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The Properties of Solid Dispersions of Indomethacin, Ketoprofen and Flurbiprofen in Phosphatidylcholine[1)]

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Solid dispersions in which the carriers were water-soluble agents have been investigated with the aim of improving the solubilities and dissolution rates of poorly water-soluble drugs. We have now examined the utility of barely soluble, but hydrophilic, phosphatidylcholine (PC) purified from hydrogenated soybean phospholipids as a carrier. As poorly water-soluble drugs, indomethacin (IM), flurbiprofen (FP) and ketoprofen (KP) were used.

The X-ray diffraction patterns suggested an amorphous state of IM when the molar ratio of IM was under 0.75. From the infrared spectra, it was considered that IM and PC had only a weak interaction with the carrier. The phase transition temperature of PC was depressed by IM and the degree of depression became larger with increasing molar ratio of IM. The solubility of IM in pH 7.0 buffer solution became 4.0 mg/ml (5 times that of IM powder), when the PC solid dispersion with an IM molar ratio in the range of 0.50—0.75 was used. However, the IM concentration decreased with time and became 2 mg/ml after 30 h.

FP and KP also had a weak interaction with PC and were present in the amorphous state, but this state was stable only when the molar ratio was under 0.50, which was lower than that in the case of IM. The solubilities of FP and KP from the PC solid dispersions were each about 1.5 times that from the powder.

PC dissolved in water to the extent of 0.1—0.5 mg/ml from the solid dispersions with IM, but the dissolution showed poor reproducibility, and no dissolution of PC was observed from FP and KP solid dispersions. Thus, the increased drug solubilities were considered to be due to the amorphous state of the drugs in the PC solid dispersions.

Keywords——phosphatidylcholine; solid dispersion; indomethacin; flurbiprofen; ketoprofen; dissolution; amorphous

Solid dispersions can be used to improve the solubilities and/or dissolution rates of poorly water-soluble drugs. In general, the carriers of such solid dispersions are water-soluble polymers such as polyethylene glycol[2)] or polyvinylpyrrolidone.[3)] They easily dissolve in water, and therefore the dispersed drugs also dissolve in water rapidly. The solubilities of the drugs are also increased owing to some interaction with the carriers.

We have examined the utility of phosphatidylcholine (PC) as a carrier. PC hardly dissolves in water but is hydrophilic, and it does interact with some kinds of drugs in water.[4)] However, PC extracted from egg or soybean is easily oxidized and sometimes forms peroxide[5)] because of its unsaturated acyl chains; it is semisolid at room temperature because its transition temperature is low, and high-purity PC is too expensive to use as a pharmaceutical additive. We have therefore worked out an improved method of PC purification from hydrogenated soybean phospholipids.[6)] PC containing several percent of phosphatidylethanolamine, but no other impurities, was obtained. Moreover, its fatty acids were palmitic and stearic acid and the composition was constant.

We used indomethacin (IM) as a poorly water-soluble drug, because the behavior of IM has already been investigated in solid dispersion.[2,3a)] Flurbiprofen (FP) and ketoprofen (KP)

were also investigated.

Experimental

Materials——PC was purified from hydrogenated soybean phospholipids (Nikko Chemicals, Lecinol S-10),[6] containing 5—7% of phosphatidylethanolamine as an impurity. The fatty acid composition of PC acyl chains was stearic acid: palmitic acid 85 : 15.

IM was obtained from Taisho Pharm. Co., and FP and KP were from Sawai Pharm. Co. They were used as obtained. Other chemicals were of reagent grade.

Preparation of Solid Dispersion——The required amounts of drug and PC were weighed out and dissolved in xylene, then the xylene was evaporated off *in vacuo*, sometimes with warming to 50 °C. The glassy film thus obtained was gathered, crushed in an electric coffee mill and sieved with a 80 mesh screen to obtain a powder. The powder was placed *in vacuo* again to remove residual xylene and stored in desiccator over silica gel at room temperature. Such a powder is described as IM-PC (0.25) for example, where the figure in parentheses is the molar ratio of the drug.

PC and a drug were also separately prepared by the same procedure, and mixed in a fixed molar ratio with a spatula (physical mixture).

Physicochemical Properties of Solid Dispersion——Powder X-ray diffraction patterns were examined in an X-ray diffractometer (Rigaku Denki Co., Geigerflex 2027 type). The X-rays were Ni-filtered CuK_α radiation (30 kV and 40 mA; scanning speed 4 degree/min). Infrared (IR) spectra were obtained on an IR spectrophotometer (Nippon Bunko A-102) by the KBr semimicro disk technique. Thermal analysis was carried out with a differential scanning calorimeter (DSC; Shimadzu DT-30 system DS-30). Scan speeds were 20 °C/min and sensitivities were ±20 mJ/s. About 5 mg of sample was sealed in an aluminum crimp cell.

Dissolution Studies——Solid dispersion equivalent to 250 mg as a drug was put into a flat-bottomed flask and 50 ml of phosphate buffer solution (PBS) pH 7.0 for IM or PBS pH 6.0 for FP and KP was added. The flask was shaken with hand to disperse the sample, placed in a water bath incubator (Yamato BT-47) and shaken at 100 rpm at 30 °C. An aliquot was passed through a 0.4 μm membrane filter (Fuji Film FR-40). After dilution, the concentrations of drugs were determined spectrophotometrically (Shimadzu UV-240 for IM and UV-160 for FP and KP) at 318 nm for IM, 247 nm for FP and 260 nm for KP. PC concentration was determined by an enzymatic method (Wako Pure Chem. Industry, Phospholipids B-Test). In the case of IM–PC, we also investigated the changes of IM concentrations of filtrates 15 min after initiation of dissolution studies with a 0.45 μm membrane filter (Toyo Roshi). All studies were done in triplicate.

Results and Discussion

Preparation of IM–PC

The melting point of distearoyl PC was reported to be above 200 °C and the transition temperature, 78 (monohydride)—97 °C (anhydride).[7] We therefore attempted to prepare solid dispersion by using a solvent method.

Ethanol, chloroform and xylene, which dissolve both IM and PC, were suitable as solvents. It was possible to prepare homogeneous yellow glassy IM–PC with any of these solvents if the molar ratio of IM was under 0.67. In the case of IM–PC (0.75), only xylene was usable. Since a high evaporating speed caused the separation of white crystals of IM, xylene with its high boiling point was preferred for the preparation of solid dispersions. IM–PC (0.80) separated out IM crystals even when xylene was used. Consequently, further investigations were done in the molar ratio range of IM from 0.25 to 0.75, and xylene was used as the solvent.

Immediately after preparation, IM–PC was obtained as a film on glass. The film of IM–PC (0.25) was slightly opaque but clearer than that of PC alone. As the IM ratio became higher, the film of IM–PC became yellower and clearer. It could be crushed and pulverized in all ranges of IM ratio at room temperature.

Physicochemical Properties of IM–PC

Figure 1 shows the powder X-ray diffraction patterns. Only one peak at $2\theta = 21°$ was found in the X-ray diffraction pattern of PC. This peak showed a short spacing, 4.2 Å,[7] and no peak with long spacing was observed. Both PC and IM peaks were observed in the physical

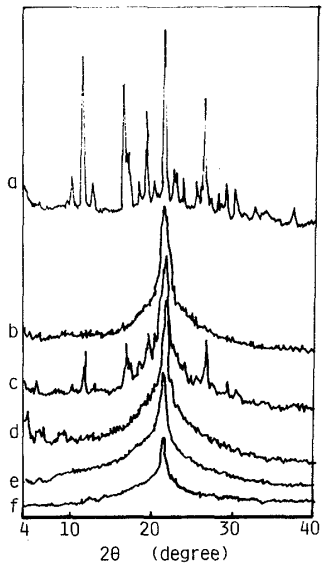

Fig. 1. X-Ray Diffraction Patterns of IM–PC and Related Samples

IM (a); PC (b); physical mixture (0.50) (c); IM–PC (0.50) (d); IM–PC (0.75) (e); IM–PC (0.75) stored for 10 months (f).

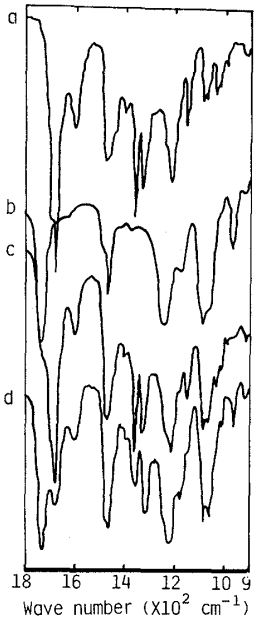

Fig. 2. IR Spectra of IM (a), PC (b), Physical Mixture (0.50) (c), and IM–PC (0.50) (d)

mixture. Only the PC peak was observed with IM–PC even if the molar ratio of IM was high as 0.75, indicating that IM is present in the amorphous state. IM–PC (0.75) stored in a desiccator for over 10 months also showed only the PC peak, so the amorphous state was considered relatively stable.

Figure 2 shows the IR spectra. The amide bands of IM, 1685 and 1385 cm^{-1}, were reduced in intensity in IM–PC compared with the physical mixture. The bands at 1100—1300 cm^{-1} of PC showed some changes. These changes were also found at other molar ratios of IM–PC.

Figure 3 shows DSC heating curves. The IM powder showed a sharp endothermic peak at 163 °C, and PC showed an endothermic peak at 85—90 °C (considered to be the phase transition temperature). No IM peak but only the PC transition endothermic peak near 90 °C was observed even in the case of the physical mixture (0.75). The transition temperature of IM–PC became lower with increasing IM molar ratio and became *ca.* 40 °C in the case of IM–PC (0.75). Since a few peaks were observed with IM–PC, IM–PC was not perfectly homogeneous. The physical mixture showed similar DSC curves with the same molar ratio of IM–PC when heated to 120 °C, cooled to 15 °C and reheated. It was considered that the physical mixture changed into a solid dispersion and IM became amorphous during the heating process, so that the IM peak was not observed.

These studies suggested that IM was present in an amorphous state in the PC solid dispersion, and that there was only a weak interaction between IM and PC.

Dissolution Studies of IM–PC

In general, water-soluble agents have been used as carriers in solid dispersions. There are also a few reports on the use of insoluble agents such as colloidal silica.[8] PC has hydrophilic character but does not dissolve in water. Venkataram and Rogers[9] reported a griseofulvin-phospholipid coprecipitate, but in this case griseofulvin was not in an amorphous state. Thus, the dissolution patterns of IM from IM–PC was examined. The phase transition might affect the dissolution,[10] so the dissolution studies were done at 30 °C to avoid the effect of transition

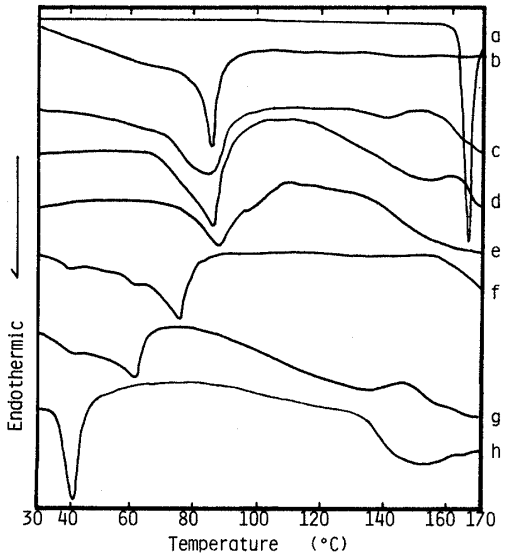

Fig. 3. DSC Curves of IM–PC and Related Samples

IM (a); PC (b); physical mixture (0.25) (c); (0.50) (d); (0.75) (e); IM–PC (0.25) (f); (0.50) (g); (0.75) (h).

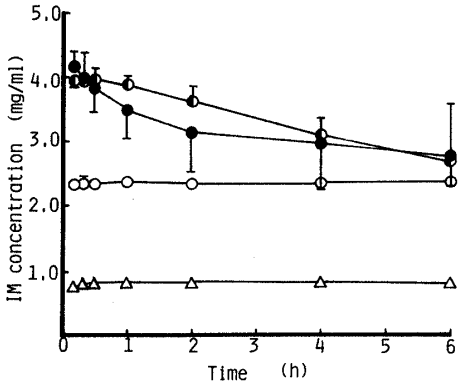

Fig. 4. Time Courses of IM Concentration with IM Powder (△), IM–PC (0.25) (○), (0.50) (◐) and (0.75) (●)

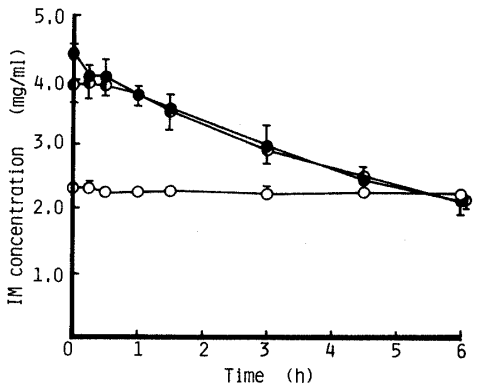

Fig. 5. Time Courses of IM Concentration of Filtrates of IM–PC (0.25) (○), (0.50) (◐) and (0.75) (●)

The suspensions for dissolution studies were filtered 15 min after the start of the experiment.

at any molar ratio of IM–PC.

Figure 4 shows the time course of IM concentration. The solubility of IM was 0.8 mg/ml. The IM concentration increased to *ca.* 4.0 mg/ml within 10 min with IM–PC (0.50, 0.67, 0.75), so that the solubility became 5 times that of IM powder. However, the IM concentration decreased with time and became 2.5 mg/ml after 6 h, and 2.0 mg/ml after 30 h. With IM–PC (0.33 and 0.25), the IM concentration became 3.4 and 2.3 mg/ml within 10 min, respectively. In these cases the initial concentrations were lower than those of IM–PC (0.75, 0.67, 0.50), but the concentrations did not change much within 6 h, though they decreased to *ca.* 2.0 mg/ml after 30 h.

It was considered that two processes occurred at the same time: precipitation from solution and dissolution from remaining IM–PC. To simplify the system, the suspension of IM–PC were filtered through a membrane filter 15 min after initiation when the IM concentrations should be maximum. Figure 5 shows the time courses of IM concentration in the filtrates. The filtrates were transparent yellow solutions immediately after filtration, but a white precipitate was observed within 30 min in the case of IM–PC (0.50, 0.67, 0.75), and its amount increased with time. The precipitate was collected and analyzed by DSC. A sharp peak was observed at 154 °C. The precipitate was dissolved in ethanol and IM was determined

by ultraviolet absorption at 318 nm; 98% of the precipitate was concluded to be IM, and PC was not detected. It was suggested that IM dissolved to form a supersaturated solution, then recrystallized and precipitated with time. The precipitate appeared after 6 h with IM–PC (0.33) and slight cloudiness was observed after 30 h with IM–PC (0.25). The rate of decrease seemed to be related to the initial IM concentration.

IM concentrations were almost the same from IM–PC (0.50, 0.67, 0.75), but they became lower as the IM molar ratio was decreased, presumably because the dissolution rate might decrease and the degree of supersaturation became low.

On the other hand, PC dissolved to the extent of 0.1—0.5 mg/ml from IM–PC but the degree of dissolution was not reproducible, and the PC concentration did not change with time in any study. PC concentrations were under 1/10 of those of IM and there was no apparent relationship between IM and PC concentrations, so it was considered that the high concentration of IM was not a result of complex formation of IM and PC in water. However, PC was precipitated when IM was removed by dialysis with Visking tubing. There appears to be some interaction between IM and PC so that PC can dissolve in water.

Preparation and Physicochemical Properties of FP–PC and KP–PC

Similar studies were done for FP and KP, which are also non-steroidal antiinflammatory drugs and have similar structures. FP–PC (0.50) and KP–PC (0.50) were obtained as glassy films which could be crushed in an electric coffee mill. The X-ray diffraction patterns showed that FP and KP were present in an amorphous state in FP–PC (0.50) or KP–PC (0.50). FP–PC (0.75) and KP–PC (0.75) were transparent semisolids immediately after evaporation of xylene, but became cloudy after 1 d. Both drug and PC peaks were observed in these cases (Fig. 6).

The IR spectrum of FP–PC (0.50) did not change remarkably compared with that of the physical mixture, but the 1695 cm^{-1} band of FP was decreased in intensity. The 1410 cm^{-1} band of FP became very weak even in the physical mixture. The 1695 cm^{-1} C=O band, and the 1420 and 1280 cm^{-1} C–O or OH bands of KP became weaker and the 1730 cm^{-1} band became stronger in the case of KP–PC (0.50) (Fig. 7).

Figures 8 and 9 show the DSC curves. As the ratio of drug increased, peaks were observed at lower temperature. Cater *et al.*[11] and Casal *et al.*[12] reported that the PC bilayer transition temperature was depressed by morphine derivatives, phenol or salicylic acid and the degree of

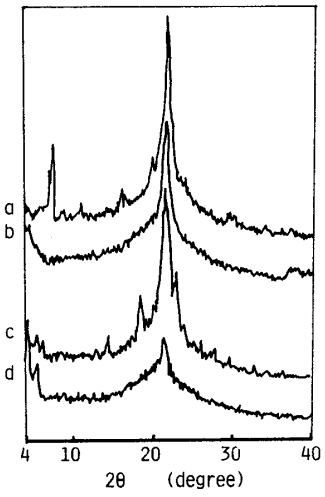

Fig. 6. X-Ray Diffraction Patterns of FP–PC, KP–PC and Related Samples

Physical mixture of FP and PC (0.50) (a); FP–PC (0.50) (b); physical mixture of KP and PC (0.50) (c); KP–PC (0.50) (d).

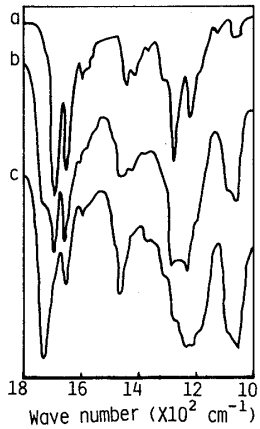

Fig. 7. IR Spectra of KP (a), Physical Mixture (0.50) (b) and KP–PC (0.50) (c)

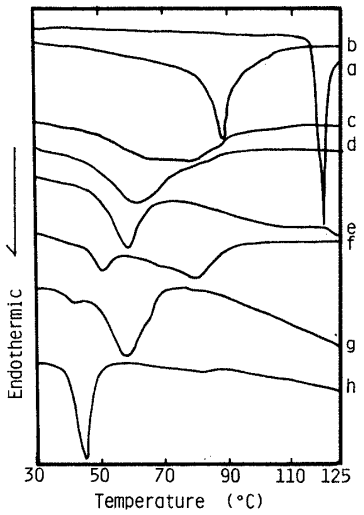

Fig. 8. DSC Curves of FP–PC and Related Samples

FP (a); PC (b); physical mixture (0.25) (c); (0.50) (d); (0.75) (e); FP–PC (0.25) (f); (0.50) (g); (0.75) (h).

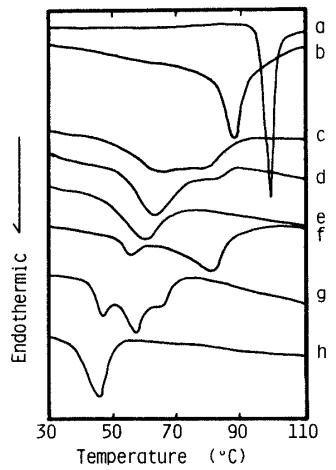

Fig. 9. DSC Curves of KP–PC and Related Samples

KP (a); PC (b); physical mixture (0.25) (c); (0.50) (d); (0.75) (e); KP–PC (0.25) (f); (0.50) (g); (0.75) (h).

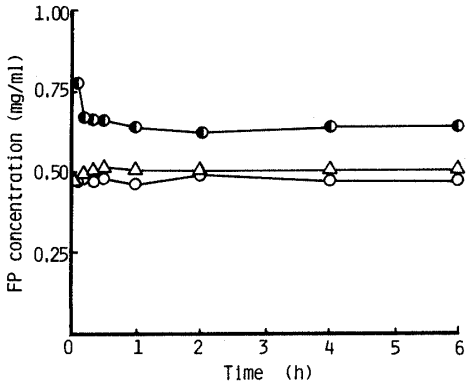

Fig. 10. Time Courses of FP Concentration with FP Powder (△), FP–PC (0.25) (○) and (0.50) (◐)

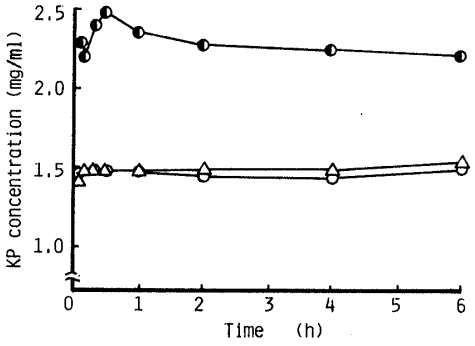

Fig. 11. Time Courses of KP Concentration with KP Powder (△), KP–PC (0.25) (○) and (0.50) (◐)

depression was dependent on the drug concentration. The phenomena were similar to those in the case of the solid dispersions. Physical mixtures also showed complex peaks, suggesting that some interaction probably occurs.

It was considered that FP and KP have some interaction with PC and are present in an amorphous state, similar to the case of IM. However, the limit of the drug molar ratio at which the amorphous state was stable was lower than that of IM.

Dissolution Studies of FP–PC and KP–PC

The solubility of FP under these conditions was 0.50 mg/ml. FP concentration increased to 0.78 mg/ml initially with FP-PC (0.50), but decreased within 1 h to 0.66 mg/ml. The dissolution behavior of FP–PC (0.25) was similar to that of FP powder (Fig. 10).

In the case of KP–PC (0.50), the KP concentration was 2.5 mg/ml at 30 min, which was 1.7 times the solubility of KP powder, but it decreased with time and became 2.2 mg/ml after 6 h. KP–PC (0.25) was no different from KP powder in dissolution behavior (Fig. 11).

PC was not detected in any case, so the high concentrations of FP and KP were due to the amorphous state of the drugs. In the cases of FP–PC (0.25) and KP–PC (0.25), the rate of

dissolution might limit the degree of supersaturation as in the case of IM–PC.

Conclusion

IM, FP and KP interact weakly with PC, probably through carbonyl or amide groups, and exist in an amorphous state in PC solid dispersions. The stability of the amorphous state differs depending on the drug. The solubilities were 1.5—5 times those of the drug powders, but the drug concentration decreased with time. PC did not dissolve in the case of FP–PC and KP–PC, but dissolved at a low concentration in the case of IM–PC. Thus, the increase of solubilities was considered to be due to the amorphous state of the drugs.

It is considered that solid dispersions in PC are available to improve the utility of poorly water-soluble drugs.

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References and Notes

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