Physical and Chemical Changes of Medicinals in Mixtures with Adsorbents in the Solid State. IV.[1] Study on Reduced-Pressure Mixing for Practical Use of Amorphous Mixtures of Flufenamic Acid

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Flufenamic acid (FFA) was mixed with magnesium aluminum silicate (MAS) at a reduced pressure of about 10 to 50 mmHg employing a commercial mixer for pharmaceutical production. An amorphous state of FFA in the mixture was efficiently achieved with this equipment, and the dissolution of FFA was enhanced in comparison with that of the physical mixture. Effects of the conditions of mixing, such as pressure, temperature and rotating speed, on dissolution of FFA were determined. Through stability tests at 40 °C under both dry and humid conditions, no change in dissolution profiles was recognized in a 5% FFA mixture stored under any conditions. On the other hand, decreases in dissolution behavior were observed in 10% and 20% FFA mixtures when they were stored under humid conditions. These results suggested that humidity should be avoided during the storage of amorphous mixtures of FFA with MAS for production purposes.

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

It is well known that, because of its higher potential energy, the amorphous form of a drug with poor solubility in water is generally more soluble than the crystalline form. Many methods have been proposed for making durgs amorphous, for example, rapid cooling of melts to a glassy state,[2] spray-drying,[3] grinding with microcrystalline cellulose or with cyclodextrins,[4] and solid dispersion in polyvinylpyrrolidone or in polyethylene glycol.[5] Unfortunately, some noncrystalline solids become crystalline depending on the storage conditions,[6] and these changes are undesirable for the manufacture of the drug.

The author has reported that some organic crystalline drugs, when mixed with adsorbents such as magnesium aluminum silicate (MAS) and treated at reduced pressure, readily become amorphous, and this change can improve the dissolution characteristics of poorly water-soluble drugs.[1a,b] Recently, equipment has been developed for pharmaceutical production that allows the inside of a container to be kept at reduced pressure. Some methods for efficient granulation of powder or coating of granules at reduced pressure employing this equipment have been proposed.[7] The goal of our investigation was to find a method, suitable for use on a production scale, of obtaining amorphous drugs by reduced-pressure mixing with an adsorbent. In the present study, flufenamic acid (FFA), a non-steroidal antiinflammatory drug with poor solubility in water, and MAS, which is used as an ingredient in pharmaceutical preparations, were mixed at a reduced pressure employing a commercial mixer for pharmaceutical production, and changes in the dispersed state of FFA and its dissolution profiles in a buffer solution were studied. Stability studies were also performed in several storage conditions to find optimum conditions for practical purposes.

Experimental

Materials MAS (Neusilin UFL₂) was purchased from Fuji Chemical Industry Co., Ltd. The specific surface area and pore size distribution have been described in a previous paper.[1b] FFA was purchased from Sigma Chemical Co., Ltd. and passed through a No. 150 sieve (mesh size: 105 μm).

Reduced-Pressure Mixing A Cross-Rotary Mixer (Meiwa Kougyou Co., Ltd.) was modified to enable powder to be mixed at reduced pressure.

A nozzle and a cock were attached to the lid of the 10-l mixing vessel in order to remove the air. Amounts of FFA and MAS suitable for making 100 g samples with 5%, 10% and 20% concentrations of FFA were weighed, and each sample was placed in the mixing vessel which was kept at a definite temperature. The lid was replaced, the vessel was evacuated of air using a vacuum pump to achieve a pressure of about 10 or 50 mmHg (or was left at atmospheric pressure), and the cock was closed. The pressure was measured with a mercury manometer connected between the nozzle and the vacuum pump. The mixing vessel was rotated within a frame supported by a rotating horizontal shaft, so that the vessel rotated around two axes at right angles to each other to mix the powder. Rotation speeds were 2.5, 10 or 25 rpm for the mixing vessel, and 2.5 rpm for the shaft.

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,[1b] but the voltage and current were 30 kV and 20 mA, respectively.

Dissolution Tests Method and conditions were as reported in our previous paper.[1b] The dissolution medium was 250 ml of a 0.1 M acetate buffer solution of pH 5.0. A sample powder equivalent to 25 mg of FFA was weighed accurately and put in the dissolution vessel in which the dissolution medium was stirred at 500 rpm at 37 °C, and the amount dissolved was determined spectrometrically (289 nm). C_{max}, the maximum concentration in dissolution curves within 20 min, was used as the index of the dissolution properties of the mixture in the study on mixing conditions. It is assumed that the higher the C_{max}, the more the FFA bacome amorphous in the mixture.

Infrared (IR) Absorption Studies Spectral data were obtained with a Hitachi IR 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 IR absorption spectrum of FFA in each mixture was determined by subtraction.

Stability Tests Samples of about 1 g to 2 g of FFA mixture prepared by reduced-pressure mixing were placed in a glass bottle and stored at 40 °C over a saturated solution of sodium chloride to obtain 75% relative humidity (RH), or $K_2CO_3 \cdot 2H_2O$ (40% RH) in laboratory desiccators. In the same way, phosphorous pentoxide was used with similar samples to keep the RH at 0%.

Thin-Layer Chromatography (TLC) The chemical stability of FFA during storage was studied using TLC developed with two solvent systems. To a quantity of mixture equivalent to 10 mg of FFA, 1 ml of methanol was added, shaken, and filtered. Filtrate samples of 10 μl were spotted on silica gel plates, which were developed with solvent systems of both *n*-butanol–water–acetic acid (4:2:1) and isopropanol–*n*-butylacetate–water–acetic acid (10:6:3:1). FFA was detected under ultraviolet (UV) light.

Results and Discussion

Studies of FFA–MAS Mixtures Mixed at Reduced Pressure In this study, a Cross-Rotary Mixer, a commercial

mixer for pharmaceutical production, was modified to allow powder mixing at reduced pressure. An amorphous mixture of FFA was prepared by reduced-pressure mixing using the equipment.

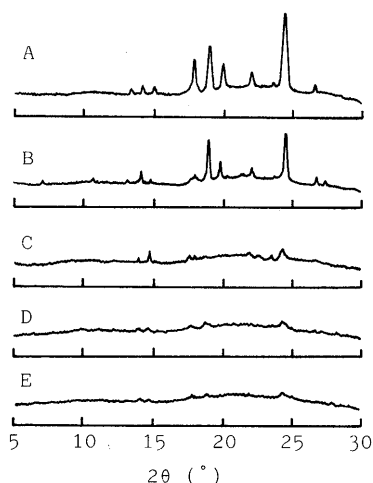Figure 1 shows change with mixing time in the X-ray

Fig. 1. Changes with Mixing Time in the X-Ray Diffraction Patterns of Mixtures of FFA with MAS

A, fresh (physical mixture); B, mixed for 20 min; C, mixed for 40 min; D, mixed for 1 h; E, mixed for 2 h. FFA and MAS (20% FFA) were mixed at 60 °C at a reduced pressure of 10 mmHg and at a rotating speed of 25 rpm.

diffraction patterns of the 20% FFA–MAS mixture. Figure 1A shows the X-ray diffraction pattern of the physical mixture in which peaks of radiation diffracted by FFA crystals can be observed. Figures 1B—E show the diffraction patterns of the mixtures during the mixing process. The peak intensity of FFA crystals decreased with mixing time and halo patterns were observed as shown in D and E.

Figure 2 shows change with mixing time in the dissolution profiles of FFA in pH 5.0 acetate buffer solution for the same mixtures as in Fig. 1. The dissolution of FFA was markedly enhanced by mixing in comparison with the simple physical mixture, and the curves for the mixture showed a typical supersaturation phenomenon. It is assumed that FFA, in mixture with MAS, had been dispersed monomolecularly in the ionic form with the mixing process[1b] and therefore enhancement in dissolution of FFA occurred. The results indicate that the FFA was efficiently changed to an amorphous state employing the commercial equipment.

The principal factors in the mixing process are the pressure in the vessel, temperature, the rotation speed and mixing time, hence the effect of these factors on changes in the dissolution properties were studied. In this study, C_{max} was used as the index of the dissolution properties of the mixture. Figure 3 shows the effect of the pressure in the vessel on the time course of C_{max} during mixing. En-
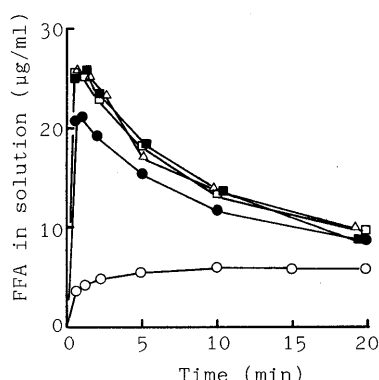

Fig. 2. Changes with Mixing Time in Dissolution Profile of FFA from Mixtures with MAS

○, fresh (physical mixture); ●, mixed for 20 min; □, mixed for 40 min; ■, mixed for 1 h; △, mixed for 2 h. FFA and MAS (20% FFA) were mixed at 60 °C at a reduced pressure of 10 mmHg and at a rotating speed of 25 rpm.

Fig. 4. Effect of Temperature during Mixing on the Time Course of Dissolution Parameter (C_{max}) of FFA

○, 60 °C; ●, 50 °C; □, 40 °C. FFA and MAS (20% FFA) were mixed at a reduced pressure of 10 mmHg and at a rotating speed of 25 rpm.
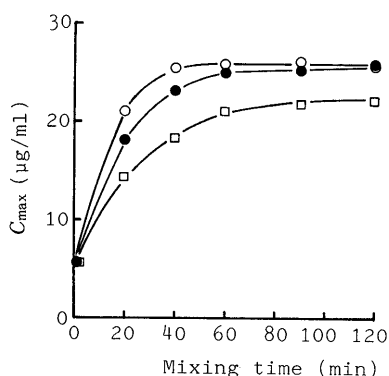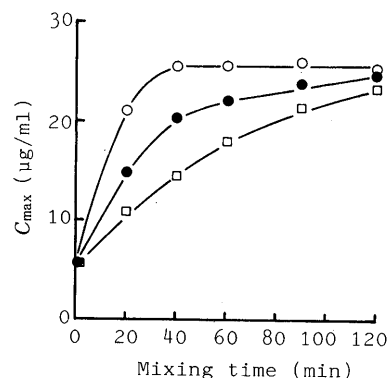

Fig. 3. Effect of Pressure during Mixing on Time Course of Dissolution Parameter (C_{max}) of FFA

○, 10 mmHg; ●, 50 mmHg; □, atmospheric pressure. FFA and MAS (20% FFA) were mixed at 60 °C and at a rotating speed of 25 rpm.
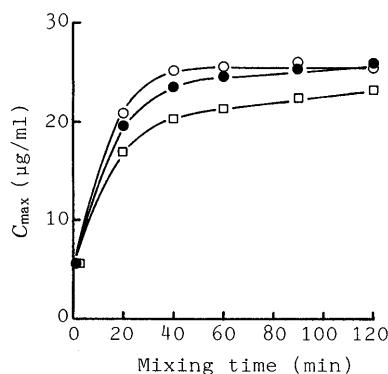

Fig. 5. Effect of Rotation Speed of Mixer on the Time Course of Dissolution Parameter (C_{max}) of FFA

○, 25 rpm; ●, 10 rpm; □, 2.5 rpm. FFA and MAS (20% FFA) were mixed at 60 °C and at a reduced pressure of 10 mmHg.

hancement in dissolution occurred more rapidly at re-
duced pressures of 10 to 50 mmHg than at atmospheric
pressure. It is clear that FFA sublimed and was transferred
to the surface or pores of MAS[1,8] in the process of the
gradual loss of the crystalline properties of FFA. Therefore,
it is reasonable to assume that the rate-determining step of
the reaction is the transfer of FFA in the gaseous phase.
The rate of mass-transfer J_1 of molecules 1 in the gaseous
mixture for steady-state diffusion is given by the following
basic equation[9]:

$$J_1 = -\frac{1}{3}\bar{v}_1\lambda_1\frac{dC_1}{dx} \tag{1}$$

where $\bar{v}_1$ is the mean velocity of the molecules 1, λ_1 is their
mean free path, and dC_1/dx is the density gradient of the
molecules 1 in the diffusion layer. Since the mean free path
λ_1 of drug molecules at reduced pressure is greater than
that at atmospheric pressure, J_1 becomes greater as the
pressure is lowered, and consequently the rate of the reaction
is accelerated at reduced pressure.

Figure 4 shows the effect of temperature on the time
course of C_{max} during mixing. As the temperature is raised,
the vapor pressure of the compound becomes higher
(Clapeyron's equation), and therefore dC_1/dx becomes
greater. Moreover, $1/3\bar{v}_1\lambda_1$ becomes greater as the
temperature is raised. These two factors combine to raise
J_1 at high temperature. Consequently, it was observed that
at higher temperature, faster enhancement of dissolution
occurred.

Figure 5 shows the effect of the rotation speed of the
mixer on the time course of C_{max} during mixing. In the
mixing of powders, the shearing force between particles
usually becomes stronger as the rotation speed is increased,
and this increases the chances of surface renewal between the
drug and adsorbent particles. The concentration of the
drug on the surface of adsorbent particles which are in
contact with drug particles, is reduced almost to zero under
high shearing forces, and hence a high value of dC_1/dx is
maintained. Consequently, it was observed that at higher
rotation speeds, faster enhancement of dissolution occurred.

These results suggested that, as long as the drug or
adsorbent are chemically stable, the mixing should be
performed at reduced pressure and at high temperature.
And, if we intend to obtain amorphous drug–adsorbent
mixtures efficiently, the mixing should be performed under
conditions of high shearing forces between particles.

Stability of Amorphous FFA–MAS Mixture Obtained by Reduced-Pressure Mixing

Three different concentrations
of FFA in mixtures with MAS were obtained by
reduced-pressure mixing at a temperature of 60 °C, a vessel
pressure of 10 mmHg, a rotation speed of 25 rpm, and a
mixing time of 2 h. Samples of each mixture were stored at
a temperature of 40 °C and at RH values of 0%, 40% or
75%. Physical and chemical changes were examined.

Figures 6, 7 and 8 show changes in the dissolution profiles
in pH 5.0 acetate buffer solutions, of 20%, 10% and 5%
mixtures, respectively, of FFA with MAS during storage.
No changes in dissolution profiles were observed in 5%
FFA mixtures stored at any RH. On the other hand,
decreased dissolution behavior was observed in 10% and
20% FFA mixtures when they were stored at 40% and 75%
RH. Nakai et al. suggested[8a] that the drug has three distinct
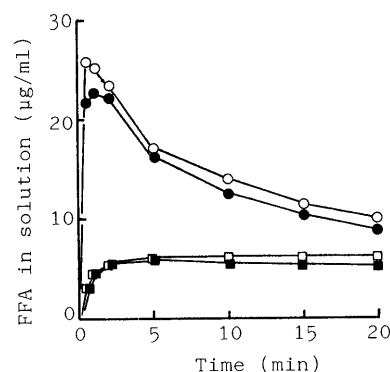

Fig. 6. Changes in Profile of FFA Dissolution from 20% Mixtures with
MAS Stored for 1 Month at Various Humidities

○, initial; ●, stored at 40 °C, 0% RH; □, stored at 40 °C, 40% RH; ■, stored
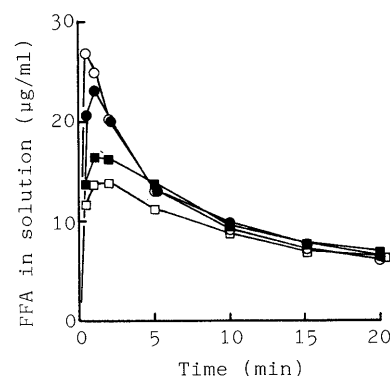at 40 °C, 75% RH. The mixture was prepared at reduced pressure.

Fig. 7. Changes in Profile of FFA Dissolution from 10% Mixtures with
MAS Stored for 1 Month at Various Humidities

○, initial; ●, stored at 40 °C, 0% RH; □, stored at 40 °C, 40% RH; ■, stored
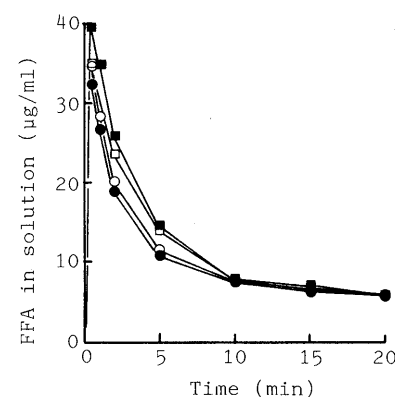at 40 °C, 75% RH. The mixture was prepared at reduced pressure.

Fig. 8. Changes in Profile of FFA Dissolution from 5% Mixtures with
MAS Stored for 1 Month at Various Humidities

○, initial; ●, stored at 40 °C, 0% RH; □, stored at 40 °C, 40% RH; ■, stored
at 40 °C, 75% RH. The mixture was prepared at reduced pressure.

phases in mixtures with porous powders such as controlled
pore glass (CPG). They showed that the drug molecules are
adsorbed on the pore walls (phase 3) at low concentrations
of about 5%, and the molecules exist partly in a disordered
structure (phase 2) and partly in phase 3 at a concentration
of about 20%. It can be presumed that differences in
stability which depend upon the concentration of FFA are
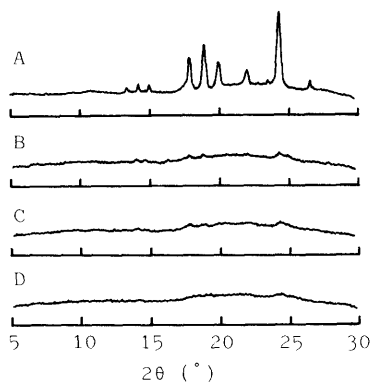related to the different phases of FFA which exist in the
mixture.

Fig. 9. Differences in the X-Ray Diffraction Patterns of 20% Mixtures of FFA with MAS Stored at 40 °C, 75% RH

A, physical mixture; B, initial; C, stored for 1 month; D, stored for 2 months. The mixture was prepared at reduced pressure of 10 mmHg.
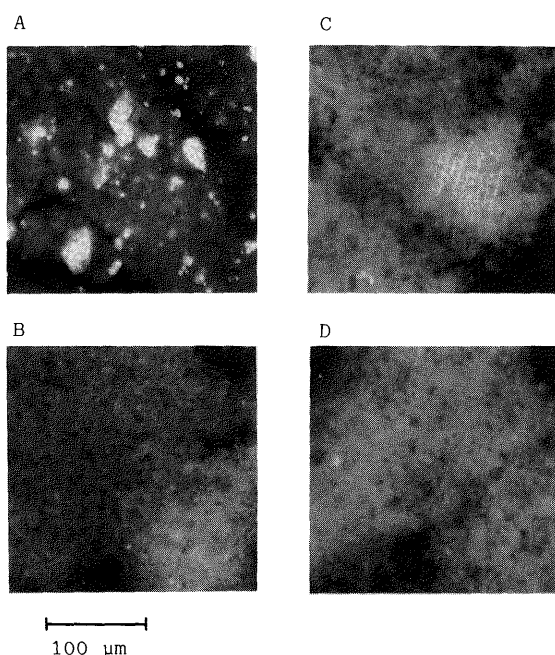

Fig. 10. Differences in Polarized Micrographs of 20% Mixtures of FFA with MAS Stored at 40 °C, 75% RH

A, physical mixture; B, initial; C, stored for 1 month; D, stored for 2 months. The mixture was prepared at reduced pressure of 10 mmHg.
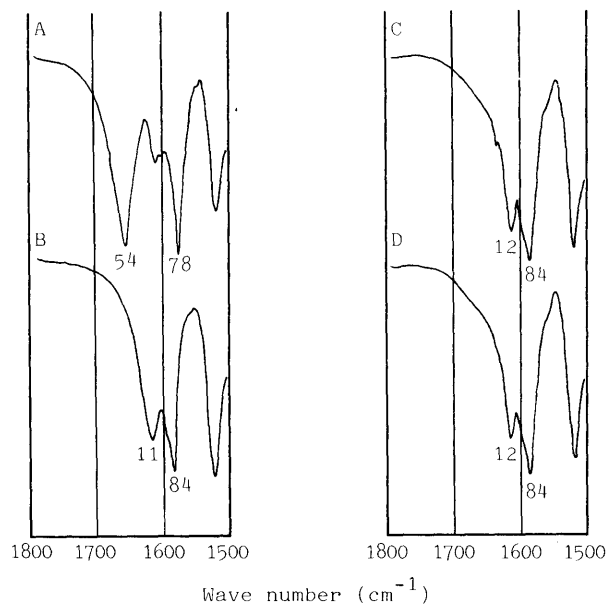

Wave number (cm^{-1})

Fig. 11. Differences in IR Spectra of FFA in 20% Mixtures with MAS Stored at 40 °C, 75% RH

A, physical mixture; B, initial; C, stored for 1 month; D, stored for 2 months. The mixture was prepared at reduced pressure of 10 mmHg.

To ascertain whether or not FFA decomposed during storage, the mixtures were tested by TLC for chemical changes. All samples gave just one spot with the same Rf value. These results indicate that decomposition did not occur during storage.

In order to obtain detailed information about physical change of FFA in the mixture, further studies were performed on the 20% FFA–MAS mixtures stored at 40 °C, 75% RH, in which decreases in dissolution were previously observed. Figure 9 shows changes in the X-ray diffraction patterns of the mixtures. Figure 9A shows the pattern of physical mixture in which peaks of radiation diffracted by FFA crystals can be observed. Figure 9B shows the diffraction pattern of the initial mixture immediately after preparation by reduced-pressure mixing in which a halo pattern was observed. Figures 9C and 9D show the patterns of the mixtures after storage for 1 month and 2 months, respectively. They were almost the same patterns as in the

initial mixture. No peaks due to FFA crystals were observed for the mixtures either before or after storage.

Figure 10 shows the changes in micrographs of the mixture obtained with a polarizing microscope. The crystals of FFA observed in the physical mixture (Fig. 10A) had almost disappeared in the initial mixture immediately after preparation by reduced-pressure mixing (Fig. 10B). Figures 10C and 10D show the micrographs of the mixtures after storage for 1 month and 2 months, respectively. They were almost the same as in the initial mixture.

Figure 11 shows changes in the IR spectra of FFA in the 20% mixtures. Curve (A) shows the IR spectral pattern of FFA in a physical mixture. It shows a strong absorption band due to carboxyl carbonyl stretching at 1654 cm^{-1}. Curve (B) shows the IR absorption of FFA in the initial mixture immediately after preparation by reduced-pressure mixing. New absorption bands, due to carbonyl anion of FFA, have appeared at 1611 and 1584 cm^{-1} accompanied with changes in the amorphous state.[1b] Curves (C) and (D) show IR absorption of FFA in the 20% mixtures with MAS after storage for 1 month and 2 months, respectively. They show absorption bands at almost the same frequencies as curve (B) does.

These results suggested that FFA in the mixture with MAS did not convert to crystalline forms during storage under humid conditions. The decrease in the dissolution of FFA from mixture with MAS, after storage in humid conditions, was therefore not caused by recrystallization of FFA. As the mechanism of the change has not been established yet, further study on this is necessary.

From the stability tests described above, it is clear that the mixtures with high concentrations of drug should not be exposed to humidity during storage when intended for use in pharmaceutical production.

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