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Stabilization of amorphous indomethacin by co-grinding in a ternary mixture

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Abstract

Mechanochemical amorphization of indomethacin (IM) was substantially enhanced by grinding with SiO_2, talc and a $Mg(OH)_2$–SiO_2 mixture. The rates of the mechanochemical amorphization were in the order of $Mg(OH)_2$–SiO_2 mixture > talc > SiO_2. Amorphous state stability of IM compounded with the carrier was examined by crystallization behavior under the condition of 30 °C and 11% relative humidity. Superiority of the binary mixture as a carrier was explained in terms of the mechanically induced strong acidic sites of the carrier. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Co-grinding; Indomethacin; Mechanochemical; Crystallization; Acidic site

1. Introduction

Stabilization of an amorphous state is particularly desirable for pharmaceutical products for higher solubility or bioavailability. To avoid any disadvantage of unstable amorphous state of a drug product, compounding with a carrier is often employed, e.g. as a solid dispersion (Chiou and Riegelman, 1971; Mosharraf et al., 1999). The term ‘solid dispersion’ is defined as the dispersion of one or more active ingredients in an inert carrier or matrix in a solid state. This is conventionally attained by melting (Bogdanova et al., 1998; Lloyd et al., 1999), dissolution into a solvent (Okonogi et al., 1997; Van den Mooter et al., 1998) or co-grinding method (Shakhtshneider et al., 1996). We have elucidated (Watanabe et al., 2001) that a ground indomethacin (IM)–SiO_2 mixture brings about a specific chemical interaction and the interaction at the interface immobilizes the IM molecules which leads to suppression of crystallization, and hence increases the stability of the amorphous state IM. The C–O–Si bridging bond, which is the origin of the chemical interaction at the drug/carrier boundary, is formed by the incipient mechanochemical acid–base reaction between IM and SiO_2 mediated by their OH groups at their interface (Watanabe et al., 2002).

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As we also reported previously (Watanabe et al., 1995, 1996) in the $Ca(OH)_2$–SiO_2 system, mechanically induced reactive acidic and basic sites interact with each other, and stronger Brønsted acidic sites are formed at their interface. Therefore, we considered that the combination of alkali earth hydroxide and SiO_2 would provide an effective carrier for improving the amorphous state stability of a drug product. Mechanochemical synthesis of complex oxide from systems containing water has already been reported in some detail (Avvakumov, 1994; Avvakumov et al., 2001). A number of reactions were found to take place more rapidly than those between simple oxides, even against expectation from the thermodynamic data (Avvakumov, 1994; Avvakumov et al., 1994). For a rapid solid state mechanochemical reaction, hydroxyl groups on the solid surface play an important role. On top of that, active sites produced by in-situ mechanical dehydration interact with each other (Watanabe et al., 1995).

In the case of the IM–SiO_2 binary mixture (Watanabe et al., 2001), inhibition of the crystallization of the amorphous IM in the ground mixture was still insufficient. For further stabilization of amorphous IM, the carrier should possess stronger interaction to suppress mobility toward relaxation, i.e. crystallization. For this purpose, we now introduce a third component as a second carrier, since we know a lot of examples of higher acidity in the field of catalytic chemistry (Pillai et al., 1991). We chose magnesium hydroxide for this purpose because of its ability to interact mechanochemically with SiO_2, to form stronger acidic sites. For the reasons given above, we examined in this study the amorphous state stability of IM compounded with a mixture of alkali earth hydroxide and SiO_2 on the basis of the acid–base interaction induced by mechanical stressing.

2. Materials and methods

2.1. Materials

A commercial reagent (Sigma Chemical Co., USA) was used as the source of IM (γ-indomethacin: 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid). As a first carrier, fumed SiO_2 powder (Aerosil 200, Nippon Aerosil Co., Japan) was used. They were the same as those used in our previous study (Watanabe et al., 2001). Magnesium hydroxide (Kyowa Chemical Industry Co., Japan), which was approved for adding to pharmaceutical products as an antacid, was employed as the second carrier for the IM solid dispersion prepared by co-grinding. As a reference for the IM–SiO_2–$Mg(OH)_2$ ternary system, a mixture of talc ($3MgO{\cdot}4SiO_2{\cdot}H_2O$, Kimura Sangyo Co., Japan) and IM was ground with a weight ratio of 1:1.

2.2. Preparation

$Mg(OH)_2$ and SiO_2 were mixed in a mortar with a molar ratio of 3:4 (0.42:0.58; w/w), which was the same cationic composition of talc, to obtain the physical mixture of the carrier (PM1). IM and a carrier, either talc or PM1, were mixed with a weight ratio of 1:1. The physical mixture (2.5 g) was put into a zirconia cylindrical vessel (100 cm^3) with 74 zirconia balls of 10 mm diameter. Grinding of the mixture was carried out using a laboratory sized vibration mill (Hi-speed Vibrating Sample Mill Model TI-100, CMT MFG. Co., Japan). The amplitude, 7 mm, and the frequency, 24 Hz, were kept constant. The resultant mass was passed through a 30 mesh sieve (opening 500 μm). Binary mixtures of IM–$Mg(OH)_2$ (1:0.42; w/w) and IM–SiO_2 (1:0.58; w/w) were also ground under the same grinding conditions.

2.3. Methods of characterization

2.3.1. Acid strength (visual color change method)

The acid strength of the ground solid was determined by the visual color change method (Tanabe, 1970). Neutral red ($pK_a = +6.8$, Tokyo Kasei Kogyo Co., Ltd., Japan), 4-(phenylazo)-1-naphthylamine ($pK_a = +4.0$, Tokyo Kasei Kogyo Co., Ltd., Japan) and 4-(phenylazo)-diphenylamine ($pK_a = +1.5$, Kanto Chemical Co., Inc., Japan) were employed as color indicators. The solvent used was dehydrated benzene (Kanto Chemical Inc., Japan). The acid strength was expressed by the Hammett acidity function, H_0.

2.3.2. Isothermal crystallization

The solid dispersions on X-ray powder diffraction sample holders were stored in a closed vessel containing saturated LiCl solution at 30 °C to keep the relative humidity (RH) constant at 11%. As reported previously, amorphous IM prepared by melt-quenching exhibits the highest rate of crystallization to γ-IM at 11% RH under this storage temperature (Andronis et al., 1997).

2.3.3. X-ray powder diffraction (XRPD)

X-ray diffraction patterns for all the samples were measured by a Geiger Flex Rint-2200 (Rigaku Co., Japan) diffractometer with Cu Kα radiation at 40 kV/40 mA. The samples were step-scanned at 0.02° intervals from 5.00 to 40.00° (2θ) at the rate of 4.00° min^{-1}.

2.3.4. Differential scanning calorimetry (DSC)

Samples of approximately 4 mg were placed in a sealed aluminum pan and scanned at 5 °C min^{-1} in a differential scanning calorimeter (Thermo Plus DSC8230C, Rigaku Co., Japan) under a nitrogen gas flow at 100 $\mathrm{cm}^3\ \mathrm{min}^{-1}$.

2.3.5. Diffuse reflectance infrared Fourier transform spectroscopy (DRIFT)

DRIFT (FTS-175, Bio-Rad Laboratories Inc., USA) was carried out to characterize the OH groups on the particles. The spectra were obtained at 2 cm^{-1} resolution by a signal averaging 128 scans.

3. Results and discussion

3.1. Changes in crystallinity due to co-grinding

As shown in Fig. 1, the XRPD peaks for IM persisted with a decrease in their intensity by co-grinding IM for up to 60 min with $Mg(OH)_2$. On the other hand, as shown in Figs. 2 and 3, the peaks of IM disappeared after co-grinding the binary mixture, i.e. with SiO_2 and talc for 60 and 30 min, respectively. This indicates that rapid amorphization of IM by co-grinding is a consequence of the interaction with SiO_2 or talc. In the case of the ternary mixture, the peaks of IM disappeared after co-grinding for only 10 min, as shown in Fig. 4. The residual peaks in the figure were assigned as $Mg(OH)_2$. It is clear by comparison with IM ground with $Mg(OH)_2$ or SiO_2 that IM ground with $Mg(OH)_2$ and SiO_2 in the ternary mixture amorphizes more rapidly than in any binary mixtures.

As reported previously (Watanabe et al., 2001, 2002), IM and SiO_2 interacted in the course of co-grinding as a consequence of the incipient mechanochemical reaction due to the acid–base reaction between their OH groups at the interface of the dissimilar particles. Judging from the in-

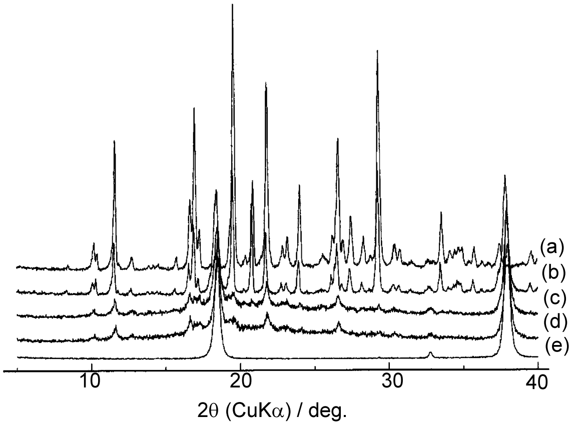


Fig. 1. XRPD profiles of IM and binary mixtures: (a) IM; (b) IM–$Mg(OH)_2$ (1:0.42; w/w) physical mixture; (c) mixture ground for 30 min; (d) 60 min; and (e) $Mg(OH)_2$.

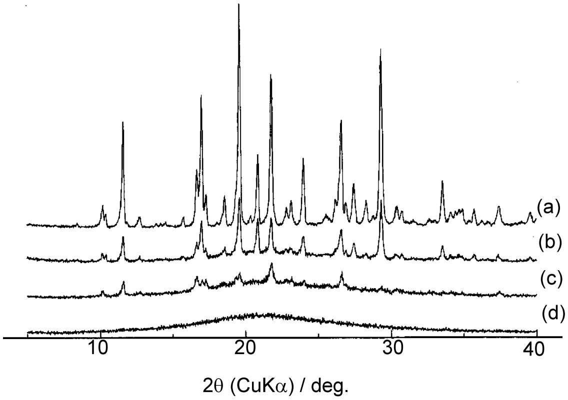


Fig. 2. XRPD profiles of IM and binary mixtures: (a) IM; (b) IM–SiO_2 (1:0.58; w/w) physical mixture; (c) mixture ground for 30 min; and (d) 60 min.

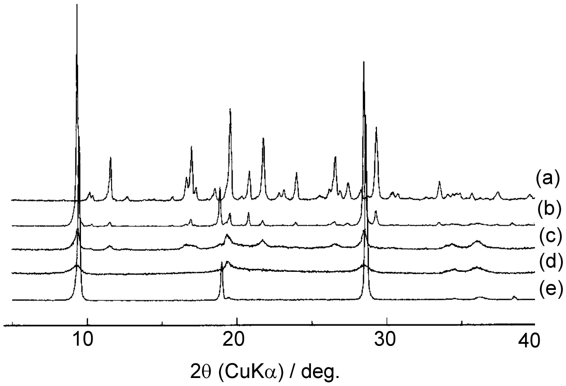


Fig. 3. XRPD profiles of IM and binary mixtures: (a) IM; (b) IM–talc (1:1; w/w) physical mixture; (c) mixture ground for 10min; (d) 30 min; and (e) talc.

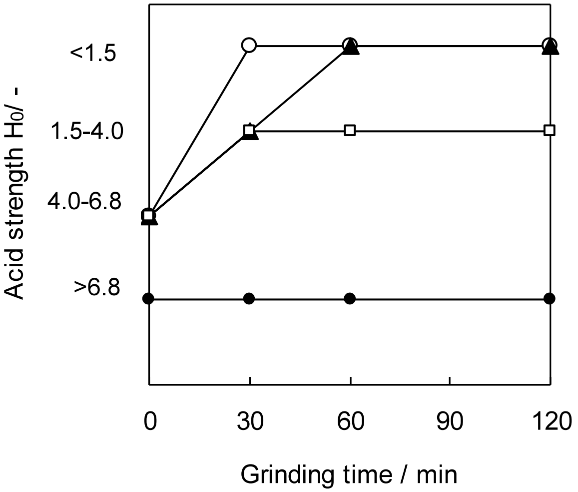


Fig. 5. Changes in the acid strength due to grinding. Symbols: ○, $Mg(OH)_2$–SiO_2 (0.42:0.58; w/w); ▲, talc; □, SiO_2; ●, $Mg(OH)_2$.

crease in the acidity of SiO_2 by mechanical stressing (Watanabe et al., 2002) and from the comparison of the amorphization profiles using SiO_2 or $Mg(OH)_2$ as the carrier in Figs. 1 and 2, it is clear that the carrier acts as an acid in this system. In order to evaluate the difference in the amorphization behavior of IM depending on the carrier, changes in the solid acidity by grinding were examined by the color change of the indicators. As displayed in Fig. 5, the acid strength of carriers increased with grinding time except for $Mg(OH)_2$. The observed order of the acid strength was the same as that of the amorphization rate, i.e. ground $Mg(OH)_2$–SiO_2 mixture > talc > SiO_2 > $Mg(OH)_2$. When a complex oxide prepared by mixing colloidal SiO_2 with $Mg(OH)_2$ was heated up to 290 °C, its acidity was increased by thermal dehydration (Tanabe, 1970). It was reported (Liao and Senna, 1992a,b) that incipient mechanochemical dehydration occurred during mechanical stressing in the $Mg(OH)_2$–SiO_2 binary mixture and talc. We therefore conclude that the mechanical dehydration by grinding leads to the increase in the acidity of the carriers, which in turn increases the acid–base interaction, leading to amorphization of IM.

In order to examine the changes in the OH group on the solid surface with grinding time, DRIFT measurement was conducted. The changes in the DRIFT spectra by ternary co-grinding are shown in Fig. 6. DRIFT preferentially detects the functional groups on the solid surface. In the case of the ground ternary mixture, the band at 3747 cm^{-1} for a free surface silanol group (Fuji et al., 1998; Shimizu et al., 1997) and that at 3377 cm^{-1} for the OH group from the carboxylic group of IM (Taylor and Zografi, 1997) disappeared by dehydration after co-grinding for 3 and 30 min, respectively. The band at 3700 cm^{-1} for the OH group of $Mg(OH)_2$ (Liao and Senna, 1993) apparently remained un-

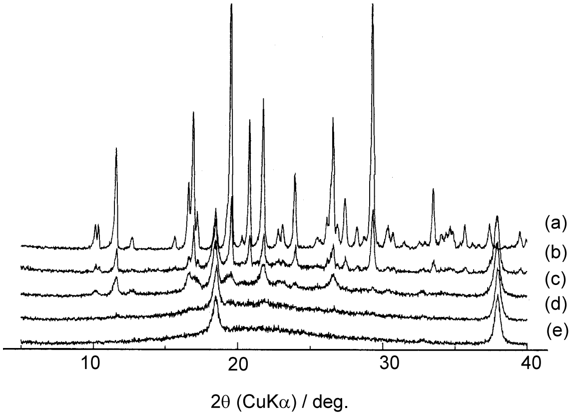


Fig. 4. XRPD profiles of IM and IM–$Mg(OH)_2$–SiO_2 (1:0.42:0.58; w/w/w) mixtures: (a) IM; (b) physical mixture; (c) mixture ground for 3 min; (d) 10 min; and (e) 30 min.

changed, since the OH group of $Mg(OH)_2$ in the bulk was not entirely consumed. The OH groups of SiO_2 and $Mg(OH)_2$ were reported to disappear due to co-grinding (Liao and Senna, 1992a, 1993). We therefore presume that mechanochemical dehydration at the interface between SiO_2 and $Mg(OH)_2$ occurred in this study by the same token. Separate grinding of SiO_2 did not bring about dehydration as we mentioned in our previous report (Watanabe et al., 2002). On the other hand, the band for the OH group from the carboxyl group of IM persisted with a decrease in their intensity on grinding IM–SiO_2, IM–$Mg(OH)_2$ and IM–talc for up to 30 min, as shown in Fig. 7. These indicate that the disappearance of the OH group from the carboxylic group of IM is associated with the acidity of the carrier. Increase in the acidity of the ground $Mg(OH)_2$–SiO_2 mixture enhances the mechanical dehydration at the interface between IM and the carrier, and hence leads to rapid amorphization.

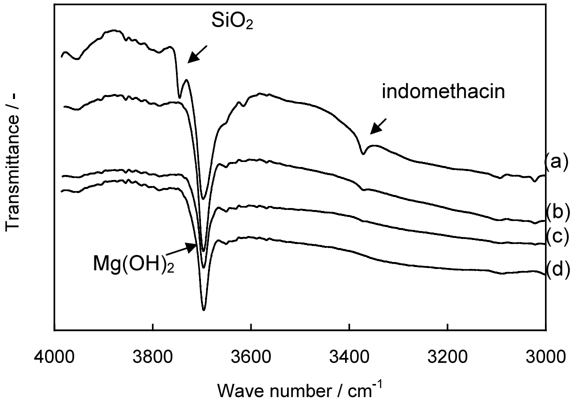


Fig. 6. DRIFT spectra of OH stretching region for IM–$Mg(OH)_2$–SiO_2 (1:0.42:0.58; w/w/w) mixtures: (a) physical mixture; (b) mixture ground for 3 min; (c) 10 min; and (d) 30 min.

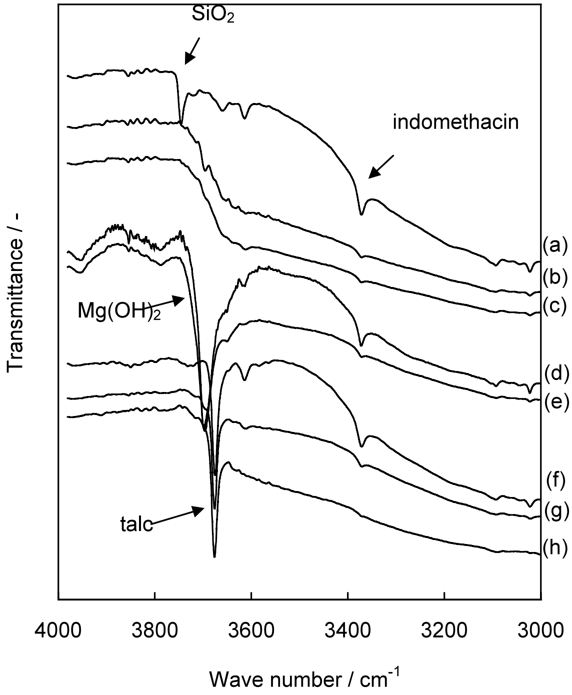


Fig. 7. DRIFT spectra of OH stretching region for binary mixtures: (a) IM–SiO_2 (1:0.58; w/w) physical mixture; (b) mixture ground for 10 min; and (c) 30min; (d) IM–$Mg(OH)_2$ (1:0.42; w/w) physical mixture; (e) mixture ground for 30min; (f) IM–talc (1:1; w/w) physical mixture; (g) mixture ground for 10 min; and (h) 30 min.

3.2. Mechanisms of strong acidic site formation

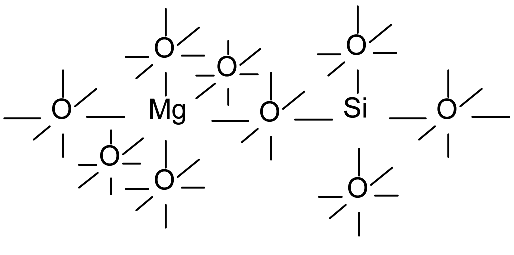
As reported previously (Watanabe et al., 2002), an increase in the acidity of the silanol group on SiO_2 is associated with a decrease in the coordination number for Si and, accordingly, with increased polarization of the OH group. As shown in Fig. 5, the $Mg(OH)_2$–SiO_2 binary carrier exhibited high acidity due to mechanical stressing. Binary metal oxides, such as SiO_2–TiO_2 and SiO_2–ZnO, are well known to exhibit high acidity in comparison with unitary oxides, and have been used as solid acid catalysts (Pillai et al., 1991). High acidity in complex oxides is caused by an excess negative or positive charge. A model structure is shown in Fig. 8 according to Tanabe's hypothesis (Tanabe et al., 1974) given below:

1. The coordination number of the cation of a metal oxide and that of a second metal oxide are maintained even in their mixture.
2. The coordination number of all the oxygen atoms of the major component is retained for all the oxygen atoms in a binary oxide.

Since the major cationic element is Ca in the amorphous precursor of the $Ca(OH)_2$–SiO_2 ground mixture (Watanabe et al., 1997), the major component in mechanically induced

$Mg(OH)_2$–SiO_2 complex is MgO, which is formed by mechanochemical dehydration of $Mg(OH)_2$. The difference in charge for one bond was 4/4 (Si–O) − 2/6 (Mg–O) = + 2/3, and for all the bonds the valence unit of + 2/3 × 4 = + 8/3 was in excess. In this case, the Lewis acidity is assumed to appear upon the presence of the excess positive charge.

Empirical proportionality between the algebraically averaged electronegativity of metal ions and the highest observed acid strengths of several binary oxides was reported (Shibata et al., 1973). The electronegativities of Mg and Si ions were calculated based on our previous report (Watanabe et al., 1998). The calculated average electronegativity between Mg and Si was 11.1 when we employed Pauling's electronegativity values. Based on the relationship between the averaged electronegativity and the empirical proportionality, the highest acid strength was calculated to be $pK_a = -2.0$, which was much higher than that of SiO_2, i.e. $pK_a = +3.3$. As mentioned above, the major cationic element seemed to be Mg in mechanically induced $Mg(OH)_2$–SiO_2 complex. On the other hand, the major cationic element of talc is Si as is mentioned in the experimental section. SiO_2–MgO complex oxide exhibits moderately strong acidic properties at higher concentration of MgO (Tanabe, 1970). The difference in the local composition between the $Mg(OH)_2$–SiO_2 ground mixture and talc explains why the acid–base interaction between IM and carriers induced from the ternary mixture is higher than that from the ground IM–talc mixture.



Charge difference: (4/4 –2/6) × 4 = 8/3

Fig. 8. Model structure of MgO–SiO_2 depicted according to postulates (1) and (2).

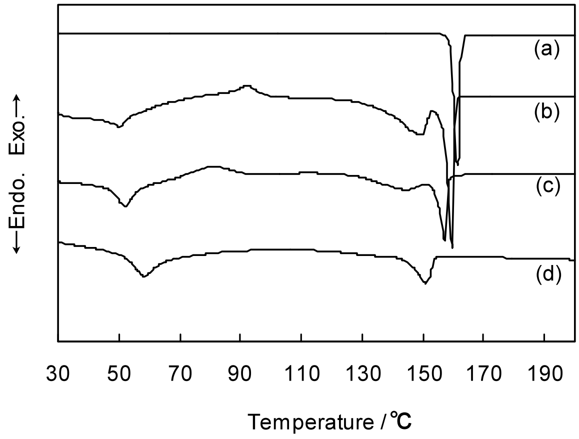


Fig. 9. DSC profiles of IM and mixtures: (a) IM; (b) IM–SiO_2 (1:0.58; w/w) ground for 60 min; (c) IM–talc (1:1; w/w) ground for 30 min; and (d) IM–$Mg(OH)_2$–SiO_2 (1:0.42:0.58; w/w/w) ground for 30 min.

3.3. Isothermal crystallization of amorphous solid dispersions

We reported previously (Watanabe et al., 2001) that high stability of amorphous IM compounded with SiO_2 was attained by prolonged co-grinding. This was explained by the stronger chemical interaction at the interface between IM and SiO_2. In Section 3.2, we discussed the IM-carrier interaction on the basis of the acid–base reaction. Therefore, we considered that the combination of alkali earth hydroxide and SiO_2, which formed stronger acidic sites by mechanical stressing than separately ground SiO_2, would be an effective carrier for improving the amorphous stability of IM. As shown in Fig. 9, when IM was heated, only an endothermic peak due to melting was detected by DSC at around 160 °C. The co-ground mixtures, in contrast, showed additional endothermic and broad exothermic peaks at around 50 °C and 60–120 °C, respectively, which were ascribed to the enthalpic relaxation just after the glass transition and the crystallization (Yoshioka et al., 1995). The glass transition temperature of the ternary ground mixture was higher than that of the binary ground mixtures. The observed order of the glass transition temperature was the same as that of the acid strength mentioned above, i.e.

ground $Mg(OH)_2$–SiO_2 mixture > talc > SiO_2. It is widely known that water absorbed onto an amorphous solid decreases the glass transition temperature, as water serves as a plasticizer to increase the molecular mobility (Andronis et al., 1997). Therefore, the increase in the glass transition temperature by ternary co-grinding in the DSC profiles seems to confirm chemical interaction at the interface between IM and the carrier, to decrease the molecular mobility of IM.

The changes in the XRPD profiles with storage time at 30 °C and 11% RH are shown in Fig. 10 for the IM–SiO_2 mixture ground for 60 min. Rapid crystallization of amorphous IM with SiO_2 during storage suggests the presence of residual micro crystalline IM after grinding, although this is not apparent on the X-ray diffractgrams (Watanabe et al., 2001). The remaining crystallites of IM, which serve as seeds for crystallization, results from the insufficient acidity and the amount of the carrier, SiO_2. As shown in Fig. 11, an apparent decrease in the rate of IM crystallization was observed for the IM–talc mixture ground for 30 min. It is important to note, however, that the mixture shows a slight crystallization of IM during storage. In the ternary mixture ground for 30 min, in contrast, no crystallization was observed during storage for up to 61 days, as shown in Fig. 12. Andronis et al. (1997) reported that crystallization of amorphous IM initiated not in the bulk but on the surface at 30 °C and below 11% RH. Apparent inhibition of crystallization in the ternary mixture suggests that the amorphous portion of IM located close to the surface is stabilized so firmly that crystallization is eventually inhibited under the above condition.

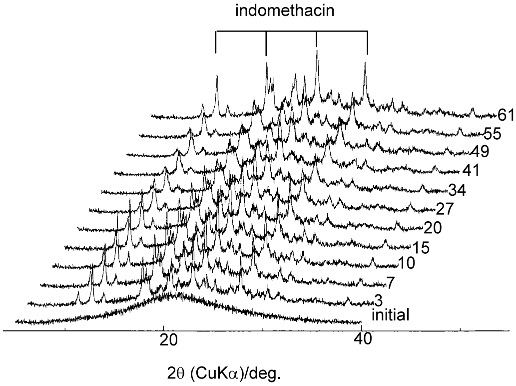


Fig. 10. Isothermal crystallization behavior of IM–SiO_2 (1:0.58; w/w) mixture ground for 60 min, stored at 30 °C and 11% RH.

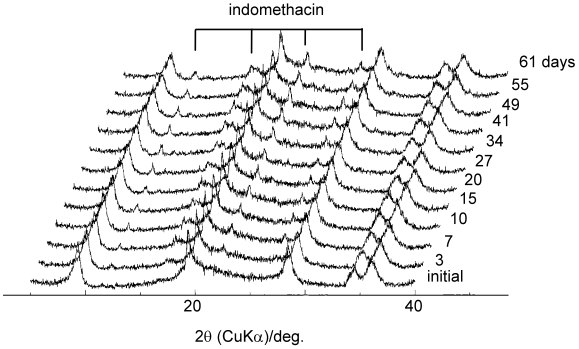


Fig. 11. Isothermal crystallization behavior of IM–talc (1:1; w/w) mixture ground for 30 min, stored at 30 °C and 11% RH.

It is noteworthy that the amorphous state stability of IM prepared by grinding with the binary carrier was higher than that with talc in spite of similar composition. Judging from the rapid increase in the acidity of SiO_2–$Mg(OH)_2$ mixture by mechanical stressing, as shown in Fig. 5, the stronger acidic sites of the carrier were formed by grinding a mixture in the IM–SiO_2–$Mg(OH)_2$ system than in the IM–talc system. The interaction exerted by the acid–base interaction between the IM and strong acidic sites formed in-situ at the SiO_2–$Mg(OH)_2$ interface brought about a de-

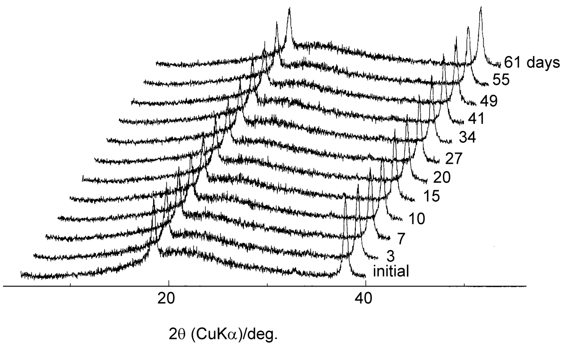


Fig. 12. Isothermal crystallization behavior of IM–$Mg(OH)_2$–SiO_2 (1:0.42:0.58; w/w/w) mixture ground for 30 min mixture, stored at 30 °C and 11% RH.

crease in the IM molecular mobility, and hence led to high stability in the amorphous state. As mentioned in Section 3.1, the interaction exerted by the solid state acid–base reaction brought about the mechanical dehydration from the mixture. Consistent with the previous report on the IM–SiO_2 system (Watanabe et al., 2002), these interactions with mechanical dehydration brought about a charge transfer, as confirmed by X-ray photoelectron spectroscopy, leading to Si–O–C bridging bond formation at the IM/SiO_2 interface. We therefore conclude that the formation of strong acidic sites enhances the mechanical dehydration between IM and the carrier, and promotes the formation of the Me–O–C (Me: Mg or Si) bridging bond, and finally reduces the molecular mobility of IM.

4. Conclusion

The amorphous state stability of IM in solid dispersion was higher for that prepared by co-grinding with a $Mg(OH)_2$–SiO_2 binary carrier than that with SiO_2 alone. DRIFT and acidity measurement showed that co-grinding the IM–$Mg(OH)_2$–SiO_2 ternary mixture brought about a chemical interaction of carboxyl groups on IM with strong acidic sites formed as a consequence of the mechanochemical reaction between $Mg(OH)_2$ and SiO_2. It was clear by comparison with talc as a carrier that the strong acidity induced by incipient mechanochemical reaction between $Mg(OH)_2$ and SiO_2 immobilized the IM molecules to suppress the crystallization, and hence to increase the amorphous state stability of IM.

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