Intercalation Compound of Diclofenac Sodium with Layered Inorganic Compounds as a New Drug Material

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The intercalation reaction of diclofenac sodium (DFS) with layered inorganic compounds, γ-titanium phosphate (γ-TiP), proton type titanium oxide (H-TiO_2) and sodium type synthetic mica (Na-TSM), was examined on. The direct reaction of DFS in ethanol–water mixed solvent resulted in the large amount accommodation of DFS. The amount of intercalated DFS was the order of γ-TiP>H-TiO_2>Na-TSM corresponding to the order of acidity. The intercalation using phospholiopids was also examined to assist the intercalation reaction. However, the amount of intercalated DFS was rather small in comparison with those in the direct reaction. DFS accommodated in γ-TiP dissolved into neutral and basic buffer solution stoichiometry while scarcely dissolved in the acidic solution. The mechanism of the intercalation and reverse dissolution was successfully accounted according to the ion-exchange mechanism between Na^+ in DFS and H^+ in γ-TiP. The dissolution from tablet of DFS/γ-TiP intercalation compound was examined by using a disintegrator. It was found that the dissolution rate appropriately controlled by mixing the disintegrator. The present results suggested the different possibilities in the clinical field to use layered inorganic compounds such as drug delivery system (DDS).

Key words intercalation; diclofenac sodium; layered compound; drug delivery system (DDS)

Two dimensional layered inorganic compounds are composed of thin lamellae that are combined with rather weak interaction such as van der Waals force and hydrogen bond. They can accommodate various organic compounds in the interlayer space to form the intercalation compounds. Typical example is the intercalation of phospholipids to form bilayers in each layered space similar to the cell membrane.[1] Authors have studied the intercalation reaction of some model drugs with layered inorganic compounds such as indometacin.[2,3] The intercalation reaction of diclofenac sodium (DFS) was also dealt with as a model drug.[4] DFS is an anti-inflammatory agent and used as various formulations such as oral drug, percutaneous drug, and ophthalmic solution. It is hygroscopic and attracts our attention from the aspect of pharmaceutical preparation.

Through the preliminary study of the intercalation reaction of DFS with the layered inorganic compounds, it was found that the amount of intercalated DFS depended on the acidity of the layered compounds. Thus it was assumed that the intercalation of DFS occurred through the ion-exchange reaction between sodium ions in DFS and protons in the layered compounds. Accordingly, three kinds of layered compounds with different acidity were selected to elucidate the above assumption. γ-Type titanium phosphate[5] was selected as a strong acid compound and proton type layered titanium oxide[6] was selected as a weak acid compound. These two compounds have protons that can participate in the ion-exchange with sodium ion in DFS. Sodium type difluorotetrasilicic mica[7] was selected as a pure neutral compound. The sodium type mica has no exchangeable proton and is impossible to convert to the proton type.

It is preferable to accommodate DFS as much as possible if the practical use were taken into consideration. The amount of DFS intercalated was rather small in the previous study.[4] Ethanol–water mixed solvent was used to increase the solubility of DFS in the present study. In addition, three intercalation procedures were examined. The first method was the direct reaction of layered compounds with DFS solution. Second was to use the hybrid compounds of layered compounds and phospholipids to expand the interlayer spacing of the layered lattice. The third was to utilize the exfoliation phenomenon of the layered compounds. It is known that each layer of the layered compound can be easily exfoliated forming monolayers due to the reaction with aqueous *n*-propyl amine or similar amine solutions. When the solvent is vaporized, the exfoliated monolayers coagulate again to form another layer structure. The large amount of DFS accommodation was expected on occasion of the coagulation.

Experimental

Layered Compounds Layered inorganic compounds selected were γ-titanium phosphate (γ-TiP), proton-type titanium oxide (H-TiO_2) and sodium-type difluorotetrasilicic mica (Na-TSM). γ-Titanium phosphate ($Ti(HPO_4)_2 \cdot nH_2O$; n is typically 2 and the formula weight about 272) was prepared by the hydrothermal reaction of amorphous titanium phosphate at 280 °C according to the method reported previously.[5] The size of hexagonal plates prepared was about 10—20 μm as observed in SEM photograph.[6] Layered proton-type titanium oxide was prepared according to the method reported by Sasaki *et al.* as follows.[7] Cs_2CO_3 and TiO_2 was mixed well and heated at 800 °C and cesium titanium oxide was prepared in advance. The product was ion-exchanged by H^+ to prepare proton-type titanium oxide ($H_{0.7}Ti_{1.825}\square_{0.175}O_4 \cdot H_2O$; □ means vacancy and the formula weight about 170). The size of fibrous particles prepared was typically 2×0.2 μm though SEM photograph is not shown. Sodium-type difluorotetrasilicic mica was prepared from 10% synthetic sodium difluorotetrasilicic mica aqueous sol that was supplied from Topy Chemical Industry Co. Ltd.[8] ($Na[Mg_{2.5}Si_4O_{10}F_2] \cdot nH_2O$; n is typically 2 and the formula weight about 426). The size of irregular particles used was about 5—30 μm.[9]

Reagents Diclofenac sodium ($C_6H_3Cl_2NHC_6H_4CH_2COONa$, DFS) was supplied from Wako Pure Chemical Industries, Ltd. Japan. Diclofenac has a pK_a value of 4.[10] Since the solubility of DFS in water is relatively low, concentrated ethanol solution was prepared in advance, 0.78 g DFS per 10 ml ethanol (about 0.25 mol/l), and used as a stock solution.[11] Reduced type phosphatidycholine (H-PC)[1] from soybeans was supplied from Nikko Chemicals Co. Ltd. L-α-Lysophosphatidylcholine from Egg York (lyso-PC) was supplied from Wako Pure Chemical Industries, Ltd. They were used to prepare the intermediate intercalation compound of lipid to assist the following intercalation of DFS.[12] They were used without further purification. *n*-Propylamine was used in order to prepare the exfoliated colloidal sol of γ-TiP. All other reagents were reagent grade and supplied from Wako Pure Chemical Industries, Ltd.

Characterization Powder X-ray diffraction analysis was used to charac-

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terize the intercalation compounds. A X-ray diffractometer equipped with CrKα (wavelength: 0.2896 nm) radiation was used for the intercalation compounds with large interlayer distance, *e.g.* phospholipid intercalation compounds (model MO3X-HF, Mac Science Co. Ltd.). CuKα (wavelength: 0.154 nm) radiation was used for others.

Thermal property was examined using thermogravimetry (TG) and differential thermal analysis (DTA) (model TAS200, TG/DTA thermal analysis system, Rigaku Co.). The heating rate was 10 °C/min and the sampling interval was 0.3 s.

The amount of intercalated DFS and dissolved DFS from the intercalation compounds was measured by the UV-visible spectrophotometer (Shimadzu model UV-1600PC system). The observed absorption maxima were 285.0 nm and 276.6 nm in ethanol and buffer solution, respectively.

Intercalation Procedures Three kinds of intercalation procedures were introduced to prepare the DFS intercalation compounds as shown schematically in Fig. 1.

(1) Direct Intercalation (Procedure 1): Each powdered layered compound was mixed with water to prepare their suspension. The suspension and DFS stock solution was mixed well and reacted with intermittent shaking for 24 h at 30 °C. The intercalated DFS was calculated from the difference between the added amount of DFS and DFS remained in the supernatant solution.

(2) Intercalation Using Exfoliation Phenomenon (Procedure 2): This procedure was applied only to γ-TiP because exfoliation of TiP layers occurs effectively by the addition of *n*-propylamine. γ-TiP was mixed with *n*-propylamine and stored for 24 h at 30 °C to prepare exfoliated and colloidal solution of γ-TiP from the analogy with γ-Zr.[13] The stock solution of DFS was then added in the colloidal solution. Reaction time was typically 24 h.

(3) Co-intercalation Using Phospholipids (Procedure 3): Each phospholipid was dissolved in chloroform and DFS stock solution was added in the lipid solution (phospholipid : DFS = 3 : 1 in mole ratio). The powdered compound was then mixed with the DFS-lipid mixed solution (layered compound : lipid = 1 : 0.8 in mole ratio). The reaction time was 24 h at 37 °C. The amount of intercalated DFS was estimated from the decrease in absorbance of the supernatant solution. The amount of intercalated phospholipids was estimated from the weight difference between the added phospholipids and the remained phospholipids.[1]

Dissolution Test Dissolution test was carried out either on the powdered intercalation compound or the molding tablet. The dissolution test was carried out in buffer solutions at pH value of 3.0 (acetic acid), 5.0 (acetic acid + sodium acetate), 7.0 (potassium dihydrogenphosphate + NaOH), and 10.0 (sodium hydrogen carbonate + NaOH), respectively. In the case of powdered sample, the sample was added in a dissolution vessel directly and stirred according to the second method in JP 14 (paddle method) with rotation rate of 500 rpm. An aliquot of the test solution was extracted from the supernatant solution at appropriate time interval, and the amount of DFS was estimated using a spectrophotometer at 276.6 nm. In the case of molding tablet, the tablet was prepared by mixing the DFS intercalation compounds and low substituted hydroxypropyl cellulose (L-HPC; Shin-Etsu Chemical Co. Ltd.) as a disintegrator. Four kinds of tablets were prepared and these mixing ratio of L-HPC were 0.0, 1.0, 3.0, and 10.0 in wt%, respectively. It was molded at a pressure of about 5 kN/m^2.[3] The dissolution test of tablets was carried out in a similar manner to the powdered sample. The test was carried out at a pH value of 7.0.

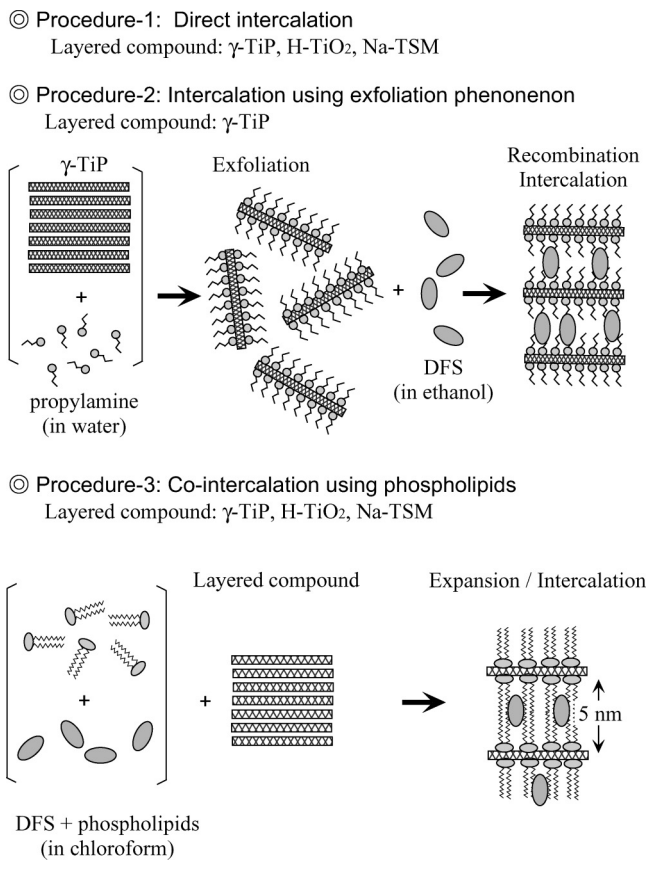

Fig. 1. Schematic Figures of Three Intercalation Procedures Used in This Study

Results and Discussion

Direct Intercalation Direct intercalation of DFS was carried out on γ-TiP, H-TiO_2, and Na-TSM (Procedure 1). They have different acidity and the acidity was found to correlate with the amount of intercalated DFS as discussed below.

The effect of ethanol on the amount of intercalated DFS was examined preliminarily on γ-TiP because the DFS solution prepared from the stock solution contained ethanol inevitably. In this examination, the concentration of DFS was fixed at 1.25×10^{-3} mol/20 ml and ethanol/water ratio was varied from 2/10—10/2 in vol%. The added amount of γ-TiP was 0.1 g, about 3.7×10^{-4} mol. It was found that the amount of intercalated DFS changed with increasing the ethanol concentration showing a maximum at ethanol/water ratio of 3/9 as shown in Fig. 2. Therefore, the intercalation was carried out at ethanol/water ratio of 3/9 for all layered compounds examined.

Figure 3 shows the amount of intercalated DFS per 1 mol of the layered compounds for each intercalation procedure. In the direct intercalation, the amount of intercalated DFS was the order of γ-TiP > H-TiO_2 > Na-TSM. The order was accountable due to the acidity of the layered compound as interpreted below.

Intercalation Mechanism of Direct Intercalation The

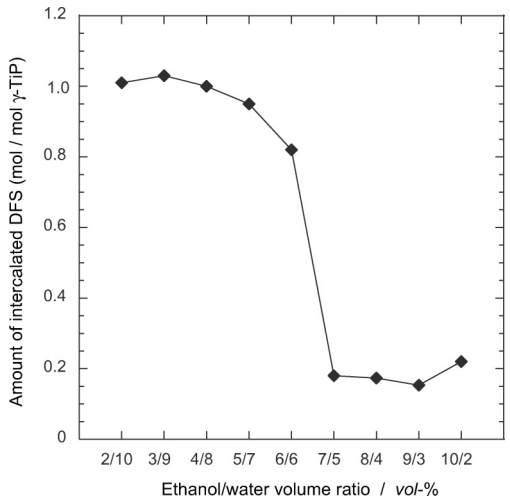

Fig. 2. Effect of Ethanol Concentration on Amount of Intercalated DFS in γ-TiP

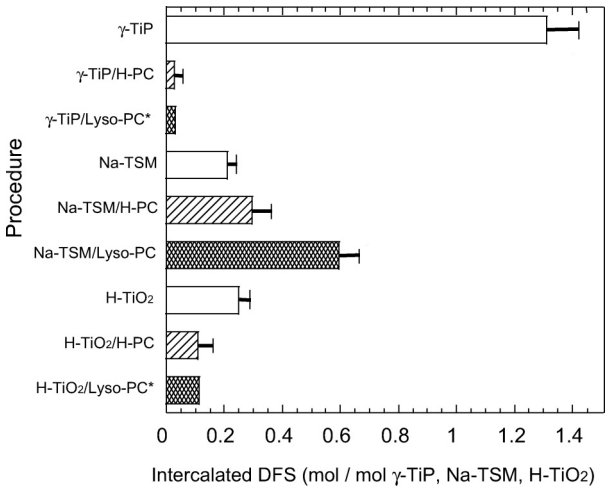

Fig. 3. Amount of Intercalated DFS in Various Layered Compounds Prepared by Three Procedures

* $n=1$, others: $n=3$.

mechanism of direct intercalation was interpreted according to the thermal analysis, X-ray diffraction analysis, and visual observation by microscope. At first, the ion-exchange mechanism was proposed because the order of γ-TiP>H-TiO_2> Na-TSM corresponded to the order of acidity of these layered compounds; γ-TiP is a strong acid, H-TiO_2 is a weak acid, and Na-TSM is a neutral compound.

The equilibrium between sodium salt DFS (DF^--Na^+) and neutral diclofenac DF (DF^--H^+) in aqueous solution is shown by Eq. 1. Intercalation of basic DFS occurred simultaneously with the ion-exchange reaction between Na^+ in DFS and H^+ in the layered material (H^+-X^-) at which DF was formed as shown in Eq. 2.

Equilibrium in solution:

$$\underset{\text{(DFS)}}{DF^-\text{-}Na^+ + H^+} \rightleftarrows \underset{\text{(DF)}}{DF^-\text{-}H^+ + Na^+} \quad (1)$$

Intercalation due to ion exchange:

$$DF^-\text{-}Na^+ + H^+\text{-}X^- \rightleftarrows DF^-\text{-}H^+ + Na^+\text{-}X^- \quad (2)$$

where X indicates the matrix of the layered compounds. Equilibrium (1) inclines to the left hand side because the solubility of DF is very low. Equilibrium (2) must incline to the right hand side with increasing the acidity of the layered compound. In fact, the pK_a value of DF is reported to be 4.0 and pH value of γ-TiP is about 1.5 in aqueous NaCl solution.[14] Firstly, DF is composed in γ-TiP matrix due to the ion exchange of Na^+ in DFS and H^+ in γ-TiP. The equilibrium in Eq. 2 tends to the right hand side because of the strong acidity of γ-TiP. If the ion-exchange mechanism is correct, the amount of DFS intercalated in H-TiO_2 must be intermediate because H-TiO_2 is a weak acid. The lowest amount must result in Na-TSM because Na-TSM is just neutral. The experimental result was consistent well with the ion exchange mechanism proposed here.

Thermal analysis was carried out in order to examine the chemical state of DFS in the intercalation compounds. Figure 4a shows a TG-DTA curve of pure DFS. The melting point of DFS is 283—285 °C and decomposition of DFS occurred simultaneously with fusion. Figure 4b shows a TG-DTA curve of the DFS intercalation compound with γ-TiP. These

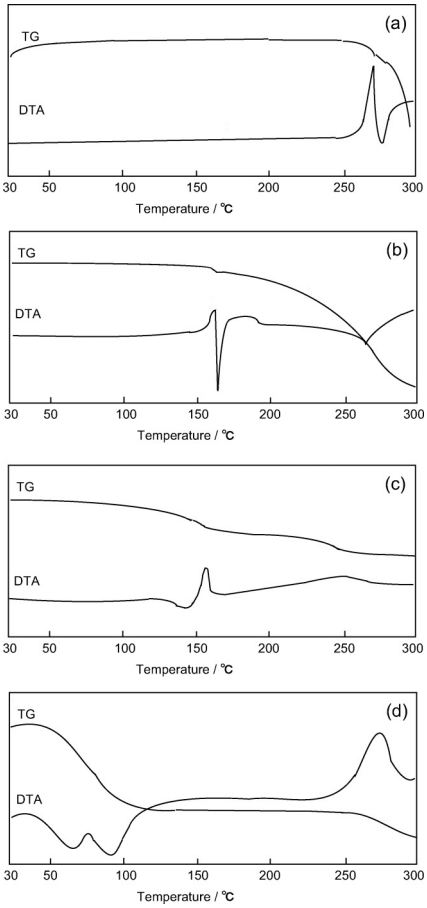

Fig. 4. Thermal Analysis Curves of DFS and Its Related Compounds Prepared under Dry Condition

DFS powder (a), γ-TiP/DFS (b), H-TiO_2/DFS (c), and Na-TSM/DFS (d) prepared by direct intercalation.

thermal analysis curves were independent of humidity showing anti-humid ability of the intercalation compounds contrary to the hygroscopic DFS powder. A small exothermic peak at 161 °C and following significant endothermic peak at about 165 °C appeared in the DTA curve. The endothermic peak may be ascribed to the neutral diclofenac DF, DF^--H^+ in Eqs. 1 and 2, as follows because the melting point of DF is reported to be 156 °C.[10] Coincidence between these two melting points suggested the plausibility of the ion-exchange mechanism although the physical state of intercalated DF is different from the ordinary DF crystal.

Figure 4c shows a TG-DTA curve of DFS intercalation compound with H-TiO_2, where a small endothermic peak at about 149 °C and following exothermic peak at 162 °C appeared. The temperature of the endothermic peak was lower than that of the exothermic peak and differed from pure DFS and DFS intercalation compound with γ-TiP. The latter peak accompanied a weight loss, presumably suggesting the presence of some chemical reaction or vaporization. The former small endothermic peak may also be ascribed to fusion of DF similar to γ-TiP because true peak point of endothermic peak must be hindered by the large exothermic peak. In the case of Na-TSM, no distinct endothermic peak was observed except for the endothermic peak due to the dehydration, Fig. 4d. The fact suggested that the intercalation reaction must differ from the ion-exchange mechanism coincident with the fact

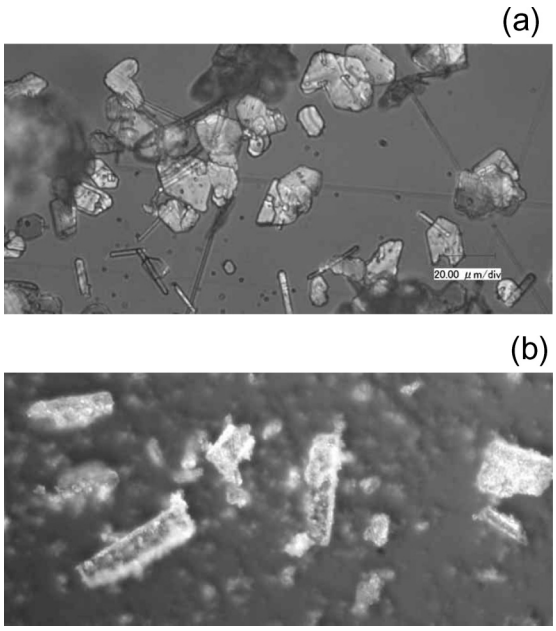

Fig. 5. Microscope Photographs of γ-TiP (a) and Intercalation Compounds of γ-TiP/DFS (b)

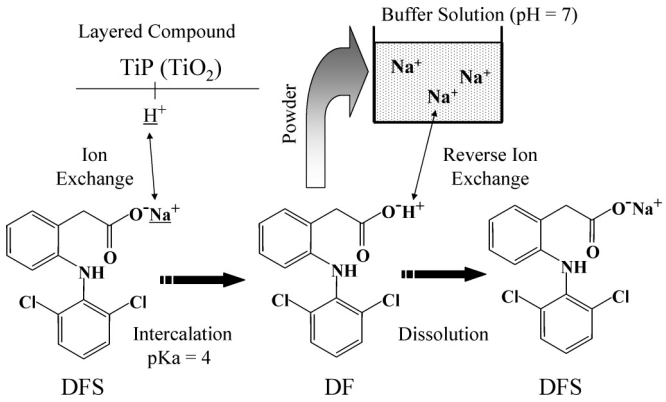

Fig. 6. Proposed Mechanism of Intercalation and Reverse Dissolution of DFS on γ-TiP

that Na-TSM contains no acidic proton.

Figures 5a and 5b show optical photographs of γ-TiP and DFS intercalated γ-TiP. It was quite certain that the crystal structure of γ-TiP changed remarkably due to the direct intercalation of DFS in ethanol solution. X-Ray diffraction patterns of γ-TiP and DFS intercalated γ-TiP were also quite different with each other although the data are not shown. However, correlation between the optical photographs and the thermal analysis was unclear within the limit of the present study.

Figure 6 shows the ion-exchange mechanism schematically. The intercalation (accommodation) of DFS (DF) occurred simultaneously with the ion-exchange between Na^+ in DFS and H^+ in γ-TiP. The reverse dissolution of intercalated DF into the neutral buffer solution containing Na^+ also occurred due to the reverse ion-exchange as illustrated. Experimentally, the reverse dissolution was found to occur quantitatively as described in the dissolution test similar to the forward ion-exchange reaction.

Table 1. Interlayer Distance of Host Layered Compounds and Lipid Intercalation Compounds

	Host layered compound	/H-PC	/Liso-PC
Na-TSM	1.54 (0.96[a])	7.2	5.6
H-TiO_2	0.93 (0.76[a])	5.6	4.4
γ-TiP	1.16 (1.11[a])	6.3	5.2

a) Interlayer distance of anhydrous compound.

Intercalation Using Exfoliation Phenomenon It has been reported that the lamellae of γ-ZrP are exfoliated in aqueous *n*-propylamine solution to form monolayer colloidal solution.[13] We have prepared the colloidal solution of γ-TiP from the analogy of γ-ZrP. On occasion of the recombination of the monolayers, papain (molecular weight: 23000) and catalase (molecular weight: 240000) could be successfully intercalated between the lamellae of the layered compounds.[12] In this study, DFS intercalation was examined in γ-TiP by changing the amount of *n*-propylamine (Procedure 2). The intercalation of DFS hardly occurred even though the concentration of *n*-propylamine changed widely (0—10 μl/10 ml). The amount of intercalated DFS decreased at *n*-propylamine larger than 10 μl contrary to our expectation.

Co-intercalation Using Phospholipids It has already been found that the interlayer gallery space of some layered compounds can be expanded remarkably by the intercalation of phospholipids to from well ordered bilayers just like in the cell membrane. The [layered compound/phospholipid] intercalation compound could successfully intercalate some drugs.[1—3] In this study, the layered inorganic compound was mixed with the chloroform solution containing DFS and phospholipids and co-intercalation of DFS on occasion of the bilayer formation of phospholipids was examined. H-PC with dual alkyl chains and lyso-PC with single alkyl chain were used to assist the intercalation of DFS (Procedure 3). The latter was used to reveal rather loose interlayer gallery space for the DFS co-intercalation.

The amount of intercalated DFS for each layered compounds is shown in Fig. 3. When lyso-PC and H-PC was used, the amount of intercalated DFS was the order of Na-TSM>H-TiO_2>γ-TiP. The combination of lyso-PC with Na-TSM could intercalate DFS twice as much as that of H-PC with Na-TSM. The interlayer distance of various layered compound are summarized in Table 1. The thickness of a covalently bonded host matrix layer of γ-TiP, H-TiO_2 and Na-TSM are 0.8—1.1 nm as estimated from the data of anhydrous compounds. On the other hand, the length of phospholipids for one molecule is about 3 nm including a hydrophilic head. The interlayer gallery height that is opened for the intercalated compounds may be estimated from these two values. The observed interlayer gallery height was 4.6 nm and 6.2 nm in Na-TSM/lyso-PC and Na-TSM/H-PC, respectively. The gallery height was 3.6 nm and 4.8 nm for H-TiO_2/lyso-PC and H-TiO_2/H-PC, respectively, and the gallery height was 4.1 nm and 5.2 nm for γ-TiP/lyso-PC and γ-TiP/H-PC, respectively.

According to the X-ray diffraction data, the structure of the intercalated phospholipids was accounted as illustrated schematically in Fig. 7. The lyso-PC intercalation compound with H-TiO_2 had a small gallery height suggesting that inter-

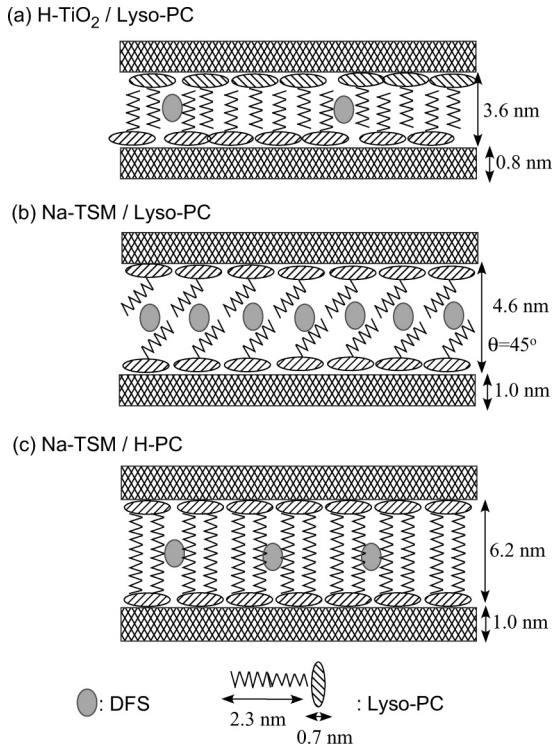

Fig. 7. Schematic Model of DFS Intercalation Compounds Prepared Using Co-intercalation with Lipids, H-TiO_2/Liso-PC (a), Na-TSM/Liso-PC (b), and Na-TSM/H-PC (c)

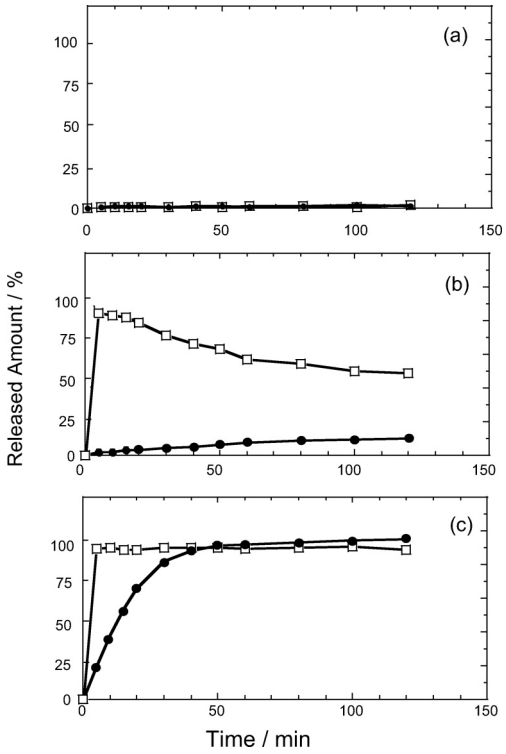

Fig. 8. Release Property of DFS from Powdered DFS (Open Square) and γ-TiP/DFS Intercalation Compound (Closed Circle) into Buffer Solution, pH=3.0 (a), pH=5.0 (b), and pH=7.0 (c)

calated lyso-PC formed a monolayer as shown schematically in Fig. 7a if the length of lyso-PC was taken into account. If such monolayer were formed, the density of *n*-alkyl chains must be rather tight as calculated from the intercalated amount of the lipid and resulted in the small amount of DFS. Lyso-PC intercalated in Na-TSM must form imperfect bialyer and inclined about 45° to the basal plane as shown in Fig. 7b. If it were true, the density of *n*-alkylchains must be loose as expected from the intercalated amount of the lipid and resulted in rather large amount of intercalated DFS. In Na-TSM/H-PC, the gallery height was large and alkyl chains of the lipids must be arranged just perpendicular to the basal plane as shown in Fig. 7c. However, the gallery space for DFS intercalation was rather narrow in comparison with Na-TSM/lyso-PC because the amount of intercalated DFS was large, and the amount of intercalated DFS in Na-TSM/H-PC was less than that in Na-TSM/lyso-PC.

Dissolution Test of DFS from Intercalation Compounds The dissolution property of DFS into aqueous solution from the intercalation compound is one of the most important information from the clinical point of view. The dissolution property was examined either in the powdered form or in the tablet form.

The dissolution property from the powdered DFS and DFS intercalation compound in various pH is shown in Fig. 8. As stated above, DFS was found to be intercalated in γ-TiP and H-TiO_2 due to the ion-exchange mechanism. The ion-exchange equilibrium of DFS and H^+ is shown as follows.

$$\text{DF-Na}^+ + \text{H}^+ \rightleftarrows \text{DF-H}^+ + \text{Na}^+$$

Neutral DF is stable and insoluble in a low pH solution such as pH 3.0. Accordingly, DFS dissolved hardly from neither the DFS powder nor the powder of γ-TiP/DF intercalation compound in acidic buffer solution of pH 3.0. On the other hand, DFS dissolved almost 100% in buffer solution for pH >7.0 because DFS dissociates into DF^- and Na^+ at pH >4 and becomes rather water soluble. In the dissolution test, DF formed in γ-TiP underwent the reverse ion-exchange reaction with Na^+ from the buffer solution to form original DFS in the solution phase. In consistent with the above discussion, the dissolution property at pH 5.0 was intermediate between pH 3.0 and pH 7.0 and 1/10 of the intercalated DFS was dissolved after 50 min. The net amount of DFS dissolved from DFS powder decreased gradually at pH 5.0. Two interpretations seem possible for the decrease in absorbance that was appeared at near pH=5. DFS molecules intercalated in γ-TiP existed in mono-dispersed state and had larger solubility than DFS crystal. Then the dissolved DFS tended to coagulate to form DFS crystal slowly and resulted in the decrease in absorbance. Another interpretation is the decomposition reaction of DFS. Former interpretation seems plausible because no factor that decomposed DFS existed in the present experimental condition. Similar decrease was observed in the imipramine chloride intercalation compound although the data are not shown.

The dissolution rate from DFS powder was fast for pH >7.0 and reached equilibrium within 5 min. The dissolution rate from γ-TiP/DFS was relatively slow and 40—60 min was required to reach a steady state. The suppressed dissolution rate of γ-TiP/DFS suggested the potential ability as a new drug delivery material for DFS. In addition, γ-TiP is chemically stable in acidic medium and decomposes into amorphous titanium hydroxide in basic medium. Accordingly, γ-TiP is considered to be safe if it were used as a drug

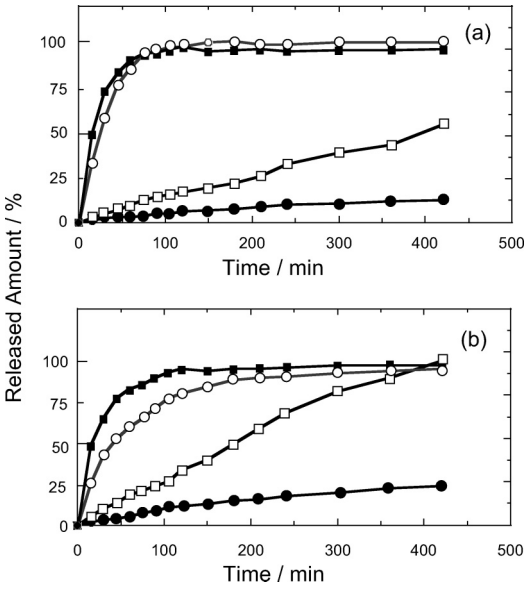

Fig. 9. Release Property of DFS from γ-TiP/DFS Tablet (a) and H-TiO_2/DFS Tablet (b) at pH 7.0

Disintegrator (L-HPC) content: 0.0% (closed circle), 1.0% (open square), 3.0% (open circle), and 10.0% (closed square). Amount of DFS contained in tablet was about 0.06 g (1.9×10^{-4} mol).

additive.

Effect of L-HPC on the Dissolution Property from Tablet The dissolution test of the molded tablets was carried out in the neutral buffer solution and the result is shown in Fig. 9. The tablet prepared from the γ-TiP/DFS powder was hard to disintegrate in buffer solution even at 420 min later. L-HPC was then added as a disintegrator. The addition of 1% L-HPC revealed an intermediate disintegration of the tablet. The tablet disintegrated completely and reached a steady state when 3% or 10% L-HPC added. The errors in time to reach 50% dissolution were roughly 10—20%. The dissolution property of H-TiO_2/DFS was almost similar to those in γ-TiP. Contrary to our expectation, the dissolution rate was controlled by the amount of added disintegrator and not by the dissolution of DFS from inside the layered compound although the dissolution rate of the powdered intercalation compound was lower than that of DFS crystal, Fig. 8c. The fact suggested that disintegration was rate determining step in the case of tablet. On the other hand, the tablet preparation was easer than that of mono-dispersed drug admixed in phospholipid from the pharmaceutical point of view. Suitable tablets could be prepared using fairly smaller amount of disintegrator than that of the phospholipid admixture.[15)]

Conclusion

Fairly large amount of DFS was intercalated in γ-TiP and H-TiO_2 due to the direct reaction with the layered compounds in ethanol–water solution. The reverse dissolution of DFS from the intercalation compounds was also satisfactory. Generally speaking, the layered materials such as used in this study are rather harmless to the human body. In addition, hygroscopic property of DFS improved significantly due to the formation of the intercalation compounds.[4)] Intercalation procedures examined in this study suggested the possibility to apply to the pharmaceuticals such as DDS.

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