Solid Dispersions of Indomethacin and Griseofulvin in Non-porous Fumed Silicon Dioxide, Prepared by Melting¹⁾

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A method of increasing the dissolution rates of glass-forming, poorly water-soluble drugs was investigated. It is based on the concept of preparing the powder form of a glassy drug dispersed in an inert carrier by melting. Indomethacin (IMC) and griseofulvin were used as model drugs, and fumed silicon dioxide was used as the carrier. The drug–silica (1:2) mixture was heated until the drug melted. The properties of the solid dispersion thus obtained were examined using powder X-ray diffractometry (XRD), differential scanning calorimetry (DSC), infrared (IR) spectroscopy, and scanning electron microscopy (SEM). XRD showed that the drugs were converted from a crystalline state to an amorphous state in the solid dispersions. On DSC thermograms, a pure IMC glass showed an endothermic peak corresponding to glass transition, then an exothermic peak corresponding to transformation to a metastable crystal and an endothermic peak corresponding to melting of the metastable form. The IMC–silica solid dispersion, however, shows no transition peak in its thermogram, indicating that a solid dispersion is more stable to heat than pure glass. The drug–silica solid dispersions showed IR spectra characteristic of pure amorphous drugs but somewhat different from those of crystalline drugs. SEM revealed that the drug–silica solid dispersions had none of the characteristics observed in crystalline drugs. The dissolution rates of drugs from the solid dispersions were much higher than those from physical mixtures and from pure crystalline drugs.

Keywords indomethacin; griseofulvin; solid dispersion; amorphous; fumed silicon dioxide; dissolution rate

Introduction

In theory, a crystalline drug can be converted to the amorphous state *via* a gaseous, liquid, or crystalline solid state. Nakai *et al.* reported that the crystalline drugs interact with porous powders or controlled pore glasses, ultimately assuming the amorphous state.^{2a–c)} They proposed a mechanism whereby the drug molecules sublime and are adsorbed onto the surface of the pores. Konno reported that the vapor pressures of drugs correlate with the rate of transformation from the crystalline state to the amorphous state in the presence of an adsorbent.^{2d)} The above studies indicate the existence of the gas route. As a typical example of the liquid route, Borka reported that a brittle, glassy amorphous mass of indomethacin was obtained by cooling the melt.³⁾ Nakai *et al.* demonstrated that all crystalline drugs become amorphous on being ground with crystalline cellulose.^{4a)} Otsuka *et al.* also reported that indomethacin (IMC) was converted to the amorphous state on grinding with an agate centrifugal ball mill.^{4b)} Such crystal modifications on grinding may suggest the existence of a crystalline solid route as well as the other routes, but clarification of this possibility will require further study.

Some drugs have been shown to be able to form glass readily upon cooling from the liquid state. Although the glass has the potential to increase the dissolution rate, it is thermodynamically unstable and is therefore transformed to a stable crystalline state by processing and environmental stresses. Several investigators reported these phenomena: the glass tended to devitrify on grinding^{5a–b)}; powdered glass did not increase the dissolution rate because of its rapid devitrification on coming in contact with water^{5c)}; and powdered glass was converted to crystal on aging much faster than untreated glass.^{5d–e)} These results indicate that pure glass is not suitable for use in formulations.

One possible approach to solving the problems caused by the grinding of the glass is to prepare the powder form of the glass dispersed in an inert carrier. In the present

study, we prepared solid dispersions of this type by melting, using IMC and griseofulvin (GRIS) as glass-forming, poorly water-soluble drugs, and non-porous fumed silicon dioxide (silica 380) as the carrier. This carrier is a pharmaceutical excipient consisting of amorphous, water-insoluble, hydrophilic, ultra-fine, spherical particles with extensive surface areas (380 m²/g). The purpose of this work was to evaluate this new approach to preparing glass powder by examining the properties of the solid dispersions using X-ray diffractometry (XRD), differential scanning calorimetry (DSC), infrared (IR), scanning electron microscopy (SEM) and dissolution testing.

Experimental

Materials Indomethacin U.S.P. grade (form I³⁾) and griseofulvin (Nakarai Chemical Co., Ltd.), and non-porous fumed silicon dioxide (aerosil 380, Nippon Aerosil Co., Ltd.) were used without further purification.

Preparation of Physical Mixtures The drug and silicon dioxide were weighed accurately in various proportions, mixed for 3 min with a Vortex mixer, and were then passed through a 200-mesh sieve.

Preparation of Triturated Mixtures The drug and silicon dioxide were manually triturated with a pestle for 5 min in an agate mortar, and were passed through a 200-mesh sieve.

Preparation of Solid Dispersion Preliminary experiments showed that the factors involved in the preparation of solid dispersion by melting are drug–silicon dioxide ratios, heating temperature and mixing methods. Since these factors are interrelated, the drug–carrier ratios required for preparation varied depending on the temperature and mixing methods used. In this study, the following conditions were employed: triturated mixtures of IMC or GRIS with silicon dioxide (1:2, w/w) were transferred to an open petri dish and heated at 150°C for 30 min and at 215°C for 30 min, respectively; they were then allowed to cool to room temperature.

Differential Scanning Calorimetry (DSC) DSC thermograms were obtained using a Perkin–Elmer DSC-1B calorimeter. The samples were placed in aluminum sealed pans, and analyzed by heating at a rate of 16°C/min in nitrogen gas. Temperature calibrations were made using stearic acid (69.4°C), benzoic acid (122.4°C), indium (155.6°C), tin (231.9°C), and lead (327.4°C) as standards. The heats of fusion were calculated by gravimetrically measuring the peak areas of the sample and the indium standard.

X-Ray Diffraction Studies Powder X-ray diffraction patterns were

recorded using a Rigaku Denki Geiger Flex 2012 diffractometer with nickel-filtered $\text{CuK}\alpha$ radiation. Voltage 35 kV, current 20 mA, receiving slit 0.15 mm, scanning speed $2^\circ/\text{min}$, chart speed 20 mm/min.

IR Spectroscopy IR spectra were recorded using KBr disks on a Hitachi 270-30 infrared spectrophotometer.

Scanning Electron Microscopy Electron micrographs were made using a scanning electron microscope (JEOL JSM-T120). The samples were coated with gold, using a direct current sputter technique.

Dissolution Studies Dissolution testing was conducted using the JP XI paddle method. The dissolution medium was 900 ml of JP XI 1st fluid (pH 1.2) at 37°C , the rotational speed of the paddle was 100 rpm, and the amount of sample was equivalent to 20 mg of the drug. At suitable time intervals, 5 ml samples of the dissolution fluid were withdrawn through a membrane filter (type HA, $0.45\ \mu\text{m}$, Millipore) and replaced with an equal volume of the dissolution fluid. The filtrates were suitably diluted and assayed spectrophotometrically at 252 nm for IMC and 260 nm for GRIS.

Results and Discussion

Figure 1 shows the powder X-ray diffraction patterns for the IMC-silica 380 (1:2) solid dispersion, physical and triturated mixtures and pure IMC crystal. The solid dispersion showed a halo pattern, and an absence of IMC diffraction peaks, indicating the presence of IMC in an amorphous form or as an extremely fine crystallite. Physical or triturated mixtures, on the other hand, showed diffraction peaks corresponding to form I of the IMC crystal. Similar results were obtained for the GRIS-silica 380 (1:2) system, as shown in Fig. 2.

When the IMC-silica 380 (1:2) mixtures were heated at 150°C for 30 min, the physical mixture still showed diffraction peaks of crystalline IMC. In contrast, the triturated mixture lost diffraction peaks, as shown in Fig. 1. At 156°C , the physical mixture required 30 min for conversion to the amorphous state, but the triturated mixture took only 20 min. To clarify the differences in solid-state properties between the physical and triturated mixtures, thermal analysis was performed using DSC.

The melting point (endothermic peak maximum) and heat of fusion (endothermic transition energy) obtained from DSC curves of IMC-silica 380 triturated mixtures decreased as the relative amount of silica 380 in the mixtures increased, as shown in Fig. 3. The lowering of these values was accompanied with broadening of the endothermic peaks corresponding to the melting of IMC. In the triturated mixture, the values fell much further than those of the

Fig. 1. Powder X-Ray Diffraction Patterns of IMC in Various Forms

A, IMC form I; B, IMC-silica 380 (1:2) physical mixture; C, IMC-silica 380 (1:2) triturated mixture; D, IMC-silica 380 (1:2) solid dispersion. a) 150°C , 30 min or 156°C , 20 min; b) 156°C , 30 min.

physical mixture. On the other hand, a slight decrease in melting point and heat of fusion was also observed for the physical mixture containing 20% silica 380, but no further decrease in these values was observed even when the amount of silica 380 was increased.

The lower melting point of the IMC in the triturated

Fig. 2. Powder X-Ray Diffraction Patterns of GRIS in Various Forms

A, crystalline GRIS; B, GRIS-silica 380 (1:2) physical mixture; C, GRIS-silica 380 (1:2) solid dispersion.

Fig. 3. The Peak Maximum and Energy of Endothermic Melting Transition of IMC-Silica 380 Mixtures as a Function of Composition

○, IMC-silica 380 physical mixture; ●, IMC-silica 380 triturated mixture.

Fig. 4. Differential Scanning Thermograms of IMC in Various Forms

A, IMC form I; B, IMC glass; C, IMC-silica 380 (1:2) solid dispersion.

Fig. 5. IR Spectra of Silica 380 and IMC in Various Forms
A, silica 380; B, IMC form I; C, IMC glass; D, IMC-silica 380 (1:2) solid dispersion.

mixture explains why the IMC in this mixture was converted to the amorphous state at a lower temperature than IMC in the physical mixture. The lower heat of fusion explains why IMC in the triturated mixture was converted to the amorphous state faster than IMC in the physical mixture. As the trituration proceeded, the color of the triturated

Fig. 6. IR Spectra of GRIS in Various Forms
A, crystalline GRIS; B, GRIS glass; C, GRIS-silica 380 (1:2) solid dispersion.

A (1000×)

C (750×)

B (1000×)

D (750×)

Fig. 7. Scanning Electron Micrographs of IMC in Various Forms
A, IMC form I; B, IMC-silica 380 (1:2) physical mixture; C, IMC-silica 380 (1:2) triturated mixture; D, IMC-silica 380 (1:2) solid dispersion.

sample changed from white to a slightly yellowish color that was characteristic of pure amorphous IMC glass, indicating that IMC becomes partly amorphous during trituration. It is likely that this crystal modification on trituration is caused by interactions between the IMC molecules and the silanol groups of the silica 380, resulting in the adsorption of some of the drug molecules onto the surface of the silica particles.^{2c)}

Figure 4 shows DSC thermograms of pure crystalline IMC, IMC glass and an IMC-silica 380 (1:2) solid dispersion. Pure crystalline IMC showed an endothermic peak corresponding to the melting transition of form I. Pure IMC glass showed an endothermic peak due to glass transition at 44 °C, then an exothermic peak around 106 °C, and an endothermic peak at 153 °C, which corresponds to the melting point of form II. Borka reported that form II crystallized from the melt at 125–135 °C on a Kofler hot bench.³⁾ Thus, the exothermic peak is due to crystallization of the amorphous form to the metastable form II. Solid dispersion, on the other hand, showed no change in its thermogram.

Silica 380 showed no transition peak over the temperature range examined, so that the thermogram of the solid dispersion should exhibit the thermal characteristics of IMC glass if no interaction occurs. The absence of a thermally detectable transition of a solid dispersion, therefore, in-

dicates that the amorphous state of IMC is stabilized by the interaction associated with hydrogen bonding with surface hydroxyl groups of silica particles. An increase in melt viscosity due to the addition of silica 380 should also contribute to the thermal stability of solid dispersion. Viscosity effect is probably attributable to inhibition of the diffusion process involved in nuclei growth for crystallization.

Figure 5 shows the IR spectra of pure IMC crystal, pure IMC glass and a IMC-silica 380 (1:2) solid dispersion. Some of the peaks of the solid dispersion were different from those of the plain crystal, but the spectrum of the solid dispersion was similar to that observed for amorphous glass in that it had less sharp peaks. Three weak bands superimposed on the broad band at 2500–2800 cm^{-1} , due to the OH stretching vibration, disappeared or were markedly weakened, and two strong bands due to the CO stretching vibration at 1680–1720 cm^{-1} showed a frequency lowering of 3–4 cm^{-1} . The strong bands at 440–490, 1000–1250 and 3450 cm^{-1} of the solid dispersion are attributed to silica 380. The hydrogen bondings between carboxylic acid groups in IMC molecules form a dimer in the crystal packing.⁶⁾ The change of IR spectra thus suggests that the state of hydrogen bonding in a solid dispersion is different from that in crystal. The results for GRIS samples are shown in Fig. 6. The IR spectra of amorphous GRIS

Fig. 8. Scanning Electron Micrographs of GRIS in Various Forms

A, crystalline GRIS; B, GRIS-silica 380 (1:2) physical mixture; C, GRIS-silica 380 (1:2) triturated mixture; D, GRIS-silica 380 (1:2) solid dispersion.

Fig. 9. Dissolution Profiles of IMC in Various Forms in JP XI 1st Fluid (pH 1.2) at 37°C

△, IMC form I; □, IMC-silica 380 (1:2) physical mixture; ■, IMC-silica 380 (1:2) triturated mixture; O, IMC-silica 380 (1:2) solid dispersion.

Fig. 10. Dissolution Profiles of GRIS in Various Forms in JP XI 1st Fluid (pH 1.2) at 37°C

△, crystalline GRIS; □, GRIS-silica 380 (1:2) physical mixture; ■, GRIS-silica 380 (1:2) triturated mixture; O, GRIS-silica 380 (1:2) solid dispersion.

and GRIS-silica 380 (1:2) solid dispersion were similar, but showed less sharp peaks than the pure crystalline GRIS.

Scanning electron microscopy (Fig. 7) of the IMC samples revealed the following: the physical mixture consisted of IMC crystal and aggregated silica particles, indicating that the intact drug crystal was randomly distributed in the inert carrier; the triturated mixture had IMC crystals to which the silica particles adhered homogeneously; and the solid dispersion showed none of the characteristics observed in the IMC crystal, but was in a state of aggregated microfine spherical particles. Similar results were obtained for the GRIS-silica 380 system (Fig. 8).

Figure 9 shows the dissolution behavior of IMC from various samples. A dramatic increase in the dissolution rate was observed for the solid dispersion relative to the pure crystalline IMC, and to the physical and triturated mixtures.

Figure 10 shows the dissolution profiles of GRIS preparations. The dissolution rate increased in the order physical mixture, triturated mixture, and solid dispersion.

In the case of IMC, the physical and triturated mixtures showed only slight improvement in the dissolution rate, while the physical and triturated mixtures of GRIS exhibited considerable improvement.

Several factors probably control the dissolution process

of solid dispersion: surface area, solubility, transformation rate from amorphous to crystalline state, change of surface area caused by crystallization, and wettability. Further study is required to clarify the actual mechanism of rapid dissolution of the solid dispersion.

Fumed silicon dioxide has been reported to increase the dissolution rate of poorly water-soluble drugs when it is used as a carrier for either surface adsorption^{7a-b)} or solid dispersion.^{7c)} The surface adsorption was carried out by solvent disposition of drugs on porous or non-porous silicon dioxide with a large specific surface area. This method has the advantage, from the formulation point of view, of having a high drug-silicon dioxide ratio (10:1),^{7a)} but the disadvantage of using organic solvents. In particular, stable IMC form I is converted to metastable form II during the preparation by this method.^{7b)} A solid dispersion was obtained by simple mixing or by fusion of a drug with porous silicon dioxide, as reported by Kim *et al.*,^{7c)} who reported, however, that the drug showed no interaction with non-porous silicon dioxide.

The present study shows that non-porous silicon dioxide can be used to prepare solid dispersions of poorly water-soluble, glass-forming drugs. Porous silicon dioxide should also be an interesting carrier and may provide further information on the drug-silica solid dispersions. The advantage of a drug-silica solid dispersion is that it not only accomplishes fast release of the drug, but also can be used in formulations of solid dosage forms without grinding because it is a powder form. The merits of the melting method used for preparing the solid dispersion are its simplicity and economy; its demerit is that it is not applicable for drugs that decompose or evaporate during the fusion process, as discussed by Chiou and Riegelman.⁸⁾ Further study is necessary to clarify the effect of aging under various storage conditions on the fast-release characteristics and on the transformation from the amorphous to the crystalline state, since the amorphous state is a thermodynamically unstable form.

References and Notes

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