Intercalation Compounds of Layered Materials for Drug Delivery Use. II. Diclofenac Sodium

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Intercalation compounds of ternary layered inorganic materials, synthetic mica (Na-TSM), with diclofenac sodium (DFS) and its drug release characteristics were investigated. Hygroscopic DFS was selected as a model drug to verify the anti-humidity and anti-oxidation of the intercalation compounds. Na-TSM powder was first mixed with the reduced-type phosphatidylcholine (H-PC) solution of chloroform or ethanol. DFS was then mixed with these solutions and heated at 37 °C to prepare the ternary Na-TSM/H-PC/DFS compound. A remarkable phenomenon was observed in the drug release study. The net amount of DFS from the DFS powder decreased apparently after 20 min arising from the decomposition of DFS in acidic medium. On the other hand, the net amount of the released DFS from the intercalation compound was invariant. Thermal analyses study indicated that DFS powder was hygroscopic and a significant endothermic peak was observed accompanied by a large weight loss due to the dehydration of adsorbed water from 40 to 90 °C. On the other hand, no significant dehydration reaction was observed in the intercalation compounds even in the sample stored under humid conditions. The present results indicated that the ternary intercalation compound was resistant to acid in addition to anti-humidity.

Key words intercalation; mica; phosphatidylcholine; diclofenac sodium; anti-humidity

Some layered inorganic compounds can accommodate polar organic compounds between the layered lamellae and form a variety of intercalation compounds. The organic compounds such as phospholipids form a bilayer sheet like cell membranes and the gallery height of the intercalation compounds can extend to 6 nm. Such a gallery will function as a specific place for chemical reactions. The intercalation technique is also available in the pharmaceutical field because several advantages are expected such as controlling the release-rate of drugs. The authors have paid attention to the interaction reaction between the host (layered materials) and guest (drugs) compounds because the new materials present an opportunity to develop various new hybrid compounds for pharmaceutical use.

The host compounds must be harmless to the human body when the intercalation compounds are applied to medical use. One promising inorganic material as a host compound is synthetic mica (sodium difluorotetrasilicate: Na-TSM). It is not only harmless but also very stable either in acidic or basic media. Since drugs with high molecular weight are hardly able to intercalate into the host inorganic compound directly, the authors have proposed to adopt the intermediate intercalation compounds such as phospholipid/mica intercalation compounds with large gallery height.[1]

Among phospholipids the reduced-type phosphatidylcholine (H-PC) is especially stable against oxidation[2] and already used as sustained release excipients in granules,[3] tablets,[4] suppositories[5] and microcapsules.[6]

We have reported the drug release characteristics of ternary intercalation compounds, where the model drugs were stable indomethacin as an oil soluble drug and imipramine chloride as a water soluble one.[7,8] In this study, we have focused on a hygroscopic drug, JP 13 diclofenac sodium (sodium[o-[(2,6-dichlorophenyl)amino]phenyl]acetate, abbreviated to DFS) to verify the anti-humidity and anti-oxidation of the intercalation compounds. The solvent method was used to prepare the Na-TSM/H-PC intermediate compound and the solvents used were chloroform and ethanol. Different Na-TSM/H-PC compounds were prepared, one as a monolayer and the other as a bilayer H-PC compound. The former is formed in ethanol solution and the latter in chloroform solution. DFS is accommodated into the Na-TSM layers simultaneously with H-PC in the present study. The ternary intercalation compounds were characterized by X-ray diffraction and thermal analysis, and the drug release property was examined.

Experimental

Materials The synthetic mica, sodium difluorotetrasilicate[9] (Na-$[Mg_{2.5}Si_4O_{10}F_2] \cdot 2H_2O$; abbreviated to Na-TSM) was used as the host inorganic layered material. The 10% Na-TSM sol, supplied from Topy Industry Co. Ltd., was washed with ultrapure water several times successively. The final precipitate was filtered and air-dried.[1] The lipid used was reduced-type soybean phosphatydilcholine and abbreviated to H-PC; Lecinol S-10EX was purchased from Nikko Chemicals Co., Ltd. JP 13 DFS (mp 283—285 °C, UV max: 276 nm in phosphate buffer, purchased from Wako Pure Chemical Ind., Ltd.) was selected as the model drug and was used without further purification. Other reagents used were reagent grade.

Preparation of Intercalation Compounds The direct method using lipid solution was adopted.[10] Two solvents were used. One was chloroform. A chloroform solution of H-PC was first prepared in a glass ampoule and Na-TSM power was mixed in the solution (H-PC : Na-TSM=0.35 : 1.0 in mole ratio). If the mixed solution was kept at 37 °C, an H-PC bilayer intercalation compound with c-lattice parameter of 7.0 nm was formed. In this study, DFS powder was mixed in the above ampoule ([Na-TSM/H-PC] : DFS=5 : 1) soon after the addition of Na-TSM powder to intercalate H-PC and DFS simultaneously. The mixture was kept at 37 °C for a day and ternary drug intercalation compound was prepared. The other solvent was ethanol. The H-PC ethanol solution was prepared first. The mole ratio was Na-TSM : H-PC=1 : 0.175 because of the low solubility of DFS in ethanol. The ethanol procedure was similar to the one using chloroform. In the case of ethanol, a monolayer like H-PC intercalation with c-lattice parameter of 4.5 nm was formed if Na-TSM was simply stored in the H-PC solution.

Characterization of Products Characterization of Na-TSM, H-PC and the intercalation compounds prepared was carried out using an X-ray diffractometer (MO3X-HF, MAC Science Co., Ltd.) equipped with Cr-$K\alpha$ radiation, λ=0.2896 nm. Thermal analysis, thermogravimetry (TG) and differential thermal analysis (DTA), was carried out using the TG/DTA thermal analysis system (TAS200, Rigaku Co.). The heating rate was 10 °C/min and the sampling interval was 0.3 s.

Humidity Control DFS and the intercalation compounds were stored under two different humidity conditions for at least 24 h. A desiccator with dried silica gel was used for low humidity. A saturated aqueous ammonium chloride solution, 79.2% at 20 °C, was used for high humidity. To distinguish the two conditions, the terms "dry" or "wet" are prefixed in the following text.

Drug Release Property The drug release rate was monitored based on the JP 13 paddle method. The pH of the buffer solution was fixed at 5.5, 7.0 and 9.0 using acetate buffer, phosphate buffer and borate buffer, respectively. The volume of the buffer solution was 500 ml and 0.032 g of drug or the intercalation compounds in which an equivalent amount of DFS was contained. Three milliliters of the test solution was sampled at fixed intervals and the amount of released drug was monitored using a spectrophotometer (UV-1600-PC, Shimadzu Corp.) at 277 nm. A small amount of surfactant was added to the buffer solution to suspend the repellent intercalation compound.

Result and Discussion

Characterization of Drug Intercalation Compounds Figure 1 shows the X-ray diffraction patterns of the host Na-TSM (a), H-PC bilayer (b), Na-TSM/H-PC (chloroform) (c), Na-TSM/H-PC (ethanol) (d), Na-TSM/H-PC/DFS (chloroform) (e) and Na-TSM/H-PC/DFS (ethanol) (f). DFS was amorphous. The thickness of the host Na-TSM lamella (covalently bonded) was about 0.95 nm which was estimated from the c-lattice parameter of anhydrous Na-TSM. Since the thickness of the guest H-PC bilayer was 6.02 nm, the c-lattice parameter of the intercalation compound should be about 7.0 nm if the H-PC bilayers were simply intercalated between Na-TSM lamellae without any structural changes. Na-TSM/H-PC prepared in chloroform had a strong diffraction peak corresponding to the c-lattice parameter of 6.95 nm as seen in Fig. 1c. Accordingly, it is obvious that the intercalation of H-PC between Na-TSM lamellae occurred forming an ideal bilayer of H-PC. On the other hand, the reaction rate of H-PC intercalation in ethanol solution was slow and the peak of the unreacted Na-TSM was still observed at 1.52 nm as seen in Fig. 1d. The c-lattice parameter of the product was 4.53 nm. In this case, the lipid bilayer must be strongly disordered and a monolayer like form of H-PC was intercalated between the host lamellae.

Various intercalation procedures have been proposed to prepare the ternary TSM/H-PC/drug intercalation compounds. In this study, the direct procedure was adopted in which the drug was added to the (H-PC+Na-TSM) solution prepared in advance and intercalated simultaneously. Figures 1e and 1f show the X-ray diffraction patterns of the ternary TSM/H-PC/DFS intercalation compounds which were prepared in chloroform and ethanol solutions, respectively. In the case of chloroform, the c-lattice parameter was about 5.0 nm which was about 2 nm shorter than that of the TSM/H-PC compound. In addition, the line width was broadened and indicated that the arrangement of the lipid bilayers was strongly distorted. The distortion was far more significant in comparison with the intercalation compound of indomethacin.[8] Since DFS used was amorphous, we could not detect the unreacted DFS from the X-ray diffraction patterns unlike indomethacin. The unreacted Na-TSM·H$_2$O (partially dehydrated form and c-lattice parameter being 1.24 nm) was also observed. On the other hand, the c-lattice parameter of the TSM/H-PC/DFS intercalation compounds expanded to 5 nm in the case of ethanol solution which was larger than the 4.53 nm for the TSM/H-PC compound. The line width was also very large and indicated that the lipid layer was distorted
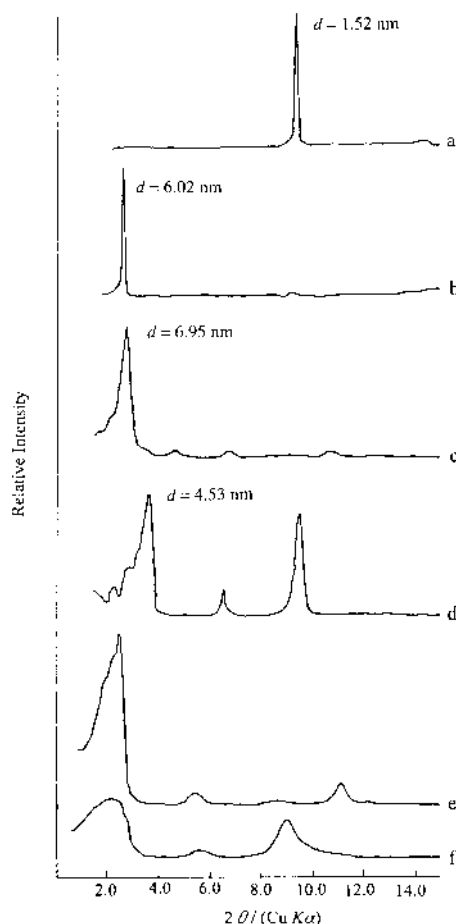

Fig. 1. Power X-Ray Diffraction Patterns of Na-TSM

Curves: a, Na-TSM; b, H-PC; c, Na-TSM/H-PC (prepared in chloroform); d, Na-TSM/H-PC (prepared in ethanol); e, Na-TSM/H-PC/DFS (prepared in chloroform); f, Na-TSM/H-PC/DFS (prepared in ethanol).

significantly, similar to that prepared in chloroform. The unreacted Na-TSM·2H$_2$O (bilayer form of H$_2$O and c-lattice parameter being 1.5 nm) was observed. The large line width in the X-ray diffraction patterns indicated that DFS was really intercalated in TSM/H-PC intercalation compounds. DFS must presumably locate within the hydrophobic alkyl chains and must disorder the good parallel arrangement of the alkyl chains in the host TSM/H-PC intercalation compound.

Thermal Analysis The TSM/H-PC/drug intercalation compounds are anticipated to have anti-humidity that protects the hygroscopic drug from moisture and enhance the effective term. The thermal analysis was carried out on TSM/H-PC/DFS intercalation compounds in comparison with DFS powder since DFS is a typical hygroscopic drug. Figures 2a and 2c show the TG/DTA curves of dry DFS and TSM/H-PC/DFS and Figs. 2b and 2d show the TG/DTA curves of wet DFS and TSM/H-PC/DFS, respectively. The data for TSM/H-PC/DFS prepared in ethanol solution are shown in Figs. 2e and 2f. DFS showed a typical hygroscopic property as shown in Fig. 2b and a large endothermic peak in DTA as well as a large weight loss in TG curve were observed from 50 to 100 °C. Both curves indicate the dehydration of coordinated water molecules. Even in dry DFS, a small change due to the dehydration reaction was observed
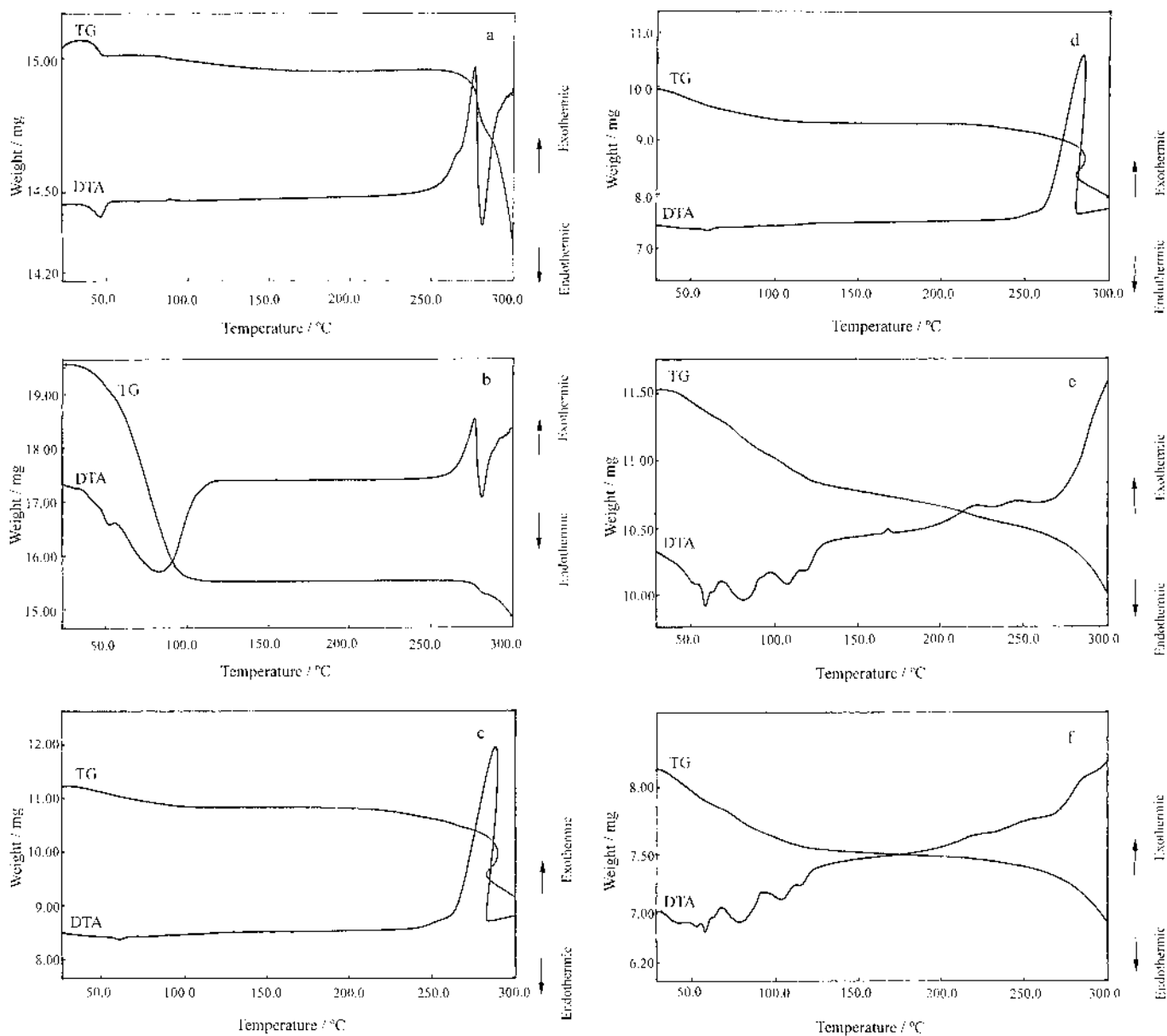
Fig. 2. Thermal Analysis

Heating rate: 10 °C/min. a, DFS stored in low humidity; b, DFS stored in high humidity; c, Na-TSM/H-PC/DFS (prepared in chloroform) stored in low humidity; d, Na-TSM/H-PC/DFS(prepared in chloroform) stored in high humidity; e, Na-TSM/H-PC/DFS (prepared in ethanol) stored in low humidity; f, Na-TSM/H-PC/DFS (prepared in ethanol) stored in high humidity.

either in DTA or TG (Fig. 2a). In the case of TSM/H-PC/DFS, the weight loss in the TG curve was rather small and the endothermic peak in the DTA curve was scarcely observed as shown in Figs. 2c and 2d even in the sample stored under humid condition (Fig. 2d). These results indicated that TSM/H-PC/DFS acquired true anti-humidity as expected. The TG and DTA curves of TSM/H-PC/DFS prepared in ethanol solution were not so different between dry (Fig. 2e) and wet (Fig. 2f) samples. The DTA curve was very complex contrary to that prepared in the chloroform solution (Figs. 2c and 2d). Various endothermic DTA peaks could be attributed to the desorption of co-intercalated ethanol molecules and residual water molecules in the unreacted TSM·2H$_2$O. In spite of such complexity, it was also concluded that TSM/H-PC/DFS prepared in ethanol was also anti-humidity since the TG and DTA curves were not so different between Figs. 2e and 2f although the desorption property was complex.

Another interesting property of the TSM/H-PC/DFS intercalation compound was observed in the thermal analyses data. Simple DFS powder showed an exothermic peak followed by an endothermic peak almost simultaneously (Figs. 2a and 2b). This result indicated that DFS began to decompose at around 280 °C (exothermic peak) and immediately DFS was fused (endothermic peak). The thermal analyses data at the decomposition temperature were quite different between the DFS powder and TSM/H-PC/DFS. Both TSM/H-PC/DFS samples prepared in chloroform and ethanol did not show any endothermic peak contrary to DFS powder. In the case of TSM/H-PC/DFS (chloroform), only a very large exothermic peak was observed accompanied by a large weight loss as shown in Figs. 2c and 2d. The good dispersion of DFS molecules in the lipid bilayer resulted in the
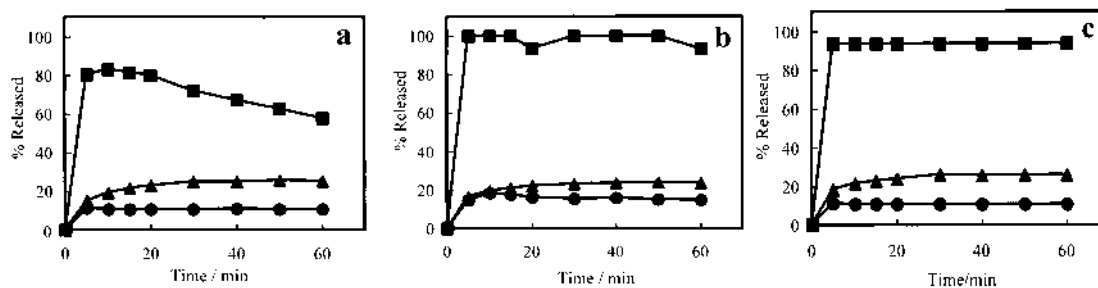
Fig. 3.   Release Property of DFS and the Intercalation Compounds at Various pHs

a, pH 5.0; b, pH 7.0; c: pH 9.0. Volume of test solution, 500 ml; weight of DFS or the intercalation compound, 0.032 g; temperature, 37 °C. Key: ■, DFS; ▲, Na-TSM/H-PC/DFS (prepared in chloroform); ●, Na-TSM/H-PC/DFS (prepared in ethanol).

disappearance of the endothermic peak, *i.e.* the disappearance of the definite melting point. The weight loss must suggest the oxidation of the –NH group and formation of volatile species. On the other hand, the exothermic peak of TSM/H-PC/DFS (ethanol) was broadened and the definite peak disappeared as shown in Figs. 2e and 2f. The weight loss was slowed down. These thermal analyses data indicated that the anti-oxidation of the intercalation compound in TSM/H-PC/DFS (ethanol) although the protection against oxygen was ambiguous in TSM/H-PC/DFS (chloroform).

Drug Release Property   The drug release property was examined to elucidate the potential of TSM/H-PC/DFS as a drug delivery system and the protective ability of drugs against various undesired atmospheres. The release property from DFS powder and DFS intercalation compounds are shown in Figs. 3a—c, where the pH of the buffer solutions were 5.0, 7.0 and 9.0, respectively. Simple DFS powder was released promptly within 5 min and almost 100% was released at pH=7.0 and 9.0. On the other hand, a remarkably different phenomenon was observed at pH=5.0 where the net amount of released DFS decreased significantly and indicated that DFS was gradually decomposed in such acidic medium. The decomposition reaction in DFS solution at pH=5.0 was proved from the decrease in the absorption peak at 277 nm. On the other hand, the release property from TSM/H-PC/DFS (chloroform) was rather slow and reached a steady state after 30 min though only 25% of the intercalated DFS was released. Very interestingly, the net amount of released DFS was increased gradually even 60 min after the start of the release experiment at pH=5.0. This fact suggests that DFS was intercalated deeply into the host interlayer, released slowly and supplemented the decomposed DFS. The difference between DFS powder and TSM/H-PC/DFS was remarkable and this fact indicates that DFS in TSM/H-PC/DFS was protective against acidic medium in contrast to DFS powder. DFS molecules must be accommodated and well dispersed in the lipid bilayer as shown schematically in Fig. 4 and the release rate was lowered and increased protection against undesired atmosphere. The release property from TSM/H-PC/DFS (ethanol) was fast and reached a steady value within 5 min. The amount of released DFS was about 15% to that of the intercalated DFS. In this case, only DFS located near the surface area is released and those intercalated deeply into the host TSM were hardly released.

It was revealed from the release property that ternary TSM/H-PC/DFS intercalation compounds had several advantages over the simple DFS powder to prepare various types of
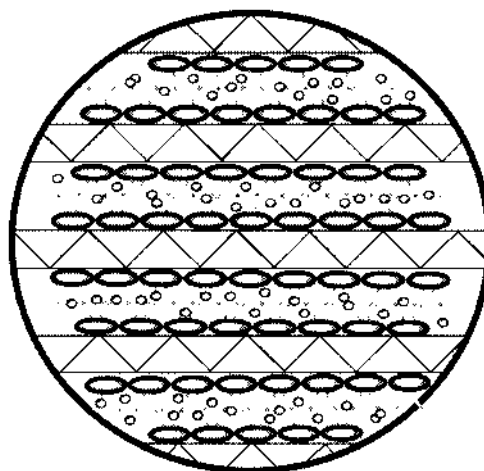

Fig. 4.   Scheme of the Intercalation Compound
△△△△, host lamellae; ○, DFS; ⬭, H-PC.

preparations although the release amount was 25% to that intercalated DFS.

Conclusion

The intercalation of a model hygroscopic drug, DFS, into layered inorganic synthetic mica, Na-TSM, was successful using a simultaneous intercalation reaction of H-PC and DFS. The TSM/H-PC/DFS intercalation compounds prepared in chloroform had several advantages over the simple DFS powder: good dispersion in the H-PC bilayers, increasing anti-humidity, stability in the acidic medium, *etc*. Using such advantagers, some improvements are anticipated in preparations. The shortcoming of TSM/H-PC/DFS was that only 25% of the intercalated DFS was released smoothly and the release rate of the rest 75% was very slow. In spite of this shortcoming, the apparent amount of released DFS in the buffer solution at pH=5.0 was kept constant according to the slow release of the remaining 75%.

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