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Physical and Chemical Changes of Medicinals in Mixtures with Adsorbents in the Solid State. I. Effect of Vapor Pressure of the Medicinals on Changes in Crystalline Properties

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It was found that some organic crystalline medicinals such as aspirin and phenacetin, when mixed with an adsorbent, gradually become amorphous during storage at room temperature (25 °C). Concomitantly, they show different dissolution patterns and decreased chemical stability. The following observations suggest that this phenomenon takes place *via* the gaseous phase, induced by the vapor pressure of the medicinals themselves. (1) Subliming crystals such as naphthalene become amorphous immediately in mixtures with adsorbents. (2) The rate of change of medicinals to the amorphous state is accelerated under reduced pressure in these systems. (3) The rate of change of the crystals to the amorphous state increases with their vapor pressure. The technique of treating crystalline medicinals at reduced pressure with an adsorbent may be a useful method of obtaining medicinals in the amorphous state without employing either solvents or excessive thermal or mechanical energy.

Keywords—adsorbent; crystalline medicinals vapor pressure; reduced pressure; amorphous; X-ray diffraction; aspirin; phenacetin; benzoic acid derivative; activated carbon; magnesium aluminum silicate

Adsorbents, which generally have a large specific surface area, have a great capacity for adsorbing gases or liquids, and are therefore used widely as drying agents for gases or as decoloring agents for solutions. In pharmaceuticals, some adsorbents, such as magnesium aluminum silicate (MAS) and anhydrous silicic acid, are used for improving the flowability of powders, and the hardness and disintegration properties of tablets.¹⁾

It is well known that the amorphous states of medicinals have different bioavailability and different pharmaceutical properties as compared with the crystalline states. Several methods have been proposed for obtaining the amorphous state in normally crystalline medicinals, for example, freeze-drying,²⁾ rapid cooling³⁾ to yield glassy products, coprecipitation,⁴⁾ and grinding of mixtures⁵⁾ with high-molecular substances.

We have recognized that some organic medicinals in mixtures with adsorbents gradually become amorphous during storage at room temperature (25 °C). This paper describes this phenomenon of physical and chemical changes in mixtures of medicinals with adsorbents, and presents some findings relating to the mechanism.

Experimental

Materials—Activated carbon (Shirasagi A, Takeda Chemical Industries, Ltd.) and MAS (Neusilin UFL₂, Fuji Chemical Industry Co., Ltd.) were passed through a No. 150 (mesh size: 105 μ m) sieve, heated at 110 °C for 3 h *in vacuo*, and kept in a desiccator containing silica gel at room temperature. Graphite was purchased from Kishida Chemical Co., Ltd. Aspirin and phenacetin of JPX grade and naphthalene, benzoic acid, *o*-, *m*- and *p*-hydroxybenzoic acid, and *o*-, *m*- and *p*-chlorobenzoic acid of special reagent grade were used.

Preparation of Mixtures—All materials were passed through a No. 150 (mesh size: 105 μm) sieve. Crystalline medicinals (aspirin and phenacetin) and crystalline organic compounds (naphthalene, benzoic acid, *o*-, *m*- and *p*-hydroxybenzoic acid, and *o*-, *m*- and *p*-chlorobenzoic acid) were each mixed well with adsorbent in a porcelain mortar in the ratio of 2:8 by weight. They were stored under the following conditions: (i) in a desiccator containing silica gel at 25 °C or at 40 °C, (ii) at 40 °C at a pressure of about 2.5 mmHg achieved by using a vacuum pump.

Measurement of Specific Surface Area of Adsorbents—A nitrogen gas adsorption apparatus was used.

Measurement of X-Ray Diffraction (Powder Method)—A Geiger Flex 2012 diffractometer (Rigaku Denki Co., Ltd.) was used with the following conditions and settings: target, Cu; filter, Ni; voltage, 30 kV, and current, 15 mA (but voltage, 35 kV and current, 20 mA for *m*-chlorobenzoic acid), receiving slit, 0.15 mm; detector, proportional counter; count range, 2000 cps; time constant, 0.5 s; scanning speed, 2 °/min; and chart speed, 20 mm/min.

Determination of Percentage Retention of Aspirin—Aspirin and its decomposition product, salicylic acid, were extracted with ethanol from the mixture with adsorbent. The solution was diluted appropriately with ethanol, the absorbances of the solution at 276 and 304 nm were determined, and the ratio of aspirin to salicylic acid was calculated.

Dissolution Test—The JP X paddle dissolution apparatus was used. The dissolution medium was 500 ml of purified water at 37 °C. The paddle velocity was 150 rpm. Mixture equivalent to 50 mg of phenacetin was added to the medium, and the amount dissolved was determined spectrometrically (243 nm).

Results and Discussion

Changes in Physical and Chemical Properties of Crystalline Medicinals in Mixtures with Adsorbents

Activated carbon, which, as is generally known, has a large surface area, and MAS, which is sometimes used as an ingredient in pharmaceutical preparations, were chosen as adsorbents. The specific surface areas of activated carbon and MAS were 960 and 375 m²/g, respectively.

Figure 1 shows the changes with time in the X-ray diffraction patterns of the mixtures of aspirin with activated carbon and with MAS (2:8 (w/w)) stored at 25 °C. Figures 1A and 1D show the diffraction patterns of newly prepared mixtures, in which peaks of radiation diffracted by aspirin crystals can be observed. Figures 1B, 1C, 1E and 1F are the diffraction patterns of the mixtures after storage at 25 °C for 3–7 d. The peak intensity of the aspirin crystals decreased with time, and halo patterns were observed.

Figure 2 shows the changes with time in the X-ray diffraction patterns of the mixtures of phenacetin with activated carbon and with MAS (2:8 (w/w)) stored at 25 °C. A similar

Fig. 1. Changes with Time in the X-Ray Diffraction Patterns of Mixtures of Aspirin with Activated Carbon and with MAS Stored at 25 °C

A, mixture of aspirin and activated carbon (original); B, mixture of aspirin and activated carbon (stored for 3 d); C, mixture of aspirin and activated carbon (stored for 7 d); D, mixture of aspirin and MAS (original); E, mixture of aspirin and MAS (stored for 3 d); F, mixture of aspirin and MAS (stored for 7 d).

Fig. 2. Changes with Time in the X-Ray Diffraction Patterns of Mixtures of Phenacetin with Activated Carbon and with MAS Stored at 25°C

A, mixture of phenacetin and activated carbon (original); B, mixture of phenacetin and activated carbon (stored for 7 d); C, mixture of phenacetin and activated carbon (stored for 14 d); D, mixture of phenacetin and MAS (original); E, mixture of phenacetin and MAS (stored for 7 d); F, mixture of phenacetin and MAS (stored for 14 d).

Fig. 3. Polarized Micrographs Showing Changes of Mixtures of Aspirin and of Phenacetin with MAS Stored at 25°C

A, mixture of aspirin and MAS (original); B, mixture of aspirin and MAS (stored for 7 d); C, mixture of phenacetin and MAS (original); D, mixture of phenacetin and MAS (stored for 14 d).

phenomenon was also observed in the mixtures of phenacetin and adsorbent, but in these cases, the decrease of the peak intensity of the crystals occurred more slowly.

Figure 3 shows changes in the micrographs of the mixtures of aspirin and of phenacetin with MAS, obtained with a polarizing microscope. It was found that the crystals of the medicinals, which were observed in the newly prepared mixture (Figs. 3A and 3C), had almost disappeared after storage at 25°C (Figs. 3B and 3D). It was difficult to check the changes of crystals of aspirin or phenacetin in mixtures with activated carbon, because these crystals were covered with black activated carbon, and therefore polarized light from the crystals could not be detected.

Figure 4 shows the percentage retention, as a function of time, of aspirin in mixtures with activated carbon and with MAS, stored at 25°C.

Fig. 4. Time Courses of Aspirin Content in Mixtures with Activated Carbon and with MAS Stored at 25°C

●, mixed with activated carbon; ○, mixed with MAS.

Fig. 5. Aqueous Dissolution Curves of Phenacetin from Mixtures with Activated Carbon and with MAS at 37°C

●, mixed with activated carbon (original); ■, mixed with activated carbon (stored for 14 d at 25°C); ○, mixed with MAS (original); □, mixed with MAS (stored for 14 d at 25°C).

Fig. 6. X-Ray Diffraction Patterns of Mixtures of Naphthalene with Activated Carbon and with Graphite

A, mixture of naphthalene and activated carbon; B, mixture of naphthalene and graphite.

Aspirin had a relatively high hydrolysis rate when mixed with these adsorbents, even though the reaction was a solid-state one. Although it is well known that some adsorbents act as chemical catalysts, they are employed for substances in the vapor or liquid phase, making use of the phenomenon of adsorption. We presumed that the rate of hydrolysis of aspirin was accelerated in mixtures with adsorbent because the medicinal became amorphous and was subject to a catalytic effect.

Figure 5 shows the dissolution patterns in water of both newly prepared and stored samples of phenacetin, in which no hydrolysis was recognized during storage, in mixtures with adsorbents. The stored samples, in which almost all the phenacetin crystals had disappeared, had a faster initial release rate of phenacetin compared with the newly prepared samples in the case of MAS mixtures. On the other hand, the stored samples had a lower initial release rate of phenacetin than the newly prepared samples in the case of activated carbon mixtures.

Behavior of Subliming Crystals in Mixtures with Adsorbent

In order to investigate the mechanism of the reduction of crystallinity in the mixtures with adsorbent, experiments using naphthalene were performed.

Figure 6A shows the X-ray diffraction pattern of a mixture of naphthalene and activated carbon, prepared within 1 h before measurement. Peaks due to naphthalene crystals were absent. It was found that, in this mixture, mass transfer of naphthalene to the surface or the pores of the activated carbon took place rapidly and the material became amorphous immediately after preparation. On the other hand, naphthalene retained its crystalline state in

Fig. 7. Changes in the X-Ray Diffraction Patterns of Mixtures of Medicinals with Activated Carbon Stored at Atmospheric and Reduced Pressures at 40 °C

A, mixture of aspirin and activated carbon (original); B, mixture of aspirin and activated carbon (stored for 2 h at reduced pressure); C, mixture of aspirin and activated carbon (stored for 2 h at atmospheric pressure); D, mixture of phenacetin and activated carbon (original); E, mixture of phenacetin and activated carbon (stored for 8 h at reduced pressure); F, mixture of phenacetin and activated carbon (stored for 8 h at atmospheric pressure).

a mixture with graphite (which is an allotropic form of activated carbon and has a small specific surface area), as shown in Fig. 6B.

Behavior of Crystalline Medicinals in Mixtures with Adsorbents at Reduced Pressure

It is well known that vaporization of liquids and the sublimation of solids take place more rapidly at reduced pressure because the mean free path of the molecules is much longer than at atmospheric pressure. If we assume that the transfer of medicinal molecules between solids takes place *via* the gaseous phase, the rate of the transfer at a reduced pressure can be expected to be increased.

Figure 7 shows the X-ray diffraction patterns of mixtures of medicinals with activated carbon stored at a reduced pressure at 40 °C in comparison with those of mixtures stored at atmospheric pressure. The crystal peaks that were detected in the newly prepared mixtures (Figs. 7A and 7D) disappeared after the mixtures had been stored at reduced pressure (Figs. 7B and 7E). On the other hand, the crystal peaks were hardly reduced at all in the mixtures stored at atmospheric pressure (Figs. 7C and 7F). As for the mixtures stored at reduced pressure, we verified spectrometrically that the medicinals had not evaporated, but remained in the mixtures.

Relation between Vapor Pressures of Crystalline Medicinals and Rates of Change from the Crystalline State during Storage

Although all non-subliming crystalline medicinals have a very small vapor pressure at room temperature, Sidgwick determined the vapor pressures of several benzoic acid derivatives in the crystalline state at 100 °C by steam distillation.⁶⁾ Table I shows the vapor pressures of benzoic acid⁷⁾ and its derivatives.⁶⁾

In order to verify that these phenomena take place *via* the gaseous phase, we studied how long crystalline substances with various vapor pressures take to become amorphous in mixtures with an adsorbent. Benzoic acid and its derivatives were used as the crystalline substances, and activated carbon as the adsorbent. After each crystalline substance had been mixed with activated carbon in a porcelain mortar, the changes in the X-ray diffraction patterns during storage were examined, and the time required for the crystal peaks to

TABLE I. Vapor Pressures and Melting Points of Benzoic Acid and Its Derivatives in the Crystalline State (from Sidgwick⁶⁾ and Washburn⁷⁾)

Compound	Vapor pressure at 100 °C (mmHg)	mp (°C)
Benzoic acid	1.26	122.7
<i>o</i> -Hydroxybenzoic acid	0.397	159.0
<i>m</i> -Hydroxybenzoic acid	0.00149	201.3
<i>p</i> -Hydroxybenzoic acid	0.00030	213.0
<i>o</i> -Chlorobenzoic acid	0.1803	140.3
<i>m</i> -Chlorobenzoic acid	0.1970	154.5
<i>p</i> -Chlorobenzoic acid	0.0450	241.5

Fig. 8. Plots of Vapor Pressure of the Crystalline Substances versus the Time Required to Become Amorphous in Mixtures with Activated Carbon

○, at 25 °C at atmospheric pressure; ●, at 40 °C at reduced pressure.

1, benzoic acid; 2, *o*-hydroxybenzoic acid; 3, *m*-hydroxybenzoic acid; 4, *p*-hydroxybenzoic acid; 5, *o*-chlorobenzoic acid; 6, *m*-chlorobenzoic acid; 7, *p*-chlorobenzoic acid.

disappear was determined.

Figure 8 shows the relation between the vapor pressure of the crystalline substances and the time required to become amorphous, plotted on a logarithmic scale. At atmospheric pressure and at 25 °C (see open circles), benzoic acid, which has the highest vapor pressure of the substances used, became amorphous within only 1 h, whereas *p*-hydroxybenzoic acid, whose vapor pressure is the lowest, changed after 8600 h. Thus, it was observed that the higher the vapor pressure, the faster the change to the amorphous state. A similar tendency was recognized at reduced pressure at 40 °C (see close circles).

The above results suggest that the phenomenon of the gradual loss at room temperature (25 °C) of the crystalline properties of some organic medicinals mixed with adsorbents takes place *via* the gaseous phase, and is induced by the vapor pressure of the medicinals themselves.

As was indicated previously, aspirin and phenacetin differed from each other in the rate of change to the amorphous state. It is presumed that an important reason for this difference is the difference in the vapor pressure of these medicinals.

This technique of treating crystalline medicinals with adsorbent at reduced pressure may be a useful method of obtaining medicinals in the amorphous state without the use of either a solvent or excessive thermal or mechanical energy.

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