Drug Release Characteristics of Ternary Mica/Phosphatidylcholine/Drug Intercalation Compounds

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The intercalation of layered inorganic materials, synthetic mica (TSM), with drugs and their drug release characteristics were investigated using intermediate intercalation compounds with phosphatidylcholine (H-PC). Oil-soluble indomethacin and water-soluble imipramine chloride were selected as model drugs. The drug intercalation compounds were prepared by two methods. The first one was the "solvent method" in which the intermediate intercalation compound of TSM with H-PC was prepared in advance using a chloroform solution of H-PC. The intermediate was then mixed with a drug and heated at 180 °C to prepare the ternary TSM/H-PC/drug compound. The second one was the "heating method" in which the mixture of (TSM+H-PC+drug) was heated at 180 °C to prepare TSM/H-PC/drug directly. The release rate was controlled using a disintegrator (L-HPC). In the case of a tablet sample, the release rate of indomethacin was controllable from 60 min (10% L-HPC) to longer than 420 min (3% L-HPC) in the case of the solvent method. A similar result was obtained in the case of imipramine chloride.

Key words drug delivery system; mica; intercalation; phosphatidylcholine; indomethacin, imipramine

Various procedures have been reported to control the release rate of drugs, *i.e.* drug delivery systems (DDS). We have proposed the use of host/guest intercalation compounds of inorganic layered compounds, where the guest drugs were accommodated into the host layered compounds and used as a DDS.[1] However, there are not very many drugs which can be accommodated into layered inorganic compounds directly to form intercalation compounds. We have then proposed to introduce the third compound which can easily form an intermediate intercalation compound, *e.g.* phospholipids. Many drugs which have difficulty in forming intercalation compounds will be accommodated more easily into the layered compounds and form ternary intercalation compounds if such intermediate compounds are introduced. Prior to their medical application, we have succeeded in forming intercalation compounds of layered inorganic compounds with alkylamines,[2] phospholipids with a bilayer form,[3,4] and enzymes.[5] The concept of the ternary intercalation compound has been applied in the case of enzyme intercalation.

One of the most promising inorganic layered compounds for medical use is synthetic mica[6] (tetrasilicic fluoro mica: TSM). It is very stable against acids and bases and is expected to be harmless to the human body. The reduced type phosphatidylcholine (H-PC), which was prepared by reducing the residual double bonds in the alkyl chains of natural soybean PC using metal catalysis, is relatively stable against oxygen and has been used as a carrier for some kinds of drugs in DDS.[7] In a previous paper, we have reported the detailed intercalation reaction of an H-PC bilayer into layered synthetic mica.[8] Considering the stability of TSM and H-PC, we have planned to intercalate indomethacin (IM) into TSM/H-PC intercalation compounds for use as a DDS; however, this proved rather unsuccessful.[1] Nevertheless, the use of TSM/H-PC intercalation compounds as DDS is now a possibility due to the following improvements reported here.

Two procedures can be used to accommodate drugs into TSM/H-PC intercalation compounds. One is the "solvent method" in which the TSM/H-PC intercalation compound was prepared in advance using an ethanol or chloroform solution of the lipid.[8] The drugs are then accommodated into the intercalation compound to form a ternary TSM/H-PC/drug intercalation compound. The other is the "heating method" in which the mixture of (TSM+H-PC+drug) is heated at an elevated temperature to prepare the ternary intercalation compound directly. The two types of products can then be used as DDS. Two model drugs are examined in this study: one is the oil-soluble IM and the other is the water-soluble imipramine chloride (IMC).

Experimental

Materials The synthetic mica, sodium tetrafluorosilicic mica[6] ($Na[Mg_{2.5}Si_4O_{10}F_4]\cdot 2H_2O$: TSM), was used as the host inorganic layered material and supplied by Topy Industry Co. Ltd. The colloidal mica was washed with deionized water and the precipitated powder of 10—50 μm diameter was gathered and dried in air. The lipid used was soybean H-PC, Lecinol S-10EX, purchased form Nikko Chemicals, Co. Ltd. IM and IMC were selected as model drugs and were used without further purification. Solvents used were reagent grade.

Preparation of Intercalation Compounds Two methods were used to prepare the ternary (TSM/H-PC/drug) intercalation compounds. One was the solvent method and in this, TSM powder was mixed with H-PC/chloroform solution (H-PC : TSM = 1.8 : 1.0, weight ratio) at 37 °C for 2 d and the intermediate H-PC/TSM intercalation compound was prepared in advance. Well defined bilayers of H-PC were formed in each gallery between TSM monolayer sheets.[8] The H-PC intercalation compound was then mixed with IM or IMC. The mixture was heated at 180 °C for 10 min and the ternary drug intercalation compound was prepared. The intercalation of IMC was examined only by the solvent method. The other was the heating method and in this, the mixture of ([TSM/H-PC] : IM = 10 : 1, weight ratio) was heated at 180 °C for 10 min to prepare the ternary (TSM/H-PC/IM) intercalation compound directly.

Characterization of Products The characterization of the (TSM/H-PC/drug) intercalation compounds prepared by the above methods was carried out using a powder X-ray diffractometer (MAC Science, Co. Ltd. MO3X-HF) and Cr$K\alpha$ radiation, $\lambda = 0.2896$ nm. Up to 9 nm of the interlayer distance was easily determined without any special technique by using Cr$K\alpha$.

Molding of Intercalation Compounds and Drug Release Release of the model drugs accommodated in the layered compound was examined using either powdered or molded materials. The drug intercalation compound was mixed with JP low substituted hydroxypropylcellulose (L-HPC) as a disintegrator in a weight ratio of 0.0, 1.0, 3.0, 5.0, and 10%, respec-

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tively. Each mixture was tableted at 500 kgf using a tablet-hitting pressure displacement measuring system (Sratt Press N-20E, Okada-Seiko, Co. Ltd.).

Drug release was monitored using the JP13 PD method. The pH of the solution was fixed at 7.0 using phosphate buffer. The amount of released drug was monitored using spectrophotometry (Shimadzu Corp. UV-1600-PC) at 320 and 250 nm, for IM and IMC, respectively.

Results and Discussion

Intercalation of Model Drugs The intercalation of model drugs was first carried out by the solvent method. Figures 1 and 2 show the X-ray diffraction pattern of the host TSM (1-a), H-PC (1-b), TSM/H-PC (1-c), IM (1-d), IMC (2-

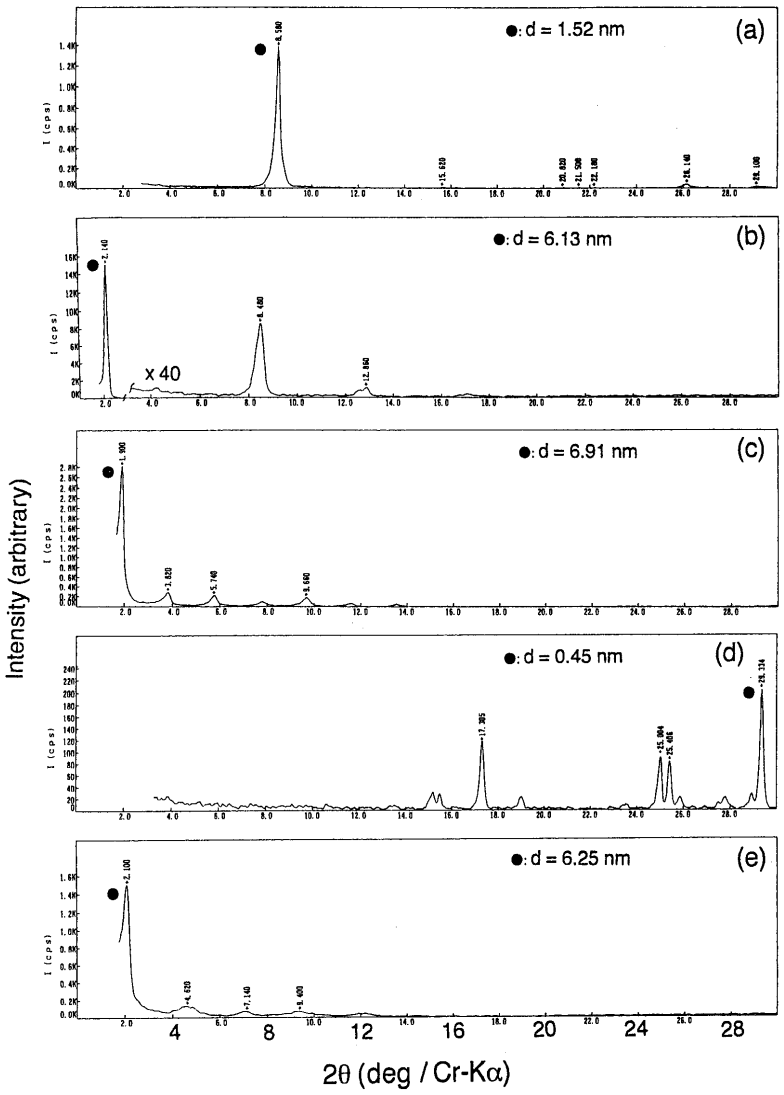

Fig. 1. X-Ray Diffraction Patterns of TSM·$2H_2O$ (a), H-PC Bilayer (b), H-PC Intercalation Compound of TSM (c), IM Powder (d), TSM/H-PC/IM Intercalation Compound after Heat Treatment at 180 °C (e)

The *d*-values which correspond to the gallery height are shown in the figure.

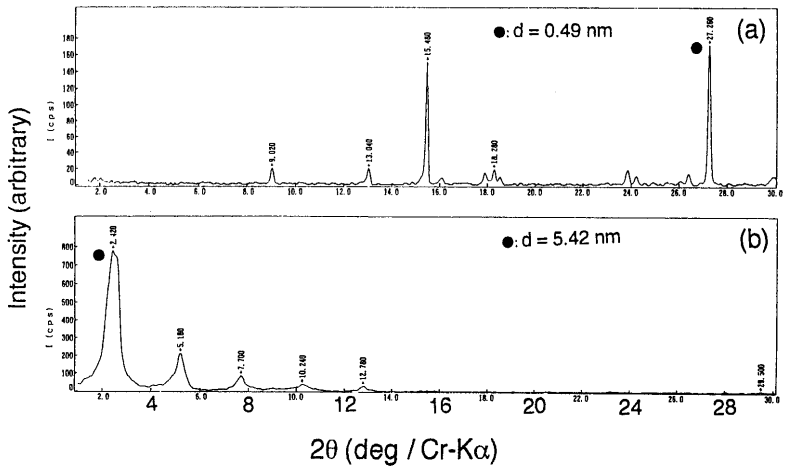

Fig. 2. X-Ray Diffraction Pattern of "as received" IMC Powder (a), and TSM/H-PC/IMC Intercalation Compound after Heat Treatment at 180 °C (b)

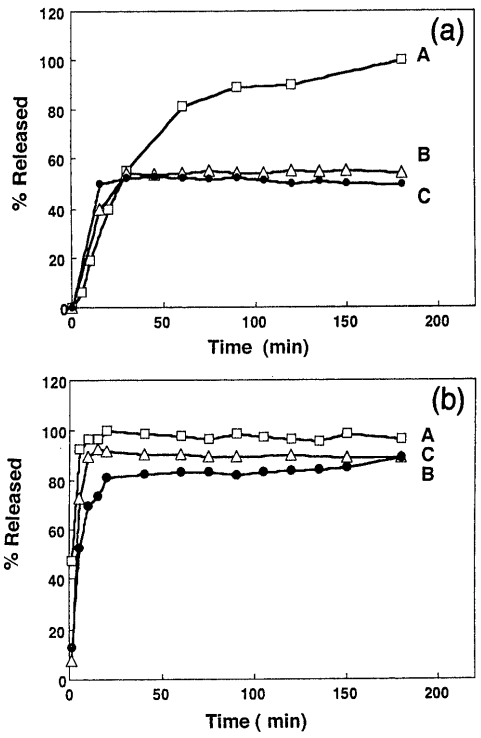

Fig. 3. Dissolution and Release Properties of IM (a) and IMC (b)

IM (IMC) powder (A), TSM/H-PC/IM(IMC) intercalation compound powder prepared by solvent method (B) and heating method (IM) or simple mixture of TSM/H-PC/IMC (C).

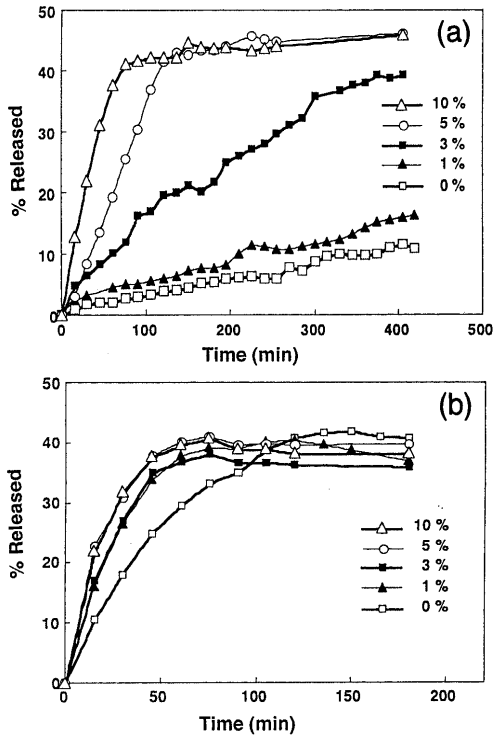

Fig. 4. Release Property of Indomethacin from Tablet TSM/H-PC/IM Intercalation Compound Prepared by the Solvent (a) and Heating (b) Methods

Numbers (%) in the figure indicate the L-HPC content in wt/%.

a), and (TSM/H-PC/IM (1-e) or IMC (2-b)) intercalation compounds. The gallery heights of the layered TSM, H-PC bilayer, TSM/H-PC, (TSM/H-PC/IM), and (TSM/H-PC/IMC) were 1.51, 6.13, 6.91, 6.25, and 5.4 nm, respectively. As seen in Fig. 1-e (solvent method), the model drugs must be intercalated completely because no peak attributable to the model drugs was observed in the ternary intercalation compounds. In the case of the heating method, the amount of intercalated IM has been confirmed either by chemical or X-ray diffraction analysis.[1] The shrinkage of the gallery height (d-value) and corresponding expansion of the line width after drug intercalation, about 1 nm, might indicate disordering of the dual alkyl chains of the H-PC bilayer caused by "squeezing" of the drug molecules. According to the careful observation of the X-ray diffraction pattern of the physical mixture of TSM/H-PC and drug, the accommodation of drug into the TSM/H-PC interlayer was expected to proceed even at room temperature, although the rate was slow.

Release Characteristics of Powdered Materials The release rate of IM and IMC into buffered aqueous solution (pH=7.0) was examined by the JP13 PD method. The added sample amount was 0.1 g, buffer solution 500 ml, stirring rate 100 rpm, and temperature 25 °C. The release characteristics of IM powder, and powdered intercalation compounds prepared by the solvent and heating methods are shown in Fig. 3a. It was found from the figure that the initial release rate was slowest for the IM powder. Very surprisingly, the initial rate of release was faster in the intercalation compounds than the simple IM powder, contrary to our expectations because IM molecules must be accommodated deeply into the layered lattice. Such an acceleration phenomenon in drug release rate has already been observed in a fused IM/H-PC mixture prepared at 180 °C.[7] In this case, IM molecules were expected to be dispersed homogeneously in the base H-PC. However, the amount of IM released was about 1/2 that of intercalated IM. Generally speaking, IM molecules must located near the tail-to-tail region of the dual chain of H-PC because IM is hydrophobic. However, some IM molecules might be buried deeply near the hydrophilic head. Presumably, the release rate of the latter molecules must be slow and we could not observe any release of these molecules within the observed time interval. A similar result for IMC is shown in Fig. 3b. In this case, simple dispersion of IMC with TMS/H-PC was examined instead of using the heating method. The initial release rate of IMC from the TMS/H-PC/IMC intercalation compound was slow compared with the oil-soluble IM. In this case, most of the intercalated IMC was released, unlike IM, Fig. 3a.

IMC molecules must be dispersed randomly in the hydrophobic tails, unlike IM molecules. In fact, both distortion (line width) and shrinking (d-value) estimated from the X-ray diffraction pattern in Figs. 1e (IM) and 2b (IMC) were significant in the IMC intercalation compound and suggested a high degree of disorder of the H-PC bilayer. The smooth release of IMC may be ascribed to such distortion in the H-PC bilayer.

Release Characteristics from Tablets The release rate of tablet IM and IMC intercalation compounds was examined using samples prepared by the solvent method as well as the heating method. The result for IM is shown in Figs. 4a and 4b. In the case of the heating method, the difference in the release rate was less sensitive to the added amount of L-HPC and most of the IM intercalated was released within 1 h. On the other hand, the release rate depended significantly on the content of L-HPC for the sample prepared by the solvent method. Addition of 5% to 10% L-HPC resulted in the

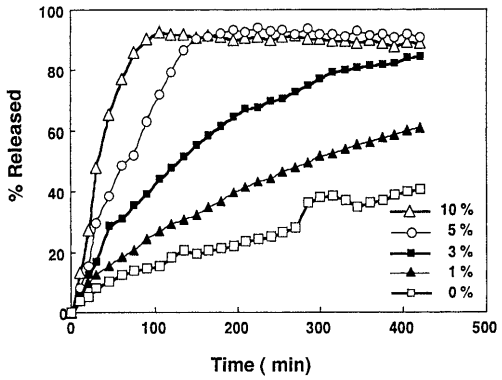

Fig. 5. Release Rate of IMC from Tablet TSM/H-PC/IMC Intercalation Compound Prepared by the Solvent Method

Numbers (%) in the figure indicate the L-HPC content in wt/%.

smooth release of IM and 120 min was required for the complete release of IM at 5% L-HPC. The release rate decreased significantly at a lower L-HPC content, and only 10% of the IM was released after 420 min (7 h) for the sample containing 1% L-HPC. Over 1000 min would be required for the tablet without L-HPC to completely release IM. It was found from these observations that the heating method is superior for the fast release of IM and the solvent method is superior for slow release. The amount of added L-HPC required to achieve a suitable release rate for TSM/H-PC/IM prepared by the solvent method corresponded to that required for the simple H-PC/IM mixture.[9] Accordingly, the tablet formation of TSM/H-PC/IM was also superior to the simple H-PC/IM mixture.

Similar results for the sample containing IMC are shown in Fig. 5. In this case, the release rate of the TSM/H-PC/IMC prepared by the solvent method was faster than that of the TSM/H-PC/IM, Fig. 4b. The amount of L-HPC required to give a similar release rate in TSM/H-PC/IMC was 2 to 3 times greater than that of TSM/H-PC/IM. The differences in release properties between the oil-soluble IM and the water-soluble IMC must be ascribed mainly to the solubility of these model drugs in neutral water, although the difference was not very significant.

Conclusion

The intercalation of model drugs, IM and IMC, into the layered inorganic material (synthetic mica: TSM) was successful using the intermediate TSM/H-PC intercalation compound prepared in advance. Tablet formation of the sample using TSM/H-PC was also satisfactory using L-HPC. Although the amount of model drugs released was about 1/2 that of the amount intercalated in the case of IM, the release rate was fast in the powdered material, and was controllable by forming tablets using a disintegrator L-HPC. The release rate was 30 min for the powdered sample to longer than 1000 min for the tablet sample.

The inorganic layered material used in this study, TSM, is chemically stable and expected to be harmless to the human body. Although the direct use of the material for DDS seems questionable under existing conditions, the gallery between the inorganic layered sheets seems protective against an oxidizing atmosphere. Such a protective atmosphere will be useful for reducing drugs.[5] The application of such inorganic layered compounds and their intercalation compounds with biologically functional compounds is espected to be a practical DDS system in the future.

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