Physicochemical Properties of Phenobarbital Solid Dispersion with Phosphatidylcholine[1)]

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We prepared a phenobarbital (PB) solid dispersion (SD) with phosphatidylcholine (PC). PB was present in an amorphous state in SD if its mole fraction was under 0.75. An infrared (IR) spectra study suggested a hydrogen bond between NH in PB and phosphate in PC, with a ratio of about 1 : 1. When the mole fraction of PB was less than 0.50, differential scanning calorimetry (DSC) curves showed endothermic peaks at 57, 90 and 145 °C, and an exothermic peak at 60 °C. The IR spectrum and X-ray diffraction pattern changed after holding at 70 °C, so at this point it is considered that the metastable state of SD changed into a stable state, and extra energy was released. When the mole fraction of PB was high, PB also arranged near hydrophobic group because an endothermic peak was observed at 46—52 °C, which was lower than fully hydrated PC.

PB is similar to indomethacin (IM) in molecular shape and to phenytoin (PHT) in chemical structure. Its DSC curve and IR spectra are similar to PHT, and the limit ratio of its amorphous state is the same as IM. It is considered that the chemical structure is an important factor in its interaction to PC, and also, the molecular shape is important to arrange into PC lattice.

Keywords phenobarbital; phosphatidylcholine; solid dispersion; X-ray diffraction pattern; infrared spectrum; thermal analysis; hydrogen bond

We investigated the physicochemical properties and dissolution patterns of indomethacin (IM), ketoprofen (KP), flurbiprofen (FP)[2)] and phenytoin (PHT)[3)] solid dispersions with phosphatidylcholine (PC) as a carrier, and found that the drugs were present in an amorphous state in PC, and their dissolution rates were improved. However, three tests—differential scanning calorimetry (DSC) curves, infrared (IR) spectra and the limit concentration of the drug present in an amorphous state— suggested that interaction between PC and IM, KP and FP (IM *etc.*) was different from that between PC and PHT.

PC has both hydrophilic and hydrophobic parts, and therefore arranges in a regular array.[4)] So the properties of solid dispersion would be effected by two factors; one is the drug affinity to the hydrophilic and hydrophobic parts of PC, another is the space size of PC and the drug molecular size. PC and drugs interact, for example, through a hydrogen bond.[2,3)] PHT has a cyclic amide group, whereas IM *etc.* have a carbonyl group as their hydrogen bond donor or receptor. The molecular shape of PHT is bulky because of its diphenyl group, whereas that of IM *etc.* are plane like. PHT and IM *etc.* are thus different in both chemical structure and molecular shape. Phenobarbital (PB) has a similar chemical structure to PHT in its cyclic amide group, yet a similar molecular shape to IM *etc.* In this paper, PB solid dispersion was studied to examine the interaction of the drug and PC.

Experimental

Materials PC was purified from hydrogenated soybean phospholipids (Nikko Chemicals, Lecinol S-10) containing 5—7% of phosphatidylethanolamine as an impurity.[5)] The fatty acid composition of the PC acyl chains was stearic acid: palmitic acid 85 : 15. So the mean molecular weight of PC was calculated as 786.

PB was a JP XI grade (Iwaki Seiyaku). Other chemicals were of a reagent grade.

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

PC and PB were also separately prepared by the same procedure and mixed in a fixed mole fraction 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 RAD-2C). The X-rays were Ni-filtered CuK_α radiation (30 kV and 40 mA; scanning speed 4 degree/min; scanning range, $2\theta = 3$—40 degrees). IR spectra were obtained on an IR spectrophotometer (Japan Spectroscopic Co., Ltd., A-102) by the KBr semimicro disk technique (scanning speed, 10 min; scanning range 4000—650 cm^{-1}). Thermal analysis was carried out with DSC (Shimadzu DT-30 system with DS-30). About 5 mg of the sample sealed in an aluminum crimp cell was heated at the speed of 20 °C/min (range ±20 mJ/s; chart speed 40 mm/min) in an atmosphere of nitrogen. Also, a micro melting point apparatus (Yanagimoto Seisakusho) was used with a microscope (× 60).

Partition Coefficient A pH 2.0 HCl/KCl buffer solution containing *ca.* 10 μg/ml of the drug (in the case of IM, 0.5 μg/ml because of its low solubility) was vigorously shaken with the same volume of hexane at 25 ± 1 °C for 2 h. The partition coefficient was determined by the drug's concentration in the water phase before and after shaking. Drug concentrations were determined by ultraviolet (UV) absorption (Shimadzu UV-160) in the cases of KP (260 nm) and FP (246 nm), and by high pressure liquid chromatography (HPLC) in the cases of PB, PHT and IM. The HPLC condition was as follows: apparatus; Waters model 510 pump, model 490 variable wavelength UV detector and model 740 data analyzer, column; μ Bondapak C_{18} 3.9 × 150 mm kept at 30 °C, mobile phase; a mixture of methanol: water acidified with phosphoric acid to pH 2.5 = 50 : 50 (PB, PHT) and 70 : 30 (IM), flow rate; 1 ml/min, retention time; 3.6 min (PB), 5.7 min (PHT) and 6.2 min (IM), wave length of detector; 230 nm (PB, PHT) and 318 nm (IM). Data were shown as the mean of three experiments.

Results

Preparation and Appearance of Solid Dispersion PB dissolved in xylene about 2 mg/ml even if it was warmed at 80 °C, but in the presence of PC, it dissolved a over 50 mg/ml. This solution showed no coprecipitation if the temperature was reduced to as low as 20 °C. The increase of solubility by PC was also observed in PHT.[3)] It suggests that PC and PB had some interaction in xylene, or that the solubilization of PB by PC was occurred.

After removing the xylene, a semiopaque film was obtained when the mole fractions of PB were 0.25, 0.33 and 0.50, and a transparent film was obtained when they were 0.67 and 0.75. PB–PC (0.80) was also a transparent film, but partly cloudy.

Powder X-Ray Diffraction Pattern Figure 1 shows powder X-ray diffraction patterns. The signals of PB crystals were changed by recrystallization from xylene. Many crystal forms have been observed in PB.[6] It indicates that PB, which was a form I crystal, changed into form III[7] through preparation.

PC which was recrystallized from xylene showed a signal of a space of acyl chains at $2\theta=21°$ ($d=4.2$ Å),[8] as well as some unspecified signals, probably related to long space, at $2\theta=5.2°$ ($d=16.8$ Å), 10.2° ($d=8.6$ Å), 13.0° ($d=6.7$ Å), which are 33 Å/n ($n=2$, 4, 5).

A physical mixture showed both PB and PC signals. PB–PC showed only PC signals and no PB signal when the mole fractions of PB were from 0.25 to 0.75. However PB–PC (0.80) often showed a small signal at 15°, which seemed to originate with PB. It indicates that PB was present in an amorphous state in PB–PC if its mole fraction was less than 0.75. When the mole fraction of PB was increased over 0.50, the diffraction angle of PC at $2\theta=21°$ showed no change, whereas the halo signal ($2\theta=13$—20°) was observed and the long space signals disappeared. These patterns reproduced for each preparation, except for PB–PC (0.50). PB–PC (0.50) often showed many unspecified signals.

IR Spectra Figure 2 shows the IR spectra of PB–PC (0.50) and related samples. PB recrystallized from xylene showed a different IR spectra from commercial PB. It also suggests the change of crystal form from form I to form III.[6] The spectrum of physical mixture was produced by the addition of PC and PB.

The spectrum of PB–PC (0.50) was compared with that of the physical mixture. PB showed a NH stretching band of oxysopyrimidine ring with an intermolecular hydrogen bond; 3200, 3150, 3080, 2960 and 2850 cm^{-1}.[6] In the spectrum of PB–PC (0.50), the peaks at 3150 and 3080 cm^{-1} disappeared. The peaks' lower frequency, 2960 and 2850 cm^{-1}, were covered by a PC–CH stretching band and not identified. The OH band of PC (3400 cm^{-1}) tended to become smaller. The peak at 3310 cm^{-1}, with hydrogen bond free NH stretching,[9] was not found. It indicates that the intermolecular hydrogen bond of PB was replaced with another molecular structure, *i.e.* PC.

In the 1800—1650 cm^{-1} range, carbonyl band, PB showed C=O peaks at 1760 and 1695 cm^{-1},[6] and PC at 1730 cm^{-1}. PB–PC (0.50) showed a peak at 1735 cm^{-1} and new shoulder peak at 1710 cm^{-1}. The peaks at 1760 and 1695 cm^{-1} disappeared. This change also suggests a change in the nature of the hydrogen bond.

PC showed a phosphate band at 1240 cm^{-1}. The phosphate band disappeared in the PB–PC (0.50) spectrum and new a peak appeared at 1160 cm^{-1}. It suggests some changes occurred in the PC molecule, too.

Other ratios of PB–PC were also investigated. Figure 3 shows the IR spectra of PB–PC (0.25, 0.67, 0.75). In the case of PB–PC (0.25), the changes observed in the bands were PB related (3200, 3150, 3080 and 1760 cm^{-1}), but no change was observed in the PC band at 1240 cm^{-1}. On the other hand, a change was observed at 1240 cm^{-1} (PC phosphate band) in the case of PB–PC (0.67) and (0.75), but no change was observed in PB bands. These data

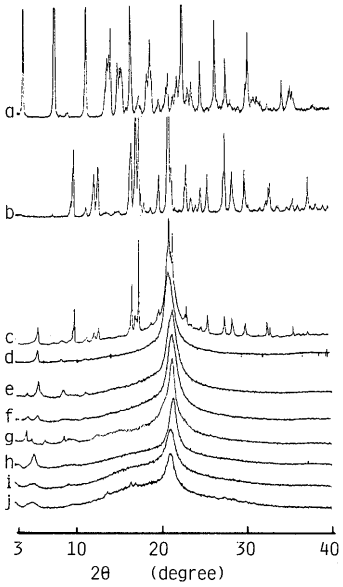

Fig. 1. X-Ray Diffraction Patterns of PB–PC and Related Samples

a, PB crystals (commercial); b, PB crystals (from xylene); c, physical mixture (0.50); d, PC; e, PB–PC (0.25); f, (0.33); g, (0.50); h, (0.67); i, (0.75); j, (0.80).

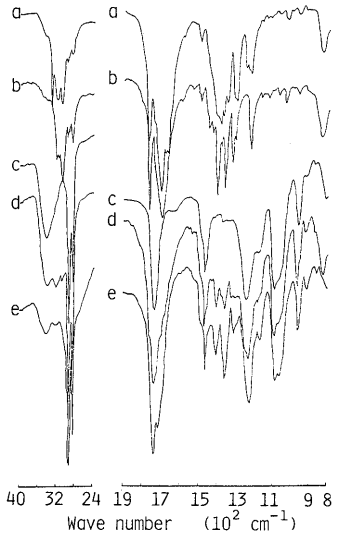

Fig. 2. IR Spectra of PB–PC (0.50) and Related Samples

a, PB crystals (commercial); b, PB crystals (from xylene); c, PC; d, physical mixture (0.50); e, PB–PC (0.50).

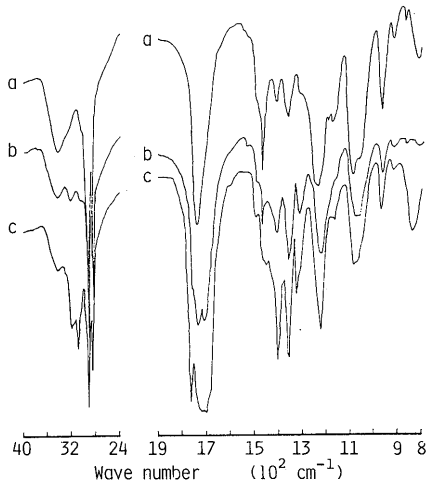

Fig. 3. IR Spectra of PB–PC (0.25) (a), (0.67) (b) and (0.75) (c)

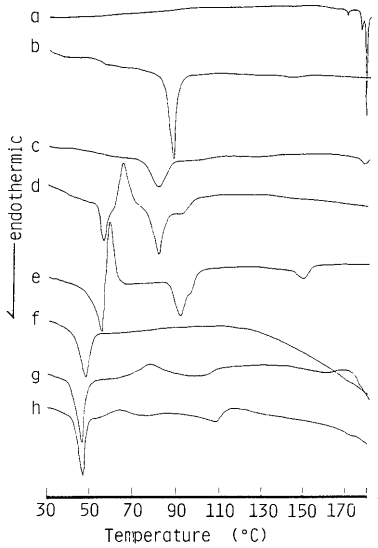

Fig. 4. DSC Curves of PB–PC and Related Samples

a, PB crystals (from xylene); b, PC; c, physical mixture (0.50); d, PB–PC (0.25); e, (0.50); f, (0.67); g, (0.75); h, (0.80).

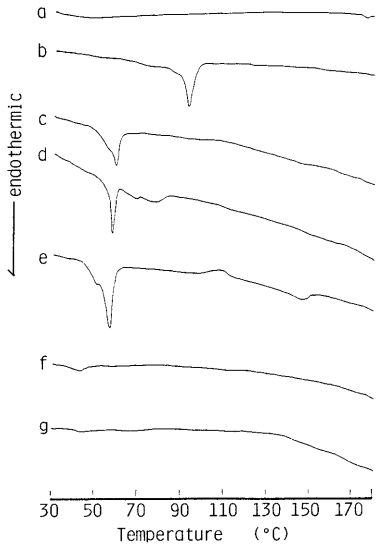

Fig. 5. DSC Second Heating Curves Immediately after Heated to 200 °C and Cooled

a, PB crystals (from xylene); b, PC; c, physical mixture (0.50); d, PB–PC (0.25); e, (0.50); f, (0.67); g, (0.75).

indicate that the hydrogen bond between NH in the oxysopyrimidine ring of PB and the phosphate of PC, and the ratio between them would be about 1 : 1.

Thermal Analysis Figure 4 shows the DSC curves of PB–PC and related samples. PB showed a melting point at 174 °C. PC showed an endothermic peak of its phase transition at 85—95 °C (solid to liquid crystalline).[10] The physical mixture showed 2 patterns; a peak in PC only, and peaks by both PC and PB. The PB–PC mixture would be prepared by heating, just like IM *etc.*–PC, but this method is not as easy as IM *etc.*–PC.

PB–PC (0.25, 0.33, 0.50) showed an endothermic peak at 57 °C, an exothermic peak at 60 °C, and endothermic peaks at 85—95 °C. PB–PC (0.50) also showed a broad endothermic peak at 145 °C. PB–PC (0.67) and (0.75) showed endothermic peaks at 52 and 46 °C respectively, and showed

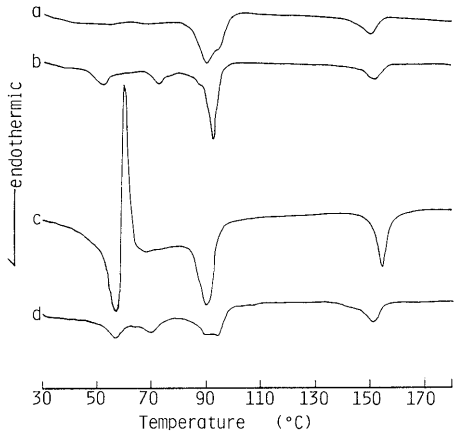

Fig. 6. DSC Second Heating Curves of PB–PC (0.50) 1 d after Heating

Holding at 70 °C (a), 120 °C (b) and 160 °C (c) for 10 min. (d) Prepared at room temperature.

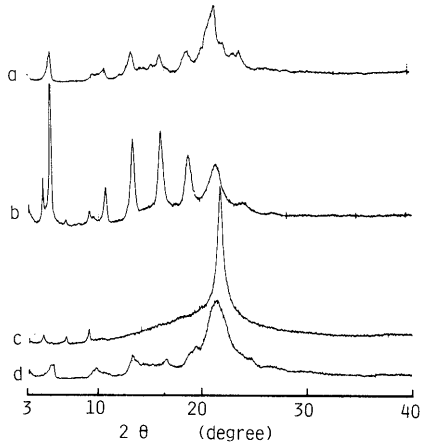

Fig. 7. X-Ray Diffraction Patterns of PB–PC (0.50) after Being Heated and Cooled

Holding at 70 °C (a), 120 °C (b) and 160 °C (c) for 10 min. (d) Prepared at room temperature.

no exothermic peak.

The appearance of the peaks was observed with transmitted light. Semiopaque PB–PC (0.50) in room temperature became transparent at 60 °C temporarily, and then became dark. About 100 °C, it became transparent again. These phenomena were not observed with IM *etc.*–PC; they became progressively clearer as the temperature increased.

PB and PC were relatively stable with heat, and no change was observed in their DSC conditions. So, second heatings were tried. Figure 5 shows the second heating curves immediate after heating at 200 °C. PB–PC (0.25, 0.50) showed only one peak at 56 °C and PB–PC (0.67, 0.75) showed no evident peaks. Second heating curves after 1 d were similar to the first curves, though in the curves of PB–PC (0.25, 0.50) the peaks were sharper.

To study this in detail, PB–PC (0.50) was held for 10 min at fixed temperatures of 70, 120 or 160 °C, which were slightly higher than the temperatures which produced the exothermic peak, PC phase transition temperature and unidentified endothermic peak at 145 °C respectively. PB–PC (0.50) then cooled and reheated immediately and after 1 d.

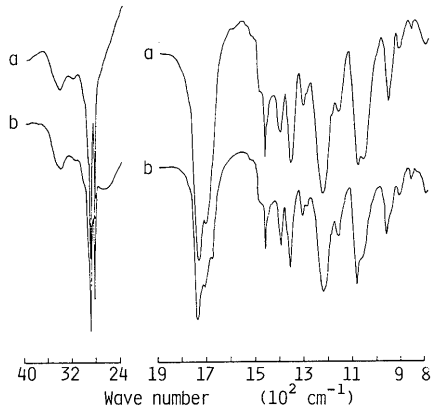

Fig. 8. IR Spectra of PB–PC (0.50) before (a) and after (b) Holding at 70 °C

Figure 6 shows the second heating curves 1 d after holding at each temperature. The peaks at 57 and 60 °C disappeared and only the peaks at 95 (PC phase transition) and 150 °C were observed after holding at 70 °C. After holding at 120 °C, endothermic peaks were observed at 58, 78, 95 and 152 °C. These second run curves were the same as those immediate after cooling. After holding at 160 °C, the second heating curve was the same as the reheating curve after heating at 200 °C. These results indicate a change in the PB and PC condition, and that condition was maintained after cooling to room temperature. So, X-ray diffraction patterns and IR spectra were determined.

Figure 7 shows the X-ray diffraction patterns of PB–PC (0.50) after it was held at a fixed temperature and then cooled. After holding at 160 °C, short PC signals at $2\theta = 21°$ showed no change, but the long-spaced signals changed to $2\theta = 4.4°$ ($d = 19.9$ Å), 6.6° (13.4 Å) and 8.8° (10.0 Å), apparently 40 Å/n ($n = 2, 3, 4$). After being held at 70 °C, the PC signals and new signals, $2\theta = 15.9°$ ($d = 5.6$ Å), 18.5 (4.8 Å), and 23.5 (3.8 Å), apparently 33 Å/n ($n = 6, 7, 8$), were observed. The diffraction pattern after holding at 120 °C was the sum of those after holding at 70 and 160 °C, and each signal became increasingly strong. It suggests the lattice of PC was changed by heating, and the orientation of the PC lattice was raised.

Figure 8 shows the IR spectra before and after holding at 70 °C. The difference occurred at 2700, 1680 and 1060 cm^{-1}. The lowered frequency of NH-stretching absorption would be attributed to a hydrogen bond formation change between PB and PC, because PB showed no crystal character by X-ray diffraction data. The carbonyl band of PB at 1680 cm^{-1} was observed, so only the 2-carbonyl vibration[9] at 1760 cm^{-1} disappeared. The absorption at 1060 cm^{-1} is also a PC phosphate band. Thus, the IR spectra also indicate a change of the PB and PC interaction by holding at 70 °C.

The above results indicate that the unusual conditions of PB–PC (0.50) were obtained due to a changed energy state. So the PB–PC (0.50) was prepared at room temperature. Broad signals similar to the one produced after the PB–PC (0.50) was held at 70 °C were observed. So the temperature and rate of removing xylene has an important effect on the PB and PC interaction pattern.

PB–PC (0.25) showed a similar change through heating, but PB–PC (0.67) and (0.75) showed no such change by heating.

Table I. Partition Coefficients of Drugs Applied for Solid Dispersion

Drug	log $P^{a)}$
PB	−1.80
PHT	−1.22
IM	0.63
KP	−0.30
FP	0.96

a) P is the partition coefficient of hexane/pH 2.0 HCl/KCl buffer solution.

Partition Coefficient The partition coefficient of the undissociated drug was determined (Table I). The coefficients of PB and PHT were considerably smaller than those of IM group.

Discussion

The limit mole fraction of PHT which was present in an amorphous state was 0.33. That of PB was considerably higher, at 0.75. This is the same as IM. PB is similar to PHT in chemical structure, but different in steric structure because of substituent groups of 5-position: PB (phenyl and ethyl) and PHT (diphenyl). It is considered that the shape of PHT is unsuitable to occupy the interstitial space of a PC lattice. A plane-like molecular shape needs to occupy the PC space in a high concentration.

PB and PC should have some interaction, because PB is present in an amorphous state. PB has two hydrogen bond donors (NH), and three acceptors (C=O). PC has a hydrogen bond acceptor, phosphate in polar head group. Craven *et al.*[11] have reported that barbiturates show only hydrogen bond donor property. Novak and Swift[12] have suggested the interaction of barbiturates and PC in chloroform. They reported a hydrogen bond between barbiturate NH protons and the ionized phosphate of PC. In our case, an IR spectra study suggests a hydrogen bond between the NH of PB and the phosphate of PC, and the ratio is about 1 : 1.

DSC curves of PB–PC showed two patterns. In the case of PB–PC (0.25, 0.33, 0.50), the first endothermic peak at a temperature of 57 °C agreed with the phase transition temperature of fully hydrated PC. It is considered that PB interacted with PC like water does: inhibited the intermolecular hydrogen bond of PC and depressed the phase transition temperature.[13] After the phase transition, an exothermic peak at 60 °C and an endothermic peak at 90 °C was observed. PB–PC (0.50), after being held at 70 °C, showed only the endothermic peak at 90 °C, and its IR spectrum and X-ray diffraction pattern changed. The results of holding at 120 and 160 °C suggest that they began to change again at temperatures over approximately 100 °C, and the change was completed at 160 °C. PB has many hydrogen bond sites and shows many hydrogen bond patterns.[9] The hydrogen bond site of PB was different and the arrangement of PB and PC was changed before and after holding at 70 °C. This indicates that PB–PC (0.50) shows two conditions: one is formed when the energy is raised by heat above 160 °C or by a solvent and heat, and another is stable a state formed with less energy. In both conditions, PB is present in an amorphous state. The high energy condition changed into a stable state at the phase transition, and the energy gap of the two conditions

represents the exothermic peak. Also, it was observed that high energy PB–PC (0.50) changes into a stable state after 6 months (data not shown). PB–PC (0.25, 0.33) are similar to PB–PC (0.50), but the PC shows two states; one interacts with PB, and the other is free.

In this way, the DSC curves of PB–PC (0.25, 0.33, 0.50) are similar to those of PHT (0.25, 0.33), and quite different to those of IM *etc.*–PC. PB and PHT have a similar chemical structure, the oxysopyrimidin ring, which has many hydrogen bond sites. IM *etc.* has only its carbonyl group as a hydrogen bond site. On the other hand, PC has both hydrophilic and hydrophobic parts, and the interaction to the polar part of PC might be superior in the cases of PB and PHT, since partition coefficients are very low. So it is considered that the chemical structure has a great influence on the interaction pattern between the drug and PC.

In the cases of PB–PC (0.67, 0.75), the endothermic peak temperature was lower than fully hydrated PC.[13] This phenomenon is similar to IM *etc.*–PC, where it was considered that PB would exist near the PC acyl chain. However, the degree of depression with PB is smaller than with IM *etc.* Menger *et al.*[14] reported that the phase transition temperature of PC was lowered by a substituent of the acyl chain and it depended on size and location. The molecular size of PB is smaller than IM but larger than KP and FP. On the other hand, it is hard to consider PB situated the end of acyl chain because the partition coefficient of PB is lower than IM *etc.* So, PB may be located near the ester linkage of acyl chains.

In conclusion, PB is present in an amorphous state in PC solid dispersion when its mole fraction is less than 0.75, to the same extent as IM. But the interaction to PC is similar to PHT. So it is considered that the molecular shape and chemical structure are both important factors for solid dispersion formation.

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References and Notes

1) A part of this work was reported at the 109th Annual Meeting of the Pharmaceuticl Society of Japan, Nagoya, April 1989.
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