Studies of Reactive Inorganic Layered Compounds with Drugs. I. Intercalation of Phosphatidylcholine Containing Indomethacin into Synthetic Mica[1)]

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The interaction between a sodium-type synthetic mica (Na-TSM), a model material of reactive layered compounds, and phosphatidylcholine (PC) in a solid dispersion (IM–PC) with indomethacin (IM), a model drug, was investigated using X-ray diffraction analysis. It was found that IM–PC interacts with Na-TSM, and can be immobilized in the interlayer space by means of heating. When IM mole fractions in IM–PC increased from 0.25 to 0.5, the amount of IM intercalated into Na-TSM increased correspondingly from 5—18%. Consequently, it was determined that inorganic layered compounds, such as Na-TSM, intercalated with drugs in PC can be obtained.

Keywords synthetic mica; intercalation; indomethacin–phosphatidylcholine solid dispersion; inorganic layered compounds; X-ray diffraction analysis

The interaction of reactive inorganic layered crystals (host material), such as mica-type layered silicates (montmorillonite and so on), crystalline silicic acids and graphite, with various organic compounds (guest material) existing among layers due to intercalation or ion exchange, has been successfully investigated.[2)] The combination of inorganic layered crystal with organic compounds offers new materials with significant physicochemical characteristics, for instance, superconductivity, catalysis, and electric or heat insulation.[3)] However, only a few studies of the interaction between these inorganic compounds and organic drugs have been carried out in the field of pharmaceutical sciences.

Recently, the interaction between crystalline medicinals and pillar interlayered montmorillonite (PILM), a porous clay, has been reported.[4)] Also, the interaction and bilayer formation of phosphatidylcholine (PC) and phosphatidylethanolamine (PE) in γ-type layered transition metal phosphate[5)] and synthetic mica[6)] by means of the solvent method utilizing $CHCl_3$, and so on, have been studied. It has been demonstrated that certain drugs, such as griseofulvin and indomethacin, form a coprecipitate[7)] or a solid dispersion[8)] with PC, which improves their dissolution behavior. If such drug-containing phospholipids were to be immobilized within an inorganic layered compound, the application of this layered compound as a novel drug carrier system might be possible. Synthetic mica,[9)] which has very stable properties in both acidic and alkaline media, is an attractive model material for reactive layered compounds.

The aim of the present study is to evaluate the interaction between synthetic inorganic mica and PC in a solid dispersion with indomethacin (IM, a model drug) *via* intercalation by means of heating, developed as a new procedure, instead of the solvent method described in previous papers. We used powder X-ray diffraction analysis because of its advantages in intercalation studies.

Experimental

Materials Sodium-type synthetic mica as a host material (Na-TSM, $Na[Mg_{2.5}Si_4O_{10}F_4]\cdot 2H_2O$) was supplied from Topy Industry Co., Tokyo, Japan. Soybean PC (Lecinol S-10EX®; PC content, 97%; acyl composition, stearic acid : palmitic acid 85 : 15) and IM (JP XII) were obtained from Nikko Chemicals, Tokyo, Japan and Nippon Bulk Yakuhin Co., Osaka, Japan, respectively. All other reagents employed were of analytical grade.

Preparation of Intercalation Compound The preparation process consisted of two steps. In the first step, to obtain PC containing IM, a solid dispersion of IM with PC (IM–PC) was prepared by means of a heating method. Briefly, an aliquot (100 mg) of powdered mixture containing IM and PC weighed in fixed mole fractions (0.25—0.5)[8)] was heated in glass tubes in a nitrogen gas atmosphere, using a dry block oven (Scinics Co., Tokyo, Japan) at a constant temperature for 6—10 min. The heated materials were cooled to room temperature by placing the tubes in ice water. These heat-processed products were then collected and crushed using a mortar. IM–PC was obtained by sieving the product through an 80-mesh screen. It was then characterized by means of X-ray diffraction analysis and differential scanning calorimetry (DSC), as described in a previous report.[8)] In the second step, IM–PC was intercalated into Na-TSM by means of the heating method without any solvent as follows. A 100-mg aliquot of a physical mixture of Na-TSM (through an 80-mesh screen) and either IM–PC or PC in various weight ratios was heated in glass tubes using the same procedure described above. Finally, the heat-processed product (an IM–PC or PC intercalation compound of Na-TSM [inorganic layered compound]) was obtained after crushing and sieving.

Thermal Analysis and X-Ray Diffraction Thermal analysis was carried out by means of DSC (Thermal Analysis System Model TAS-200 equipped with DSC8230D, Rigaku Corporation, Tokyo, Japan). Approximately 3 mg of the sample sealed in an aluminum crimp cell was heated at the rate of 10 °C/min in an atmosphere of nitrogen. The intercalation of the products was characterized by means of X-ray diffraction analysis (Powder X-ray Diffractometer, MAC Science (Yokohama, Japan): CrK_α radiation ($\lambda = 2.29$ Å) using monochromator).

IM Content in the IM–PC Intercalation Compound of Na-TSM For the determination of IM content in the IM–PC intercalation compound, the heat-processed products stated above were filtered with qualitative filter paper in order to remove any free IM-PC which did not intercalate into Na-TSM. A rinsed product was obtained after the removal of chloroform. To determine the content of IM intercalated into Na-TSM, the product (IM–PC intercalation compound of Na-TSM) was suspended in heated ethanol (approximately 60 °C). After being cooled to room temperature, the IM-dissolved supernatant obtained following centrifugation was analyzed by means of UV spectrophotometry at 318 nm.

Results and Discussion

Intercalation of IM–PC or PC into Na-TSM From the data of DSC thermograms (Fig. 1), the formation of a solid dispersion (IM–PC) between IM and PC was characterized. To facilitate the intercalation of IM into Na-TSM, IM–PC was used in the heating method, since the intercalation of PC into Na-TSM by means of a solvent method has been observed previously.[6] Figure 2 illustrates the X-ray diffraction profiles of Na-TSM (the host material), and the physical mixture of IM–PC and Na-TSM before heat processing, as well as the products of Na-TSM with IM–PC after heating at a constant temperature (180 °C) and then cooling to room temperature. Only basal plane diffraction was observed for Na-TSM. The interlayer spacing of Na-TSM, estimated from the *d*-value of the X-ray diffraction pattern (represented by curve 3 in Fig. 2), was approximately 1.4 nm (Table I). This value corresponds to the interlayer spacing of the Na-TSM monodehydrate formed by heating, or the solvent used in a previous study.[10] In the case of IM–PC with Na-TSM after heating, the characteristic reflections for the $n\lambda$ sequence ($n=1,2,3...$) of curve 1 obviously differed from those of Na-TSM (curve 3) or the physical mixture of IM–PC with Na-TSM before heating (curve 2). The interlayer spacing (*d*-value) of the heat-processed product (IM–PC intercalation compound of Na-TSM) was estimated to be 5.6 nm (Table I).

These results clearly indicate that the interlayer spacing of Na-TSM was elongated (the *d*-value increased approximately four-fold) by the intercalation of IM–PC. As shown in Fig. 3, a similar phenomenon of elongated interlayer spacing (5.5 nm) was observed in the intercalation of PC without IM (Table I). It was previously reported that the diffraction curves and the intensity sequence of the basal plane reflection of Na-TSM with egg PC were similar to those of the egg PC bilayer, and that the *d*-value of 5.16 nm for PC increased to 5.54 nm for Na-TSM with egg PC.[5,6] The interlayer spacings (*d*-values) of 5.6 nm with IM–PC and 5.5 nm with soybean PC obtained using the heating method in this study are in general agreement with the spacing (5.54 nm) observed with egg PC. Consequently, it may be presumed that IM–PC intercalated into Na-TSM forms a bilayer structure. It was confirmed that the IM–PC intercalation compound of Na-TSM was obtained by means of the heating method.

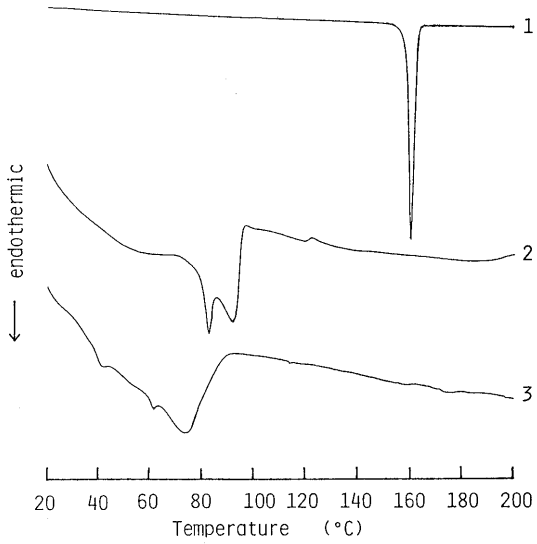

Fig. 1. Thermograms of IM, PC and IM–PC Determined by the DSC Method

IM mole fraction in IM–PC: 0.25. Curves: 1, IM; 2, PC; 3, IM–PC.

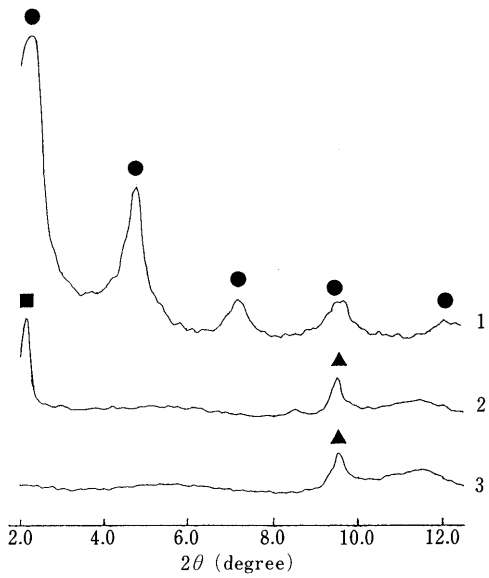

Fig. 2. X-Ray Diffraction Patterns of Na-TSM, the Physical Mixture of IM–PC and Na-TSM, and the IM–PC Intercalation Compound of Na-TSM (Heat-Processed Product) Obtained by the Heating Method

Curves: 1, IM–PC intercalation compound of Na-TSM (IM–PC with Na-TSM after heating at 180 °C for 6 min); 2, physical mixture (IM–PC with Na-TSM before heating); 3, Na-TSM. Key: ●, peak for IM-PC intercalation compound of Na-TSM; ▲, peak for Na-TSM; ■, peak for PC.

Table I. Diffraction Peaks and *d*-Spacing Values Obtained from X-Ray Diffractograms (Figs. 2 and 3) of the IM–PC or PC Intercalation Compound of Na-TSM Prepared by the Heating Method

$n\lambda$ sequence	IM–PC			PC			Na-TSM		
	2θ (degree)	*d* (nm)	Basal spacing $n\times d$	2θ (degree)	*d* (nm)	Basal spacing $n\times d$	2θ (degree)	*d* (nm)	Basal spacing $n\times d$
1	2.3	5.7	5.7	2.3	5.7	5.7	9.5	1.38	1.38
2	4.8	2.73	5.46	5.0	2.62	5.24			
3	7.2	1.82	5.46	7.3	1.80	5.40			
4	9.2	1.42	5.68	9.5	1.38	5.52			
5	12.0	1.10	5.50						
		Mean	5.56		Mean	5.47			

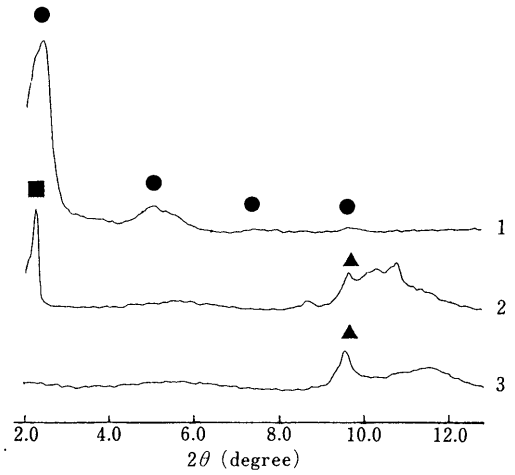

Fig. 3. X-Ray Diffraction Patterns of Na-TSM, the Physical Mixture of PC and Na-TSM, and PC Intercalation Compound of Na-TSM (Heat-Processed Product) Obtained by the Heating Method

Curves: 1, PC intercalation compound of Na-TSM (PC with Na-TSM after heating at 180 °C for 6 min); 2, physical mixture (PC with Na-TSM before heating); 3, Na-TSM. Key: ●, peak for PC intercalation compound of Na-TSM; ▲, peak for Na-TSM; ■, peak for PC.

TABLE II. IM Content (%) in the Prepared IM–PC Intercalation Compound of Na-TSM (Rinsed Product)

IM mole fraction[a)]	Processing temperature	
	180 °C	130 °C
0.25	5	3
0.5	18	15

a) IM mole fraction in IM–PC for preparation of intercalation compound of Na-TSM. Weight ratio in powdered mixture, IM–PC : Na-TSM = 1 : 1. IM content (%) is expressed as the mean of the results from two experiments.

IM Content in the IM–PC Intercalation Compound of Na-TSM To elucidate evidence for existence of IM in the intercalation compound, the heat-processed product (IM–PC intercalation compound of Na-TSM) was rinsed with chloroform in order to remove any free IM–PC which did not intercalate into Na-TSM, and the IM content in these products was determined. The IM content (%) in the IM–PC intercalation compound of Na-TSM processed at 130 and 180 °C is summarized in Table II. When a higher IM mole fraction (0.5) was used, an increased IM content (approximately four-fold) was obtained.

The X-ray diffraction profiles of the IM–PC intercalation compound of Na-TSM after rinsing changed slightly (Fig. 4). The interlayer spacings (*d*-values) of the rinsed IM–PC intercalation compound of Na-TSM were estimated to be 5.3 and 4.5 nm. The lower value of 4.5 nm suggests that the change in the PC bilayer structure (a monolayer structure may be partially formed) was presumably caused by the partial removal of PC due to rinsing.

Concerning the effect of temperature used in the heat processing on formation of the IM–PC intercalation compound of Na-TSM, an increase in processing temperature tended to increase the content of IM in the intercalation compound (Table II). However, as shown in

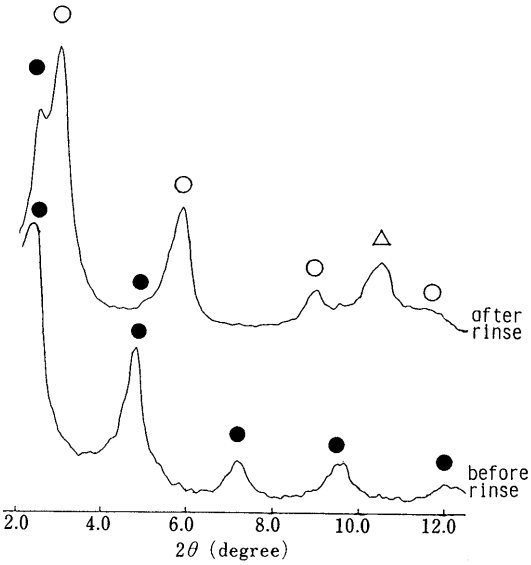

Fig. 4. X-Ray Diffraction patterns of the IM–PC Intercalation Compound of Na-TSM (Heat-Processed Product) before and after Rinsing with Chloroform

Key: ● and ○, peaks for the IM–PC intercalation compound; △, peak for the Na-TSM dehydrate.

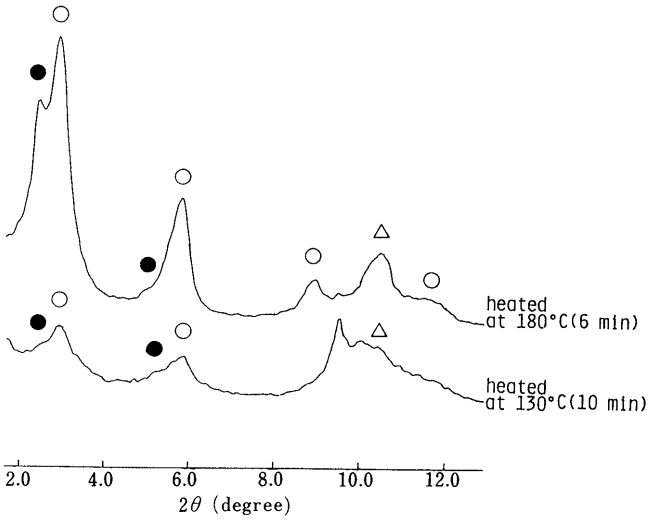

Fig. 5. X-Ray Diffraction Patterns of the IM–PC Intercalation Compound of Na-TSM (Rinsed Product) Obtained by the Heating Method at 130 and 180 °C

Key: ● and ○, peaks for the IM–PC intercalation compound; △, peak for the Na-TSM dehydrate.

Fig. 5, no significant difference was observed in the values (5.3 and 4.5 nm (180 °C): 5.1 and 4.4 nm (130 °C)) of interlayer spacing between the two IM–PC intercalation compounds obtained after heating at different temperatures.

In conclusion, we have found that IM–PC interacts with Na-TSM and is immobilized in the interlayer space. It is possible to prepare the intercalation compound (layered compound) of Na-TSM with varying contents of IM. It may be concluded that inorganic layered compounds such as Na-TSM containing IM in PC, a novel drug carrier mechanism, can be obtained by means of the heating method.

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References and Notes

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10) Unpublished data.