Molecular Behavior of Flufenamic Acid in Physical and Ground Mixtures with Florite

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The molecular behavior of flufenamic acid (FFA) was investigated in the physical and ground mixtures with two types of florite, florite R (FR) and florite S (FS). FR is mainly composed of porous calcium silicate while the main component of FS is porous silicon dioxide. The interaction of FFA and nonporous calcium silicate was also studied. Analyses were performed by differential scanning calorimetry, powder X-ray diffraction, and infrared-spectroscopy. Storage and grinding of the mixtures of FFA and FR resulted in the transformation of FFA to the amorphous ionic state, predominantly to calcium salt, and the amorphous state of the drug was found to be more stable in mixtures of higher FR content. In the mixture of FFA and FS, longer storage or grinding was necessary to obtain the amorphous state of FFA, and no change in its chemical state was observed. Differences of the FFA molecular state in the mixtures with FR and FS were attributed to differences of the chemical composition of these additives. Nonporous calcium silicate was found to have limited ability to induce transformation of FFA to the amorphous state as it has small surface area and lacks a porous structure. Stored or ground mixtures of FFA and FR showed marked enhancement in the dissolution behavior of FFA due to the existence of FFA in the amorphous ionic form.

Keywords amorphous; calcium silicate; flufenamic acid; florite; grinding; dissolution; X-ray diffraction analysis; differential scanning calorimetry; solid state interaction

When drugs which are poorly soluble in water are administered in solid dosage forms, the dissolution rate is often considered as a rate-limiting factor in the absorption process. The rate of dissolution of these drugs depends upon the effective surface area and the energy state within the drug crystals. Concomitantly, the amorphous form of the drug can exhibit a much higher dissolution rate and better bioavailability than the crystalline form. Various techniques have been used to reduce the crystallinity or to obtain the amorphous form of a crystalline drug. These include freeze-drying,[2,3)] spray-drying,[4)] solid dispersion,[5–8)] and molecular dispersion which was obtained by grinding the drug with certain additives such as microcrystalline cellulose,[9–13)] chitin or chitosan,[14)] cyclodextrins,[15,16)] gelatin, polyvinylpyrrolidone or methyl cellulose.[17)] It has been reported that some crystalline medicinals in mixtures with adsorbents[18–21)] or porous powders[21–24)] gradually became amorphous during storage at moderate temperatures.

We earlier reported that benzoic acid, when mixed with porous calcium silicate (florite R), was transformed to an amorphous ionic state within a few hours after mixing.[24)] In the present work, we compared the molecular behavior of flufenamic acid (FFA) in its physical and ground mixtures with two types of florite of different chemical composition, and with commercial calcium silicate. The relationship between the physicochemical properties of the additive and the molecular behavior of the drug in mixtures with additives was discussed. The influence of the molecular state of FFA on the dissolution pattern was also investigated.

Experimental

Materials Florite R and florite S (Tokuyama Soda, Tokyo) and calcium silicate (Wako Pure Chemical Industries Co., Tokyo) were used after drying in vacuum at 120 °C for 3 h. The main specifications of each sample are presented in Table I. FFA (Sigma Chemical Co.) was used as received. Other materials and solvents were of analytical reagent grade.

Preparation of the Physical Mixtures A drug with a particle size of 90—125 μm was uniformly mixed with the dried excipient in certain ratios using an agate mortar and pestle. The prepared mixtures were kept at 40 °C and 0% relative humidity (RH).

Preparation of the Ground Mixtures The ground mixtures were prepared using a vibration mill (Heiko Seisakusho TI-200). The sample chamber was made of alumina and had a volume of 140 cm^3. The rod was also made of alumina and had a height of 65.7 mm. The weight of each sample was about 2 g.

Stability of the Amorphous State of FFA in the Ground Mixtures with Florite R Samples of the 3 min ground mixture of 30% FFA and the 10 min ground mixture of 50% FFA were kept at 40 °C over P_2O_5 (0% RH), or over the saturated aqueous solution of KBr (79.6% RH). Samples of the stored mixtures were taken for powder X-ray diffraction analysis at 10 d intervals.

Powder X-Ray Diffraction Analysis The powder X-ray diffraction patterns were obtained using a Rigaku Denki 2027 diffractometer. Operating conditions were the same as those reported previously.[24)]

Differential Scanning Calorimetry (DSC) The samples were sealed in the aluminum liquid sample pans and the measurements were carried out on a DuPont 910 differential scanning calorimeter coupled with 9900 computer/thermal analyzer. The heating rate was 10 °C/min under nitrogen gas flow of 60 ml/min. After the furnace was equilibrated at 40 °C, the temperature was raised to 140 °C (1st run). Following the 1st run, the sample pan was removed from the furnace, both furnace and sample pan were allowed to cool to room temperature, and then the measurement was repeated (2nd run).

Infrared (IR)-Spectroscopy IR-spectra were obtained by KBr disk method using a computer mediated Fourier transformed infrared (FT-IR) spectrometer (Nicolet 5ZDX, U.S.A.). Since the used additives have absorption bands in the range of 1800 to 1200 cm^{-1}, the absorption spectra of FFA were determined by subtracting the spectrum of each additive from that of the corresponding mixture.

Dissolution Studies The dissolution of FFA from the samples was carried out according to the paddle method (JP XI). The dissolution medium was 300 ml of JP XI disintegration medium No. 1 (pH 1.2)

TABLE I. Specifications of Additives

	Florite R	Florite S	Calcium silicate
Main composition	Porous calcium silicate	Porous silicon dioxide	Nonporous calcium silicate
Specific surface area (m^2/g)	140	170	12
Mean particle diameter (μm)	15—20[a)]	15—20[a)]	10—15[b)]
Apparent density (g/cm^3)	0.08—0.12	0.12—0.15	0.41—0.43

a) Nominal. *b)* Determined by optical microscope.

placed in a 400 ml glass beaker, which was maintained at 37 °C by means of thermostated water bath. Each mixture was passed through a No. 150 sieve (mesh size 105 μm) before measurement. The sample powder was transferred into the dissolution medium, which was immediately stirred at 300 rpm using a rotatable shaft with two blades (40 mm long). The shaft was adjusted so that a distance of 10 mm was maintained between the lower end of the blades and the bottom of the vessel. At appropriate intervals, 5 ml samples were taken and replaced by the same volume of dissolution medium at 37 °C. The samples were filtered through a 0.2 μm membrane filter. One ml of the filtrate was appropriately diluted with 0.1 N NaOH solution. The drug concentrations were determined spectrophotometrically using a double beam spectrophotometer (Shimadzu, UV-160) at 289 nm.

Results and Discussion

Molecular Behavior of FFA in the Stored and Ground Mixtures Figure 1 shows the changes in the X-ray diffraction patterns of the physical mixtures of 20% FFA and 80% of either florite R or florite S. In the FFA and florite R mixture, a halo pattern was observed after storage for 7 d at 0% RH and 40 °C. In the mixture of FFA and florite S, the halo pattern was attained after about 10 d. Thus in the stored mixtures of FFA and either type of florite, FFA existed in an amorphous state. These results are in good agreement with those reported by Konno and Kinuno who used magnesium aluminum silicate as additive.[19] Figure 2 shows the changes in the X-ray diffraction patterns of the physical mixtures of 20% FFA and 80% of calcium silicate after storage at 0% RH and 40 °C. There was no appreciable change in the intensity of the X-ray diffraction peaks due to FFA crystals after storage of the physical mixture for 1 month. Figure 3 shows changes in the X-ray diffraction patterns of the physical mixtures of 30% FFA and 70% of either florite R or florite S after storage at 0% RH and 40 °C. In the mixture of FFA and florite R, the intensities of X-ray diffraction peaks due to FFA crystals gradually decreased with period of storage and a halo pattern was observed after 5 weeks. These X-ray diffraction peaks were, in contrast, still observed in the FFA–florite mixture even after storage for 8 weeks, though the crystallinity of FFA was reduced.

The X-ray diffraction data indicated that florite R has a greater ability to induce the transformation of FFA to the amorphous state than does florite S. This may be due to the difference in the chemical composition of the two additives. Although florite R and commercial calcium silicate have the same chemical composition, the latter did not induce amorphization of FFA because it has a limited surface area and lacks the porous structure of florite. Nakai *et al.*[25] discussed in detail the possible mechanism behind the interaction between porous powder and crystalline medicinals. They proposed that when the

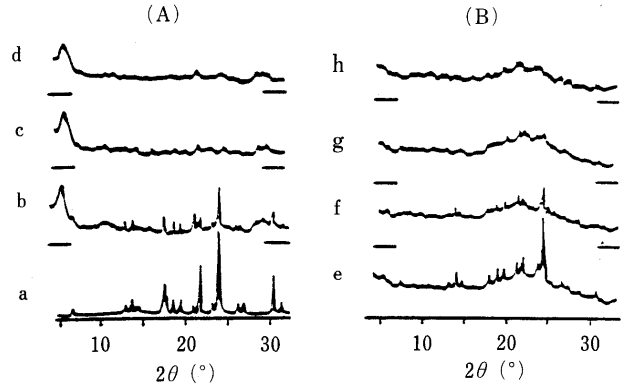

Fig. 1. Changes in X-Ray Diffraction Patterns of the Physical Mixtures of 20% FFA and 80% of Either Florite R (A) or Florite S (B) after Storage at 0% RH and 40 °C

a, FFA crystals; b, fresh mixture with florite R; c, stored for 7 d; d, florite R; e, fresh mixture with florite S; f, stored for 7 d; g, stored for 10 d; h, florite S.

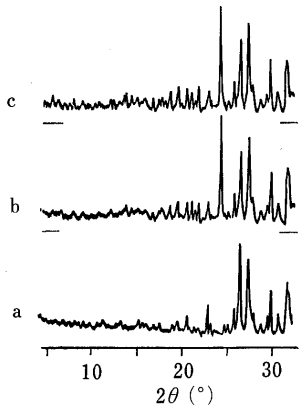

Fig. 2. Changes in X-Ray Diffraction Patterns of the Physical Mixtures of 20% FFA and 80% of Calcium Silicate after Storage at 0% RH and 40 °C

a, calcium silicate; b, physical mixture; c, mixture stored for 1 month.

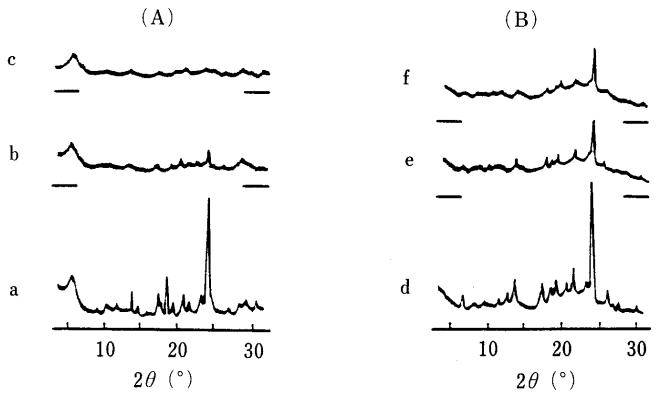

Fig. 3. Changes in X-Ray Diffraction Patterns of the Physical Mixtures of 30% FFA and 70% of Either Florite R (A) or Florite S (B) after Storage at 0% RH and 40 °C

a, fresh mixture with florite R; b, stored for 4 weeks; c, stored for 5 weeks; d, fresh mixture with florite S; e, stored for 4 weeks; f, stored for 8 weeks.

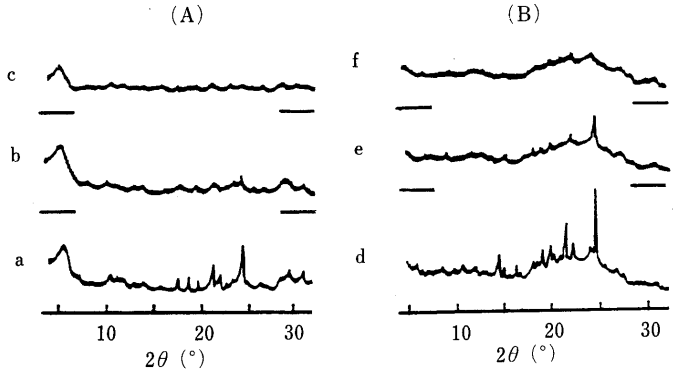

Fig. 4. X-Ray Diffraction Patterns of the Physical and the Ground Mixtures of 20% FFA and 80% of Either Florite R (A) or Florite S (B)

a, physical mixture with florite R; b, ground for 0.5 min; c, ground for 1 min; d, physical mixture with florite S; e, ground for 1 min; f, ground for 2 min.

crystalline drugs were mixed with porous powder, the drug molecules penetrated into the capillaries. These molecules have higher adsorption rate than those colliding with flat surfaces, since the molecules experience a greater number of collisions with walls in the capillary. Thus, the molecules would easily lose their kinetic energy during the collisions and rapidly become adsorbed on the capillary walls, providing a sink condition at the surface of the porous powders. Grinding is a process commonly used for size reduction or to obtain the amorphous state of a drug. It has been recently reported that grinding not only reduced particle size but also caused a change in the molecular behavior of a drug in the solid state.[26] In the present study we investigated the effect of grinding with porous powders on the molecular behavior of FFA. Figure 4 shows the X-ray diffraction patterns of the physical and the ground mixtures of 20% FFA and 80% of either florite R or florite S. The mixture with florite R showed a halo pattern after grinding for 1 min, while the mixture with florite S displayed the halo pattern after grinding for about 2 min. It is obvious that the amorphous state of FFA was attained easily by grinding with both types of florite, due to the porous structure and large specific surface area of either florite acting synergistically with the mechanical effect of grinding to induce this rapid transformation. Figure 5 shows the X-ray diffraction patterns of the physical and the ground mixtures of 20% FFA and 80% of calcium silicate. The grinding of the mixture for 2 min induced slight reduction of the crystallinity of both FFA and calcium silicate, but the amorphous state was not attained even after grinding for 10 min. Thin layer chromatographic (TLC) analysis indicated that FFA was subjected to partial decomposition in the mixture ground for 5 or 10 min (less than 1.0%), while no decomposition of FFA was observed in the physical mixtures during storage. The X-ray diffraction patterns of the physical and the ground mixtures of 30% FFA and 70% of either florite R or florite S are shown in Fig. 6. In the mixture with florite R, the X-ray diffraction peaks due to FFA crystals disappeared after grinding for 3 min. In the mixtures with florite S, grinding resulted in reduction of the crystallinity of FFA, but complete amorphization was not achieved even after grinding for 20 min. The mixture of FFA and florite R in 1 : 1 weight ratio also showed a halo pattern after grinding for 10 min. The amorphous state of FFA was obtained by grinding with florite R in a relatively short time even in the mixtures containing higher ratios of FFA.

Thermal Behavior of FFA by DSC Figure 7 shows the DSC curves of the physical mixtures of FFA and florite R in various mixing ratios. In the 1st run, FFA crystals showed a sharp endothermic peak at 135.5 °C due to the melting of FFA crystals. In the 2nd run they showed two endothermic peaks at 120 and 128 °C, which were attributed to the melting of the crystalline polymorphs of FFA.[27] In the 1st runs, the mixture of 10% FFA showed no peak, while the mixtures of 20—30% FFA showed a broad endothermic peak between 90—135 °C. The mixtures containing 40—60% FFA showed two overlapping endothermic peaks; the first peak was broad and observed at low temperature and the second peak was due to the melting of FFA crystals. The temperatures of the second peaks were lower than the melting point of FFA as a result of crystallinity changes, similar to benzoic acid in an

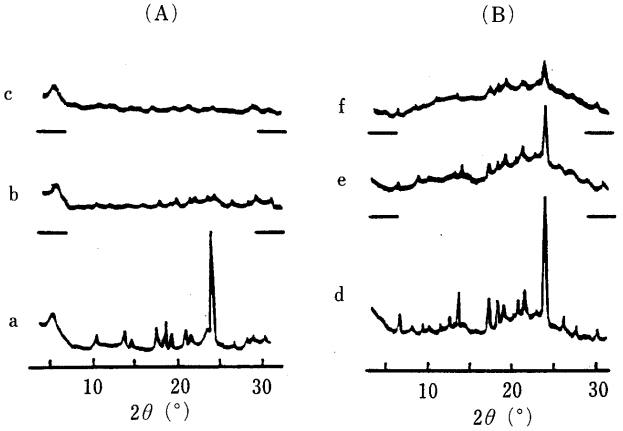

Fig. 6. X-Ray Diffraction Patterns of the Physical and the Ground Mixtures of 30% FFA and 70% of Either Florite R (A) or Florite S (B)

a, physical mixture with florite R; b, ground for 2 min; c, ground for 3 min; d, physical mixture with florite S; e, ground for 3 min; f, ground for 20 min.

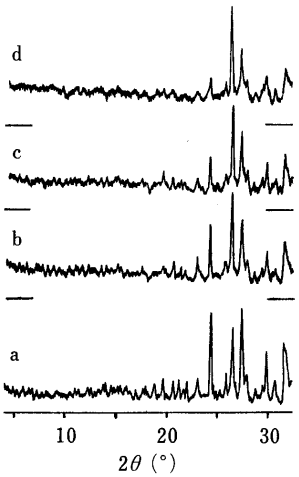

Fig. 5. X-Ray Diffraction Patterns of the Physical and the Ground Mixtures of 20% FFA and 80% of Calcium Silicate

a, physical mixture; b, ground for 2 min; c, ground for 5 min; d, ground for 10 min.

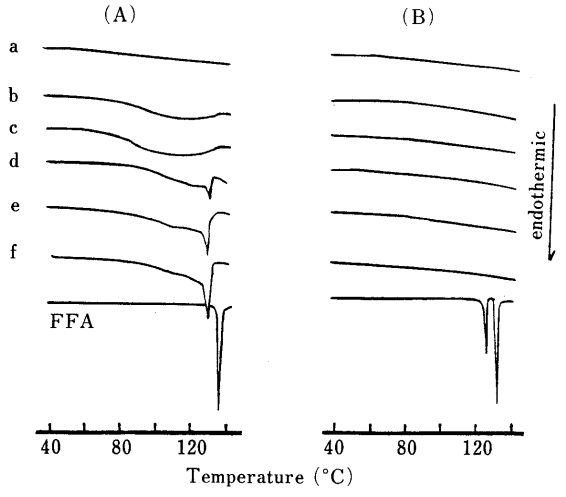

Fig. 7. DSC Curves of the Physical Mixtures of FFA and Florite R in Various Mixing Ratios (% FFA)

(A) 1st run; (B) 2nd run. a, 10%; b, 20%; c, 30%; d, 40%; e, 50%; f, 60%.

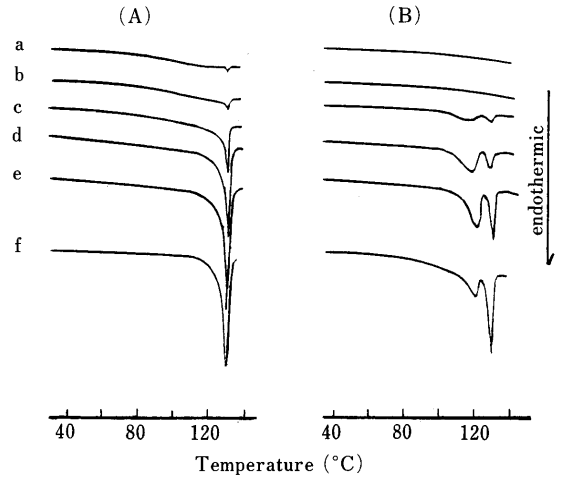

Fig. 8. DSC Curves of the Physical Mixtures of FFA and Florite S in Various Mixing Ratios (% FFA)

(A) 1st run; (B) 2nd run. a, 10%; b, 20%; c, 30%; d, 40%; e, 50%; f, 60%.

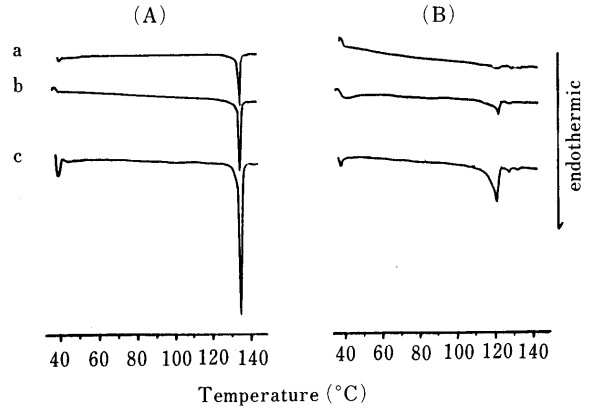

Fig. 9. DSC Curves of the Physical Mixtures of FFA and Calcium Silicate in Various Mixing Ratios (% FFA)

(A) 1st run; (B) 2nd run. a, 5%; b, 10%; c, 20%.

aerosil mixture reported previously.[21] By increasing the mixing ratio of FFA, the area of the broad peak was reduced while the second peak became more prominent. None of the mixtures showed any peaks in the 2nd runs.

The DSC curves of the physical mixtures of FFA and florite S in various ratios are shown in Fig. 8. In the 1st runs, the mixtures of 10—20% FFA showed two small endothermic peaks at about 90—135 °C and at 135 °C, but showed no peak in the 2nd runs. In the 1st runs, the mixtures containing FFA in a ratio of 30—60% showed a sharp endothermic peak due to melting of FFA at 135 °C. In the 2nd runs, they showed two endothermic peaks, the first peak attributable to the disordered FFA in the pores and the second to melting of the crystalline FFA.

Figure 9 shows the DSC curves of the physical mixtures of FFA and calcium silicate in various ratios. In the 1st runs, all mixtures showed a sharp endothermic peak due to FFA melting, while there was only a slight reduction in the heat of fusion of FFA in the 2nd runs, indicating the absence of strong interaction between FFA and commercial calcium silicate.

The DSC results confirmed that florite R had the greatest ability to induce the transformation of FFA to the amorphous state. They also indicated that FFA had the

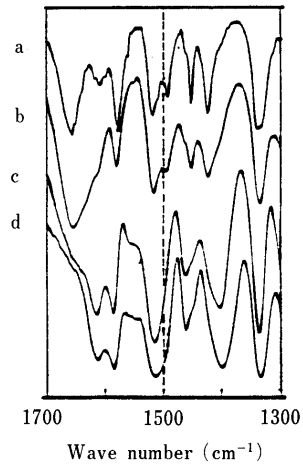

Fig. 10. Changes in the IR-Spectra of the Physical Mixture of 20% FFA and 80% Florite R after Storage at 0% RH and 40 °C for 7 d

(A) 1st run; (B) 2nd run. a, FFA; b, fresh mixture; c, stored mixture; d, calcium flufenamate.

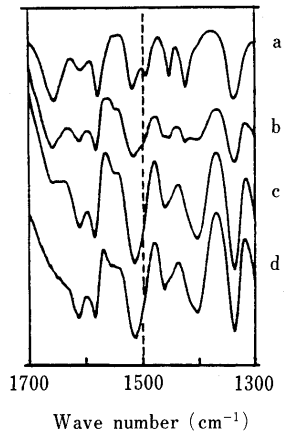

Fig. 11. Effect of Grinding on the IR-Spectra of the Physical Mixture of 20% FFA and 80% Florite R

a, intact; b, ground for 2 min; c, ground for 4 min; d, ground for 5 min.

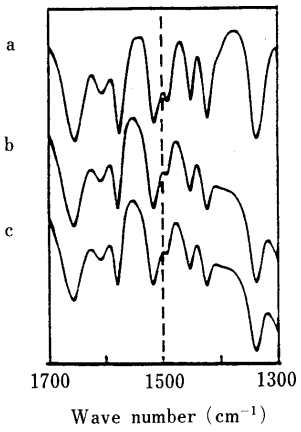

Fig. 12. Changes in the IR-Spectra of the Physical Mixtures of 20% FFA and 80% Florite S after Storage at 0% RH and 40 °C or after Grinding for 5 min

a, physical mixture; b, mixture stored for 10 d; c, mixture ground for 5 min.

following three phases in the mixture with porous powders: a crystalline state which showed a sharp endothermic peak, a disordered state which showed a broad endo-

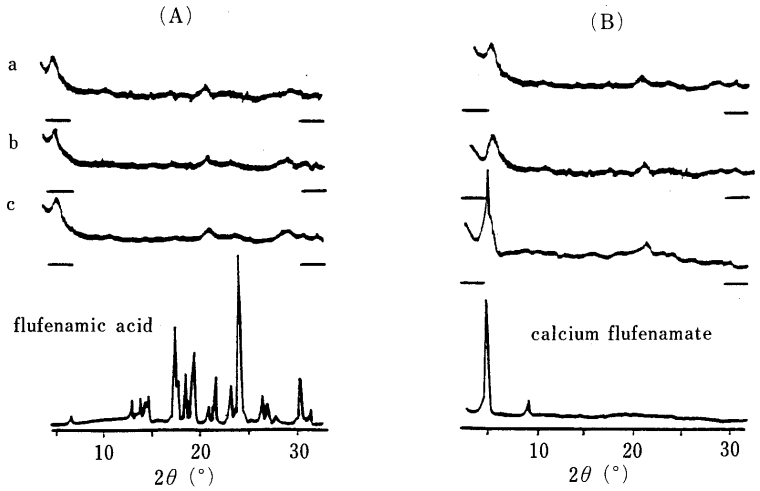

Fig. 13. Changes in X-Ray Diffraction Patterns of the Ground Mixtures of FFA and Florite R after Storage for 2 Months at Different RHs and 40 °C

(A) mixture of 30% FFA ground for 3 min; (B) mixture of 50% FFA ground for 10 min. a, before storage; b, after storage at 0% RH; c, after storage at 79.6% RH.

thermic peak at low temperature and an amorphous state which showed no peak.

Changes of IR-Spectra of the Stored and Ground Mixtures of FFA Changes in the IR-spectra of the mixture of 20% FFA and 80% florite R after storage at 0% RH and 40 °C for 7 d are shown in Fig. 10. The fresh mixture showed the carbonyl stretching band of FFA at about 1656 cm^{-1}. The stored mixture did not show this band, but showed a carbonyl anion band at about 1400 cm^{-1}. In a stored mixture of FFA and florite R, FFA was thus transformed to an ionic form, predominantly calcium salt. Konno and Kinuno[19] reported that storage of the physical mixture of FFA and magnesium aluminum silicate under reduced pressure resulted in the transformation of FFA to an amorphous ionic form.

The effect of grinding on the IR-spectra of the physical mixture of 20% FFA and 80% florite R is shown in Fig. 11. The IR-spectra of the mixture ground for 2 min showed both the carbonyl band of FFA at about 1656 cm^{-1} and the carbonyl anion band at about 1400 cm^{-1}. With increase in grinding time, the intensity of the FFA carbonyl band gradually decreased, while the carbonyl anion band became more prominent. The mixture ground for 5 min showed only the carbonyl anion band. The large specific surface area and the porous structure of florite R enhanced the effect of grinding to induce the rapid transformation of FFA to the amorphous state. The amorphous FFA molecules were adsorbed on the surface of florite R, where they interacted with calcium cations to form the amorphous calcium flufenamate. Figure 12 shows the IR-spectra of the physical mixtures of 20% FFA and 80% florite S after storage at 0% RH and 40 °C for 10 d or after grinding for 5 min. No significant difference was observed among the IR-spectra of the fresh, stored, or ground mixtures. Similarly, there was no significant difference among IR-spectra of the physical, stored or ground mixtures of FFA and nonporous calcium silicate.

The IR-spectral results indicated that in the mixtures of FFA and florite R, storage or grinding induced the transformation of FFA to the amorphous ionic state,

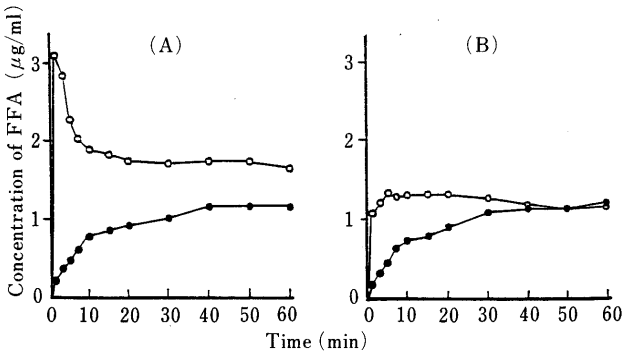

Fig. 14. Dissolution Profiles of FFA from the Physical and the Stored Mixtures with Either Florite R or Florite S in pH 1.2 Solution at 37 °C

(A) mixtures of 20% FFA and 80% florite R; (B) mixtures of 20% FFA and 80% florite S. ●, physical mixture; ○, mixture stored for 10 d at 0% RH and 40 °C.

while in the corresponding mixtures of FFA and florite S, there was no change in the molecular state of the drug. This was attributed to the difference in the chemical compositions of florite R and florite S: florite R being composed primarily of porous calcium silicate and florite S of porous silicon dioxide.

Stability of the Amorphous State of FFA in the Ground Mixtures with Florite R Figure 13 shows the changes in the X-ray diffraction patterns of the ground mixtures of FFA and florite R after storage for 2 months at 0 and 79.6% RHs at 40 °C. Florite R showed diffraction peaks at $2\theta = 5.5°$ and 21.0°. The ground mixture of 50% FFA stored at 79.6% RH showed an X-ray diffraction pattern which coincided with that of the crystalline calcium flufenamate. In contrast, there was no significant change in the X-ray diffraction pattern when the mixture was stored at 0% RH. In the ground mixture of 30% FFA, no change was observed in the X-ray diffraction pattern after storage at either 0% or 79.6% RH. These results indicated that the amorphous calcium flufenamate was more stable in mixtures containing higher ratios of florite R or in those stored at lower RH.

Dissolution Behavior of FFA Figure 14 shows the dissolution profiles of FFA from the physical and the stored

mixtures with either florite R or florite S in pH 1.2 solution at 37 °C. The stored mixture of FFA and florite S exhibited a greater dissolution rate than the physical mixture, due to the presence of the drug in an amorphous state. The observed leveling of the concentration of FFA after the first 10 min is attributed to the stable crystalline state of FFA.[28] However, when florite R was used, the stored mixture showed the greatest enhancement in the dissolution rate of FFA due to the existence of FFA in an amorphous ionic state. The observed decrease in the concentration of FFA after its initial fast dissolution may be due to the conversion of the calcium flufenamate to the molecular form. The 5 min ground mixture of 20% FFA and 80% florite R showed a dissolution pattern which was almost the same as that of the stored mixture.

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