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Stability of amorphous indomethacin compounded with silica

Tomoyuki Watanabe [a,*], Naoki Wakiyama [a], Fusao Usui [a], Masaru Ikeda [a], Tetsuhiko Isobe [b], Mamoru Senna [b]

[a] *Product Development Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[b] *Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Yokohama 223-8522, Japan*

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Abstract

The stability of indomethacin (IM) compounded with SiO_2 either by co-grinding or by melt-quenching was examined by recrystallization kinetics under the conditions 30 °C and 11% relative humidity. A decrease of the recrystallization rate with and without an appreciable induction period was observed in both compounds. Higher stability of amorphous IM compounded with SiO_2 was attained by prolonged co-grinding than by melt-quenching. This was explained by the stronger chemical interaction at the interface between IM and SiO_2 by co-grinding, as revealed by ^{29}Si and ^{13}C solid state NMR. Incomplete co-grinding with the rest of the crystalline state, however, made the amorphous state appreciably unstable, since the remaining crystallites serve as seeds for recrystallization.

Keywords: Crystallization; Solid-state NMR; Indomethacin; Co-ground mixture; Interaction

1. Introduction

An increase in the rate of dissolution is desired in many industrial fields like hydrometallurgy or pharmaceuticals where people are almost always dealing with sparingly soluble solids. Rates of dissolution are increased conventionally by changing physical states by size reduction, phase transformation or amorphization. Changes in the chemical states by compounding with foreign substances could also accelerate the dissolution process. A typical example of the latter is compounding of a drug with a carrier like silica. When these physical and chemical changes are achieved simultaneously, e.g. by compounding and amorphization, a synergism of both effects is expected. In view of the instability of the amorphous state, compounding with a carrier may stabilize the amorphous state. Stabilization of an amorphous state is particularly desirable for pharmaceutical products. For practical purposes, it is particularly important to optimize a subtle balance between amorphization and stabilization. To observe this kind of balance as a consequence of

* Corresponding author. Tel.: +81-03-3492-3131; fax: +81-03-5436-8568.
E-mail address: watatm@shina.sankyo.co.jp (T. Watanabe).

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compounding, we need well focused analytical tools.

Solid state NMR spectroscopy is a versatile tool for characterizing novel solid forms of medicinal compounds (Middleton et al., 1997). Solid state cross-polarization magic-angle-spinning (CP/MAS) NMR for ^{13}C has been used to evaluate drug polymorphs (Kimura et al., 1999; Stephenson et al., 1997; Matsunaga et al., 1999; Gao, 1998), drug–buffer interaction of commercial tablets (Chang et al., 1986), interaction between drug and polymer microspheres (Vachon and Nairn, 1998), and properties of crystalline drugs in a drug–polyethylene glycol solid dispersion (Markovich et al., 1997). The same technique for ^{29}Si distinguishes the coordination number of Si atoms with different chemical shifts. ^{29}Si CP/MAS NMR is used to detect resonance from silicate species near the hydroxyl groups on the following basis. Magnetization is generated by excitation of ^{1}H nuclei, and then transfer to the observation nuclei, so that the nuclei species located in the vicinity of protons on a nanometer scale are preferentially observed by CP/MAS spectroscopy (Brei, 1994; Leonardelli et al., 1992). Since the proton locates on the surface of an SiO_2 particle, the ^{29}Si CP/MAS NMR spectrum gives information on ^{29}Si nuclei near the surface of SiO_2. However, the ^{13}C CP/MAS NMR spectrum detects ^{13}C nuclei not near the surface but in the bulk of organic materials because of the presence of ^{1}H nuclei in the bulk.

We previously reported an NMR study on an inorganic binary system (Watanabe et al., 1997), where we examined the mechanochemical reaction between $Ca(OH)_2$ and SiO_2 by co-grinding, and revealed the formation of an amorphous precursor with a short-range order of hydrated calcium silicates near the surface of SiO_2 particles. We, therefore, think these analyses suitable to elucidate the changes in the microstructure and interatomic interactions in a drug–carrier solid dispersed system as well. When an amorphous drug is compounded with silica, as a carrier, to form an amorphous solid dispersion, the atomic-scale local structure of the drug and carrier may be examined in detail by combining ^{13}C and ^{29}Si CP/MAS NMR methods.

Indomethacin (IM, γ-indomethacin; 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid), being sparingly soluble in aqueous media, is one of the most widely used non-steroidal anti-inflammatory drugs. Solid dispersion or complexes between IM and carriers have been studied extensively, e.g. compounds formed between IM and β-cyclodextrin by a co-precipitation method (Casella et al., 1998a,b) or by a mechanochemical treatment (Nozawa et al., 1997); investigations of the interaction between IM and nicotinamide (Bogdanova et al., 1998), or an IM, citric acid and polyvinylpyrrolidone (PVP) ternary system prepared by a solvent evaporation technique (Lu and Zografi, 1998). Although some compounding methods are effective, changes in the dissolution characteristics and amorphous state stability have rarely been studied from physicochemical viewpoints.

The purpose of the present study is to examine the stability of amorphous IM compounded with SiO_2 on the basis of the chemical interaction exerted in a solid state by means of detailed analyses on an atomic scale.

2. Materials and methods

2.1. Materials

Reagents. A commercial reagent (Sigma Chemical Co.) was used as the source of γ-indomethacin. The raw crystalline drug was passed through a 100 mesh (150 μm) sieve. As SiO_2 source, fumed silica nanoparticles (Aerosil 200, Nippon Aerosil Co.) was used. Specific surface areas of the sieved IM and SiO_2 were 0.84 $m^2\ g^{-1}$ and 191 $m^2\ \mu g^{-1}$, respectively, as determined by a BET method with N_2 gas adsorption (Quantasorb, Quantachrome Co.).

2.2. Preparation

2.2.1. Grinding

IM and SiO_2 were mixed in a mortar with a weight ratio of 1:1 to obtain a physical mixture. 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.). 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). Separately ground samples of IM and SiO_2 were prepared under the same grinding condition.

2.2.2. Melt-quenching

Melt-quenching was carried out by modifying the technique reported by Andronis et al. (1997). The same physical mixture used for co-grinding was heated up to 165 °C, which is slightly above the melting point of γ-IM (162 °C), and kept for 5 min. The heated mixture was dropped into a cool trap (Neo Cool Trap, Yamato Co.) at − 101 °C. The quenched solid mass was lightly pulverized in a mortar and passed though the same 30 mesh sieve used above. Melt-quenched IM without SiO_2 was prepared separately in the same manner.

Co-grinding and melt-quenching methods did not change the chemical purity of IM in a solid dispersion, as confirmed by high performance liquid chromatography (HPLC) by a method prescribed in The Japanese Pharmacopoeia (1996).

2.3. Methods of characterization

2.3.1. Isothermal crystallization

The amorphous solid dispersions and IM 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%. Under this RH, amorphous IM prepared by melt-quenching exhibits the highest rate of crystallization to γ-IM at 30 °C, well below its glass transition temperature (Andronis et al., 1997).

2.3.2. X-ray powder diffraction (XRPD)

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

2.3.3. Differential scanning calorimetry (DSC)

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

2.3.4. Solid state nuclear-magnetic-resonance

Cross polarization magic-angle-spinning (CP/MAS) NMR spectra were obtained using a 300 MHz spectrometer (CMX-300, Chemagnetics Inc.). For ^{13}C, the following conditions were adopted: frequency of 75.6 MHz, 90° proton pulse 5 μs, contact time 1.5 ms, pulse delay 5 s, spinning rate 3.5 kHz, spectral width 25 kHz, and acquisition time 40 ms. The chemical shifts were calibrated indirectly to the higher field adamantane peak (29.5 ppm relative to tetramethylsilane, TMS). For ^{29}Si, the observation frequency was 59.6 MHz, pulse delay 7 s and the contact time 5 ms. Polydimethylsilane was used as the secondary standard with a chemical shift of − 34.0 ppm from TMS. The assignment of NMR peaks is shown as Q_N in each figure, where the subscript N denotes the coordination number of Si atoms.

3. Results and discussion

3.1. Changes in the crystallinity due to co-grinding and melt-quenching

As shown in Fig. 1, the XRPD peaks for γ-IM disappeared after co-grinding for 30 min (curve (f)). Melt-quenched IM samples with and without SiO_2 mixture were also amorphous (curves (i) and (j)). On grinding IM for up to 180 min without the presence of SiO_2, diffraction peaks of γ-IM persisted with a mere decrease in their intensity (curve (b)). This indicates that rapid amorphization of IM by co-grinding is associated with the interaction with SiO_2.

When a physical mixture was heated, only an endothermic peak due to IM melting was detected by DSC at around 160 °C. Typical DSC profiles are shown in Fig. 2. The co-ground or melt-quenched mixtures, in contrast, showed additional endothermic and exothermic peaks at around 50

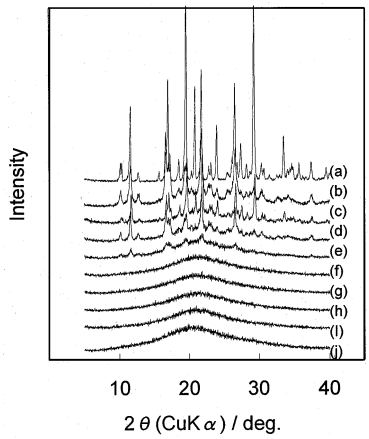

Fig. 1. profiles of physically mixed, co-ground and melt-quenched indomethacin–SiO_2 (1:1); (a) indomethacin, (b) indomethacin ground for 180 min, (c) physical mixture, (d) co-ground for 3 min, (e) 10 min, (f) 30 min, (g) 60 min, (h) 180 min, (i) melt-quenched mixture and (j) melt-quenched indomethacin.

and 60–120 °C, which were ascribed to the enthalpic relaxation just after the glass transition and crystallization, respectively (Yoshioka et al., 1995). The crystallization peak of the co-ground mixtures shifted toward higher temperature and the shift increased with grinding time. The crystallization temperature of the mixture ground for

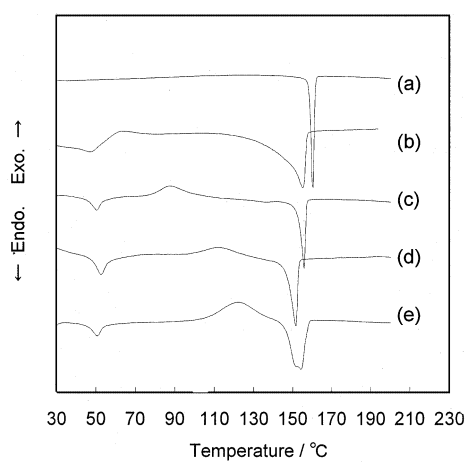

Fig. 2. DSC profiles of physically mixed, co-ground and melt-quenched indomethacin–SiO_2 (1:1); (a) physical mixture, (b) co-ground for 10 min, (b) co-ground for 60 min, (b) co-ground for 180 min and (c) melt-quenched mixture.

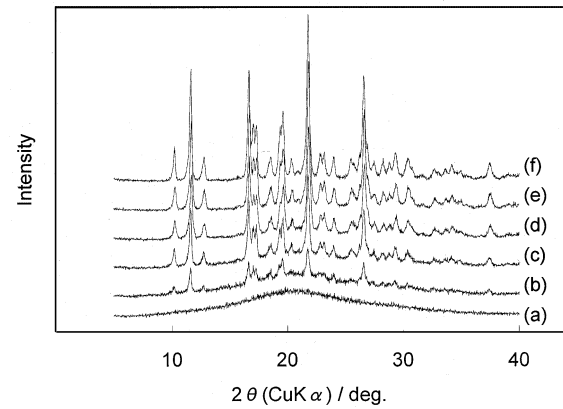

Fig. 3. XRPD profiles of separately melt-quenched indomethacin, stored at 30 °C, 11% RH; (a) initial, (b) 5, (c) 10, (d) 20, (e) 35 and (f) 63 days.

180 min was closer to that of the melt-quenched mixture than that of the mixture ground for 10 or 60 min. Since grinding or melt-quenching develops many lattice defects, the melting point of the ground or melt-quenched mixtures is lower than that of the physical mixture (Otsuka et al., 1986).

3.2. Isothermal recrystallization of amorphous solid dispersions and amorphous indomethacin

The changes in the XRPD profiles with storage time at 30 °C and 11% RH are shown in Fig. 3 for separately melt-quenched IM. The amorphous IM without a carrier crystallized rapidly during storage. 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) reported that crystallization of amorphous IM was restricted to the surface region when RH was less than 11% at 30 °C. Therefore, suppression of molecular mobility on the surface is essential for inhibition or retardation of recrystallization under this condition. Here, inhibition implies the existence of the fraction of IM which does not recrystallize itself at all. Retardation, in contrast, expresses the decrease of the rate of recrystallization, including the appearance of an induction period.

We evaluated recrystallization behaviors by a modified Herman's method (Usui et al., 1998). The results are shown in Fig. 4. In this method, the crystallinity was determined by comparing the ratio of the peak area of the composites with that of the physical mixture or raw IM. We estimated the crystallinity three times, and the data were well reproducible with relative standard deviation not more than 4%. The polymorph in the crystallized phase was γ-IM (Zannetti et al., 1986), irrespective of the sample. An apparent decrease in the rate of crystallization for the mixture ground for 180 min or melt-quenched suggests that a part of the amorphous portion of IM is stabilized so firmly that it is eventually inhibited to recrystallize under the present conditions. A decrease in the initial rate of recrystallization, on the other hand, suggests a different kind of drug crystallization kinetics. It is important to note that co-grinding for 30 min brings about a slight inhibition but the initial rate of recrystallization is much higher than that of the others. In contrast, melt-quenching or prolonged grinding of a mixture brought about retardation with a substantial induction period for crystallization and inhibition at the same time. The extent of inhibition became much larger by prolonged co-grinding than by melt-quenching.

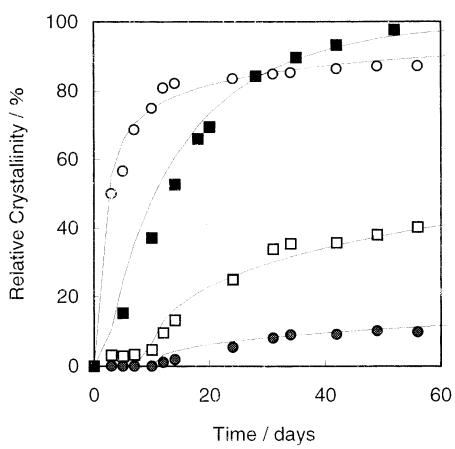

Fig. 4. The behaviors of crystallization under 30°, 11% RH; (■) separately melt-quenched indomethacin, (□) melt-quenched mixture, (○) co-ground mixture for 30 min and (●) co-ground mixture for 180 min.

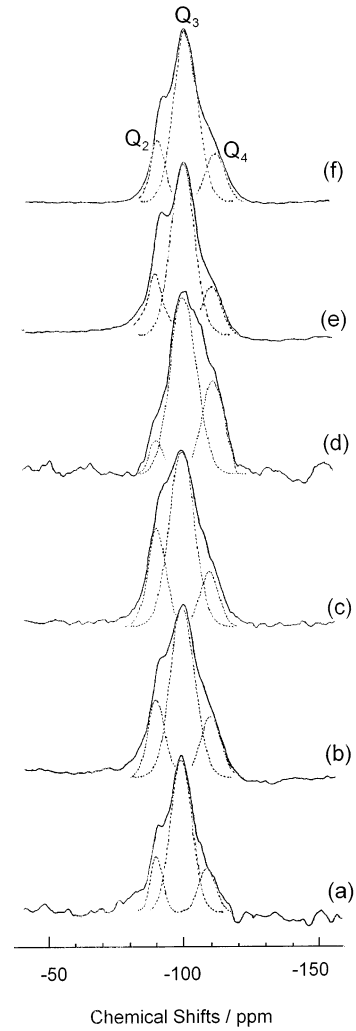

Fig. 5. ^{29}Si CP/MAS NMR spectra of physically mixed, co-ground and melt-quenched indomethacin–SiO_2 (1:1); (a) physical mixture, (b) co-ground for 30 min, (c) co-ground for 180 min, (d) melt-quenched mixture, (e) SiO_2 ground for 30 min and (f) SiO_2 ground for 180 min.

3.3. Changes in the Si coordination states in solid dispersion

In Section 3.2, we demonstrated a difference in the stability of amorphous IM, in spite of no appreciable difference in the X-ray diffractograms. Changes in the Si coordination states are visualized in Fig. 5 by the chemical shift of the ^{29}Si CP/MAS NMR spectrum. A ^{29}Si CP/MAS

NMR spectrum provides information preferentially for Si atoms near the silanolic proton on the surface. A Q_3 peak at -100 ppm for surface silanol groups of SiO_2 was predominant in the physical mixture, while a Q_2 peak at -90 ppm, assigned as Si atoms in silanediol groups (geminal type hydroxyl silanol groups) (Brei 1994; Leonardelli et al., 1992), appeared as a small peak. A Q_4 peak (Brei 1994; Leonardelli et al., 1992) at -110 ppm, from a Si atom linked to four other SiO_4 tetrahedra, was hardly detected. The observation described above implies that most of the near-surface silicon atoms are linked to Si–OH groups in the physical mixture of IM and SiO_2. By grinding the mixture, the Q_2 peak intensity increased from that of the physical mixture.

In order to visualize the changes in the SiO_2 coordination state with grinding time, the resonance peaks of the ^{29}Si CP/MAS NMR, shown in Fig. 5, were subjected to deconvolution by assuming the chemical shifts (Q_2 -90, Q_3 -100 and Q_4 -110 ppm, respectively) and Gaussian distribution to obtain the fraction of each Q_N group. These chemical shifts fitted well to the deconvolution and literature results (Brei 1994; Leonardelli et al., 1992). As shown in Fig. 5, the Q_2 state increased and the Q_3 state decreased with grinding time of the mixture, while the coordinated states of silicon remained unchanged in the separately ground SiO_2. Therefore, the changes in the intensity of the Q_2 and Q_3 peaks in the ground mixtures, shown in Fig. 5, must be a characteristic consequence of co-grinding. There were remarkable differences in the Q_N states between the co-ground and melt-quenched mixtures as shown in Fig. 5. By deconvolution, we obtained Q_2 9%, Q_3 74% and Q_4 17% in the melt-quenched mixtures, while we obtained Q_2 26%, Q_3 62% and Q_4 12% in the mixture co-ground for 180 min.

Taylor and Zografi (1997) reported that hydrogen bonds were formed between PVP amide carbonyl and IM carboxylic acid hydroxyl in the amorphous solid dispersion prepared by co-precipitation. These hydrogen bonds inhibit crystallization from the amorphous state. The difference in the crystallization behavior of melt-quenched IM with and without SiO_2 indicates the existence of molecular interaction at the interface IM–SiO_2. In contrast to the results of the physical mixture in the ^{29}Si CP/MAS NMR spectrum, as shown in Fig. 5, the fraction of Q_2 state was much smaller and that of the Q_4 state was larger in the melt-quenched mixture. Judging from the decrease in the Q_2 state and the increase in the Q_4 state on melt-quenching, chemical interaction at the IM–SiO_2 interface between geminal hydroxyl groups of SiO_2 and the polar region of IM, such as carboxyl groups, leading to dehydration is most probably dominant in the melt-quenching method. The interaction exerted by such dehydration at the interface brings about the decrease in IM molecular mobility, and hence leads to higher stability in the amorphous state than in separately melt-quenched IM.

The difference in the changes in the fraction of Q_N by co-grinding and separate grinding of SiO_2 indicates mechanochemical reaction between SiO_2 and IM by co-grinding. The increase in the Q_2 state does not imply an increase in the geminal type surface silanol. An increase in the fraction of the Si atoms with low coordination number, and a decrease in the silanol groups on SiO_2 by co-grinding, have been found by ^{29}Si-MAS and CP/MAS NMR in the $Ca(OH)_2$–SiO_2 system (Watanabe et al., 1997). The results indicate that Ca^{2+} and O^{2-} ions from the hydroxide migrate into the near-surface region of the SiO_2 by co-grinding. By the same token, the increase in Q_2 and the simultaneous decrease in Q_3 shown in Fig. 5 indicate that IM reacts preferentially with the silanol groups on the SiO_2 surface. Since separate grinding of SiO_2 did not change the Q_2 state, the decrease in the Si coordination number is attributed to the chemical interaction of IM with siloxane bonds to increase Q_2. Siloxane bonds are broken by mechanical stressing, forming dangling bonds, like E′ or NBOHC (Fukuchi, 1993). We assume from the increase in the Q_2 state by co-grinding for 180 min that an oxygen atom from either methoxy or carbonyl groups of the IM molecule compensate the oxygen vacancies formed by the breakage of siloxane bonds. The mechanical compounding restricts the molecular mobility of IM more strongly than that of silanol-carboxyl groups observed in the melt-quenched mixture. The more severe reduction of IM molec-

ular mobility by co-grinding explains why the fractional inhibition of recrystallization from amorphous IM prepared by co-grinding is higher compared with melt-quenching. IM molecules reacted with SiO_2 at the IM–SiO_2 interface are eventually immobilized as a result of strong chemical interaction mentioned above, so that they inhibit or retard the recrystallization in the surface region of IM, as mentioned in Section 3.2.

3.4. Comparison of samples with varying co-grinding time

The initial crystallization rate (Fig. 4) of the mixtures ground for 30 min was much higher than that of mixtures groound for 180 min. In order to discuss the difference in the recrystallization rate, changes in the IM chemical state by grinding were further examined by ^{13}C solid state NMR. The changes in the ^{13}C CP/MAS NMR spectra due to co-grinding and melt-quenching are shown in Fig. 6. The differences in the chemical shifts (peak position) of the NMR peaks between crystalline (physical mixture) and amorphous states were not significant, although the peaks of the latter were much broader. Peak broadening by amorphization is simply attributed to the broader distribution of the molecular orientation (Markovich et al., 1997). The NMR spectrum of the mixture co-ground for 180 min was similar to that of the melt-quenched IM or mixture. On the other hand, the peak shape clearly differed between the mixtures co-ground for 30 min and for 180 min. Solid-state NMR is known to be a sensitive tool to assess crystalline and amorphous materials (Gustafsson et al., 1998). The presence of sharp peaks in the spectra of the sample co-ground for 30 min as well as that of the physical mixture suggests the presence of residual microcrystalline IM after grinding for a short period, although they are not apparent on the X-ray diffractograms shown in Fig. 1. Existence of microcrystalline IM is also supported by the crystallization behavior in Fig. 4. In a recrystallization of amorphous molecular crystals, the activation energy for nucleation is much higher than that for growth, e.g. in amorphous lactose prepared by spray drying (Schmitt et al., 1999). The remaining microcrystallites dispersed in an amorphous matrix could serve as seeds for recrystallization from the amorphous portion to expedite crystallization. As a matter of fact, Yoshioka et al. (1994) reported that the rate of crystallization from an amorphous state IM increased with residual seed crystals formed by the slow cooling of the molten IM. The remaining microcrystallites, however, do not explain the partial inhibition of recrystallization shown in Fig. 4; the relative crystallinity of a mixture ground for 30 min does not exceed 90%. The inhibition can only be explained rationally by irreversible immobilization by a strong chemical interaction at the interface between IM and SiO_2. The recrystallization inhibition in isothermal or the increase in the recrystallization temperature with the grinding time in the DSC profiles, as mentioned in Section 3.1, seems to result from both the disappearance of the microcrystallites and the chemical interaction. Disappearance of the microcrystallites by a prolonged co-grinding was clearly demonstrated by ^{13}C CP/MAS NMR.

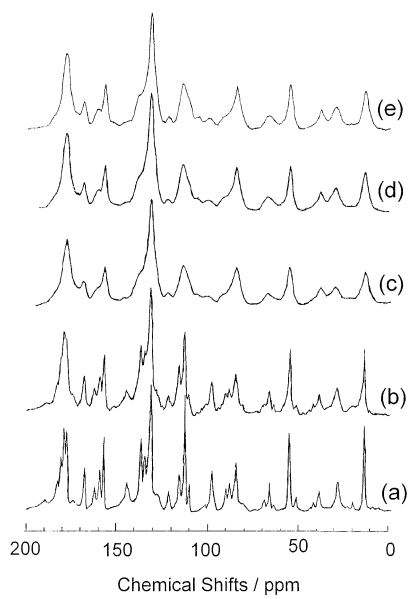

Fig. 6. ^{13}C CP/MAS NMR spectra of melt-quenched indomethacin, physically mixed, co-ground and melt-quenched indomethacin–SiO_2 (1:1); (a) physical mixture, (b) co-ground for 30 min, (c) co-ground for 180 min (d) melt-quenched mixture, and (e) melt-quenched indomethacin.

Table 1
Changes in the T_g value and percentage SiO_2

	Melt-quenched IM	Melt-quenched mixture	Co-ground for 30 min	Co-ground for 60 min	Co-ground for 180 min
T_g (°C)	43.2	43.2	46.7	47.5	48.6
Percentage SiO_2		0.0	2.5	3.0	3.7

However, the difference in the chemical interaction between a mixture ground for 180 min and a melt-quenched mixture could not be explained from comparison of the ^{13}C CP/MAS NMR spectra. The similarity in the ^{13}C CP/MAS NMR spectra between a mixture ground for 180 min and a melt-quenched mixture, in contrast with ^{29}Si CP/MAS NMR as mentioned Section 3.3, is presumably attributed to the contribution of carbon atoms not only on the surface but also in the bulk of IM. Therefore we further examined the changes in the chemical states of the drug and the carrier at their interface.

3.5. Evaluation of the mechanochemical interaction

Co-grinding or melt-quenching were carried out with the weight ratio IM:SiO_2 = 1:1. As mentioned above, the interaction is most probably dominated at the interface between SiO_2 and IM particles. Moreover, the specific surface area of SiO_2 is much higher than that of IM. This indicates that not all SiO_2 molecules interact with IM. Therefore, the Gordon–Taylor equation (Gordon and Taylor, 1952) was employed to estimate the ratio of SiO_2 molecules interacted with IM in the ground mixture from the glass transition temperature, T_g, as

$$T_{gmix} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2} \quad (1)$$

where T_{g1}, T_{g2} and T_{gmix} are the glass transition temperatures, in Kelvin, of components 1, 2 and the mixture, and w_1 and w_2 are the weight fractions of each component. The constant K can be approximated as

$$K \approx \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \quad (2)$$

where ρ_1 and ρ_2 are the densities of each component. The densities used in this study were taken from previous reports (Yoshioka et al., 1995; Aerosil, 1992). The T_g values of the amorphous IM and SiO_2 are 323 K (Yoshioka et al., 1995) and 1473 K (Brückner, 1970), respectively. The observed T_g values from DSC profiles are summarized in Table 1. The T_g value of the melt-quenched mixture was identical with that of the separately melt-quenched IM, indicating the amorphous IM to be immiscible with SiO_2 by melt-quenching. An increase in the T_g value by co-grinding, on the other hand, demonstrates a significant drug–carrier interaction. The percentage SiO_2 reacted with amorphous IM was predicted by fitting the T_g values. As shown in Table 1, the percentage SiO_2 was not more than 4% after co-grinding for 180 min.

^{13}C CP/MAS NMR gives information for ^{13}C nuclei not near the surface but in the bulk, as mentioned above. We consider that the reduction of the percentage IM in a mixture, leading to the increase in the relative surface area to the bulk in the amorphization process, enhances the information from the carbon of IM at the IM–SiO_2 interface. Therefore, co-grinding and melt-quenching of the mixture in the ratio IM:SiO_2 = 4:96, which was the inverse ratio of above result, were carried out by the same preparations described in Section 2. Changes in the carbon chemical states in the solid dispersion (IM:SiO_2 = 4:96) are visualized by the chemical shift of the ^{13}C CP/MAS NMR spectrum shown in Fig. 7. Each peak for the physical mixture in Fig. 7 corresponded well with that of the IM:SiO_2 = 1:1 physical mixture in Fig. 6. As shown in Fig. 7, the peaks of carbon bound to methoxy groups and carbonyl groups, which are interpreted on the basis of previous reports of liquid phase ^{13}C

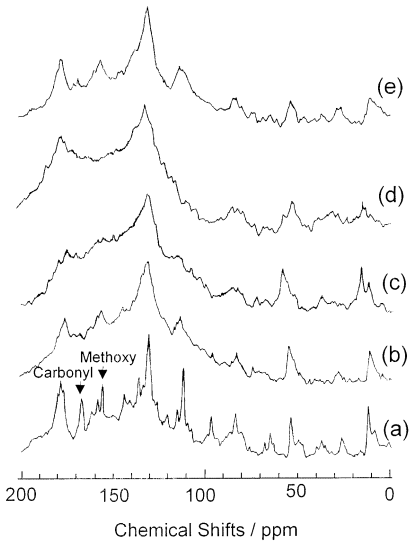

Fig. 7. ^{13}C CP/MAS NMR spectra of physically mixed, co-ground and melt-quenched indomethacin–SiO_2 (4:96); (a) physical mixture, (b) co-ground for 10 min, (c) co-ground for 30 min, (d) co-ground for 180 min and (e) melt-quenched mixture.

NMR (Rusu et al., 1998; Lin, 1992), were decreased or disappeared on co-grinding. In contrast, such a decrease of peak intensity was not detected in the melt-quenched mixture. According to the ^{29}Si solid state NMR (Section 3.3), co-grinding for 180 min brought about a chemical interaction of IM molecules with siloxane bonds of the SiO_2 particles, which was not observed in the melt-quenched mixture. From the foregoing, it is clear that the interaction of siloxane bonds at SiO_2 particles with the oxygen of methoxy or carbonyl groups in IM molecules is specific to co-grinding.

On the other hand, the ^{13}C NMR spectrum of the melt-quenched mixture is similar to that of separately melt-quenched IM, indicating that the thermal treatment dose not achieve the kind of strong chemical interaction observed in co-ground mixtures between IM and SiO_2. Obviously, the mechanically induced interaction restricts the molecular mobility of IM more strongly than that induced by thermal treatment. The presence of the former interaction by co-grinding explains why the fractional inhibition of recrystallization from amorphous IM is higher than that of amorphous IM prepared by melt-quenching.

3.6. Interpretation of the differences in the recrystallization behavior

The solid line in Fig. 4 denotes the fit of the data to the Kolmogorov–Johnson–Mehl–Avrami (KJMA) equation (Price, 1990), which is widely known in recrystallization studies;

$$f = 1 - \exp[-\beta(t-\tau)^n] \quad (3)$$

where f is the fraction recrystallized, $\beta^{1/n}$ is the apparent nuclei-growth rate constant (Andronis et al., 1997), τ is the induction period, and n is the constant derived from the time-dependent exponents for growth and nucleation. From the linearized form of Eq. (3),

$$\ln[-\ln(1-f)] = \ln\beta + n\ln(t-\tau) \quad (4)$$

n, τ and $\beta^{1/n}$ were determined and are summarized in Table 2. The constant, n, being one of the most important parameters associated with the mechanisms of recrystallization, can be separated into two components (Price, 1990).

$$n = a + b(1+q),\ 0 > q > -1 \quad (5)$$

The parameter a is the nucleation rate component that varies from $a = 0$ for instantaneous nu-

Table 2
Changes in the parameters of the KJMA equation

	Melt-quenched IM	Melt-quenched mixture	Co-ground for 30 min	Co-ground for 180 min
n (–)	1.12	0.60	0.27	0.62
$\beta^{1/n} \times 10^{-3}$ (day^{-1})	64.4	7.7	316.0	0.7
τ (day)	2	10	1	11

cleation to $a = 1$ for a constant nucleation rate, while b defines the dimensionality of growth, and q is the growth exponent including contributions from various types of power-law controlled reactions.

The lowest n value of the mixture obtained by co-grinding for 30 min can be explained by the existence of nucleation seeds leading to instantaneous nucleation. The n values of the mixtures ground for 180 min and melt quenched are similar. This suggests the similarity of their recrystallization mechanisms. A lower rate of recrystallization of the co-ground mixture than that of melt-quenching reflects the higher restriction of the molecular mobility by co-grinding. The difference in the induction period of each recrystallization behavior can be explained, if partly, by the sorption of water, since water serves as a plasticizer to increase the molecular mobility. The sorbed water is concentrated primarily at the polar region, such as carboxyl groups on IM or silanol groups on SiO_2. These polar functional groups at the interface between IM and SiO_2 are consumed by melt-quenching or co-grinding, reducing the extent of H_2O sorption. Interactions between IM and SiO_2 generated by co-grinding or melt-quenching decrease the molecular mobility of IM not only directly, but also indirectly by blocking the sorption of water.

4. Conclusion

The stability of amorphous indomethacin in solid dispersion with SiO_2 is higher for those mixtures prepared by prolonged co-grinding than for those prepared by melt-quenching. ^{29}Si and ^{13}C CP/MAS NMR show that co-grinding the IM–SiO_2 mixture brings about a chemical interaction of indomethacin molecules with surface silanol groups and mechanically damaged siloxane bonds of SiO_2 particles. The latter interaction is not observed in the melt-quenched mixture. It is clear by comparison with separately melt-quenched IM that the interactions at the interface immobilize the indomethacin molecules to suppress recrystallization, and hence to increase the stability of the amorphous indomethacin. Incomplete co-grinding with the rest of the crystalline state, however, made the amorphous state appreciably unstable, since the remaining crystallites serve as seeds for recrystallization.

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