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Physical and Chemical Changes of Medicinals in Mixtures with Adsorbents in the Solid State. II.[1)] Application of Reduced Pressure Treatment for the Improvement of Dissolution of Flufenamic Acid

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Flufenamic acid (FFA) was mixed with magnesium aluminum silicate (MAS) and stored at 60 °C at a reduced pressure of about 2.5 mmHg. After storage, when its concentration was not more than 20%, FFA was observed by X-ray diffraction and polarizing microscopy to be amorphous. The dissolution of FFA was thus enhanced in comparison with that of a freshly prepared mixture. Furthermore, the dissolution curves showed a typical supersaturation pattern, and the supersaturation state continued longer, the higher the pH value of the dissolution medium. Flufenamic acid, in a mixture with MAS, became amorphous more rapidly at reduced pressure than at atmospheric pressure, and therefore the effect of improved dissolution appeared earlier at reduced pressure. Infrared spectral studies suggested that FFA, after storage at a reduced pressure with MAS, was dispersed monomolecularly in an ionic form. The technique of treating crystalline medicinals, that have poor solubility in water, with adsorbent at reduced pressure may be useful for improving their dissolution characteristics.

Keywords adsorbent; flufenamic acid; magnesium aluminum silicate; amorphous; dissolution; reduced pressure; X-ray diffraction; IR

In the previous paper,[1)] we reported that some organic crystalline medicinals such as aspirin and phenacetin, when mixed with an adsorbent, gradually became amorphous during storage at room temperature. At the same time, their physical and chemical properties were changed. We recognized on examination that the vapor pressure of the medicinals affected this reaction, and change of physical and chemical properties took place more rapidly at reduced pressure than at atmospheric pressure. Nakai *et al.*[2)] have already investigated in detail the physicochemical changes of medicinals in the solid state. They have studied the interaction between medicinals and porous powder or light anhydrous silicic acid by X-ray diffractometry, infrared spectroscopy and differential scanning calorimetry.

In the present study, we have tried utilizing these phenomena so as to improve the dissolution of flufenamic acid (FFA), a nonsteroidal antiinflammatory drug with poor solubility in water. Flufenamic acid was mixed with magnesium aluminum silicata (MAS) and stored at reduced pressure. The dissolution of the medicinals into various media was measured, and the dispersed state of the medicinals in the mixture was studied by X-ray diffraction and infrared (IR) spectroscopy.

Experimental

Materials MAS (Neusilin UFL$_2$, Fuji Chemical Industry Co., Ltd.) was passed through a No. 150 (mesh size: 105 μm) sieve, heated at 110 °C for 3 h *in vacuo*, and kept in a desiccator containing silica gel at room temperature. The specific surface area of MAS determined by the B.E.T. method with nitrogen gas was 375 m^2/g, and the pore size distribution was calculated by the Cranston–Inkley method,[3)] with the results shown in Fig. 1. FFA was purchased from Sigma Chemical Co., Ltd. Benzoic acid and sodium benzoate of special reagent grade were used.

Preparation of Mixtures FFA and benzoic acid, passed through a No. 150 (mesh size: 105 μm) sieve, were each mixed well with MAS in a porcelain mortar in suitable ratios. They were stored under the following conditions: (i) at 60 °C at atmospheric pressure, and (ii) at 60 °C at a reduced pressure of about 2.5 mmHg achieved by using a vacuum pump.

Measurement of X-Ray Diffraction (Powder Method) A Geiger Flex 2012 diffractometer (Rigaku Denki Co., Ltd.) was used. The measurement conditions were the same as those reported in the previous paper.[1)]

Dissolution Tests A cylindrical vessel with an inside diameter of 85 mm, and a height of 110 mm was used. A rotatable shaft with blades as defined in the JP XI paddle method was used. The rotatable shaft was fixed to the bearing so that a distance of 10 mm was maintained between the lower end of the blades and the bottom of the vessel. The dissolution media were JP XI disintegration medium No. 1 (pH 1.2), 0.1 M citrate buffer solution (pH 3.0), and 0.1 M acetate buffer solutions (pH 4.0 and 5.0). The mixture were passed again through a No. 150 (mesh size: 105 μm) sieve before testing. A sample powder equivalent to 25 mg of FFA was weighed accurately and put in the dissolution vessel, in which 250 ml of dissolution medium was stirred at 500 rpm at 37 °C, and the amount dissolved was determined spectrometrically (289 nm).

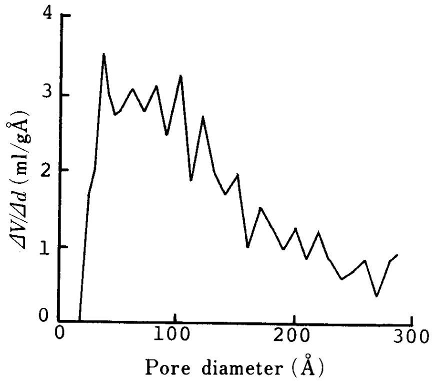

Fig. 1. Pore Size Distribution of MAS Calculated According to Cranston and Inkley[3)]

IR Absorption Studies Spectral data were obtained with a Hitachi 270-30 double-beam spectrophotometer according to the KBr disk method in the range of 1800 to 1500 cm^{-1}. Since MAS has an absorption band in this range, the absorption spectra of the medicinals in the mixtures were determined by subtracting the spectra of MAS from that of each mixture.

Results and Discussion

Changes in Physical and Chemical Properties of FFA in Mixtures with MAS when Stored at a Reduced Pressure

Magnesium aluminum silicate, which is sometimes used as an ingredient of pharmaceutical preparations, was chosen as the adsorbent. Figure 2 shows the changes in the X-ray diffraction patterns of the mixtures of FFA with MAS (20% FFA) stored at a reduced pressure at 60 °C. Curve B presents the diffraction pattern of a freshly prepared mixture, exhibiting peaks of diffraction by FFA

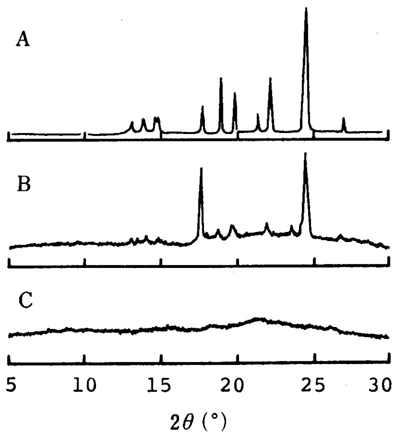

Fig. 2. Changes in the X-Ray Diffraction Patterns of Mixtures of FFA with MAS

A, FFA crystals; B, mixture (20% FFA, fresh); C, mixture (20% FFA, stored for 5 h at a reduced pressure at 60 °C).

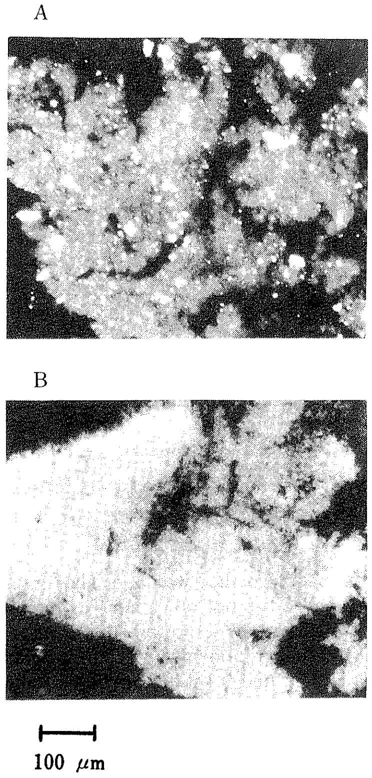

Fig. 3. Polarized Micrographs of Mixtures of FFA with MAS Stored at a Reduced Pressure at 60 °C

A, mixture (20% FFA, fresh); B, mixture (20% FFA, stored for 5 h at a reduced pressure at 60 °C).

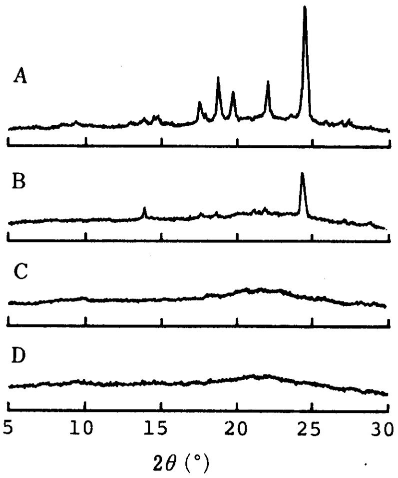

Fig. 4. X-Ray Diffraction Patterns of Various Mixtures of FFA with MAS Stored at a Reduced Pressure at 60 °C

A, 40% FFA; B, 30% FFA; C, 20% FFA; D, 10% FFA.

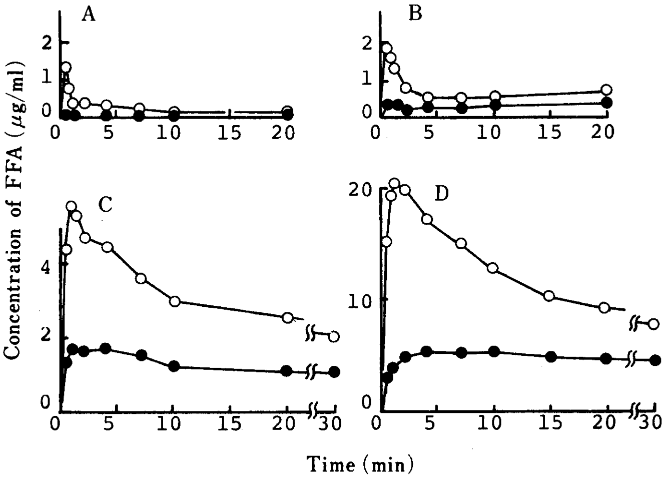

Fig. 5. Dissolution Profiles of FFA from Mixtures with MAS into Various Dissolution Media at 37 °C

●, 20% FFA, fresh; ○, 20% FFA, stored for 5 h at a reduced pressure at 60 °C. A, pH 1.2 solution (JP 1st fluid); B, pH 3.0 citrate buffer solution; C, pH 4.0 acetate buffer solution; D, pH 5.0 acetate buffer solution.

crystals (curve A); and curve C presents the diffraction pattern of the mixture after storage at a reduced pressure at 60 °C for 5 h. The crystal peaks had disappeared and a halo pattern was observed.

Figure 3 shows the changes in micrographs of a mixture of FFA with MAS (20% FFA), obtained with a polarizing microscope. The crystals of FFA observed in the fresh mixture (Fig. 3A) had almost disappeared after storage at a reduced pressure at 60 °C for 5 h (Fig. 3B). The FFA was therefore considered to have been changed to an amorphous state after being mixed with MAS and stored at reduced pressure at 60 °C.

Figure 4 shows the X-ray diffraction patterns of the mixtures of FFA with MAS in various weight ratios after storage at a reduced pressure at 60 °C for 5 h. The crystal peaks of FFA disappeared completely when the concentration of FFA was not more than 20%.

Figure 5 shows the dissolution profiles of FFA into various dissolution media. The dissolution profiles of FFA mixtures with MAS stored at a reduced pressure were compared with those of fresh mixtures. Since FFA was an acid with a pK_a value of 3.9,[4] the amount of FFA dissolved changed markedly in this pH region. Furthermore, in mixtures with MAS stored at a reduced pressure, the concentration of FFA became higher than in the case of freshly prepared mixtures, and the concentration then decreased gradually, showing a typical supersaturation phenomenon. The supersaturated state continued longer, the higher the pH value of the medium. Takayama *et al.*[5] reported that the dissolution profiles of FFA from a solid dispersion system showed the same supersaturation pattern. It was considered that, just as they proposed, the decrease of FFA concentration was due to a phase transition to stable forms accompanied with crystallization.

Comparison of Reduced Pressure with Atmospheric Pressure during Storage on Changes in Physical and Chemical Properties of FFA In order to investigate the effects of reduced pressure during storage on changes in the physical and chemical properties, the 20% mixture of FFA with MAS was stored both at a reduced pressure (2.5 mmHg) and at atmospheric pressure, and the X-ray diffraction patterns and dissolution profiles were then compared. Each sample was stored at 60 °C for 0.5—5 h. Figure 6 shows the X-ray diffraction patterns of these mixtures. The peaks due to FFA crystals were already absent after 2 h in the mixture stored at a reduced pressure. After storage at atmospheric pressure, on the other hand, the peak intensity of the FFA crystals in the mixture decreased slowly, and these peaks still remained to a slight degree even after 5 h.

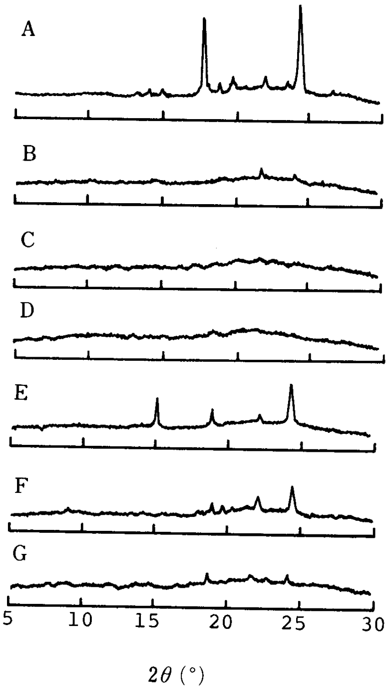

Fig. 6. X-Ray Diffraction Patterns of Mixtures of FFA with MAS Stored at Reduced and Atmospheric Pressures at 60 °C

A, fresh; B, stored for 1 h at a reduced pressure; C, stored for 2 h at a reduced pressure; D, stored for 5 h at a reduced pressure; E, stored for 1 h at atmospheric pressure; F, stored for 2 h at atmospheric pressure; G, stored for 5 h at atmospheric pressure.

Figure 7 shows the dissolution profiles of FFA in these mixtures stored at reduced and atmospheric pressures. After storage for 0.5—1 h, the concentration of dissolved FFA became higher for the mixtures which were stored at a reduced pressure than those stored at atmospheric pressure. As the storage period was increased, the concentration of dissolved FFA stored at atmospheric pressure approached the concentration after storage at a reduced pressure, so that there was little difference in the dissolution patterns of FFA in the mixtures stored for 5 h.

It was found that FFA, in the mixtures with MAS, became amorphous more rapidly at reduced pressure than at atmospheric pressure, and therefore the improvement in dissolution appeared earlier at the reduced pressure. As was discussed in the previous report,1) it is believed that the above change was accelerated at reduced pressure because the change took place *via* the gaseous phase induced by the vapor pressure of the medicinals themselves. It is considered that the vapor pressure of FFA is important to estimate the transition of the molecules in the mixture with MAS. It is also conjectured that transfer of water molecules remaining in the pores of MAS takes place when such mixtures are stored at reduced pressure, and this transfer

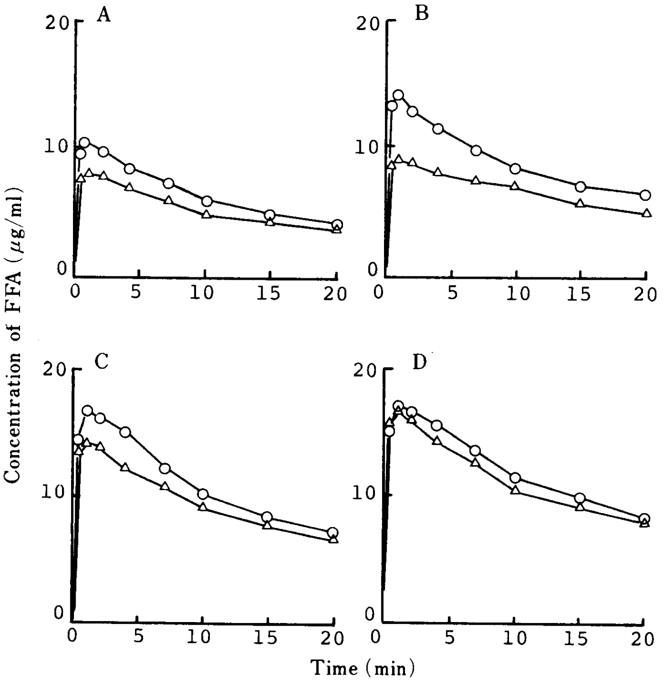

Fig. 7. Dissolution Profiles of FFA from Mixtures with MAS Stored at 60 °C into pH 5.0 Acetate Buffer Solution

○, stored at a reduced pressure; △, stored at atmospheric pressure. A, stored for 0.5 h; B, stored for 1 h; C, stored for 2 h; D, stored for 5 h.

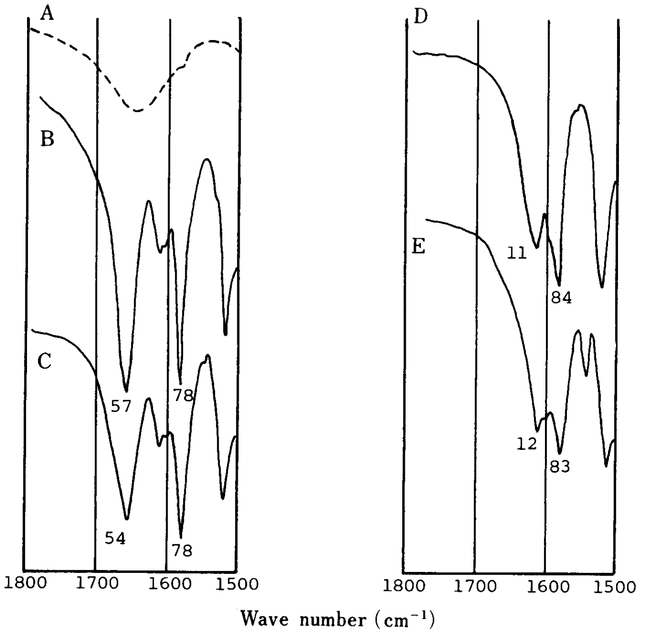

Fig. 8. IR Spectral Changes of FFA in Mixtures with MAS

A, MAS; B, FFA crystals; C, FFA in mixture (20% FFA, fresh); D, FFA in mixture (20% FFA, stored for 5 h at a reduced pressure at 60 °C); E, precipitates from equimolar solution of FFA and sodium hydroxide.

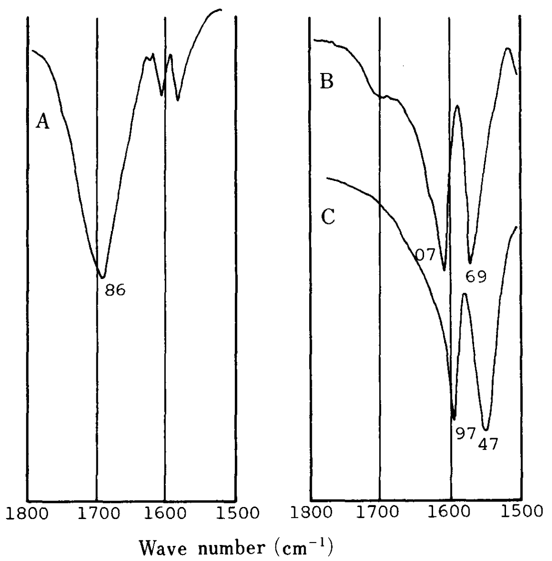

Fig. 9. IR Spectra of Benzoic Acid in Mixture with MAS

A, benzoic acid crystals; B, benzoic acid in mixture (20% benzoic acid, stored for 2 h at a reduced pressure at 60 °C); C, sodium benzoate crystals.

may participate in the acceleration of the transition of the molecules of the compound.

Study of IR Absorption of FFA in the Mixture Since the carbonyl stretching band in the IR spectrum of a carbonyl compound shifts sensitively according to changes in the electrostatic environment of the molecules, it can offer information of various kinds about the molecules. Nakai *et al.*[2b)] studied the dispersed state of medicinals in mixtures with porous clay, and reported that bezoic acid was ionized on heating in certain pillar interlayer montmorillonite mixtures. In the present paper, the IR spectrum of FFA in the region of the carbonyl stretching band (1800—1500 cm^{-1}) was measured to obtain information about the dispersed state of FFA in the mixtures with MAS. MAS has an absorption band in this range, and so the absorption spectra of the components of the mixtures were determined by subtraction.

Figure 8 shows the IR spectral changes of FFA in the mixtures with MAS. Curve (A) shows the IR spectral pattern of MAS. Curve (B) shows that of FFA crystals, which show a strong absorption band due to carboxyl carbonyl stretching at 1657 cm^{-1}. The carboxyl carbonyl stretching of FFA in a freshly prepared mixture has an absorption band at almost the same frequency as do FFA crystals (curve (C)). Curve (D) shows the IR absorption of FFA in the mixture with MAS after storage at a reduced pressure. The carbonyl stretching band at 1654 cm^{-1}, which was observed in the fresh mixture, has disappeared and new absorption bands have appeared at 1611 and 1584 cm^{-1}.

In order to obtain detailed information on this change in absorption bands, the IR spectral changes of benzoic acid, the aromatic carbonic acid with the most basic chemical structure, in a mixture with MAS were studied (Fig. 9). The molecules in the crystals of benzoic acid are strongly linked to their neighbors by hydrogen bonding between oxygen atoms and hydroxy groups. The carbonyl stretching band of benzoic acid crystals appeared at 1686 cm^{-1} as shown in curve (A). Curve (B) indicates the IR pattern of benzoic acid in the mixture with MAS after storage at a reduced pressure, where benzoic acid was confirmed by X-ray diffraction to be amorphous. The band at 1686 cm^{-1} had disappeared, and new absorption bands appeared at 1607 and 1569 cm^{-1}. Generally, the carbonyl anion has a strong asymmetric vibration in the range of 1610—1550 cm^{-1}.[6)] Curve (C) shows the IR absorption of sodium benzoate, an ionic form of benzoic acid, which has absorption bands at 1597 and 1547 cm^{-1}. These results suggest that benzoic acid had been dispersed in the ionic form monomolecularly, concomitantly with a change to the amorphous state. As to the mixture of FFA with MAS, the IR spectrum of FFA after storage at a reduced pressure was almost the same as that of an ionic form of FFA, which was obtained by precipitation from an equimolar solution of FFA and sodium hydroxide (Fig. 8E). The results suggested that FFA, in the mixture with MAS, was dispersed monomolecularly in the ionic form. It is considered that not only the amorphous state of FFA, but also the dispersed state in ionic form affected the dissolution characteristics of FFA from mixtures which were stored at reduced pressure.

The above results lead to the conclusion that the technique of mixing an adsorbent at reduced pressure with crystalline medicinals having poor solubility in water may be useful for improving their dissolution characteristics. This technique may facilitate the transition of crystalline medicinals to the amorphous state as the vapor pressure of the medicinals and the specific surface area of the adsorbent increase. As was suggested by Takayama *et al.*,[5)] the addition of water-soluble polymers as the third component of the mixture may be useful in practice in order to maintain the supersaturated state of FFA in the dissolution medium.

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