The Solid Dispersion of Benzodiazepins with Phosphatidylcholine.¹⁾ The Effect of Substituents of Benzodiazepins on the Formation of Solid Dispersions

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Solid dispersions of four benzodiazepins, nitrazepam (NZP), nimetazepam (NMP), diazepam (DZP) and medazepam (MZP), with phosphatidylcholine (PC) were prepared to investigate the effect of functional groups of benzodiazepins. These benzodiazepins were present in an amorphous state immediately after preparation of the solid dispersion. The limit mole fractions for the amorphous state were 0.50 (NZP), 0.25 (NMP), 0.25–0.40 (DZP) and 0.25 (MZP). Infrared spectra and thermal analysis suggested an interaction, probably a hydrogen bond, between PC and NZP. In contrast, no interaction was suggested between PC and NMP, DZP or MZP, because they have no functional donor groups for the hydrogen bond. NZP solid dispersion showed no change after 1 year, but NMP, DZP and MZP solid dispersion showed recrystallization of drugs after 1 year. Thus, it was considered that some interaction between PC and the drug was needed to prevent the recrystallization. Dissolution of NZP in pH 7.0 phosphate buffer solution was much faster from NZP solid dispersion than from NZP crystals, and there was no aging effect of the solid dispersion. Dissolution of DZP also improved with the formation of a solid dispersion, but the dissolution rate became slower with time.

Keywords solid dispersion; phosphatidylcholine; benzodiazepin; aging; thermal analysis; X-ray diffraction pattern; dissolution

Solid dispersion is a method for improving the dissolution rate of poorly water soluble drugs by dispersing the drug in a carrier as an ultramicrocrystal or amorphously.²⁾ The bioavailability of poorly water soluble drugs, which limited absorption from the gastro-intestine track by dissolution rate, was improved,³⁾ and the dose could be reduced.⁴⁾ Some cases showed no aging effect,^{3a)} though some cases showed a drug condition change, agglomeration or recrystallization, with time and improvement of the dissolution rate decreased.⁵⁾ The reason for the different aging effect must be clarified. Thakker *et al.*⁶⁾ reported that nabilone and polyvinylpyrrolidone (PVP) interacted with a hydrogen bond in solid dispersion, and polymorphism was prevented for more than 2 years. Doherty and York⁷⁾ defined a furosemide–PVP interaction in solid dispersion, and a hydrogen bond may account for the formation and stability of the amorphous form in solid dispersion.

We have been studying the solid dispersion, the carrier of which is phosphatidylcholine (PC), and reported indomethacin (IM), ketoprofen (KP), flurbiprofen (FP),⁸⁾ phenytoin (PHT),⁹⁾ and phenobarbital (PB)¹⁰⁾ solid dispersions. These drugs exist in an amorphous state in solid dispersion and show no recrystallization with time. Infrared (IR) spectra and differential scanning calorimetry (DSC) curves suggested a weak interaction, probably a hydrogen bond, between the drug and PC. However, the interactions between PC and IM, KP or FP with a carbonyl group were different from those between PC and PHT or PB with an oxopyrimidin ring. On the other hand, the limit mole fractions of PHT and PB for the amorphous state were quite different, 0.33 and 0.75, respectively, in spite of similar chemical structures. So the steric structure also affects the formation of a solid dispersion.

In this report, four benzodiazepins which have the same skeleton but different substituents were used to investigate the effect of functional groups on the formation of solid dispersions without taking into account steric factors.

Experimental

Materials PC was purified by the method described in an earlier

report.¹¹⁾ Its purity was above 95% and the fatty acid composition was palmitic acid:stearic acid=15:85. The structure and abbreviations of benzodiazepins are listed in Table I. Nitrazepam (NZP) and nimetazepam (NMP) were the kind gift of Toyo Jozo Co., Ltd. and Sumitomo Pharmaceutical Ltd., respectively. Diazepam (DZP) and medazepam (MZP) were provided by Nippon Bulk Yakuhin Co., Ltd. Other chemicals were of a reagent grade.

Preparation of Solid Dispersion The required amounts of drug and PC were weighed out and dissolved in xylene. The xylene was then evaporated off *in vacuo*, sometimes warming to 80°C. The glassy film thus obtained was crushed and sieved with an 80-mesh screen. This powder was placed *in vacuo* again to remove residue xylene. The solid dispersion thus obtained was described as drug–PC (mole fraction of drug). Drugs were obtained from xylene and sieved with an 80-mesh screen. The physical mixture (P-mix) was prepared by mixing drug and PC with a spatula. It was stored in a desiccator over silica gel at 25±2°C.

Physicochemical Properties of Solid Dispersion IR spectra were obtained on an IR spectrophotometer (Japan Spectroscopic, Ltd., FT/IR-8000) by the diffuse reflectance method with no dilution. The base lines were corrected. Also, the IR spectra of the CHCl₃ solution (5×10⁻² M) were measured. DSC curves and X-ray diffraction patterns were measured by the same condition as previously reported.¹⁰⁾ Measurements were performed within 1 week after preparation. To investigate the aging effect, the solid dispersions packed in sample tubes were stored in the dark in a desiccator over silica gel at 25±2°C. After 1, 3, 6 and 12 months, the X-ray diffraction patterns were measured.

Dissolution Studies The dissolution patterns of NZP and DZP were tested in a JP XI dissolution test apparatus. As 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 sample equivalent to 10 mg of the

TABLE I. Benzodiazepins Used in This Study

Drug	Abbreviation			
		R ₁	R ₂	R ₇
Nitrazepam	NZP	H	=O	NO ₂
Nimetazepam	NMP	CH ₃	=O	NO ₂
Diazepam	DZP	CH ₃	=O	Cl
Medazepam	MZP	CH ₃	H, H	Cl

drug was dispersed in a test solution. An aliquot of the test solution was withdrawn periodically and immediately filtered through a $0.20\text{ }\mu\text{m}$ membrane filter (Dismic-25, Advantec Toyo). The same volume of PBS was added to the test solution. The NZP concentration was determined by the absorbance at 258 nm after dilution with pH 7.0 PBS. The DZP concentration was determined by the absorbance at 241 nm after dilution with 0.1 N HCl solution. The solubilities were determined by dispersing the equivalent to 25 mg of the drug in 50 ml of pH 7.0 PBS at $37 \pm 0.1^\circ\text{C}$. The test was performed within 1 week after preparation. All studies were done in triplicate.

Results and Discussion

IR Spectra NZP-PC and MZP-PC were a slightly yellow powder, and NMP-PC and DZP-PC were white powder.

The IR spectra of solid dispersions and P-mix were compared. Each P-mix showed the sum of the drug and PC spectra. NZP-PC showed some difference from the P-mix (Fig. 1). PC the phosphate band at 1170 cm^{-1} showed some change. The NZP amide NH bands at 3350 and 3225 cm^{-1} , and NZP absorption at 1917 and 1025 cm^{-1} disappeared. NZP absorption at 1620 and 1342 cm^{-1} showed some change. These changes were also observed in CHCl_3 solution. The NZP amide C=O band at 1712 and 1685 cm^{-1} was observed only at 1685 cm^{-1} in P-mix. On the other hand, this band was observed only at 1715 cm^{-1} in NZP-PC. This band in CHCl_3 solution is at 1699 cm^{-1} . The above changes indicated not only an amorphous state of NZP but also some interaction between NZP and PC.

NMP and DZP also have an amide, but NMP-PC showed no evident difference from the P-mix, and DZP-PC sometimes showed some difference at 1700 cm^{-1} only

immediately after preparation. MZP-PC showed the same spectra with P-mix.

DSC Curves Figure 2 shows the DSC curves of solid dispersions and related materials. Heating was carried out under 200°C because PC decomposes above 200°C even if its atmosphere is N_2 . The melting point of NZP is above 200°C (225°C), so its DSC curve is not shown. The P-mix of NZP and PC showed an endothermic peak at 85°C , which was considered the phase transition of PC (anhydride-monoanhydride).¹²⁾ The base line drifted at above 150°C , which suggested that some change occurred. The appearance was observed with a micro melting point apparatus, and melting occurred gradually from 150°C . NZP-PC (0.25) showed endothermic peaks at 63 and

Fig. 1. IR Spectra of NZP-PC and Related Materials
a, NZP; b, PC; c, P-mix (0.50); d, NZP-PC (0.50).

Fig. 2. DSC Curves of Solid Dispersions and Related Materials

(I) NZP; (II) NMP; (III) DZP; (IV) MZP. a, drug; b, PC; c, P-mix (0.25); d, solid dispersion (0.25); e, 0.33; f, 0.50; g, 0.67.

Fig. 3. X-Ray Diffraction Patterns of Solid Dispersions and Related Materials

(I) NZP; (II) NMP; (III) DZP; (IV) MZP. a, drug; b, PC; c, P-mix (0.25); d, solid dispersion (0.25); e, 0.33; f, 0.40; g, 0.50; h, 0.67.

75 °C, and NZP-PC (0.50) at 54 and 63 °C. By increasing the mole fraction of drug, a lowering of the peak temperature was observed. This phenomenon was also observed in DSC curves of IM-PC, KP-PC and FP-PC, and the degree of temperature depression was almost the same if the mole fraction of the drug was the same.⁸⁾ Therefore, it was suggested that NZP and PC had some interaction so that the PC phase transition temperature was lowered. NZP-PC (0.67) showed endothermic peaks at 63 and 78 °C, and the degree of depression of the phase transition temperature was not significant as with NZP-PC (0.50).

In contrast, NMP-PC, DZP-PC and MZP-PC showed an endothermic peak at 85 °C, the same as PC only, and they showed no base line drift at high temperature. It was suggested that NMP, DZP and MZP have no interaction with PC which affects the PC phase transition, as does NZP. An NMP melting peak was observed if the mole fraction of NMP was above 0.33, and DZP and MZP melting peaks were observed for mole fractions above 0.50. The drug crystals remained in solid dispersion in these cases.

X-Ray Diffraction Patterns Figure 3 shows the X-ray diffraction patterns of solid dispersions and related materi-

TABLE II. The Change in the X-Ray Diffraction Patterns of Solid Dispersions

	Time after preparation (months)				
	0	1	3	6	12
NZP-PC (0.25)	—	—	—	—	—
(0.50)	—	—	—	—	—
(0.67)	+	+	+	+	+
NMP-PC (0.10)	—	—	—	—	—
(0.25)	—	±	±	±	±
(0.33)	+	+	+	+	+
DZP-PC (0.10)	—	—	±	±	+
(0.25)	—	—	+	+	+
(0.33)	±	+	+	+	+
(0.40)	±	+	+	+	+
(0.50)	+	+	+	+	+
MZP-PC (0.10)	—	+	+	+	+
(0.25)	±	+	+	+	+
(0.33)	+	+	+	+	+

—, no drug signals; ±, drug signals were sometimes observed; +, drug signals were always observed.

als. NZP-PC showed only PC signals, and the amorphous state of NZP in solid dispersion was suggested. NZP-PC (0.50) also showed no NZP signals, suggesting the

amorphous state of NZP. However some signals which did not fit with either PC or NZP were observed at $2\theta = 4.4^\circ$ ($d = 20.1 \text{ \AA}$), 6.6° ($13.4 \text{ \AA}$) and 8.8° ($10.0 \text{ \AA}$). These signals were also observed in the X-ray diffraction patterns of PB-PC (0.50). The long space of the lamellar phase of PC, in which the acyl chains are C_{18} , was reported $60\text{--}63 \text{ \AA}$ (anhydride-mono-hydrate).¹³ $62 \text{ \AA}/n$ ($n = 4, 6, 8$) signals were observed in our case, and these signals changed into $80 \text{ \AA}/n$ ($n = 4, 6, 8$), probably due to arranging NZP into a PC lattice. NZP-PC (0.67) showed both NZP and PC signals. If the mole fraction of NZP was under 0.50, NZP was considered to be present in an amorphous state.

In the case of NMP, NMP-PC (0.33) showed NMP signals clearly. DZP-PC (0.25) showed only PC signals. DZP-PC (0.33) and (0.40) showed only PC signals in some cases, but both PC and DZP signals in other cases, and the reproducibility of the preparation was poor. DZP-PC (0.50) consistently showed both PC and DZP signals. The patterns of MZP-PC (0.25) were observed in two cases, for PC signals only and for both PC and MZP signals. MZP-PC (0.33) exhibited both PC and MZP signals.

As mentioned above, the limit mole fractions of the drugs present in the amorphous state were about 0.50 (NZP), 0.25 (NMP), 0.25–0.40 (DZP) and 0.25 (MZP). However, reproducibility was poor in the cases of DZP and MZP, unlike that of other drugs which had been investigated. Next, the changes of X-ray diffraction patterns with time were studied, and the results are shown in Table II. NZP-PC showed no change after 1 year (Fig. 4I). However, in the cases of NMP-PC, DZP-PC and MZP-PC, the solid dispersion which had shown no drug signals immediately after preparation, showed drug signals after some months. The change of DZP-PC (0.25) is shown in Fig. 4II as a typical example.

To sum up their physicochemical properties, the solid dispersions were divided into two groups; one was NZP and the other was NMP, DZP and MZP. The amorphous state of NZP is stable with time, but those of NMP, DZP and MZP are unstable and recrystallization occurs.

NZP has H as R_1 and $=O$ as R_2 , a lactum ring. This structure contributes to the hydrogen bond. Actually, the

Fig. 4. Change of X-Ray Diffraction Patterns of NZP-PC and DZP-PC as a Function of Time

(I) NZP-PC: a, 0.67; b, 0.67 after 12 months; c, 0.50; d, 0.50 after 12 months. (II) a, DZP-PC (0.25); b, after 1 month; c, after 3 months; d, after 6 months; e, after 12 months; f, P-mix (0.25).

IR spectra show some change in amide, and the PC phase transition temperature was lowered. This indicates an interaction between NZP and PC. In the case of NMP, in which R_1 substituent is replaced with CH_3 , its tertiary amide group, $C=O$, does not contribute to the hydrogen bond. The nitro group at the 7-position contributes little to the hydrogen bond. The IR spectra show no change in either the amide band (1680 cm^{-1}) or the nitro band ($1520, 1340 \text{ cm}^{-1}$), and DSC curves show the PC phase transition peak at the same temperature as PC alone. Thus, it was considered that there was no interaction between PC and NMP. DZP and MZP were also considered to have no interaction with PC for the same reason.

For the above reason, NZP is present in an amorphous state in NZP-PC like IM, PHT or PB; however, NMP, DZP and MZP are temporarily present in an amorphous state by coprecipitation with PC, but there is no interaction for stabilizing the amorphous state, so those drugs change into a crystal form, which is a more stable energy state.²⁾

Dissolution Studies It became apparent that NZP was present in an amorphous state in NZP-PC but NMP, DZP and MZP were recrystallized over time even if they were present in an amorphous state immediately after preparation. Although it is not necessary for drugs to exist in an amorphous state, they will be undesirable for use if their dissolution patterns result in recrystallization. Therefore, the dissolution pattern was tested for NZP-PC and DZP-PC as typical examples of recrystallizing drugs.

The solubility of NZP was $35 \mu\text{g/ml}$. It raised above

Fig. 5. Dissolution Patterns of NZP in a pH 7.0 Phosphate Buffer Solution

Δ , NZP crystals; $\blacksquare$, P-mix (0.50); $\circ$, NZP-PC (0.25); $\bullet$, 0.50. —, immediately after preparation; ---, after 12 months. Each point represents the mean $\pm$ S.D. of three experiments.

Fig. 6. Dissolution Patterns of DZP in pH 7.0 Phosphate Buffer Solution

Δ , DZP crystals; $\blacksquare$, P-mix (0.40); $\circ$, DZP-PC (0.25); $\bullet$, 0.40. —, immediately after preparation; ---, after 1 month; - - - -, after 3 months; ..... after 12 months. Each point represents the mean $\pm$ S.D. of three experiments.

100 µg/ml with NZP-PC, though recrystallization of NZP in solution was very fast. DZP-PC also temporarily raised the solubility of DZP from 50 to 73 µg/ml.

Figure 5 shows the dissolution patterns of NZP. NZP-PC (0.25) and (0.50) showed similar dissolution patterns; 50% of NZP dissolved within 5 min, 80% within 30 min. The dissolution rate was much higher than that from NZP crystals. These improved dissolution patterns showed no change after 1 year. It was suggested that NZP-PC may be used to improve the NZP dissolution rate.

Figure 6 shows the dissolution patterns of DZP. DZP dissolved 40% within 5 min and 80% within 30 min from DZP-PC (0.25). From DZP crystals, only 14% of the DZP dissolved within 5 min and 40% within 30 min. Thus, the dissolution rate of DZP was improved by the formation a solid dispersion, as well as NZP-PC. DZP-PC (0.40) also improved the dissolution rate of DZP, but not as much as DZP-PC (0.25).

The change of dissolution pattern with time was investigated with DZP-PC (0.25). After 1 month, while DZP signals were not observed in X-ray diffraction patterns, the dissolution slowed compared with the rate immediately after preparation. The dissolution became slower and slower with time, and after 1 year, DZP dissolved only 19% within 5 min, which was half the rate immediately after preparation. Thus, it was considered that the improvement of the dissolution rate by forming a solid dispersion was not maintained for a long time in the case of DZP, which recrystallized with time.

In conclusion, some interaction between PC and a drug is required to keep the drug in an amorphous state. And

some functional group is needed. If the amorphous state of the drug is stable, the improvement of the dissolution rate shows no change with time. In this case, solid dispersion is efficiently improves the dissolution of a drug which does not dissolve well in water.

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References and Notes

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