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Synthesis and properties of Mg_2Al layered double hydroxides containing 5-fluorouracil

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Abstract

A pharmaceutically active compound, 5-fluorouracil (5-FU) has been firstly intercalated into layered double hydroxide with the restructure method. Powder X-ray diffraction and spectroscopic analysis indicate that 5-FU molecule is stabilized in the host interlayer by electrostatic interaction and intermolecular interaction, and that the orientation of 5-FU is different when changing the pattern of aging treatment or the swelling agent. The release studies show that a rapid release of the drug during the first 40 min is followed by a more sustained one, and that the total amount of drug released from hybrid material into the aqueous solution is almost 87% and 74% at pH 4 and 7, respectively. The studies mentioned above suggest that layered double hydroxide might be used as the basis of a tunable drug delivery carrier.

Keyword: Hydrotalcite; Layered double hydroxide; 5-Fluorouracil; Hybrid material; Controlled release

1. Introduction

Nanohybrid systems have attracted considerable interest due to their synergistic effects and potential applications [1,2]. Recently, bioinorganic hybrid systems, as an important subject in the area of hybrids, have deeply fascinated chemists [3]. In these systems, the inorganic host framework lends stabilization and drug delivery, and the biomolecular guest species provide biological functions.

As an important class of inorganic matrix, layered double hydroxides (LDHs), also known as anionic clays or hydrotalcite-like compounds, represented by the general formula $[M_{1-x}^{II}M_x^{III}(OH)_2]^{x+}A_{x/m}^{m-}\cdot zH_2O$, where M^{II} and M^{III}, i.e., di- and tri-valent metal cations, respectively, are capable of occupying the octahedral interspaces of brucite-like sheet. A^{m-}anions between the layers can compensate the positive charges of the layer structures and these interlayer regions may contain water molecules [4]. Owing to the rich intercalation chemistry of LDHs, these materials have extensive applications as catalysts, catalyst precursors and supports, adsorbents, optical and electric functional materials, and flame retardants and polymer stabilizers [5]. Recently, particular attention has been focused on the LDH-based controlled release systems. Although many biomolecules/LDH hybrid complexes have been reported, only a few examples have been studied as drug delivery carriers [6–8]. Furthermore, the potential applications of these hybrid compounds ranging from drug delivery vehicles and controlled release to the improvement of drug solubility have greatly enhanced their significance. Thus, there is an urgent need to enrich the bioagents–LDH controlled release system. To date, the construction of bio-LDH hybrid systems has been achieved by three strategies, i.e., electrostatic reaction [3], hydrogen bonds [7] and encapsulation with an

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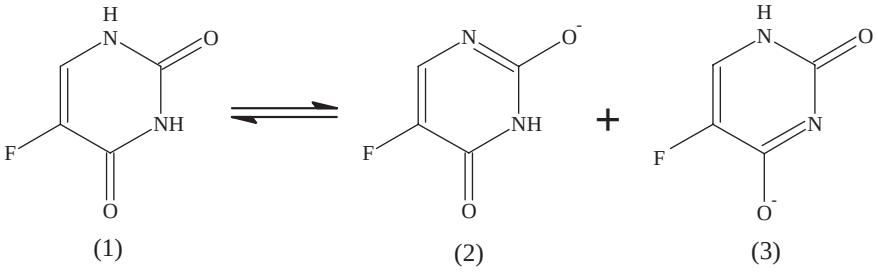

Scheme 1. Resonance structure.

anionic micelle [8]. They are suitable for intercalation of bioagents with negative charge, rich hydroxyl groups and general charge neutral, respectively.

The present work is to build up a charge-neutral, highly pharmaceutically active drug-intercalated LDHs in an attempt to gain a novel therapeutic delivery system, Mg_2Al–5-FU–LDH. 5-Fluorouracil (5-FU) is an antimetabolic drug used extensively in cancer chemotherapy [9]. However, the toxicity of 5-FU may bring adverse effects on the body. Choosing a proper controlled release system can improve its anticancer activity and then decrease the toxic effect. Here Mg_2Al–LDH was chosen as the system. However, 5-FU is a neutral weak acid, and it is thereby difficult for it to be intercalated into the chosen host. After treatment with alkali, interestingly, the resulting conjugate base is anionic and can be intercalated in the LDH. In Scheme 1, structures (**2**) and (**3**) are tautomers of the conjugate base of acid (**1**) [10].

As a result, it is possible to choose an appropriate LDH host to encapsulate 5-FU molecule by this means.

Here the "calcination-restructure method" was used to synthesize the Mg_2Al–5-FU–LDH hybrid system. The composite was characterized by powder X-ray diffraction (XRD), Fourier transform infrared spectra (FTIR), thermogravimetric analysis (TG) and UV spectra. As will be described, the interlayer arrangement of 5-FU depends on various patterns of aging treatment and different swelling solvents. The release behavior of 5-FU will also be discussed.

2. Experiment section

2.1. General procedures

All chemicals were commercially purchased and used without further purification. (Note: 5-FU is photo-labile and care should be taken to protect samples against photo-oxidation [11]) Element analysis was obtained using an inductively coupled plasma-atomic emission spectrometry, Labtest Equipment Co. Model 710 Plasmascan. The XRD analysis was conducted using a Rigaku D/max-IIB X-ray diffractometer at a scanning rate of 4°/min, using Cu$K\alpha$ radiation ($\lambda = 1.5418$ Å). FTIR were recorded using a Perkin–Elmer Model 1725X spectrophotometer in the range of 400–4000 cm^{-1}. The profile of 5-FU released from LDHs was determined with a Perkin–Elmer UV–visible spectrophotometer Lambda 20. TG curve was recorded under airflow at a heating rate of 10 °C/min.

2.2. 5-FU release study

The release of 5-FU from LDHs into the media (phosphate buffer solution with various initial pH values) was performed by adding about 0.05 g of LDHs into 250 mL of the buffer solutions at 37 °C. The accumulated amount of 5-FU released into the solution was measured momentarily using UV–visible spectrophotometer at 265 nm. The tests were made in triplicate and the results were recorded as an average.

2.3. Preparation of the Mg–Al–CO_3–LDH

This compound was prepared with a coprecipitation method as described by Miyata [12]. Typically, a mixed solution of 1 M $MgCl_2$ and 1 M $AlCl_3$ (Mg/Al ratio = 2) was added dropwise to 1 M Na_2CO_3 solution under vigorous stirring, and pH was then adjusted with 1 M NaOH to 10 ± 0.3. The gel-like mixture was aged for 18 h at 65 °C. The resulting product was separated by filtration, washed with deionized water and dried at 60 °C.

2.4. Preparation of the 5-FU–LDH

After calcining the starting LDH at 500 °C for 4 h, the Mg–Al oxide precursor was prepared. In the test for the uptake of 5-FU, a 30 mL 5-FU solution dissolved with diluted ammonia solution was mixed with 0.1 g of the Mg–Al oxide precursor and aged for 2 days under various conditions. The precipitate obtained was filtered, washed with 200 mL deionized water, and dried in a vacuum desiccator at 60 °C overnight. When the aging temperature was changed, compounds **1** and **2** were obtained at 60 °C and hydrothermal 70 °C, respectively, and when the solvent was changed to glycerol,

compound **3** was obtained. The experiments were actually carried out in the N_2 atmosphere.

3. Results and discussion

3.1. Powder X-ray diffraction

Table 1 gives the chemical formulae and the unit-cell parameters of the samples. It indicates that all the Mg/Al ratios equal about 2. Fig. 1 gives the XRD patterns for all the samples. It shows that the basal spacing (d_{003}) of the pristine Mg_2Al–CO_3 is 7.7 Å. The layered structure was destroyed when heating the LDH at 500 °C for 4 h, which is indicated by the disappearance of (003) and (006) reflections in the XRD pattern of the Mg–Al oxide LDH in Fig. 1b, and these values are in good agreement with the literature [12]. The Mg_2Al–LDHs containing 5-FU shows expanded structures. Interestingly, the basal spacings of the compounds varied according to the aging treatment and swelling solvent. Compound **2** has an 8 Å basal spacing as shown in Fig. 1c. However, compound **1** has both 8 and 10.6 Å basal spacings, and 10.6 Å phase was dominant, see Fig. 1d. When adding glycerol to the reaction system, larger basal spacing, 12.4 Å was formed as shown in Fig. 1e. The observed basal spacings of the compounds, 8 and 10.6 Å, resulted from the horizontal (parallel to the layer) or monolayer vertical (perpendicular to the layer) orientation of the incorporated 5-FU (Fig. 2). Given that the thickness of 5-FU is approximately 3 Å, a basal spacing of 8 Å would be explained in terms of a horizontal orientation by adding the thickness of the LDH layer (4.8 Å) (Fig. 2a). The long axis length is about 5.3 Å, the basal spacing would be 10.6 Å for a monolayer with vertical-arranging 5-FU (Fig. 2b). As for the example with the basal spacing 12.4 Å, the gallery height is close to 7.6 Å when subtracting the thickness of the host layer, 4.8 Å, from the corresponding basal spacing (d_{003}) value. This gallery height may result from the bilayer arrangement of 5-FU anion in it (Fig. 2c) [13].

It has been reported in the literature that adding glycerol as swelling agent was beneficial for the intercalation of large species. However, this is the first example to study the effect of glycerol on the guest orientation [14,15]. The bi-layer was produced in the interlayer region because the swelling effect of glycerol makes the gallery height expand and then makes intercalation convenient. The same phenomenon was

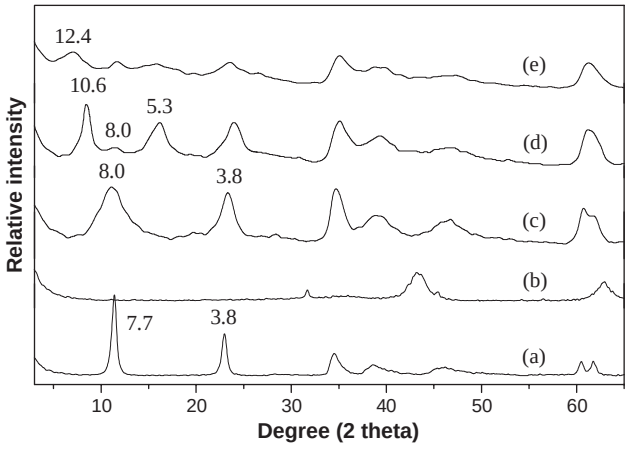

Fig. 1. XRD patterns for oriented film samples of the LDH intercalate: (a) Mg_2Al–CO_3, (b) Mg–Al-oxide, (c) compound **2**, (d) compound **1**, and (e) compound **3**.

Table 1
Chemical formulae and unit-cell parameters for drug hybrid materials

Samples	Chemical formulae	Elemental analysis				a (Å)	c (Å)
		Found	(%)	Calcd.	(%)		
1	$Mg_{0.67}Al_{0.32}(OH)_2(5\text{-FU})_{0.33}\cdot 0.8H_2O$	Mg	16.20	Mg	16.28	3.03	31.78
		Al	8.70	Al	8.63		
		C	15.95	C	15.84		
		N	9.33	N	9.24		
		F	6.19	F	6.27		
2	$Mg_{0.68}Al_{0.34}(OH)_2(5\text{-FU})_{0.38}\cdot 1.0H_2O$	Mg	16.41	Mg	16.52	3.05	24.02
		Al	9.30	Al	9.17		
		C	18.33	C	18.24		
		N	10.81	N	10.64		
		F	7.12	F	7.22		
3	$Mg_{0.67}Al_{0.32}(OH)_2(5\text{-FU})_{0.30}\cdot 1.1H_2O$	Mg	16.16	Mg	16.28	3.04	37.11
		Al	8.69	Al	8.63		
		C	15.91	C	15.84		
		N	9.35	N	9.24		
		F	6.01	F	6.27		

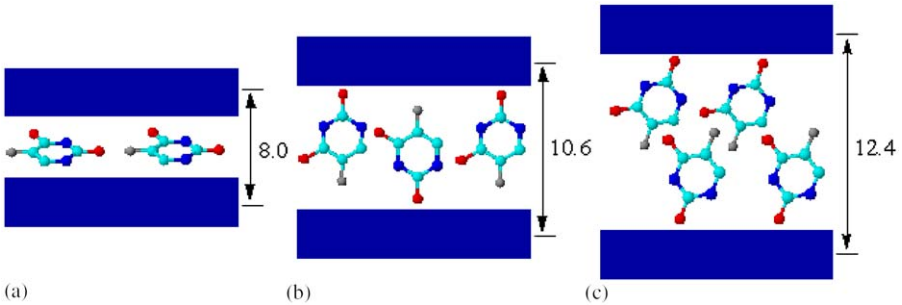

Fig. 2. Schematic illustration of the orientation of 5-FU intercalates.

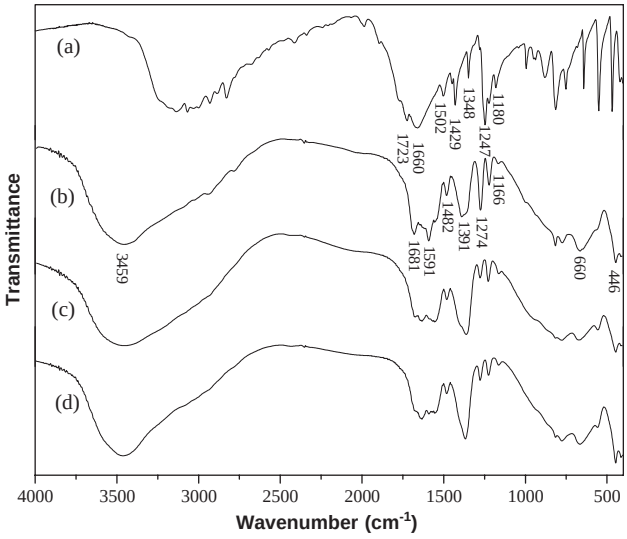

Fig. 3. FTIR of (a) 5-FU, (b) compound **1**, (c) compound **2**, and (d) compound **3**.

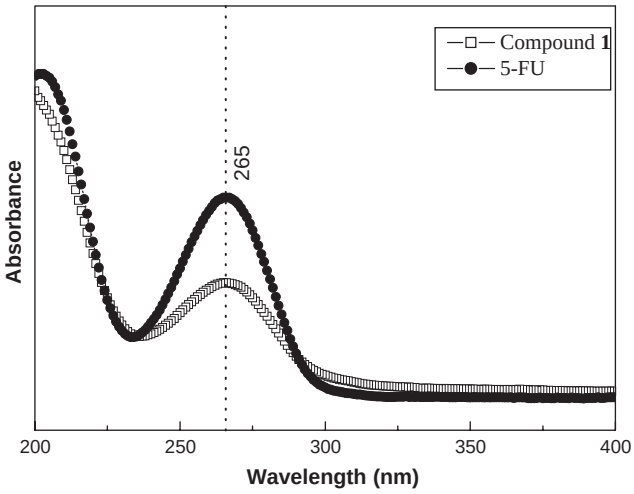

Fig. 4. UV–vis absorption spectra for the 5-FU and compound **1**.

also observed in the intercalation of some other species, and this work is now in progress. Additionally, the characteristic peak of the glycerol was not observed in Fig. 3. Besides the electrostatic interaction, intermolecular interactions, hydrogen bond (H–F, H–N) between the guest molecules and the host layers may simultaneously exist [16].

3.2. Fourier transform infrared spectroscopy

FTIR spectra of the drug–LDH hybrid, compared with that of the pristine LDH, are in some way different as shown in Fig. 3, i.e., the broad absorption band around 1500–1680 cm^{-1} is due to the overlap of peaks (C=C, C=N, C=O); the C=O absorption band at 1723 cm^{-1} shifts to 1680 cm^{-1}; the strong absorption bands at 1482 and 1391 cm^{-1} can be attributed to the vibration of the multi-substituted pyrimidine compound, and the strong absorption band at 1274 and 1166 cm^{-1} can be assigned to the vibration of C–O and C–N, respectively. These results indicate that 5-FU takes the form that has negatively charged oxygen (Scheme 1). The broad absorption band around 3400 cm^{-1} is due to the stretching of the hydroxyl groups (from the layers and the water molecules). In the low-frequency region, the bands at 660 and 446 cm^{-1} are attributed to the lattice vibration of *M*–O and *M*–O–*M* (*M* = Mg, Al) in the matrices. It clearly shows that the intercalation reactions are accomplished without any degradation of the drug molecule.

Fig. 4 shows the UV–vis absorption spectra of compound **1**. The drug molecules show the same characteristic absorption bands in 265 nm. The result also verifies that the drug molecules are stabilized by electrostatic interaction with the positively charged LDH. The compounds **2** and **3** also exhibit the same results.

3.3. Thermal stability analysis

The TG curve shows two steps with noticeable weight loss in Fig. 5. The first step is attributed to the removal of surface-adsorbed water and interlamellar water up to about 240 °C. The second step from 300 to 600 °C was due to the decomposition of intercalated 5-FU and dehydroxylation of the host layers. These temperatures

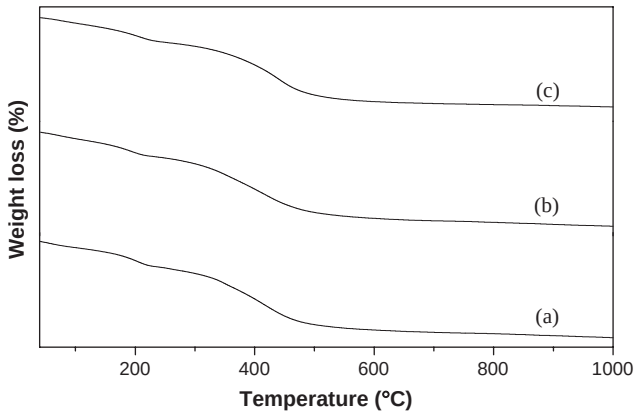

Fig. 5. TG curves for the 5-FU and hybrid material.

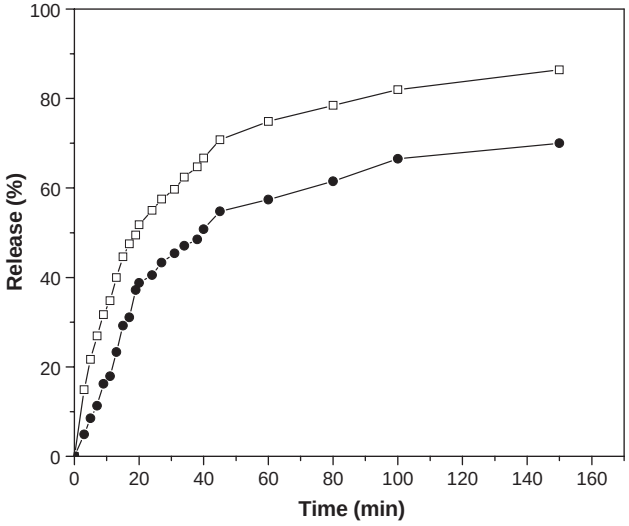

Fig. 6. Release profiles of 5-FU from compound **1** into various initial pH aqueous solutions. Key: (□) pH 4, and (●) pH 7.

are somewhat higher than the decomposition temperature (281–283 °C) of pure 5-FU. The result indicates that the LDH host enhances the thermal stability of 5-FU.

3.4. Controlled release of 5-FU in aqueous solutions

Given that 5-FU can be released from the layers material without losing its pharmaceutical activity, the pristine LDH then can be considered as an effective drug delivery vehicle and a controlled release system. Hence, we quantitatively monitored the controlled release process of the guest anions under conditions that would resemble physiological conditions through a series of experiments.

Fig. 6 shows the release profile plots for the deintercalation of 5-FU from compound **1** on addition of the buffer aqueous solutions with various pH values. It is worth noting that the rapid release during the first 40 min is followed by a more sustained release of the drug, and 65% and 50% amount of 5-FU is released from the LDH at pH 4 and 7, respectively. Such a discrepancy may be due to a possible different mechanism for the release of the interlayer anion. At pH 7, the mechanism of the modified drug release has been interpreted on the basis of the ion-exchange process between the 5-FU anion pillared in the lamella host and phosphate anions in the buffer solution [6b]. However, the faster release of 5-FU happening at pH 4 is probably because parts of LDH begin to dissolve at acidic pH so that the release can occur through ion-exchange and the removal of inorganic host. At equilibrium, it was estimated that almost 87% and 74% amount of 5-FU could be released from LDH into the aqueous solution at pH 4 and 7, respectively. In addition, the concentration of the buffer solution should also affect the rate of release. Further study is still needed to explain the reason for this preliminary observation. The release behaviors of compounds **2** and **3** are similar to that of compound **1**.

4. Conclusions

A new drug delivery was prepared with a calcination-restructure method for the intercalation of the non-ionized biomolecule, 5-FU, into the interlayer LDH. The present results demonstrated that the LDH could be an excellent biocompatible inorganic host for drug reservoirs and delivery carriers.

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