Article

Intercalation Compounds of Layered Titanium Phosphate for Drug Delivery Use

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Abstract

Layered inorganic material, γ -titanium phosphate (γ -TiP), was applied as a host material for drug delivery use. Hygroscopic diclofenac sodium (DFS) was selected as a model drug to improve its anti-humidity and anti-oxidation. The intercalation was carried out in ethanol solution of DFS. Propylamine was used as the third compound to expand interlayer gallery and/or exfoliate lamellae. The amount of intercalated DFS was almost independent on the concentration of propylamine added. The drug release characteristics was also investigated. The release rate of DFS from the intercalation compound was slower than DFS powder and almost all DFS intercalated was released within 120 min.

1 Introduction

Some layered inorganic compounds can accommodate polar organic compounds between the layered lamellae and form a variety of intercalation compounds. The host compounds must be harmless to the human body when the intercalation compounds were applied to medical use. One of the promising inorganic materials as such host compound is layered γ -titanium phosphate, $\text{Ti}(\text{HPO}_4)_2 \cdot 2\text{H}_2\text{O}$ (γ -TiP). Figure 1 shows SEM photograph of crystalline titanium phosphate prepared hydrothermally. γ -TiP is known to exfoliate by the topo chemical reaction in the presence of *n*-propylamine similar to α -zirconium phosphate.[1] The exfoliated γ -TiP lamellae is reassembled again to remove solvent (Fig.2). The intercalation of molecules with a large molecular weight to γ -TiP can occur during the exfoliation-reassemble process. In this study, we have focused on a hygroscopic drug as a guest compound to verify the anti-humidity and anti-oxidation of the molecules accommodated in the interlayer space. The drug was diclofenac sodium abbreviated to DFS; sodium[*o*-(2,6-dichlorophenyl)amino]phenyl]acetate. DFS is widely used as an anti-inflammatory agent, especially for the rheumatism.

Fig. 1 SEM photograph of titanium phosphate

Fig. 2 SEM photograph of exfoliated titanium phosphate

2 Experimental

2.1 Precursor

Amorphous titanium phosphate was prepared in advance as reported.[2] Crystalline dihydrated titanium(IV) phosphate was obtained by hydrothermal synthesis as follows.[3] 1.0 g of amorphous titanium phosphate and 20 cm³ of 10 mol dm⁻³ H₃PO₄ were placed in a glass tube and sealed. The tube was then put in an autoclave. Hydrothermal synthesis was carried out at 270 °C and 7 x 10⁶ Pa for 36 h.

2.2 Model drug

DFS (m.p. 283 – 285 °C, UV max: 276 nm in phosphate buffer, purchased from Wako Pure Chemical Ind., Ltd.) was selected as a model drug and was used without further purification.

2.3 Intercalation

Intercalation was carried out in two processes to utilize the exfoliating phenomenon of the lamellae of the host γ -TiP layer.

Method 1: 2~35 mm³ of n-propylamine was added into suspended solution of γ -TiP (0.1 g γ -TiP in 10 cm³ ultra purified water). Then 5 cm³ of saturated ethanol solution of DFS (3.6 x 10⁻² mol dm⁻³) was added in the suspension. According to the mixing, a suspension of γ -TiP appeared to indicate the formation of exfoliated lamellae. The reaction time was 24 h and gel-like precipitate was formed. The precipitate was served for further measurement

Method 2: 0.058 g of DFS and a known amount of amine were dissolved in 10 cm³ ethanol in advance. Then 0.1 g of γ -TiP powder was added in the ethanol solution containing DFS. N-propylamine, n-amylamine, n-heptylamine n-decylamine and n-tetradecylamine were used. The reaction time was 24 h and the precipitate was served for further measurement.

In both processes, an aliquot of the supernatant solution containing residual DFS was taken out at a fixed period of time and the amount of DFS was measured by a spectrophotometer to calculate the amount of intercalated DFS.

For comparison, DFS intercalation was examined on synthetic mica (TSM)-phosphatidylcholine (PC) intercalation compound as a precursor in which intercalation of indomethacin was successfully occurred.[4] In this case, two procedures were also examined. In one procedure, TSM-PC intercalation compound was prepared in ethanol solution of PC. It had an interlayer gallery height of about 5 nm. Saturated ethanol solution of DFS was then added in the solution to prepare TSM-PC-DFS intercalation compounds. In another procedure, ethanol solution of DFS-PC mixture was prepared in advance and Mica powder was added in the mixed solution. Co-intercalation of DFS was expected on the occasion of PC intercalation.

2.4 Characterization

The products were characterized by using of a powder X-ray diffractometer (MO3X-HF, MAC Science Co., Ltd., Japan) equipped with monochromized Cu-K α .

2.5 Drug Release Property

Drug release rate was monitored based on the Japanese Pharmacopoeia Thirteenth Edition paddle method. The pHs of the buffer solution were fixed at 3.0, 5.0, 7.0 and 10.0. The volume of the buffer solution was 500 cm³ and 0.032 g of drug or the intercalation compounds in which equivalent amount of DFS were contained. 3 cm³ of the test solution was sampled at fixed intervals and the amount of released drug was monitored using a spectrophotometer (UV-1600PC, Shimadzu Co., Japan).

3 Results and Discussion

3.1 XRD patterns of products

Figure 3 shows the powder X-ray patterns of products prepared. The interlayer distance of γ -TiP expanded to 1.61 nm by the intercalation of n-propylamine (b). γ -TiP + n-propylamine + DFS intercalation compound prepared by *Method 1* has the diffraction peaks at $2\theta = 4.6$ and 6.8 with the interlayer distances of 1.90 nm and 1.29 nm, respectively. The intercalation compound of γ -TiP and DFS ethanol solution had the diffraction peak at $2\theta = 6.8$ (data is not shown). From this fact, the interlayer distance of 1.29 nm was assigned to a γ -TiP/DFS compound without amine. It is confirmed that the amount of intercalated DFS did not participate in n-propylamine discussed below.

Fig. 3 Powder X-ray diffraction patterns. a: γ -TiP, b: γ -TiP + n-propylamine, c: γ -TiP + n-propylamine + DFS.

3.2 Amount of intercalated DFS

Method 2 was examined first for various n-alkyl amines. However, no decrease in absorbance of DFS was observed in the supernatant solution. The fact meant no intercalation of DFS into γ -TiP occurred by *Method 2*. As a consequence, *Method 1* was used in the rest of the present study.

To elucidate the superiority of the present intercalation procedures, DFS intercalation was examined on TSM in advance. Figure 4 shows the amount of DFS intercalated in TSM-PC intercalation compounds. The reaction was very slow and two days were necessary to reach equilibrium. The amount of DFS was very low comparing with indomethacin intercalation, about a few mg in 0.1 g of Mica.

The result obtained by *Method 1* is shown in Fig. 5 in which the amount of intercalated DFS was examined at various concentration of n-propylamine. The intercalation of DFS reached equilibrium with in 12 h for all cases. The amount of intercalated DFS in γ -TiP was about fourteen times larger than that in TSM shown in Fig. 4. No significant difference was observed up to 10 mm³ of n-propylamine added. The

Fig. 4 Uptake of DFS to TSM-PC

Fig. 5 Uptake of DFS to γ -TiP with various concentration of n-propylamine

Added amount of n-propylamine, given in mm³

—●— 2	—■— 5	---▲--- 10
—×— 20	—*— 35	

amount of DFS intercalated decreased a little with increasing the volume of n-propylamine when n-propylamine added exceeded 20 mm³. DFS was found to intercalate even in the absence of n-propylamine. This result indicated that intercalation of DFS was assisted mainly by coexisting ethanol. The effect of propylamine and other n-alkyl amines was low contrary to our expectation. The phenomenon is completely different from the DFS intercalation on TSM (Fig. 4) and also indomethacin on TSM.[4]

3.3 Drug Release Property

The anti-humidity and anti-oxidation ability of DFS intercalated in TSM has already been proved.[5] Accordingly, the release property into solution phase was examined to elucidate the potentiality of γ -TiP-DFS intercalation compound as a drug delivery system. The release property from DFS powder and DFS intercalation compounds in neutral solution is shown in Fig. 6. DFS released from DFS powder into the buffer solution was fast and reach equilibrium within 5 min. On the other hand, the release rate from γ -TiP-DFS intercalation compound was rather slow and over 40 min was necessary to reach a steady state. Similar property was observed in the buffer solution at pH 10.0. On the other hand, DFS was hardly released from neither DFS powder nor γ -TiP-DFS intercalation compound in the acidic buffer solution at pH 3.0.

Fig. 6 Release property at pH 7.0

—◆— Intercalation compound
—■— DFS powder

It was found from above results, γ -TiP-DFS intercalation compound prepared by *Method 1* seems superior method for drug delivery use because γ -TiP used were all harmless to the human body in addition to its simplicity and high accommodated amount. In addition, release rate was also suppressed slow in comparison with DFS powder. Furthermore, the anti-humidity and anti-oxidation ability were also improved. DFS is one of the most efficient non-steroidal anti-inflammatory drug used in various diseases and is expected to develop new drug delivery method. Present intercalation seems to have a potentiality as a practical use in medical field.

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