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Synthesis and characterization of 5-fluorocytosine intercalated Zn–Al layered double hydroxide

Chunxia Liu [a], Wanguo Hou [a,b,*], Lifang Li [c], Yan Li [a], Shaojie Liu [a]

[a] Key Laboratory for Colloid & Interface Chemistry of Education Ministry, Shandong University, Jinan 250100, PR China
[b] College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, PR China
[c] College of Chemistry and Material Science, Shandong Agriculture University, Taian 271018, PR China

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ABSTRACT

In this paper, the intercalation of 5-fluorocytosine (5-FC) into a layered inorganic host, Zn–Al layered double hydroxide (LDH), has been carried out using coprecipitation method to obtain 5-FC/LDH nanohybrids. The intercalated amount (A_{In}) of 5-FC into the LDH is remarkably dependent on the molar ratio ($R_{F/M}$) of 5-FC to metal ions and the pH of coprecipitation system. The morphology of 5-FC molecules in 5-FC/LDH nanohybrids is dependent on the A_{In}. It is interestingly found that the morphology of the nanohybrid particles may be changed with the increase of $R_{F/M}$ from hexagonal plate particles to threadlike particles. The in vitro drug release from the nanohybrids is remarkably lower than that from the corresponding physical mixture and pristine 5-FC at either pH 4.8 or pH 7.5. In addition, the release rate of 5-FC from the nanohybrid at pH 7.5 is remarkably lower than that at pH 4.8, this is due to a possible difference in the release mechanism. The obtained results show these drug-inorganic nanohybrids can be used as a potential drug delivery system.

1. Introduction

Layered double hydroxides (LDHs), or the so-called hydrotalcite-like compounds (HTlc), are a family of layered solids with structurally positively charged layers and interlayer balancing anions [1,2]. LDHs may be represented by the general formula $[M^{II}_{1-x}M^{III}_{x}(OH)_2]^{x+}[A^{n-}_{x/n}]^{x-}\cdot mH_2O$, where M^{II} and M^{III} are di- and trivalent metal cations, respectively, A^{n-} are interlayer anions (or galley anions) of charge n, x is the molar ratio of $M^{III}/(M^{II}+M^{III})$ and m is the number of moles of co-intercalated water per formula weight of the compound. LDHs contain brucite (magnesium hydroxide)-like layers, where some divalent metal cations have been isomorphically substituted by trivalent metal cations to form positively structurally charged layers, and the structural positive charge density can be adjusted easily by changing the molar ratio of M^{III}/M^{II}. In the gallery space, monovalent anions such as NO_3^- and Cl^- are much easily replaced by almost any desired anions, organic or inorganic, by utilizing the ion-exchange method [3–5]. Owing to a good anion-exchange property and other physico-chemical properties, LDHs have widespread applications in many areas such as anion adsorbents, medicine carriers, ion exchangers, catalyst supports, catalysts and membranes [6–12].

More recently, LDHs are attracting much attention in drug delivery and gene therapy because of their biocompatibility, anion-exchange property, nontoxicity, etc. [13–16]. Choy and coworkers [13] developed the DNA/LDHs nanohybrids for efficient gene delivery. It was shown that the DNA molecules could be easily intercalated into LDHs by anion exchange, and LDHs could protect the DNA from degradation, which might enhance the DNA delivery efficiency. Although LDHs have been used as host for a number of drug delivery systems [17,18], it is still urgent to expand the kinds of drugs that can combine with LDHs to form the safe and efficient drug delivery systems. More importantly, the mechanisms of the drug–LDHs interactions, drug controlled release and delivery efficiency, are still far to be fully understood.

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, 5-fluorocytosine (5-FC)/LDHs. 5-FC (4-amino-5-fluoro-2-pyrimidone) is a member of the antimetabolite type of antifungal drugs [19]. It was originally developed as an anticancer drug but was found to have considerable activity against *Candida* spp., *Cryptococcus neoformans* and *Chromomycosis* spp. [20,21]. However, the toxicity of 5-FC may bring adverse effects on the body. Choosing a proper controlled release system can improve its activity and then

* Corresponding author at: Key Laboratory for Colloid & Interface Chemistry of Education Ministry, Shandong University, 27 Shanda nanlu, Jinan 250100, PR China. Fax: +86 531 8564750.
E-mail address: wghou@sdu.edu.cn (W. Hou).

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decrease the toxic effect. Here nanohybrids based on Zn_2Al LDH were chosen as the system. However, 5-FC is a neutral weak acid, and it is difficult to be directly intercalated into the host LDHs. After treatment with alkali, the resulting conjugate base is anionic, as shown in Scheme 1 [22], and can be intercalated into LDHs.

Here the coprecipitation method was used to synthesize 5-FC/LDH nanohybrids. The nanohybrids were characterized by inductively coupled plasma mass spectrometry (ICP-MS), powder X-ray diffraction (XRD), Fourier transform infrared spectra (FT-IR), transmission electron microscope (TEM) and UV spectra. The intercalated amount of 5-FC into LDHs and the release behavior of 5-FC from the nanohybrids were investigated, and the interaction mechanism between 5-FC and LDHs was discussed.

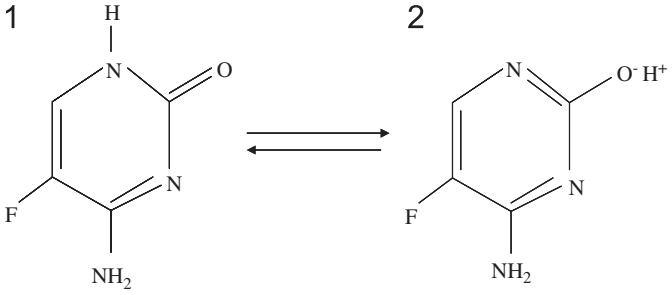
2. Experimental

2.1. Materials

5-Fluorocytosine sample was supplied by Shandong Medicinal Biotechnology Centre and used without further purification. Deionized water from which carbon dioxide was removed by boiling under nitrogen was used in all experiments. All other chemical reagents used were A.R. grade.

2.2. Preparation and characterization of 5-fluorocytosine/LDHs nanohybrids

The 5-FC/LDHs nanohybrids were synthesized by the coprecipitation method. Under a N_2 atmosphere, a mixed salt solution containing 5.95 g (0.020 mol) of $Zn(NO_3)_2 \cdot 6H_2O$ and 3.75 g (0.010 mol) of $Al(NO_3)_3 \cdot 9H_2O$ in 35 ml of deionized H_2O was prepared. A known weight of 5-FC was dissolved in a known volume of diluted ammonia water (6 wt%) to obtain a 5-FC ammonia solution. Then the 5-FC ammonia solution was added to the mixed salt solution under stirring. The desired pH of the system was adjusted by 2 M NaOH or 2 M HCl. The precipitate was aged for 3 h in the mother solution at 40 °C and then filtered and washed with deionized water. The filter cakes held in a glass bottle were peptized at a constant temperature of 60 °C in an oven for about 24 h to obtain 5-FC/LDH nanohybrids. The above procedure was repeated, altering the pH value and the amount of 5-FC added while keeping other reaction conditions constant, to obtain a series of 5-FC/LDH nanohybrids (see Table 1).



Scheme 1. Resonance structure of 5-FC.

The metal contents of the 5-FC/LDHs nanohybrids were determined by inductively coupled plasma mass spectrometry (ICP-MS). C/H/N elemental microanalyses were analyzed with a Desert Analytics instrument. The morphology of the nanohybrids were determined using a JEM-100cxII model transmission electron microscope. Powder X-ray diffraction (PXRD) data were obtained on a D/max-rA model diffractometer with Cu$K\alpha$ radiation (40 kV and 80 mA). FT-IR spectra were recorded on a Bruker Vector 22 model spectrometer in air at room temperature. The sample was pressed into a disc with KBr.

2.3. Measurement of intercalated amount and release amount of 5-fluorocytosine

The intercalated amount of 5-FC in the 5-FC/LDH nanohybrids was determined by an HP-8453 model UV–vis spectroscopy using the following method. A known weight of the nanohybrids was placed in a 10 ml volumetric flask, then 0.5 ml 6 M HCl solution was added, and the balance filled with phosphate buffer solution (0.02 M). Then the concentration of 5-FC in solution was determined by monitoring the absorbance at $\lambda_{max} = 275$ nm with UV–vis spectroscopy to calculate the intercalated amount of 5-FC into the nanohybrids. The concentration was calculated by regression analysis according to the standard curve obtained from a series of standard solution of 5-FC in phosphate buffer solution.

To measure the amount of 5-FC released from 5-FC/LDH nanohybrids, the in vitro drug release test was performed at constant temperature (37 ± 0.5 °C) by suspending 0.02 g 5-FC/LDH nanohybrids in 300 ml either a pH 4.8 or 7.5 buffer solution. The concentration of the phosphate buffer of pH 7.5 and phosphate–citrate buffer of pH 4.8 were 0.02 and 0.05 M, respectively. The solid/liquid ratio of 0.02 g/300 ml was chosen according to the solubility of 5-FC at this pH value. Aliquots (4 ml) of supernatant

Table 1
Synthesis conditions, chemical compositions and intercalated 5-FC amount of 5-FC/LDH nanohybrids

Sample	$R_{F/M}$	pH	Zn%	Al%	C%	H%	N%	Chemical formula	Intercalated amount of 5-FC (wt%)[a]
1	0.33	8.5	33.85	9.13	1.16	2.75	3.51	$[Zn_{0.60}Al_{0.40}(OH)_2](5\text{-FC})_{0.03}(NO_3)_{0.20}(OH)_{0.17} \cdot 0.70H_2O$	2.49 (3.11)
2	0.33	9.0	29.73	13.23	1.28	2.76	2.62	$[Zn_{0.48}Al_{0.52}(OH)_2](5\text{-FC})_{0.03}(NO_3)_{0.10}(OH)_{0.39}$	2.69 (3.44)
3	0.33	9.5	22.38	15.95	2.74	2.95	2.56	$[Zn_{0.32}Al_{0.68}(OH)_2](5\text{-FC})_{0.06}(OH)_{0.62} \cdot 0.09H_2O$	6.26 (7.37)
4	0.33	10	37.16	11.85	0.853	2.59	2.31	$[Zn_{0.56}Al_{0.44}(OH)_2](5\text{-FC})_{0.02}(NO_3)_{0.10}(OH)_{0.32} \cdot 0.10H_2O$	1.84 (2.29)
5	0.50	8.0	34.00	6.73	5.50	2.55	6.60	$[Zn_{0.67}Al_{0.33}(OH)_2](5\text{-FC})_{0.14}(NO_3)_{0.19} \cdot 0.70H_2O$	14.35 (14.32)
6	0.50	8.5	29.66	6.57	7.61	2.66	7.86	$[Zn_{0.65}Al_{0.35}(OH)_2](5\text{-FC})_{0.23}(NO_3)_{0.12} \cdot 1.20H_2O$	20.46 (20.45)
7	0.50	9.0	29.86	8.15	7.99	2.69	7.99	$[Zn_{0.60}Al_{0.40}(OH)_2](5\text{-FC})_{0.22}(NO_3)_{0.09}(OH)_{0.09} \cdot 0.72H_2O$	19.68 (21.47)
8	0.50	9.5	31.62	9.06	3.97	2.68	5.39	$[Zn_{0.59}Al_{0.41}(OH)_2](5\text{-FC})_{0.10}(NO_3)_{0.17}(OH)_{0.14} \cdot 0.70H_2O$	12.83 (10.68)
9	0.50	10	33.37	10.02	4.51	2.66	5.20	$[Zn_{0.58}Al_{0.42}(OH)_2](5\text{-FC})_{0.11}(NO_3)_{0.09}(OH)_{0.22} \cdot 0.42H_2O$	9.62 (12.13)
10	0.67	8.0	28.14	5.75	11.91	2.67	11.72	$[Zn_{0.67}Al_{0.33}(OH)_2](5\text{-FC})_{0.38}(NO_3)_{0.13} \cdot 0.64H_2O$	29.79 (32.03)
11	0.67	8.5	30.37	6.73	10.75	2.74	10.45	$[Zn_{0.65}Al_{0.35}(OH)_2](5\text{-FC})_{0.31}(NO_3)_{0.05} \cdot 0.40H_2O$	29.25 (28.91)
12	0.67	9.0	33.73	7.63	10.57	2.75	10.70	$[Zn_{0.65}Al_{0.35}(OH)_2](5\text{-FC})_{0.28}(NO_3)_{0.12}$	26.57 (28.42)
13	0.67	9.5	30.61	7.71	10.70	2.75	10.02	$[Zn_{0.62}Al_{0.38}(OH)_2](5\text{-FC})_{0.30}(NO_3)_{0.05}(OH)_{0.03} \cdot 0.33H_2O$	26.64 (28.77)
14	0.67	10	25.09	5.90	12.74	2.73	11.78	$[Zn_{0.64}Al_{0.36}(OH)_2](5\text{-FC})_{0.44}(NO_3)_{0.08} \cdot 1.15H_2O$	30.49 (34.26)

[a] The values in brackets are the results obtained by C/H/N elemental analysis.

were taken at desired time intervals, and filtered through a 0.45-μm syringe filter. The 5-FC content was determined by UV absorption at $\lambda_{max} = 275$ nm to calculate the release amount of 5-FC from the nanohybrids.

3. Results and discussion

3.1. Elemental chemical analyses

Synthesis conditions, chemical compositions and intercalated 5-FC amounts of 5-FC/LDH nanohybrids prepared are shown in Table 1. It can be seen from Table 1 that the Zn/Al molar ratios in samples decrease with the increase of synthesis pH, showing the contrary trend as reported for Zn/Al-CO_3 LDHs [23]. The NO_3^- anions have not been removed completely, which has been observed by other authors in studies of intercalation of large anions in Mg/Al-NO_3 LDH precursors [24].

The intercalated amounts (A_{In}) of 5-FC in various 5-FC/LDHs nanohybrids increases with the increase of molar ratios of 5-FC/(Zn^{2+}+Al^{3+}) ($R_{F/M}$) in raw materials. In addition, the A_{In} results obtained by UV–vis measurements are close to those obtained by C/H/N analysis. A unified change tendency of A_{In} with the pH value change of coprecipitation systems was not obtained.

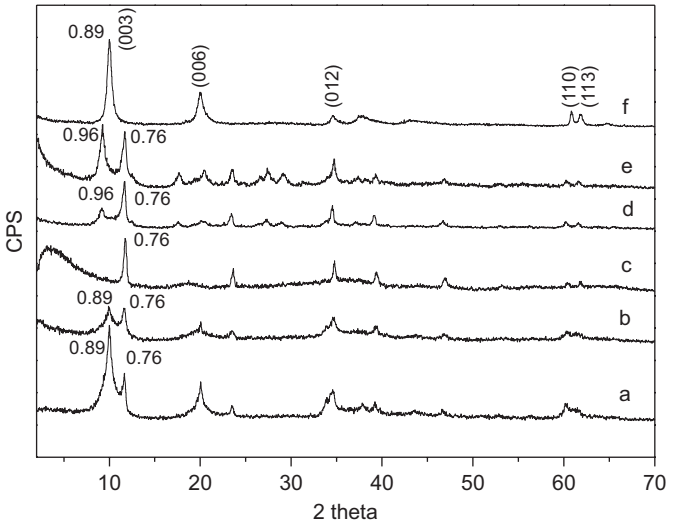


Fig. 1. Powder XRD patterns of 5-FC/LDHs nanohybrids with different intercalated amount of 5-FC: (a) 2.49%, (b) 2.69%, (c) 6.26%, (d) 20.64%, (e) 29.25% and (f) pristine Zn–Al LDH.

3.2. XRD analysis

Fig. 1 illustrates the PXRD patterns of the 5-FC/LDH nanohybrids and pristine LDH sample. For the pristine LDH sample (Fig. 1f), the three intense lines in its PXRD patterns at low 2θ angle correspond to diffractions by planes (003), (006) and (012), and two peaks between 60 and 65° (2θ) are due to (110) and (113) plane diffractions [25]. These sharp and symmetric peaks demonstrate the formation of a well-crystallized LDHs. The interlayer distance (d_{003}) value of the pristine LDH sample (Fig. 1f) is 0.89 nm, showing the same value as reported for nitrate-LDH [26]. The intercalation of 5-FC in the pristine LDH sample induce the division or shift of the 0 0 3 basal reflection pattern. For all the 5-FC/LDH nanohybrids, a new diffraction pattern at $d_{003} = 0.76$ nm appears. With the increase of A_{In} value, another new diffraction pattern at $d_{003} = 0.96$ nm appears gradually as shown in Fig. 1d and e, while the diffraction pattern at $d_{003} = 0.89$ nm disappeared gradually as shown in Fig. 1a and b. The change of 0 0 3 basal reflection pattern of 5-FC/LDH nanohybrids comparing with the pristine LDH sample indicates the successful preparation of 5-FC/LDH nanohybrids, i.e., the 5-FC is indeed intercalated into the gallery of the LDH.

Given that the thickness of the brucite-like layer of LDHs is about 0.48 nm [25], the gallery heights corresponding to the diffraction patterns of $d_{003} = 0.76$ and 0.96 nm are 0.28 and 0.48 nm, respectively. The thickness and length of 5-FC molecule is about 0.30 and 0.48 nm, respectively [22]. According to the gallery heights of the 5-FC/LDH nanohybrids and the size of 5-FC molecule, a probably morphology of 5-FC molecules in 5-FC/LDH nanohybrids may be proposed, as illustrated in Fig. 2. At lower A_{In} value, 5-FC molecules are intercalated into the gallery of LDH with a horizontal orientation, and 5-FC molecules and NO_3^- anions coexist in the interlayer region of LDH, which form two 0 0 3 basal reflection patterns at $d_{003} = 0.89$ nm for the NO_3^- anions and at $d_{003} = 0.76$ nm for the horizontal orientation 5-FC molecules, respectively. The coexistence of intercalated phase and pristine LDH cophase was observed when intercalating bulk anions in the interlayer space of LDHs [27,28]. At higher A_{In} value, part of 5-FC molecules are intercalated into the gallery of LDH with a horizontal orientation, and part of 5-FC molecules with a vertical-arranging monolayer, the coexistence of 5-FC molecules with horizontal orientation and vertical-arranging monolayer induces the appearances of two 0 0 3 basal reflection patterns at $d_{003} = 0.96$ nm for the vertical-arranging of 5-FC molecules and at $d_{003} = 0.76$ nm for the horizontal orientation of 5-FC molecules, respectively. The diffraction peaks of intercalated materials became broad and decreased in intensities, indicating that the ordered arrangement of the sheet decreased after intercalation. The disappearance of diffraction pattern at $d_{003} = 0.89$ nm for

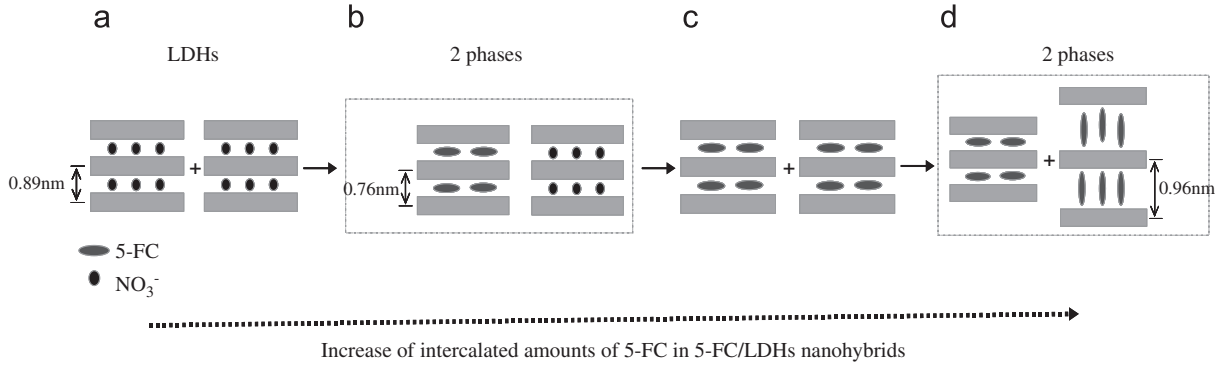


Fig. 2. Schematic structure representation of 5-FC/LDHs nanohybrids with different intercalated amount of 5-FC.

5-FC/LDH nanohybrids with higher A_{In} value is probably due to disordered arrangement of the intercalated nitrate anions or that nitrate anions are exchanged out of LDH gallery.

3.3. FT-IR spectra

FT-IR spectra of the 5-FC/LDH nanohybrids, the pristine LDH sample and pure 5-FC sample are shown in Fig. 3. Precise ascription of the bands is very difficult, due to the very large number of bands recorded [29]. It can be seen from Fig. 3 that some characteristic absorption peaks, such as at 1644, 1554, 1337 and 1280 cm^{-1} [22], of pure 5-FC appeared in the spectra of the 5-FC/LDH nanohybrids, indicating the presence of 5-FC molecules in the 5-FC/LDH nanohybrids. FT-IR spectra of nanohybrid, compared with that of the pure 5-FC, are also in some way different, the characteristic C=O stretching vibration at 1682 cm^{-1}(ketone) [30] has vanished in the nanohybrid, and this result indicates that 5-FC takes the form that has negatively charged oxygen (Scheme 1) in the nanohybrid interlayers. The intensities of characteristic absorption peaks corresponding to 5-FC of 5-FC/LDH nanohybrid sample 3 (Fig. 3c) are lower than those of 5-FC/LDH nanohybrids samples 8 and 13 (Fig. 3d and e), which arises from the lower A_{In} value of the sample 3 (see Table 1).

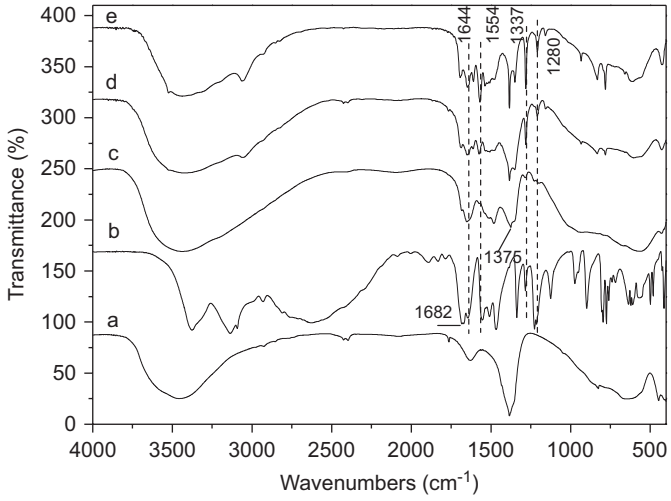


Fig. 3. FT-IR spectra of 5-FC/LDHs nanohybrids and pristine LDH and 5-FC: (a) pristine Zn–Al LDH, (b) pure 5-FC, (c) nanohybrid sample 3, (d) nanohybrid sample 8 and (e) nanohybrid sample 13.

3.4. TEM images

TEM images of 5-FC/LDH nanohydrids are shown in Fig. 4, it is interestingly found that the morphology of the nanohybrid particles may be changed with the increase of $R_{F/M}$. The nanohybrid samples reveal hexagonal plate particles at $R_{F/M}$ = 0.33 (Fig. 4a), hexagonal plate and threadlike particles coexisting at $R_{F/M} = 0.5$ (Fig. 4b) and unitary threadlike particles at $R_{F/M} = 0.67$ (Fig. 4c). The diameter and length of the threadlike particles are about 20 nm and several micron, respectively. Generally, the LDHs with hexagonal platelet morphology are almost obtained by traditional synthesis methods; it is noteworthy that the intercalation process modifies the morphology and the size of microcrystals. But the mechanism of the morphological change of the nanohybrid particles with $R_{F/M}$ is not clear yet.

3.5. 5-Fluorocytosine release from 5-fluorocytosine/LDH nanohybrids

Typical release kinetic curves of 5-FC from the 5-FC/LDH nanohybrid sample 5, sample 14, physical mixture of 5-FC and the pristine LDH, and pristine 5-FC at different pH are shown in Fig. 5. Similar release kinetic curves were obtained for the other nanohybrid samples. As can be seen from Fig. 5, the physical mixture and pristine 5-FC exposed to 0.02 M Na_2HPO_4–NaH_2PO_4 buffer solution (pH 7.5) release 5-FC quickly, the release being complete within 5 min. The release rate of 5-FC from the nanohybrid is obviously lower than that from the physical mixture and pristine 5-FC. In addition, the release rate of 5-FC from the nanohybrid is obviously dependent on pH, and the release rate at pH 7.5 is remarkably lower than that at pH 4.8. The percent release of 5-FC from the nanohybrid reaches about 100% within about 60 min when exposed to a pH 4.8 environment. When the pH is changed to 7.5, the release rate of 5-FC from the nanohybrids is obviously lower. The time taken for 90% of the drug to be released from the nanohybrids is about 40 and 55 min for

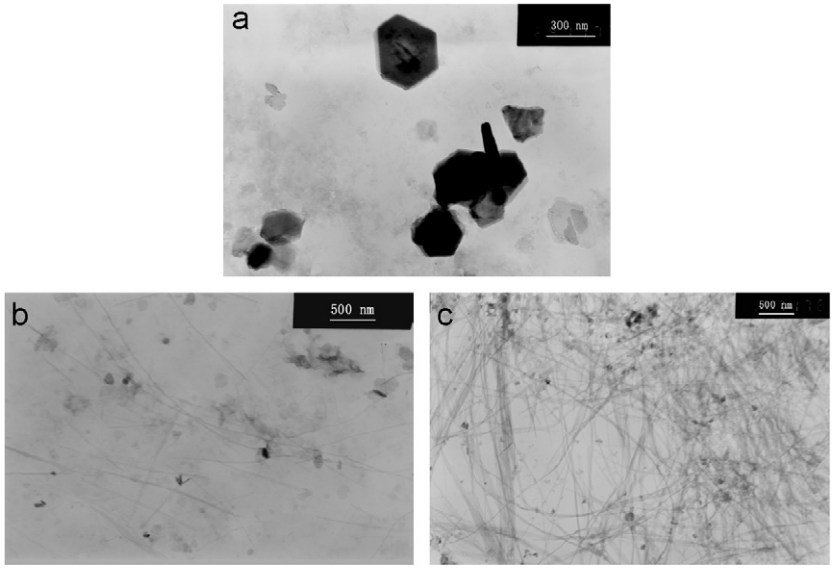


Fig. 4. TEM images of 5-FC/LDHs nanohybrids prepared with different molar ratio of 5-FC to metal ions: (a) 0.33, (b) 0.50 and (c) 0.67.

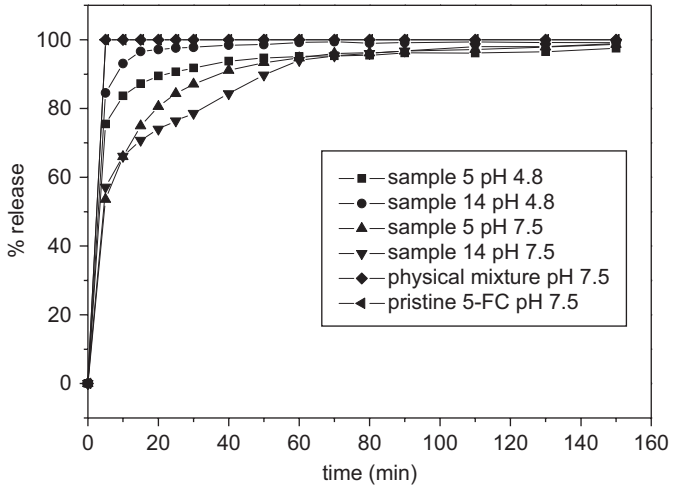


Fig. 5. Release of 5-FC from nanohybrids, the physical mixture and pristine 5-FC at pH 4.8 and pH 7.5.

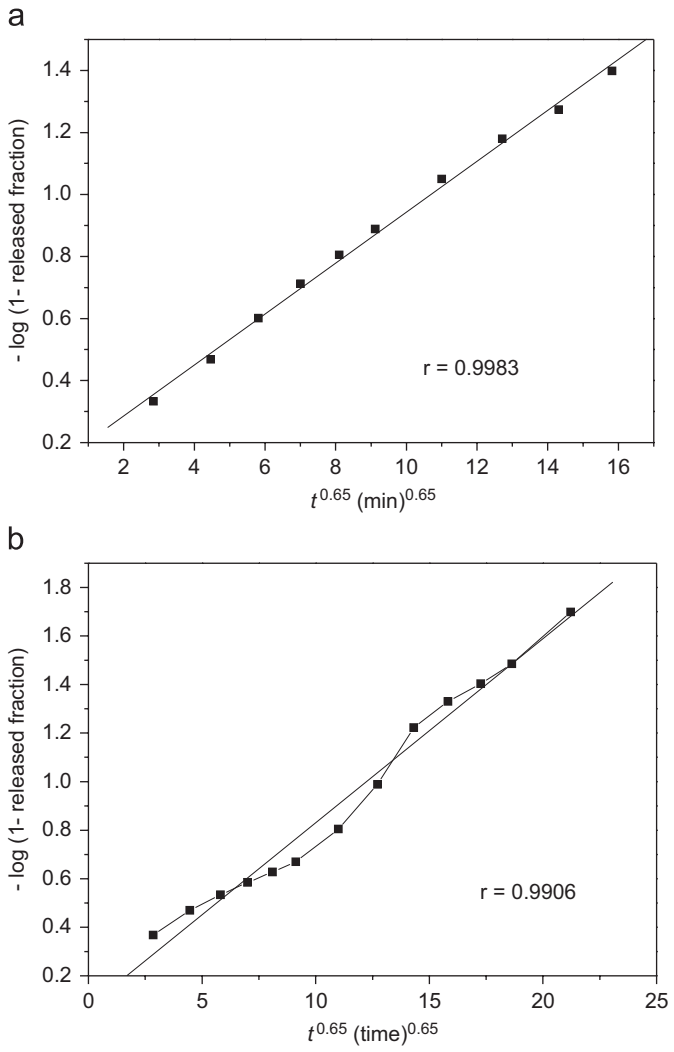


Fig. 6. Release of 5-FC from the nanohybrid as a function of time$^{0.65}$ at pH 7.5: (a) sample 5 and (b) sample 14.

samples 5 and 14, respectively, and that taken for total drug content to be released is about 150 min for both, which indicate that an increase in drug load increased the extent of 5-FC release. The lower release rate of 5-FC from the 5-FC/LDHs nanohybrids at

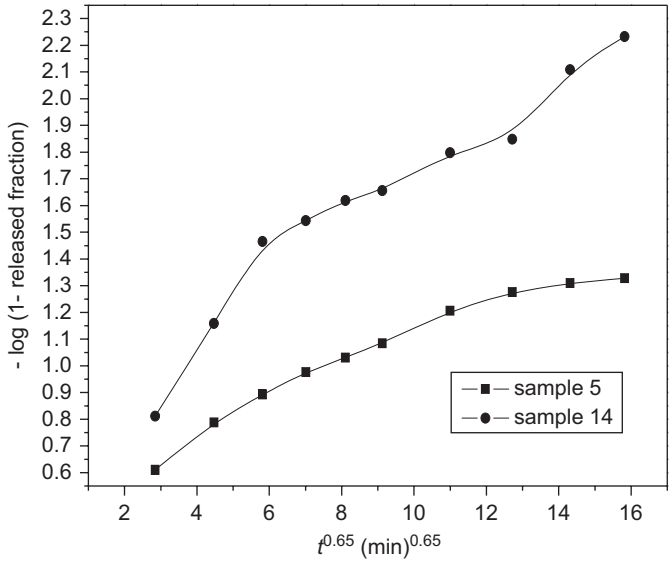


Fig. 7. Release of 5-FC from the nanohybrid as a function of time$^{0.65}$ at pH 4.8: (a) sample 5 and (b) sample 14.

pH 7.5 indicates that the 5-FC/LDHs nanohybrids are indeed a potential drug delivery system. Such a discrepancy of the release rate at pH 4.8 and pH 7.5 may be due to a possible difference in mechanism for the release of 5-FC from the nanohybrid [18]. At acidic pH, LDHs begin to dissolve. This would indicate that release of an interlayer molecule should occur mainly through the removal of inorganic host. At above pH 7, the LDH should be more stable, and as a result, release may be attributed to the restricted motion of 5-FC molecules arising from steric effect of LDHs and the electrostatic interaction between 5-FC anions and positively charged LDHs layers. That is to say, the mechanism of release in the pH 4.8 environment should be through both the dissolution of LDH layers and the ion exchange; while for the pH 7.5 release, the mechanism should be primarily through ion exchange with the ions in the buffer solution [18].

To confirm the difference in mechanism for the release of 5-FC at pH 4.8 and pH 7.5, the direct proportionality between log(1−released fraction) and $t^{0.65}$ is checked as done by Ambrogi [31]. This method is applied to our experimental data. The results are depicted in Figs. 6 and 7. A linear relationship was evident in the case of the two different drug-loaded nanohybrids for pH 7.5 release (Fig. 6a and b), while in the pH 4.8 environment such a line cannot be obtained (Fig. 7) for both samples. Results of this study suggest the importance of diffusion through the LDH particle in controlling the drug release rate as described by Bhaskar et al. [32].

4. Conclusions

The intercalation of 5-fluorocytosine (5-FC) into a layered inorganic host, Zn–Al LDH, has been carried out using coprecipitation method to obtain 5-FC/LDH nanohybrids. The intercalated amount (A_{In}) of 5-FC into the LDH is remarkably dependent on the molar ratio ($R_{F/M}$) of 5-FC to metal ions and the pH of coprecipitation system. It is interestingly found that the morphology of the nanohybrid particles may be changed with the increase of $R_{F/M}$ from hexagonal plate particles to threadlike particles. The in vitro drug release from the nanohybrids is remarkably lower than that from the corresponding physical mixture and pristine 5-FC at either pH 4.8 or pH 7.5 environments. In addition, the release rate of 5-FC from the nanohybrid at pH 7.5 is remarkably

lower than that at pH 4.8, this is due to a possible difference in the release mechanism. For the pH 7.5 release, the mechanism is primarily through ion-exchange; while for the pH 4.8 release, that is through both the dissolution of LDH layers and ion-exchange. The obtained results show these drug-inorganic nanohybrids can be used as a potential drug delivery system.

Acknowledgments

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