Preparation of the Solid Dispersion of Indomethacin with Phosphatidylcholine by Heating Method[1)]

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The solid dispersion (SD) preparation method of indomethacin (IM, mp 161 °C) with phosphatidylcholine (PC) was investigated. The melting point of PC is high, above 200 °C, making a melting method inapplicable. However, PC shows a phase transition at about 100 °C when its acyl chains are stearic acid and it is an anhydride. In the case of mole fraction of IM in SD being 0.50, X-ray diffraction patterns suggest that IM is in an amorphous state after heating at 90 °C for 1 h, at 110 °C for 10 min or at 180 °C for 6 min. When the mole fraction of IM is as low as 0.25 or 0.33, IM is also present in an amorphous state after heating at 70 °C for 2 h and at 90 °C for 10 min. The obtained SD showed endothermic peaks from about 40 °C to 70 °C upon thermal analysis. It is possible to prepare SD above 70 °C, but this requires a long heating time; therefore, heating at above the phase transition temperature is most suitable. The dissolution patterns of IM from SD compressed into tablet form were fitted to Higuchi's square root equation and the dissolution rate was found to be 1.5-fold that from a physical mixture of the same composition.

Keywords solid dispersion; heating method; phosphatidylcholine; indomethacin; thermal analysis; dissolution

There are two typical preparation methods for solid dispersion (SD); one is the solvent method and the other is the melting (or fusion) method, each one having its advantages and disadvantages.[2)] The solvent method is used for various drug-carrier combinations, but selecting the solvent is difficult, and residual solvent is sometimes a problem. Venkataram and Rogers reported that the solubility of griseofulvin was changed depending on the residual solvent.[3)] On the other hand, the melting method is easy, but can only be used when the melting points of the drug and carrier are relatively low and they are not degraded by heat.

We have investigated the properties of SD where the carrier is phosphatidylcholine (PC).[4)] PC is different from other carriers of SD, in that it is not water-soluble. SD is available to improve the solubility of poorly water-soluble drugs, because drugs are present in an amorphous state in SD. SD has been prepared by the solvent method; the drug and PC were dissolved in ethanol or xylene and the solvent was removed. Since removal of the solvent required a long time, we tried the melting method. The melting point of PC is high, above 200 °C.[5)] However, PC shows a phase transition, at which the acyl chains of PC melt, at temperature considerably lower than the melting point. We used PC in which the main acyl chains are stearic acid and the phase transition temperature (Tc) is 78 (monohydride)—*ca.* 100 °C (anhydride).[6)] Also, decrease of the Tc was observed when SD was formed.[4)] Hence, there is the possibility of forming SD by heating at a temperature lower than the melting point (heating method). We used indomethacin (IM) as the model drug, because its SD had already been formed by the solvent method.[4a)] The properties of SD were also investigated.

Experimental

Materials PC was provided by Nikko Chemicals (Lecinol S-10 EX, PC content 97%, fatty acyl composition; stearic acid: palmitic acid = 85 : 15). IM and flurubiprofen (FP) were JP grade, and ketoprofen (KP) was purchased from Nippon Bulk Yakuhin. Other chemicals were of reagent grade.

Preparation Method of SD First, a physical mixture (PM) was prepared; IM (or other drug) and PC were weighed in a fixed mole fraction, and mixed well in a mortar. One hundred mg of PM was heated in a glass tube in a dry block bath (Scinic Co. AL-500) at a fixed temperature and time in a nitrogen atmosphere, cooled in ice, crushed with a coffee mill or mortar and passed through an 80-mesh sieve. Also, 1—2 g of PM was heated in a glass beaker in an oven, followed by the same procedure described above. The figure in parenthesis following SD or PM is the mole fraction of the drug.

Stabilities and Homogeneities of IM PM and SD were dissolved in ethanol 40 μg/ml equivalent to IM. IM concentrations were determined by UV absorption at 318 nm.[7)] The residual % was calculated as IM concentration of SD to that of PM. Determinations were done in triplicate.

Physicochemical Properties of SD Powder X-ray diffraction patterns were examined in an X-ray diffractometer (Rigaku Denki Co., Geigerflex RAD-2C). The X-rays were Ni-filtered CuK_α radiation (40 kV and 30 mA; scanning speed 4 degrees/min; scanning range, $2\theta = 3$—40 degrees). Thermal analysis was carried out with differential scanning calorimetry (Rigaku Denki Co., Thermoflex TAS-200 DSC 8230D). About 5 mg of SD prepared 3 d prior to measurement and sealed in an aluminum crimp cell was heated at the rate of 10 °C/min in an atmosphere of nitrogen.

Dissolution Studies Eighty mg of SD or PM was compressed by a tableting machine (Okada Seiko N-20E) at 500 kgf and made into tablet form (diameter 7 mm, thickness 2 mm, surface area 1.2 cm^2). The dissolution patterns were tested in a JP XII dissolution test apparatus. As the test solution, 500 ml of pH 7.0 phosphate buffer solution (PBS) was kept at 37 ± 0.1 °C with stirring at 100 rpm by a paddle. A tablet was put into the test solution and an aliquot of the solution was withdrawn periodically and immediately filtered through a 0.20 μm membrane filter (Dismic-25, Advantec Toyo). The same volume of PBS was added to the test solution. The IM concentration was determined by the absorbance at 318 nm. All experiments were done in triplicate.

Results and Discussion

Preparation Temperature We first investigated the possibility of preparation of SD by the heating method with PM (0.50). IM is yellow when it melts or dissolves in solvent. PM (0.50) showed no change when it was heated at 60 °C for 24 h, but became yellow when heated at 70 °C. This indicates that SD was formed when PM (0.50) was heated above 70 °C. Hence we tried preparing SD at the following 4 temperatures: 70 °C, the peak end temperature of DSC curves of SD (0.50) prepared by the solvent method; 90 °C, slightly higher temperature than Tc of monohydrated PC;

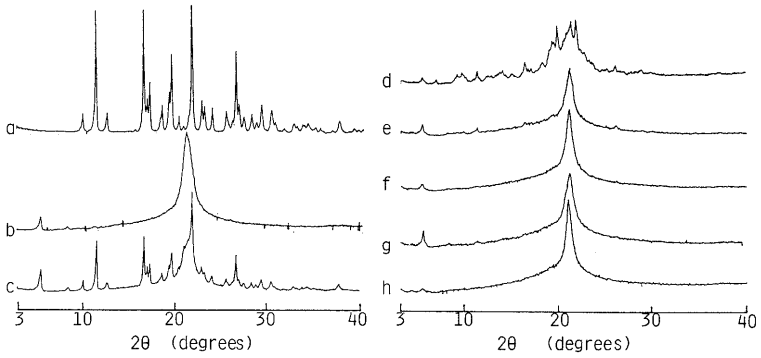

Fig. 1. Powder X-Ray Diffraction Patterns of SD (0.50) Prepared at Various Temperatures and Times

a, IM; b, PC; c, PM (0.50); d, SD (0.50) prepared at 70 °C for 2 h; e, at 90 °C for 20 min; f, at 90 °C for 1 h; g, at 110 °C for 10 min; h, at 180 °C for 6 min.

TABLE I. Residual Percent of Indomethacin after Preparation of Solid Dispersion

Mole fraction of IM	Conditions of preparation			
	180 °C 6 min	110 °C 10 min	90 °C 1 h	70 °C 2 h
0.25	99.7±0.3	98.8±0.8	99.4±0.5	97.8±0.6
0.33	100.0±0.4	99.9±0.6	99.1±1.0	99.1±0.6
0.50	100.6±0.5	99.4±0.7	101.0±0.1	100.6±0.1[a]
0.67	98.7±1.5	98.5±3.0[a]	—	—
0.75	99.6±1.5	99.3±4.3[a]	—	—

Each data listing represents the mean±S.D. of 3 determinations. *a*) IM crystals observed in X-ray diffraction patterns.

110 °C, slightly higher than Tc of anhydrated PC; and 180 °C, above the melting point of IM.

Figure 1 shows the X-ray diffraction patterns of SD and related materials. For preparation at 70 °C, the X-ray diffraction pattern showed IM crystals after 2 h of heating, although PM became yellow. At 90 °C, X-ray diffraction patterns indicate a small amount of residue of IM crystals after 20 min heating, but no crystals after 60 min heating. Only 10 and 6 min were needed to obtain an amorphous state of IM when PM was heated at 110 °C and 180 °C, respectively.

Other mole fractions of SD were investigated. In the case of low mole fraction of IM such as 0.25 or 0.33, IM changed to an amorphous state after 2 h heating at 70 °C or 10 min heating at 90 °C. It is suggested that SD can be prepared at lower temperature and in a shorter time when the IM ratio is low. On the other hand, for ratios of IM above 0.50, PM became yellow at 60 °C, but IM crystal signals were observed even after 1 h heating at 110 °C. When PM (0.67) or (0.75) was heated at 180 °C, X-ray diffraction patterns suggested that IM was present in an amorphous state. But SD (0.80) showed IM crystal signals. The limit of IM concentration to show an amorphous state is 0.75 which is the same as that of SD prepared by the solvent method.[4a)]

The IM content in SD was determined and is shown in Table I. In all cases, no degradation of IM was observed and IM existed in a homogenous state in SD.

To prepare a large amount of SD, PM was spread in a beaker and put in a oven with a fixed temperature of 110 °C or 180 °C. In this case, the atmosphere was air. The limit of IM concentration showing an amorphous state prepared at 110 °C and 180 °C were 0.50 and 0.75, respectively, and

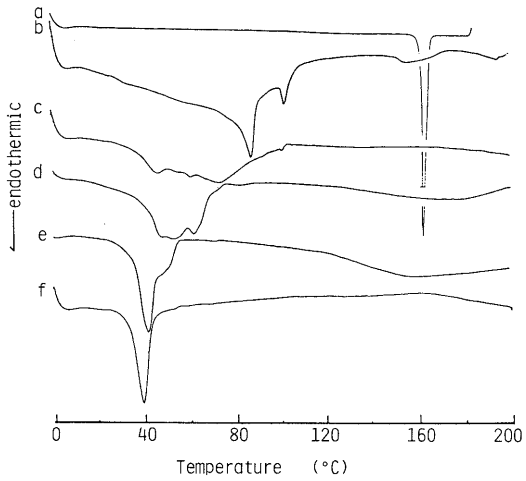

Fig. 2. DSC Curves of SD with Various Mole Fractions of IM Prepared at 180 °C for 6 min

a, IM; b, PC; c, SD (0.25); d, (0.50); e, (0.67); f, (0.75).

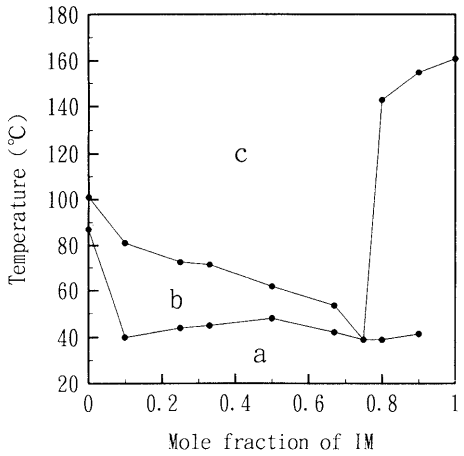

Fig. 3. Phase Diagram of IM–PC System

a, solid; b, solid + liquid crystalline; c, liquid crystalline.

no degradation was observed except SD (0.75) prepared at 180 °C.

Thus, the heating method is applicable for preparation of SD, and optimal temperatures are 110 °C and 180 °C for SD of IM, because these temperatures require only a short time.

Thermal Analysis SD obtained by the heating method was characterized by thermal analysis. Figure 2 shows DSC

curves of SD with various mole fractions of IM prepared by heating for 6 min at 180 °C. The mole fraction of IM became higher, the peak temperature became lower. This phenomenon was also observed in the SD prepared by the solvent method. Figure 3 shows a phase diagram of SD produced by peak temperatures of DSC curves. A eutectic-like phenomenon is shown at the composition when the mole fraction of IM was 0.75, although a phase transition (not melting) was exhibited. Ford and Rubinstein reported that if a drug-carrier combination shows a eutectic point, it is possible to prepare SD at the eutectic temperature.[8] But the IM–PC combination, PM which molar ratio of IM were under 0.75, showed a broad endothermic peak from 40 °C to 100 °C, and also around 150 °C in the case of PM (0.80) and (0.90); SD could not be prepared at lower as 45 °C.

Preparation temperature slightly affected DSC curves. For example, in SD (0.50) in which IM was present in an amorphous state, endothermic peaks were observed at 49 °C, 55 °C and 62 °C for preparation at 180 °C, and also at 46 °C and 61 °C for preparation at 90 °C and 110 °C.

Preparation of SD of KP and FP It was verified that SD of IM with PC can be prepared by the heating method as well as by the solvent method. Thus whether SD of other drugs can be prepared by the heating method was of interest, and KP and FP, of which SD with PC has also been made by the solvent method,[4a] were studied.

The melting point of KP is 97 °C, and PM showed a glass-like form when heated at 80 °C. KP was present in an amorphous state after 10 min heating at 80 °C or 110 °C when its mole fraction was under 0.67. This upper limit of the mole fraction agreed with SD obtained by the solvent method. The DSC curves of the obtained SD (0.50) showed endothermic peaks at 43 °C and 62 °C, similar to SD of IM.

FP, of which the melting point is 117 °C, was present in an amorphous state after 10 min heating at 80 °C or 110 °C when its mole fraction was under 0.50. This limit also agreed with SD obtained by the solvent method. PM showed a homogenous transparent glass-like form at 110 °C, but FP crystal signals were observed in the X-ray diffraction pattern when the mole fraction was 0.67 and 0.75. This phenomenon was also observed using the solvent method.

The DSC curves of SD (0.50) showed endothermic peaks at 36 °C and 51 °C, suggesting that the state of SD was different from those of IM and KP.

Thus, SD could be prepared at lower temperature when the drug melting point was low.

Dissolution Studies Dissolution of IM from SD and PM were compared. SD and PM were compressed and made into a tablet of which the surface area was 1.2 cm^2. In all cases, no disintegration was observed within 23 h, although there was slight expansion because of the absorption of water.

Figures 4 and 5 show the dissolution of IM from PM and from SD prepared by heating at 180 °C for 6 min, respectively. The dissolution profiles showed good correlation between the cumulative amount of dissolution and square root of time except SD (0.67), and the dissolution became faster when the IM mole fraction became larger. The amount of dissolution from SD within 6 h was about 20% and at 23 h was about 40% of each quantity of IM.

In general, dissolution from SD is fast and of 0-order dissolution, because the carrier is water-soluble.[9] It was

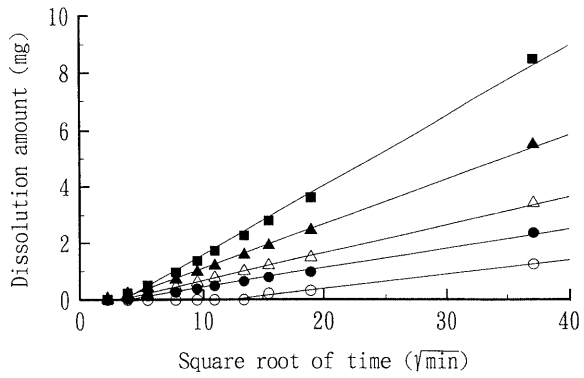

Fig. 4. Dissolution of IM from PM Compressed at 500 kgf

IM mole fractions in PM are 0.10 (○), 0.25 (●), 0.33 (△), 0.50 (▲), and 0.67 (■). The surface area of tablets is 1.2 cm^2.

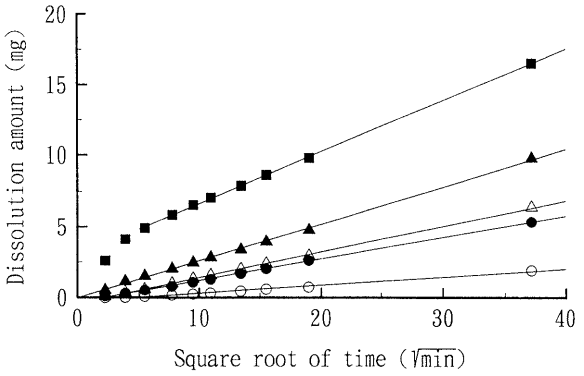

Fig. 5. Dissolution of IM from SD Prepared at 180 °C for 6 min and Compressed at 500 kgf

IM mole fractions in SD are 0.10 (○), 0.25 (●), 0.33 (△), 0.50 (▲), and 0.67 (■). The surface area of tablets is 1.2 cm^2.

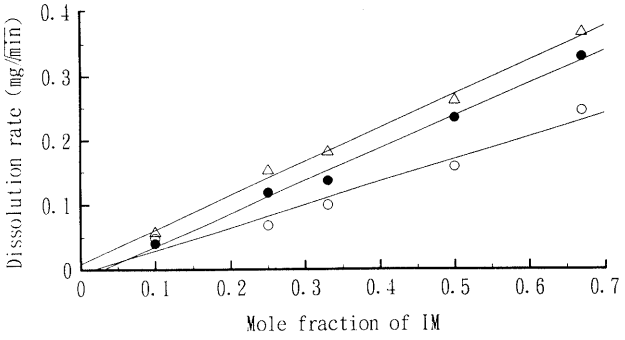

Fig. 6. The Relationship between Dissolution Rate and Mole Fraction of IM

PM (○), SD prepared at 110 °C (●), prepared at 180 °C (△).

reported[10] that release from an insoluble matrix can be described by the Higuchi square root equation.[11] PC is a kind of lipid and insoluble in water, so dissolution from PM and SD fitted the Higuchi equation. Dissolution profiles from PM showed a lag time, probably due to wetting, but those of SD did not because IM in an amorphous state at the surface of tablet dissolved quickly. SD (0.67) showed initial fast dissolution and a good fit with the Higuchi plot after 1 h. The reason is not completely clear, but was probably because when the mole fraction of IM was high, amorphous IM near the tablet surface burst into water followed by insoluble matrix type release. Also, Higuchi square root

type dissolution was observed in the SD prepared by heating at 110 °C.

The dissolution rate was calculated by the least-squares method with time from 10 min to 23 h, except SD (0.67) which was done with time from 1 to 23 h. Figure 6 shows the relationship between dissolution rate and mole fraction of IM; both PM and SD showed good correlation between these two factors. Generally, the ratio of drug in SD rose and dissolution rate lowered, because crystallization or aggregation of the drug occurred.[2,12] In SD with PC, the dissolution rate was proportional to the mole fraction of IM from 0.1 to 0.67 (*ca.* 4—50%). The value of dissolution rate/mole fraction of IM was 0.339 ($r=0.9776$) for PM, and 0.544 ($r=0.9964$) and 0.473 ($r=0.9938$) for SD prepared at 180 °C and 110 °C, respectively. The dissolution rate from SD was thus about 1.5-fold that from PM. The dissolution from powder SD was very fast (above 90% within 5 min), so the rate-limiting factor seems to be water diffusion into the tablet. It was reported that addition of a water-soluble substance to a water insoluble matrix caused fast release of drug because of pore formation after dissolution of the former.[13] IM in an amorphous state dissolved quickly, and consequently water diffused rapidly due to the formation of pores.

Conclusion

The heating method is applicable to the preparation of SD of which the carrier is PC, as is the solvent method. Optimal heating temperature differs according to a drug's characteristics, but is generally about 110 °C which is above Tc of PC. The method is very simple, making it convenient for preparing SD with a drug which is stable against heat.

Dissolution from powder SD was very fast, but that from tablet form was slow and fitted a diffusion equation for a matrix system because PC does not dissolve in water.

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References and Notes

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