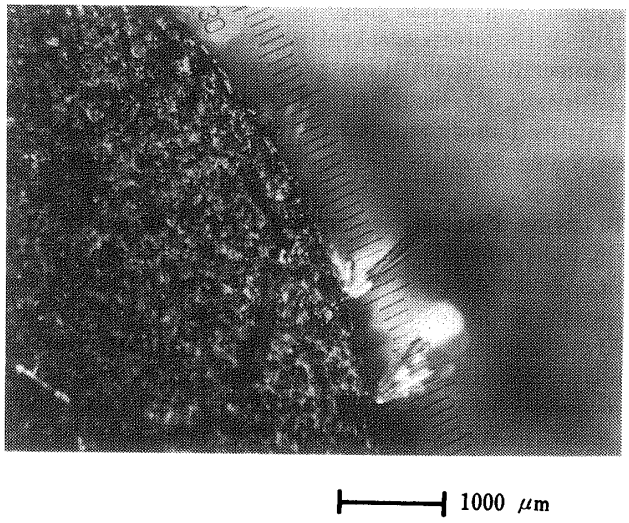

Fig. 3. Growth of Whiskers on the Tablet Surface

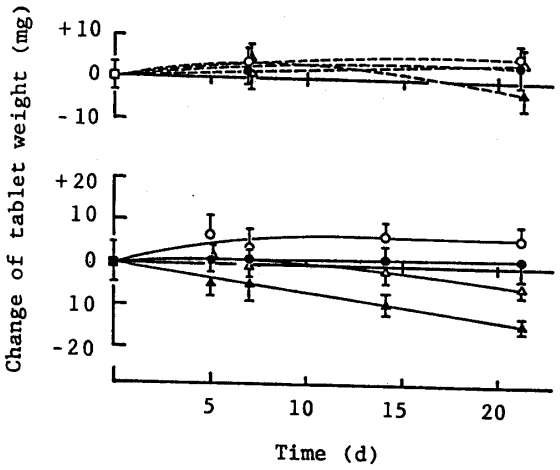

Fig. 4. Time Course of Tablet Weight

□, initial tablet (A:M=30:70); ■, initial tablet (A:C:M=15:15:70); ----, A:M=30:70; ——, A:C:M=15:15:70; ○, room temp.; ●, 40 °C; △, 50 °C; ▲, 60 °C. Each point represents the mean ± S.D. for ten tablets.

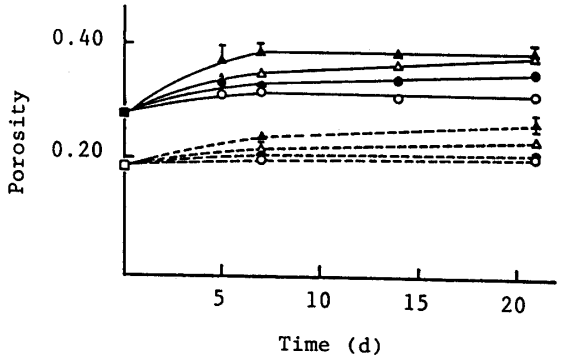

Fig. 5. Time Course of Porosity of the Tablets

□, initial tablet (A:M=30:70); ■, initial tablet (A:C:M=15:15:70); ----, A:M=30:70; ——, A:C:M=15:15:70; ○, room temp.; ●, 40 °C; △, 50 °C; ▲, 60 °C. Each point represents the mean ± S.D. for ten tablets.

As shown in Fig. 3, in the experiments on the time course of the hardness and friability of the tablets, the growth of columnar or needle-like crystals, the so-called whiskers, was apparent with the naked eye on the tablets containing activated carbon which were stored at 50 and 60 °C, on the 2nd or 3rd d after the start of storage.

The time course of the tablet weight is shown in Fig. 4. Taking into account the standard deviations of the weight of the tablets, the weight of the tablets containing no activated carbon did not change. With the tablets containing activated carbon, the higher the temperature, the greater the degree of decrease. As the tablet weight was measured after removing the whiskers from the tablet, this decrease in the tablet weight is thought to be mainly due to the whisker removal.

Figure 5 shows the time course of porosity. In the tablets containing no activated carbon the porosity gradually increased, and the higher the temperature, the greater the degree of the increase. As for the tablets containing activated carbon, the porosity also increased. The increase was fast for the first week, and very slow after that. In this case, too, the higher the temperature, the greater the degree of the increase. The degree of the increase in the tablets containing activated carbon was greater than that in the tablets containing no activated carbon. These results are thought to reflect the increase in the tablet volume induced by the absorption of moisture, the thermal expansion and the delay of elastic recovery of the tablets, as well as by the decrease in the tablet weight induced by whisker growth.

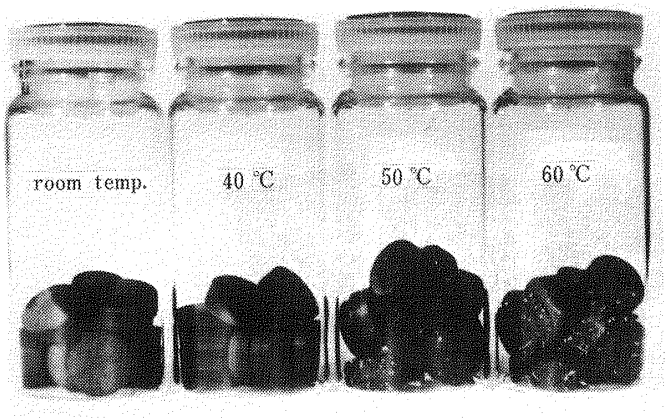

Fig. 6. Effect of Temperature on Whisker Growth

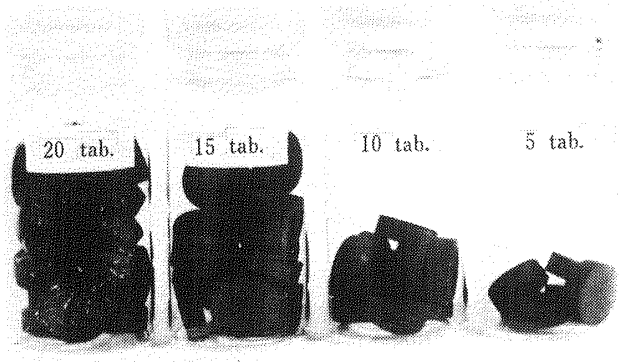

Fig. 7. Effect of Number of Tablets on Whisker Growth

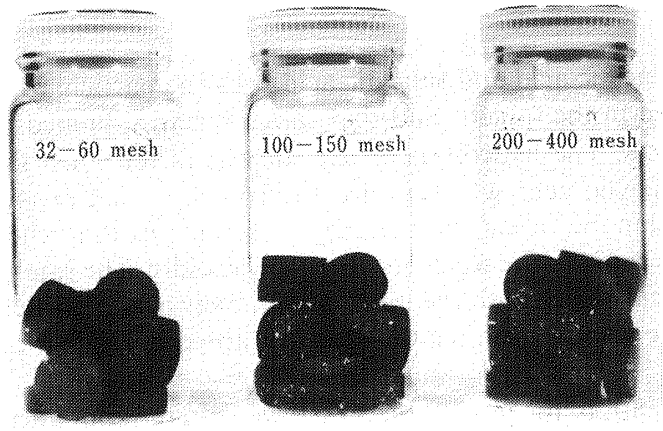

Fig. 8. Effect of Particle Size of Aspirin on Whisker Growth

The Composition and Growth Mechanism of Whiskers

In every experiment on the time course of hardness, friability, tablet weight or porosity, whisker growth was observed on the tablet surface. As it was considered that the results in the above experiments were strongly affected by this whisker growth, the composition and growth mechanism of the whiskers were investigated. Aspirin, activated carbon and microcrystalline cellulose powder, in a ratio of 15%: 15%: 70% were mixed and tableted. The tablets were kept in glass containers and stored at four different temperatures. Figure 6 shows a photograph taken a week after the start of storage. Furthermore, when the storage containers were opened, the more whiskers present on the tablets, the stronger the odor of acetic acid.

When the whiskers on the tablets were collected and analyzed by DSC, the melting point of these whiskers coincided with that of salicylic acid. It was presumed from these results that

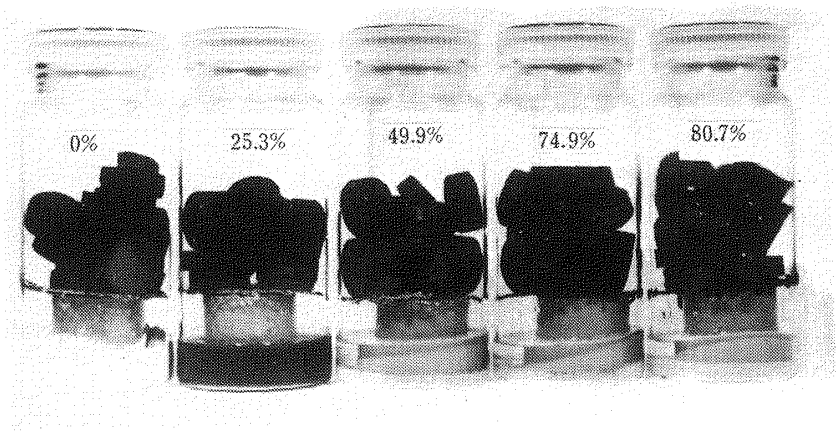

Fig. 9. Effect of Relative Humidity on Whisker Growth

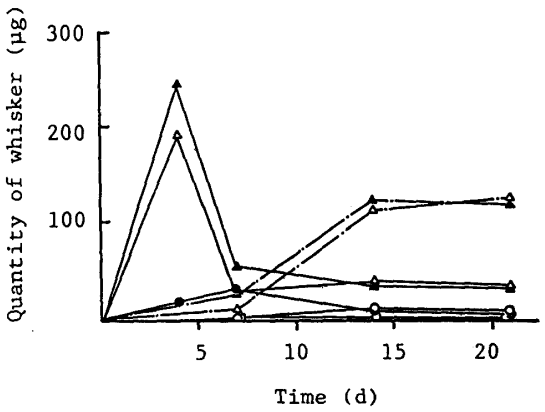

Fig. 10. Time Course of Whisker Growth at Various Levels of Relative Humidity

—·—, A:M=15:85; ——, A:C:M=15:15:70; □, 0%; ○, 25.3%; ●, 49.9%; △, 74.9%; ▲, 80.2%.

aspirin in the tablets was hydrolyzed into acetic acid and salicylic acid with the participation of the small amount of moisture contained in the tablets, and that salicylic acid sublimed to form whiskers on the surface of the tablets. The hydrolysis of aspirin was faster when the temperature was higher. Thus, if the salicylic acid whiskers are the so-called non-proper whiskers which are formed by salicylic acid in the vapor phase, it may be speculated that when the vapor density of salicylic acid increases rapidly, the whiskers also grow rapidly. The rate of increase of the vapor density of salicylic acid varied with the number of tablets or the particle size of aspirin contained in the tablets. The results when the tablets were stored at 60 °C for a week are shown in Figs. 7 and 8.

The results supported the above speculation; the more tablets there were in the containers (Fig. 7), and the smaller the particle size of aspirin contained in the tablets (Fig. 8), the faster the whiskers grew. It became clear from these results that these salicylic acid whiskers were non-proper whiskers which were formed on the surface of the tablets when the vapor density of salicylic acid became supersaturated.

The effects of moisture on the growth rate of salicylic acid whiskers are shown in Fig. 9. Here, the tablets used were composed of 15% aspirin, 15% activated carbon and 70% microcrystalline cellulose. They were stored under five relative humidities at 60 °C. The photograph in Fig. 9 was taken on the 4th d after the start of the storage.

The whiskers grew faster when the relative humidity was higher. The reason was thought to be that more moisture could participate in the hydrolysis of aspirin when the relative humidity was higher. This experiment was continued for three weeks, and the results are shown in Fig. 10.

In the tablets containing activated carbon, at the relative humidities of 74.9% and 80.2%

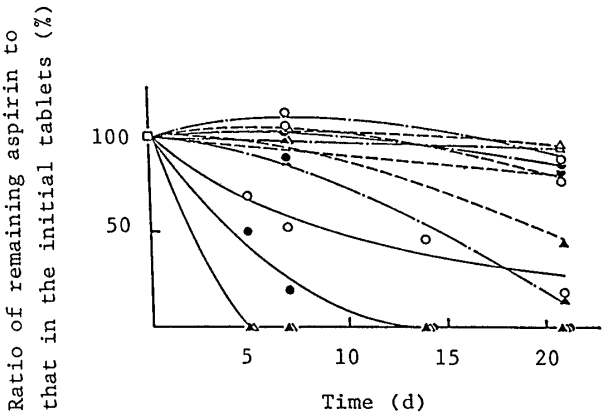

Fig. 11. Time Course of Remaining Aspirin in the Upper Part of the Tablet

□, initial tablets (A : M = 30 : 70), (A : M = 15 : 85) or (A : C : M = 15 : 15 : 70); ----, A : M = 30 : 70; —·—, A : M = 15 : 85; ——, A : C : M = 15 : 15 : 75; ○, room temp.; ●, 40 °C; △, 50 °C; ▲, 60 °C.

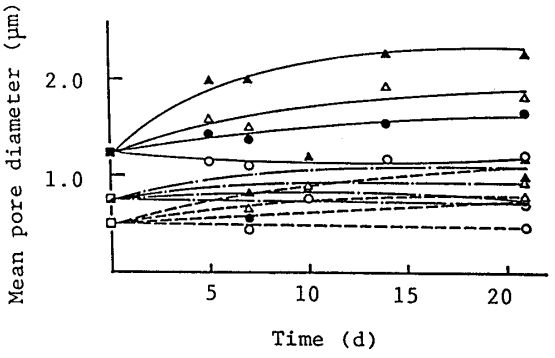

Fig. 12. Time Course of Mean Pore Diameter in the Tablet

□, initial tablet (A : M = 30 : 70); ◪, initial tablet (A : M = 15 : 85); ■, initial tablet (A : C : M = 15 : 15 : 70); ----, A : M = 30 : 70; —·—, A : M = 15 : 85; ——, A : C : M = 15 : 15 : 70; ○, room temp.; ●, 40 °C; △, 50 °C; ▲, 60 °C.

the weight of whiskers increased markedly and reached the maximum at the 4th d; after that the weight decreased. In the tablets containing no activated carbon, at the relative humidities of 74.9% and 80.2% the weight increased gradually until two weeks from the start, then the increase stopped. These results can not be explained clearly, but the following mechanisms may be involved. Although aspirin before hydrolysis has intermolecular hydrogen bondings, salicylic acid produced by the hydrolysis has intramolecular hydrogen bondings, so that salicylic acid can be more easily sublimed or water-distilled.[10] Salicylic acid and acetic acid may dissolve in the saturated solutions of the salts used to maintain the relative humidities.

Ratio of Remaining Aspirin in the Upper Part of the Tablet

The ratio of the remaining aspirin in the upper part of the tablets to that in the initial tablets was examined by measuring the endothermic peak area for aspirin at four different temperatures, and the results are shown in Fig. 11.

With the tablets containing activated carbon, the decrease of aspirin was faster than in the tablets containing no activated carbon. With the tablets stored at 50 and 60 °C, the endothermic peak of aspirin had already disappeared by the 5th d of the storage. With the tablets containing no activated carbon stored at room temperature, 40 and 50 °C, the decrease of aspirin was small, but with the tablets containing 15% or 30% of aspirin stored at 60 °C, the aspirin decreased to a half of the initial level in three weeks. These results suggest that the decrease of aspirin was accelerated by the addition of activated carbon, and by higher temperature.

Changes in the Internal Structure of the Tablet

Figure 12 shows the changes in the mean pore diameter in the tablets at four different temperatures. Although there was no change in any of the tablets at room temperature, the increase in the mean pore diameter was faster when the temperature was higher. The increases of the mean pore diameter from those of the initial tablets, mixed at the ratios of A : C : M = 15 : 15 : 70, A : M = 30 : 70 and A : M = 15 : 85, at the 3rd week of the storage at 60 °C, were about 1, 0.5 and 0.3 μm, respectively. The greater increase of the mean pore diameter in the tablets containing activated carbon clearly indicates that the addition of activated carbon accelerated the hydrolysis of aspirin. The increase of the mean pore diameter in the tablets containing 30% of aspirin without activated carbon was about twice that in the tablets containing 15% of aspirin without activated carbon, and this was presumably caused by the

loss of aspirin. The large increase of porosity in the tablets containing activated carbon (Fig. 5) is also thought to have been caused by the same mechanism. Taking into consideration that the mean pore diameter was measured by using the whole tablet, it is likely that the hydrolysis of aspirin did not occur in the upper part of the tablet alone, but in all the aspirin particles. We proposed previously, on the basis of the accordance between the capillary volume obtained by mercury porosimetry and the void volume calculated from the porosity, that all the voids in tablets prepared by the direct compression method communicated with the outside of the tablets.[11] Therefore, it is presumed that the vapor of acetic acid and salicylic acid produced by the hydrolysis can diffuse to the outside of the tablets, and that salicylic acid vapor can crystallize as whiskers on the surface of the tablets.

Whisker Growth and Mechanical Strength of the Tablet

From the above findings, it is conjectured that the addition of activated carbon accelerates the hydrolysis of aspirin into acetic acid and salicylic acid, and that the produced acetic acid diffused into the storage container as vapor, while salicylic acid also diffused as vapor at first, but after reaching the supersaturated vapor density, formed non-proper whiskers on the surface of the tablets by sublimation or crystallization. Although the mechanism of the acceleration of hydrolysis by the addition of activated carbon is not yet clear, we assumed previously that ethenzamide and caffeine anhydride whiskers, which may have the same non-proper growth mechanism as the salicylic acid whiskers described in this paper, were produced by capillary condensation in the voids in the tablets.[1] Nakai *et al.* also recently suggested that capillary condensation results in whisker formation, based on a study in which the molecular state in the capillary was examined by using porous glass.[12] As the activated carbon used in this study is also a porous material, the tablets containing activated carbon showed reduced mechanical strength, and the amount of whiskers was large, the hydrolysis of aspirin and growth of salicylic acid whiskers may occur by the capillary condensation, not in the voids formed by the tableting, but in the capillaries in the activated carbon.

The decrease in the mechanical strength of the tablets, which was reflected by the decrease in hardness and the increase of friability, was thought to be caused by the decrease in the number of contact points and in the contact area between the aspirin particles and those of the admixed substances owing to the hydrolysis of the aspirin. The increase in porosity and the mean pore diameter may be similarly explained.

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