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Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method

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Abstract

The solid dispersion particles of indomethacin (IMC) were prepared with different types of silica, non-porous (Aerosil 200) or porous silica (Sylysia 350) by using spray-drying method. Powder X-ray diffraction analysis showed that IMC in solid dispersion particles is in amorphous state irrespective of the type of silica formulated. In DSC analysis, the melting peak of IMC in solid dispersion particles with Sylysia 350 shifted to lower temperature than that in solid dispersion particles with Aerosil 200 although the peak of each solid dispersion particles was much smaller than that of original IMC crystals. Dissolution property of IMC was remarkably improved by formulating the silica particles to the solid dispersion particles. In comparing the effect of the type of the silica particles, the dissolution rate of solid dispersion particles with Sylysia 350 was faster than that with Aerosil 200. The formulation amount of IMC did not affect on the amorphous state of IMC in the resultant solid dispersion particles in powder X-ray diffraction patterns. However, the area of the melting peak of IMC in the solid dispersion particles increased and an exothermic peak owing to recrystallization was observed with increasing the IMC content in the DSC patterns. The dissolution rate of IMC from the solid dispersion particles with Sylysia 350 was faster than that of Aerosil 200 irrespective of IMC content. In stability test, amorphous IMC in the solid dispersion particles with each silica particles did not crystallize under storing at severe storage conditions (40 °C, 75% RH) for 2 months, while amorphous IMC without silica easily crystallized under same conditions.

Keywords: Indomethacin; Solid dispersion particles; Amorphous; Spray-drying; Porous silica

1. Introduction

There are many poorly water soluble drugs which have been developing in pharmaceutical field. To solve this problem, several methods have been studying as

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pharmaceutical engineering techniques such as simple grinding (Kaneniwa et al., 1973), grinding with additive (Yamamoto et al., 1974), and formation of salt (Berge et al., 1977), or inclusion compound with cyclodextrin (Kimura et al., 2000). Solid dispersion system where drug molecules are dispersed in the carrier such as PVP (Simonelli et al., 1969) or PEG (Chiou and Riegelman, 1969) is an alternative useful method.

Indomethacin (IMC) is one of the poorly water soluble drugs (solubility in water: 5 μg/mL, Hancock and Parks, 2000) which is often used as a model drug for the solid dispersion. The property of the amorphous state of IMC was examined extensively by many workers (Imaizumi et al., 1979; Fukuoka et al., 1986). Zografi et al. reported the interaction of IMC and PVP in molecular level, and the effect of PVP on the inhibition of crystallization of amorphous IMC in the solid dispersion system (Taylor and Zografi, 1997; Matsumoto and Zografi, 1999). Yoshioka et al. (1994) also reported that crystallization of IMC from amorphous state below and above its glass transition temperature.

Takeuchi et al. (1987, 2003, 2004) also reported the solid dispersion particles with colloidal silica or porous silica prepared by spray-drying method could improve the dissolution property of tolbutamide and IMC. In this system, porous silica played an important role to control the polymorphs and stabilize meta-stable crystals in the solid dispersion particles under the severe storage conditions. Recently, the interaction between IMC molecules and silica surface, as well as the dissolution property and stability of the amorphous state of IMC, was extensively investigated by Watanabe et al. (2001, 2002, 2003).

In general, porous material has special properties such as decrease of melting point and making non-frozen water in the pores (Enüstün et al., 1978; Etzler and White, 1987). These properties were also applied for pharmaceutical engineering field to decrease crystallinity of drugs, i.e. amorphous state. Nakai et al. has reported the interaction between drug molecules and porous carriers, such as controlled pore glass (Matsumoto et al., 1994; Nakai et al., 1984) and porous cellulose (Matsumoto et al., 1998) in adsorption method by mixing or heating of it. In these cases, the state of drug changed from crystalline state to amorphous state and the dissolution property was improved.

In this study, we tried to prepare solid dispersion particles with IMC and porous silica (Sylysia 350) by spray-drying method and compared it to that with non-porous silica (Aerosil 200). We also examined the effect of the ratio of IMC to silica on the physicochemical property and dissolution property of solid dispersion particles.

2. Experimental

2.1. Materials

IMC was a gift from Sumitomo Pharmaceuticals Co. Ltd., Japan. Two types of silica (Aerosil 200, Nihon Aerosil Co. Ltd., Japan, Sylysia 350, Fuji Silysia, Chemical Ltd., Japan) were used as obtained. Aerosil 200 is non-porous silica and Sylysia 350 is porous silica. The property of carrier is shown in Table 1. All other chemicals and solvents were of reagent grade.

2.2. Preparation of solid dispersion particles

The solid dispersion particles of IMC with fine silica particles were prepared using the spray-drying (SD) method. One gram of silica was suspended in 100 mL of ethanol solution into which 1.0 g of IMC had been dissolved. After ultrasonication for 5 min, this suspension was fed to a spray dryer (GS31, Yamato Scientific Co., Ltd., Japan) at rate of 10 mL/min and sprayed into the chamber from a nozzle with a diameter of 406 μm

Table 1
Physicochemical properties of Aerosil 200 and Sylysia 350

Sample	Porous or non-porous	Particle size (μm)	Specific surface area (m^2/g)	Pore size (nm)	Pore volume (mL/g)
Aerosil 200	Non-porous	0.012	2.0×10^2	–	–
Sylysia 350	Porous	3.9	3.0×10^2	21.0	1.6

The values were obtained from the catalog of Aerosil (Nihon Aerosil), Sylysia (Fuji Silysia).

at a pressure of 0.12–0.15 MPa. The inlet and outlet temperatures of the drying chamber were maintained at 100 and 70 °C, respectively. The spray-dried IMC particles were prepared from the ethanol solution of IMC under the same conditions. All the particles were dried in the desiccator with blue silica gel under reduced pressure for 1 day before testing their properties. Meta-stable IMC (α-form) was prepared by following the method of Borka (1974). Amorphous IMC was also prepared by immersion of melted IMC into liquid nitrogen.

2.3. Physicochemical property of solid dispersion particles

The size of the solid dispersion particles was measured by laser diffraction size analyzer (LDSA-2400A, Tonichi Computer, Japan). The particle shape was observed by scanning electron microscopy (JSM-T330A, Nihon Denshi, Japan). The specific surface area of solid dispersion particles was also measured by the N_2 adsorption method (Gemini; Shimadzu Co., Japan) after degassing the sample powder at 40 °C overnight (Flow Prep060; Shimadzu Co., Japan). The crystalline form of IMC in solid dispersion particles was measured by powder X-ray diffraction method (RAD-IC, Rigaku Denki, Japan) and differential scanning calorimetry (DSC6200, Seiko Instruments Inc., Japan). In DSC analysis, 1.0–1.5 mg of sample powder was put in the aluminum sample pan. The increasing rate of temperature was 10 °C/min.

2.4. Dissolution test

The dissolution test was carried out according to Japanese Pharmacopoeia XIV. Sample (25 mg of IMC or 50 mg of solid dispersion particles) was added to 900 mL of no. 2 medium (pH 6.8) for a disintegration test with paddle stirring at a rotation speed of 100 rpm at 37 °C, as specified in JPXIV. The drug concentration in the medium was measured spectrophotometrically at 320 nm (UV-160A; Shimadzu Co., Japan).

2.5. Stability test

The sample particles were stored in desiccator with 75% RH (saturated solution with NaCl) at 40 °C. The crystalline form of IMC in solid dispersion particles was measured by powder X-ray diffraction method (RAD-IC, Rigaku Denki, Japan) after 2 months.

3. Results and discussions

Table 2 shows the average particle size of spray-dried IMC and IMC solid dispersion particles with Aerosil 200 or Sylysia 350. The size of spray-dried IMC and IMC solid dispersion particles was much smaller than that of original IMC crystals. The size of the solid dispersion particles with Aerosil 200 is larger than that with Sylysia 350. It means that Aerosil 200 formed matrix structure with IMC in the particles. The size of IMC solid dispersion particles is almost the same as that of Sylysia 350. The same tendency has already been observed for tolbutamide solid dispersion particles with Sylysia 350 prepared by spray-drying (Takeuchi et al., 2004).

The SEM photographs of these particles shown in Fig. 1 confirmed the same particle size of these solid dispersion particles. The solid dispersion particles with Aerosil 200 were smaller than the agglomerated Aerosil 200 particles, which suggested that the

Table 2
Particle size of solid dispersion particles with Aerosil 200 or Sylysia 350

Sample	Particle size (μm)		
	D_{16}	D_{50}	D_{84}
Original IMC	8.0 ± 0.7	32.3 ± 4.3	128.8 ± 47.3
Spray-dried IMC	3.8 ± 0.1	7.2 ± 0.3	18.4 ± 2.8
Solid dispersion particles with Aerosil 200	3.3 ± 0.1	6.3 ± 0.2	10.2 ± 0.3
Solid dispersion particles with Sylysia 350	1.8 ± 0.0	3.5 ± 0.0	5.5 ± 0.0

The data are the average values of four runs.

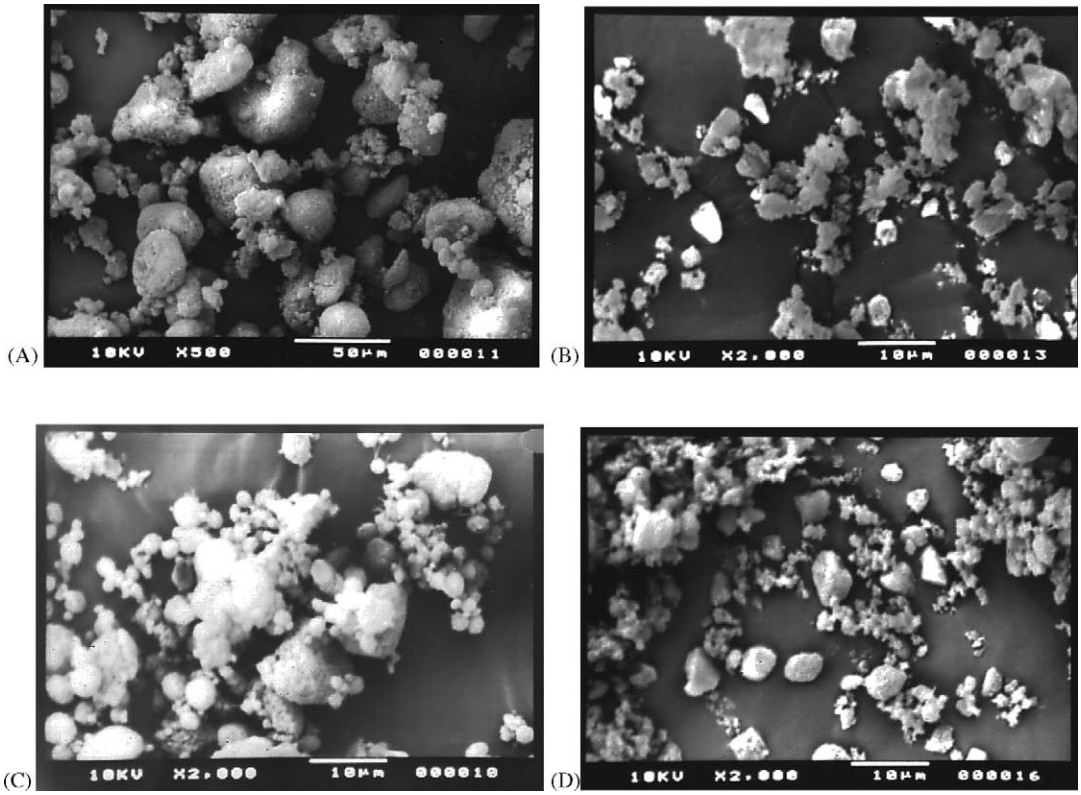

Fig. 1. The particle shape of solid dispersion particles prepared with Aerosil 200 or Sylysia 350: (A) Aerosil 200; (B) Sylysia 350; (C) solid dispersion particles with Aerosil1 200; (D) solid dispersion particles with Sylysia 350.

Aerosil 200 particles were well dispersed in the solid dispersion particles.

The powder X-ray diffraction analysis clarified that the crystalline form of the spray-dried IMC was mixture of meta-stable form (α-form) and stable form (γ-form), while the original IMC crystals are stable form (γ-form) (Fig. 2). The crystallinity of spray-dried IMC was decreased probably because of the rapid drying rate from the ethanol solution. On the other hand, the crystallinity of IMC in solid dispersion particles with silica remarkably decreased irrespective of the type of silica formulated. Comparing the powder X-ray diffraction charts of these solid dispersion particles, small peaks were observed in the solid dispersion particles with Sylysia 350. There are various reports about the interaction between drug molecules and silanol group of silica (Takeuchi et al., 1987, 2003, 2004; Watanabe et al., 2001, 2002, 2003). In these reports, silanol group on the surface of silica particles tends to form hydro-

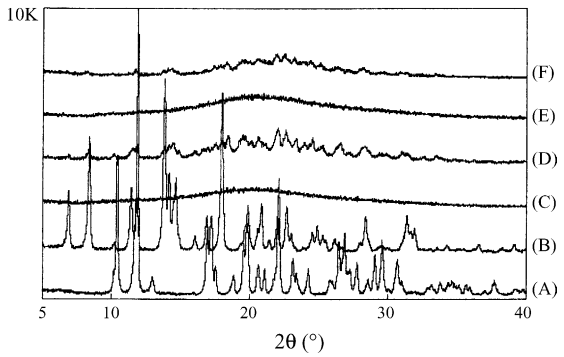

Fig. 2. Powder X-ray diffraction patterns of various types of IMC and solid dispersion particles with Aerosil 200 or Sylysia 350: (A) original IMC crystals (γ-form); (B) meta-stable IMC crystals (α-form); (C) amorphous IMC; (D) spray-dried IMC; (E) solid dispersion particles with Aerosil1 200; (F) solid dispersion particles with Sylysia 350.

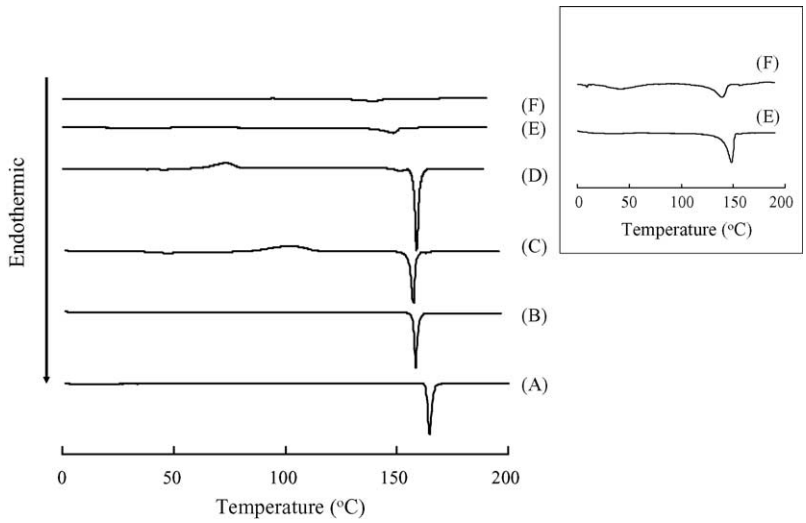

Fig. 3. DSC patterns of various types of IMC and solid dispersion particles with Aerosil 200 or Sylysia 350: (A) original IMC crystals (γ-form); (B) meta-stable IMC crystals (α-form); (C) amorphous IMC; (D) spray-dried IMC; (E) solid dispersion particles with Aerosil1 200; (F) solid dispersion particles with Sylysia 350.

gen bonding with carbonyl group of drug. When the porous silica (Sylysia 350) was formulated in the solid dispersion system, the drug molecules might form the hydrogen bonding in its pore. It leads to good dispersion of drug molecules in the solid dispersion particles.

DSC patterns of various types of IMC and IMC in solid dispersion particles are shown in Fig. 3. As observed in the powder X-ray diffraction analysis, IMC might be in an amorphous state in the solid dispersion particles. However, a very weak endothermic peak was observed for IMC in the solid dispersion particles, although the peak observed was a trace and the peak position was shifted to lower side of temperature compared to the melting endothermic peak for the stable or meta-stable IMC crystals. Comparing the trace peak for the two types of solid dispersion particles with different types of silica, the area of melting peak of IMC in solid dispersion with Sylysia 350 is smaller and its position of peak is lower than that with Aerosil 200. In general, the melting point of drug molecules in the pore is lower than that in bulk state (Enüstün et al., 1978; Etzler and White, 1987). Nakai et al. reported this phenomenon with porous silica or porous cellulose as carrier in the mixing system of drug crystals and the porous materials (Matsumoto et al., 1994, 1998; Nakai et al., 1984).

Fig. 4 shows the dissolution profile of IMC from the solid dispersion particles with Aerosil 200 or Sylysia 350. The dissolution rate of spray-dried IMC particles was faster than that of original IMC crystals because of decrease in particle size and crystallinity and change in crystalline form. However, 100% of spray-dried IMC could not dissolve within 60 min. On the other hand, the dissolution profile of IMC in the solid dispersions particles was remarkably improved irrespective of the type of silica formulated. This might be due to the improvement in wettability and dispersibility in the medium as

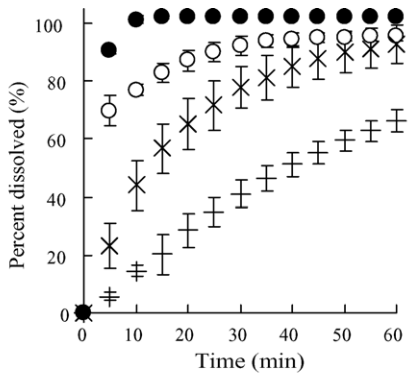

Fig. 4. Dissolution profiles of IMC from solid dispersion particles with Aerosil 200 or Sylysia 350: (+) original IMC crystals (γ-form); (×) spray-dried IMC; (◯) solid dispersion particles with Aerosil 200; (●) solid dispersion particles with Sylysia 350.

well as the decrease in particle size and crystallinity of IMC in the particles as followed in the previous report with tolbutamide solid dispersion with Aerosil 200 (Takeuchi et al., 1987). Comparing the dissolution profiles of solid dispersion particles with Aerosil 200 and Sylysia 350, the dissolution rate of IMC from solid dispersion particles with Sylysia 350 was faster than that with Aerosil 200. The difference in the drug crystallinity may be responsible for the difference in the drug dissolution rate of the two different types of the solid dispersion particles.

It is preferable that the drug content in the solid dispersion is higher to reduce the dose amount. To examine the effect of drug content in the solid dispersion particles on their physicochemical properties including its drug dissolution property, we prepared the additional two types of solid dispersion particles having different drug contents (drug to silica = 3 to 1 and 1 to 3). Fig. 5 shows the morphology of IMC solid dispersion particles prepared with the different IMC contents. In case of solid dispersion particles with Sylysia 350, a needle shape of IMC was observed when the drug content was increased to 75% (drug to silica = 3 to 1). It indicated that the excess of IMC was precipitated outside the pores of Sylysia 350. On the other hand, the shape of the solid dispersion particles with Aerosil 200 was similar in any IMC content. It means that the solid dispersion particles formed matrix structure with IMC and Aerosil 200 even at high IMC content in the formulation.

The particle size of solid dispersion having different IMC contents was measured by a laser diffraction size analyzer. The size of solid dispersion particles with Sylysia 350 was similar irrespective of IMC content as shown in Table 3. However, in comparing their specific surface area, that of the solid dispersion particles of the ratio of IMC to Sylysia 350 = 3 to 1 ($45.5 \pm 3.1\ m^2/g$) was smaller than that in the ratio of 1 to1 ($99.5 \pm 1.5\ m^2/g$). This discrepancy could be explained by their morphological difference described

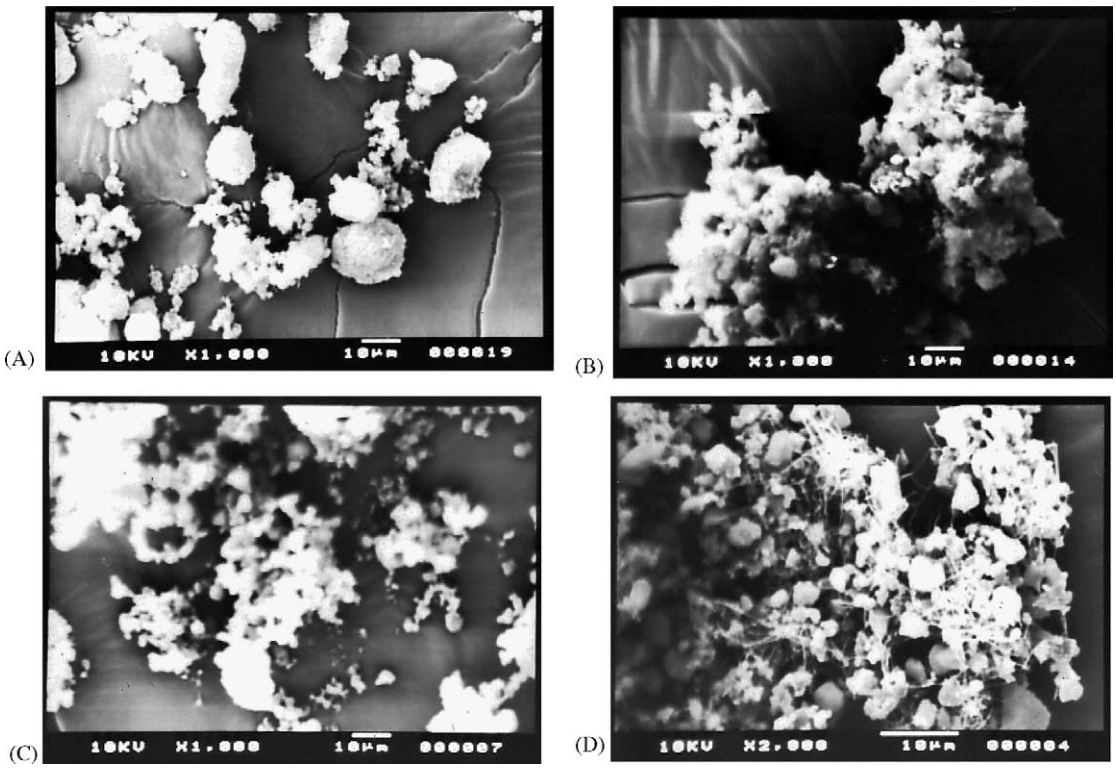

Fig. 5. Effect of IMC content on the particle shape of solid dispersion particles with Aerosil 200 or Sylysia 350: (A) IMC:Aerosil 200 = 1:3; (B) IMC:Aerosil 200 = 3:1; (C) IMC:Sylysia 350 = 1:3; (D) IMC:Sylysia 350 = 3:1.

Table 3
Effect of IMC content on the particle size of solid dispersion particles with Aerosil 200 or Sylysia 350

Sample, IMC:silica	Particle size (μm)		
	D_{16}	D_{50}	D_{84}
Aerosil 200			
1:3	4.0 ± 0.1	7.2 ± 0.2	11.5 ± 0.6
1:1	3.3 ± 0.1	6.3 ± 0.2	10.2 ± 0.3
3:1	2.4 ± 0.1	4.5 ± 0.1	6.9 ± 0.4
Sylysia 350			
1:3	1.8 ± 0.0	3.2 ± 0.1	5.0 ± 0.1
1:1	1.8 ± 0.0	3.5 ± 0.0	5.5 ± 0.0
3:1	2.2 ± 0.1	4.3 ± 0.1	6.7 ± 0.2

The data are the average values of four runs.

above. On the other hand, the size of solid dispersion particles with Aerosil 200 decreased with increasing the IMC content (Table 3). This result is well corresponding to SEM observation (Fig. 5), where aggregates of small particles were observed when the ratio of IMC to Aerosil 200 was 3 to 1. In addition, the size of spray-dried Aerosil 200 particles without drug is almost the same as that of solid dispersion particles at the ratio of IMC to Aerosil 200 = 1 to 3 (D16 = 4.0 μm, D50 = 7.0 μm, D84 = 10.7 μm). These results suggested that excess of Aerosil 200 particles in the solid dispersion formulation tend to form larger particles of Aerosil 200.

The effect of IMC ratio on the crystalline state of IMC in solid dispersion particles was examined by powder X-ray diffraction analysis (Fig. 6). Even at the formulation of IMC to silica = 3 to 1, the peaks attributed to crystalline IMC in the X-ray diffraction chart of the solid dispersion particles with Sylysia 350 were still small. The hallow patterns were observed irrespective of the drug content in the solid dispersion particles with Aerosil 200. It means that IMC in the solid dispersion particles could effectively interact with silica surface to form an amorphous state within the range of this drug content. As estimated with Fig. 5, a part of IMC might be solidified outside the pores of Sylysia particles at higher content of the drug in the formulation of solid dispersion particles. Based on the powder X-ray diffraction analysis, a large part of IMC in solid dispersion particles with Sylysia 350 was in amorphous state even outside the pores of Sylysia 350.

To confirm the amorphous state of IMC in the solid dispersion particles having different IMC contents, DSC analysis was carried out (Fig. 7). The melting peak of IMC was not observed for the solid dispersion particles with Sylysia 350 of the drug content of 25% (ratio of IMC to Sylysia 350 = 1 to 3). A small melting peak was detected in that with Aerosil 200 having the same drug content. When the drug content was 50%, the drug melting peak was observed for each solid dispersion particle. In comparing the two types of silica in solid dispersion particles, Sylysia and Aerosil, the melting peak of the former solid dispersion was smaller than that of latter, and its position was shifted to lower temperature side. When the excess amount of IMC was formulated as in the formulation of IMC to silica = 3 to 1, the endothermic and exothermic peaks were observed around 50 and 80 °C, respectively. The endothermic and exothermic peaks might be attributed to the glass transition point of the amorphous IMC and its crystallization point, respectively (Yoshioka et al., 1994). The same exothermic peak was also observed in the DSC pattern of spray-dried IMC without silica. This result suggested that the solid dispersion particles having higher content of IMC consist of both amorphous IMC interacted with silica surface and unstable amorphous or meta-stable crystalline IMC. In comparing the two types of silica as the carrier of the solid dispersion, the porous Sylysia 350 might be more suitable to obtain the larger amount of stable amorphous state of drug.

Fig. 8 shows the effect of IMC ratio on the dissolution profile of IMC from the solid dispersion particles. There is a difference between Aerosil 200 and Sylysia 350 as carrier in the effect of IMC content on the dissolution profile. In case of Aerosil 200, the dissolution profile slightly changed depending on the IMC content, and its dissolution rate was slower than that of Sylysia 350 at any IMC content. On the other hand, the dissolution profile of solid dispersion particles with Sylysia 350 was very rapid irrespective of IMC content. It is concluded that Sylysia 350 is preferable carrier to improve the dissolution property of IMC compared with Aerosil 200.

Fig. 9 shows the stability of amorphous IMC in the solid dispersion particles stored at 75% RH and 40 °C for 2 months. Amorphous IMC without silica was easily crystallized to meta-stable form, while amorphous IMC in both solid dispersion particles was unchanged. We already reported that Sylysia 350 had strongly stabilizing effect on the meta-stable tolbutamide in solid

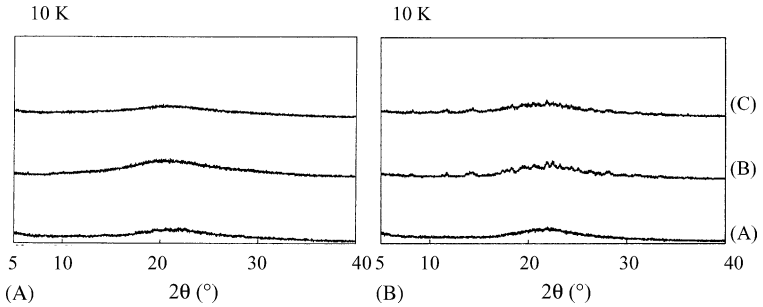

Fig. 6. Effect of IMC content on the crystalline form of IMC in solid dispersion particles with Aerosil 200 or Sylysia 350 in powder X-ray analysis: (A) Aerosil 200; (B) Sylysia 350. IMC:silica—(A) 1:3; (B) 1:1; (C) 3:1.

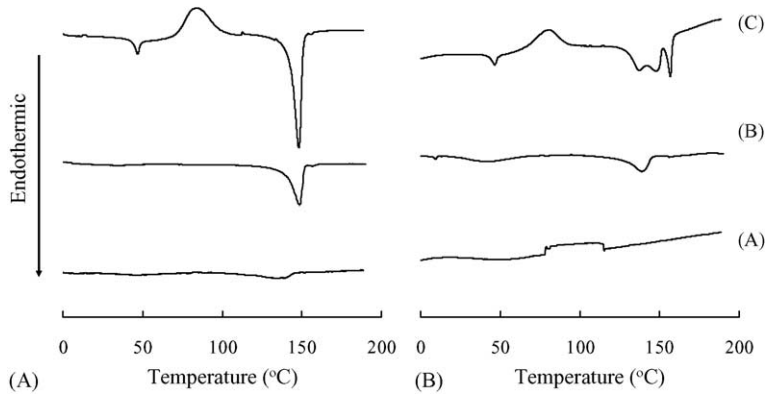

Fig. 7. Effect of IMC content on the crystalline form of IMC in solid dispersion particles with Aerosil 200 or Sylysia 350 in DSC analysis: (A) Aerosil 200; (B) Sylysia 350. IMC:silica—(A) 1:3; (B) 1:1; (C) 3:1.

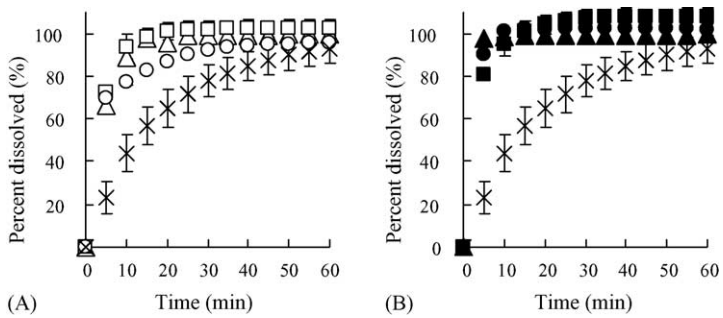

Fig. 8. Effect of IMC content on the dissolution profile of IMC from solid dispersion particles with Aerosil 200 or Sylysia 350: (A) Aerosil 200; (B) Sylysia 350; (×) spray-dried IMC crystals; open symbol: solid dispersion particles with Aerosil 200 (IMC:Aerosil 200 = 1:3 (△), 1:1 (◯), 3:1 (□)); close symbol: solid dispersion particles with Sylysia 350 (IMC:Sylysia 350 = 1:3 (▲), 1:1 (●), 3:1 (■)).

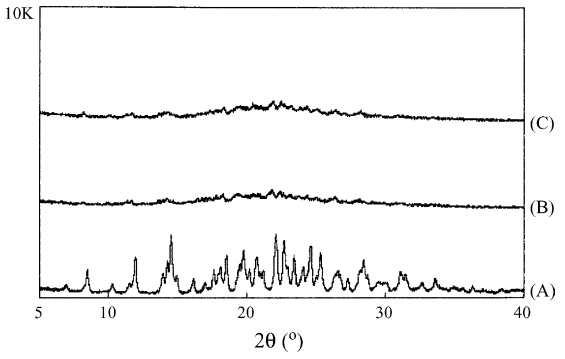

Fig. 9. Stability of amorphous IMC, IMC in solid dispersion particles with Aerosil 200 or Sylysia 350 stored at 75% RH and 40 °C for 2 months: (A) amorphous IMC; (B) solid dispersion particles with Aerosil 200; (C) solid dispersion particles with Sylysia 350.

dispersion particles compared with Aerosil 200 at severe conditions probably because of their porous structure (Takeuchi et al., 2004). In the present case, no difference was observed between Sylysia 350 and Aerosil 200 in the stabilizing effect. This might be due to that IMC molecules have a stronger interaction with silica irrespective of the structure type of silica.

4. Conclusion

The solid dispersion particles of IMC with fine porous silica, Sylysia 350, were prepared by spray-drying method. The average particle size (D_{50}) of solid dispersion particles could be controlled between 3 and 5 μm. This system could transform the crystal form of IMC to amorphous state and remarkably improve the dissolution property of IMC. Comparison of dissolution rate between Sylysia 350 and Aerosil 200 found that the dissolution rate of IMC in solid dispersion particles with Sylysia 350 was faster than that with Aerosil 200 irrespective of the drug content. The amorphous state of IMC in the solid dispersion particles was kept even under the severe conditions for 2 months.

References

Berge, M.S., Bighley, D.L., Monkhouse, S.D., 1977. Pharmaceutical salts. J. Pharm. Sci. 66, 1–19.

Borka, L., 1974. The polymorphism of indomethacin. New modifications, their melting behavior and solubility. Acta Pharm. Suec. 11, 295.

Chiou, W.L., Riegelman, S., 1969. Preparation and dissolution characteristic of several fast-release solid dispersions of griseofulvin. J. Pharm. Sci. 58, 1505–1509.

Enüstün, B.V., Sentürk, H.S., Yurdakul, O., 1978. Capillary freezing and melting. J. Colloid Interf. Sci. 65, 509–516.

Etzler, F.M., White, P.J., 1987. The heat capacity of water in silica pores. J. Colloid Interf. Sci. 120, 94–99.

Fukuoka, E., Makita, M., Yamamura, S., 1986. Some physical properties of glassy indomethacin. Chem. Pharm. Bull. 34, 4314–4321.

Hancock, B.C., Parks, M., 2000. What is the true solubility advantage for amorphous pharmaceuticals? Pharm. Res. 74, 397–404.

Imaizumi, H., Nambu, N., Nagai, T., 1979. Stability and several physical properties of amorphous and crystalline forms of indomethacin. Chem. Pharm. Bull. 28, 2565–2569.

Kaneniwa, N., Ikekawa, A., Hashimoto, K., 1973. Influence of operational variables on ball-milling of sulfadimethoxine and white alundum. Chem. Pharm. Bull. 21, 676–681.

Kimura, K., Hirayama, F., Arima, H., Uekama, K., 2000. Effect of aging on crystallization, dissolution and adsorption characteristics of amorphous tolbutamide-2-hydroxypropyl-β-cyclodextrin complex. Chem. Pharm. Bull. 48, 646–650.

Matsumoto, K., Nakai, Y., Yonemochi, E., Oguchi, T., Yamamoto, K., 1994. Physicochemical characteristics of porous crystalline cellulose and formation of an amorphous state of ethenzamide by mixing. Int. J. Pharm. 108, 167–172.

Matsumoto, K., Nakai, Y., Yonemochi, E., Oguchi, T., Yamamoto, K., 1998. Effect of pore size on the gaseous adsorption on ethenzamide on porous crystalline cellulose and the physicochemical stability of ethenzamide after storage. Chem. Pharm. Bull. 46, 314–318.

Matsumoto, T., Zografi, G., 1999. Physical properties of solid molecular dispersions of indomethacin with poly (vinylpyrrolidone) and poly (vinylpyrrolidone-co-vinyl-acetate) in relation to indomethacin crystallization. Pharm. Res. 16, 1722–1728.

Nakai, Y., Yamamoto, K., Terada, K., Ichikawa, J., 1984. Interaction of medicinals and porous powder. I. Anomalous thermal behavior of porous glass mixtures. Chem. Pharm. Bull. 32, 4566–4571.

Simonelli, A.P., Metha, S.C., Higuchi, W.I., 1969. Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. J. Pharm. Sci. 58, 538–549.

Takeuchi, H., Handa, T., Kawashima, Y., 1987. Spherical solid dispersion containing amorphous tolbutamide embedded in enteric coating polymers or colloidal silica prepared by spray-drying technique. Chem. Pharm. Bull. 35, 3800–3806.

Takeuchi, H., Nagira, S., Hiromitsu, Y., Kawashima, Y., 2003. Design of solid dispersion particles of drug with fine porous carriers. J. Soc. Powder. Technol., Jpn. 40, 157–162.

Takeuchi, H., Nagira, S., Hiromitsu, Y., Kawashima, Y., 2004. Solid dispersion particles of tolbutamide prepared with fine silica particles by the spray-drying method. Powder Technol. 141, 187–195.

Taylor, L.S., Zografi, G., 1997. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm. Res. 14, 1691–1698.

Watanabe, T., Wakiyama, N., Usui, F., Ikeda, M., Isobe, T., Senna, M., 2001. Stability of amorphous indomethacin compounded with silica. Int. J. Pharm. 226, 81–91.

Watanabe, T., Ono, I., Wakiyama, N., Kusai, A., Senna, M., 2002. Controlled dissolution properties of indomethacin by compounding with silica. S.T.P. Pharm. Sci. 12, 363–367.

Watanabe, T., Hasegawa, S., Wakiyama, N., Kusai, A., Senna, M., 2003. Comparison between polyvinylpyrrolidone and silica nanoparticles as carriers for indomethacin in as solid state dispersion. Int. J. Pharm. 250, 283–286.

Yamamoto, K., Nakano, M., Takaichi, A., Nakai, Y., 1974. Dissolution rate and bioavailability of griseofulvin from a ground mixture with microcrystalline cellulose. J. Pharm. Biopharm. 2, 487–493.

Yoshioka, M., Hancock, B.C., Zografi, G., 1994. Crystallization of indomethacin from amorphous state below and above its glass transition temperature. Pharm. Res. 83, 1700–1705.