

Preparation of 5-Fluorouracil/ β -Cyclodextrin Complex Intercalated in Layered Double Hydroxide and the Controlled Drug Release Properties

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Hydrophobic anticancer drug 5-fluorouracil (5-FU) has been included in the carboxymethyl modified β -cyclodextrin (CMCD), and the inclusion complex (5-FU/CMCD) was further intercalated into galleries of a zinc aluminum layered double hydroxide (ZnAl-LDH) by the ion-exchange method. Powder X-ray diffraction (XRD), Fourier transform infrared (FT-IR), and UV-vis spectroscopy indicate a successful intercalation of 5-FU/CMCD into the LDH gallery. The release behavior of 5-FU from drug/CMCD-LDH composite at different pH values was studied. It was found that 5-FU was released faster in pH 7.2 than in the acidic mediums (pH 4.8), and the released amount was higher. The introduction of CMCD into the LDH matrix could prolong the drug release time in comparison to that from LDH without CMCD, which can be attributed to the inclusion of 5-FU by the CMCD cavity. Studies on mathematical modeling of drug release show that the release of 5-FU from the drug/CMCD-LDH composite follows the Korsmeyer-Peppas equation very well at different pH values. The drug/CMCD inclusion complex intercalated LDH composite in this work provides a supramolecular formulation for controlled release behavior, which can be potentially applied for nonionic and hydrophobic drugs.

1. Introduction

The hydrophobic drug 5-fluorouracil (5-FU) has been used as a chemotherapeutic agent against colorectal cancer for many years. Because of its erratic oral bioavailability, 5-FU is currently used by intravenous administration.^{1,2} This will cause severe gastrointestinal, neural, cardiac, and dermatological toxic effects because of 5-FU cytotoxicity.³ Additionally, the limited aqueous solubility restricts the use of 5-FU. Therefore, the rate-controlled 5-FU delivery is expected to reduce systemic side-effects and to provide an effective therapy for colorectal cancer with reduced dose and duration of therapy. At present, a great deal of research work has been concerned about the controlled release of 5-FU by using different drug delivery systems. Rotello et al. reported the light-controlled release of 5-FU from a nanoscale gold nanoparticle carrier.⁴ Huang demonstrated a proof-of-concept approach for producing genipin-gelatin microcapsules, and it can enhance the effect of controlled release of 5-fluorouracil.⁵ In addition, a lot of polymeric nanoparticles, such as poly (*N*-isopropylacrylamide-co-acrylic acid), poly-(2-hydroxyethyl methacrylate), and chitosan/polyethylene glycol, were also used as carriers of 5-fluorouracil.^{6–9} However, the degradation of synthetic polymers has been shown to cause unwanted toxic effects.¹⁰

Among the drug delivery systems, inorganic materials, such as layered double hydroxides (LDHs), have attracted attention in recent years because LDHs have many advantages, including good biocompatibility, nontoxicity, and adjustable controlled-release property.^{11–13} With the general formulation of $[M^{2+}_{1-x}M^{3+}_x(OH)_2]^{x+}(A^{n-})_{xn} \cdot mH_2O$, LDHs are a large class of host-guest layered inorganic materials consisting of positively charged brucite-like layers and exchangeable interlayer anions. Therefore, a series of pharmaceutically active compounds, such as ibuprofen, fenbufen, and diclofenac, have been intercalated into LDHs and exhibited the feasibility of LDH-based tunable drug delivery systems.^{14–16} The 5-FU drug, through the

treatment with alkali, has been first intercalated into MgAl LDH, and its release behavior was discussed.¹⁷ However, the research on the application of drug-LDHs as a delivery system is still at its early stage, and the regulation of the amount and rate of drug release is not easy to obtain.¹⁸ Further development to achieve successful controlled delivery systems remains an important task.

β -Cyclodextrin (β -CD) is a torus-shaped cyclic oligosaccharide with seven 1,4-linked D-glucopyranose units. It can form an inclusion complex with many organic molecules through a host-guest interaction. By forming the drug/ β -CD inclusion complex, the physicochemical properties of the drug such as aqueous solubility, stability, and bioavailability increased. Meanwhile, the drug's gastrointestinal or ocular irritation, unpleasant taste, and smell were reduced or eliminated.¹⁹ So this capability of β -CD has been exploited in pharmacy, drug release, food, and cosmetic industry.^{20–22} Recently, Nakayama reported the intercalation of sulfobutyl ether β -CD (SBE- β -CD) into MgAl-LDH, and the controlled release of drug prazosin from SBE- β -CD-LDH has also been studied.²³ In our previous studies, the carboxymethyl-modified β -cyclodextrin (CMCD) intercalated ZnAl LDH has been used for selective adsorption of nucleosides.²⁴ To the best of our knowledge, a study about CMCD and LDH as a controlled release system for 5-FU has not been reported.

On the basis of our previous work about CMCD-LDH, herein the present research will involve developing and characterizing a delivery system of 5-FU by using CMCD and ZnAl (molar ratio: 2/1) layered double hydroxide as a carrier. The inclusion complex of 5-FU/CMCD intercalated into NO₃-ZnAl-LDH has been prepared by the ion-exchange method. X-ray diffraction (XRD), Fourier transform infrared (FT-IR), and UV-vis spectroscopy indicate a successful intercalation of the inclusion complex. The release behavior of the resulting composite at different pH buffers has been studied, demonstrating that this drug/CMCD-LDH composite can be used as an excellent controlled release formulation. We focus on the structure and controlled release property of as-synthesized 5-FU/

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CMCD-LDH composite intended for providing the potential application in the field of controlled release of 5-FU. In addition, the possible release kinetic mechanism involved is also studied.

2. Experimental Section

2.1. Reagents. 5-Fluorouracil (5-FU) and β -CD were purchased from Aldrich. Other analytical grade chemicals including $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, NaOH, NH_4OH (1%), and chloroacetic acid were purchased from the Beijing Chemical Co. Ltd. and used without further purification. Phosphate-citrate buffer solutions were used at 37 °C.

2.2. Preparation. Synthesis of Carboxymethyl- β -cyclodextrin, CMCD (3.6). CMCD (3.6) was synthesized according to the procedure described previously,²⁵ and the average number of carboxylate groups per CMCD was calculated to be 3.6 by ^1H NMR.²⁶

Preparation of 5-FU/CMCD Intercalated NO_3 -ZnAl-LDH. NO_3 -ZnAl-LDH (Zn/Al molar ratio 2:1) precursor was synthesized by the hydrothermal method reported previously.²⁷ The pH of aqueous solution (200 mL) containing 0.08 mol of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and 0.04 mol of $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ was adjusted to 8.5 with $\text{NH}_3 \cdot \text{H}_2\text{O}$, and then it was aged in an autoclave at 140 °C for 10 h. The precipitate was centrifuged and washed thoroughly with water. Subsequently, the inclusion complex of 5-FU/CMCD intercalated into NO_3 -ZnAl-LDH was prepared by the ion-exchange method as follows: 3.0 g of CMCD was dissolved in 30 mL of deionized and CO_2 -free water, and then the saturated solution of 5-FU was added until the solution became suspended. After being stirred at 60 °C for 48 h, the dispersion was filtered, and the filtrate containing soluble 5-FU/CMCD inclusion complex was transferred into the NO_3 -ZnAl-LDH (2.0 g) solution. The solution pH value was maintained at 7.0, and the resulting gel was aged under a nitrogen atmosphere at 70 °C for 48 h. The product mixture was filtered, and the resulting white solid (denoted as 5-FU/CMCD-LDH) was extensively washed with deionized water and dried.

2.3. In Vitro Drug Release Study. To measure the release performances of 5-FU from 5-FU/CMCD-LDH, 2.5 g of 5-FU/CMCD-LDH composite powder was added to 500 mL of phosphate citrate buffer solutions (pH 4.8 and pH 7.2, respectively) and was stirred at 37 °C. At specified time intervals, 5 mL of solution was removed and filtered through a 0.2 μm syringe filter. The accumulated amount of drug released into the solution was measured momentarily using a UV-vis spectrophotometer at $\lambda_{\text{max}} = 266$ nm of 5-FU. Runs were performed in triplicate. The release profiles were plotted as the relative release percentages of 5-FU against time.

2.4. Characterization. Powder X-ray diffraction data were recorded by a Shimadzu XRD-6000 power X-ray diffractometer using Cu K α radiation ($\lambda = 0.154$ nm) at 40 kV, 30 mA, a scanning rate of 10° min⁻¹, and a 2 θ angle ranging from 2° to 70°. A UV-vis spectrophotometer (Shimadzu UV-2501PC) was employed to measure the absorbance spectra of 5-FU in the 200–350 nm wavelength range. FT-IR spectra were recorded using a Vector 22 (Bruker) spectrophotometer using the KBr pellet technique in the range 4000–400 cm⁻¹, with 2 cm⁻¹ resolution and accumulation of 32 scans.

3. Results and Discussion

3.1. Characterization of the 5-FU/CMCD-LDH Composite. The powder X-ray diffraction patterns of 5-FU/CMCD-LDH are shown in Figure 1, with NO_3 -ZnAl-LDH precursor and

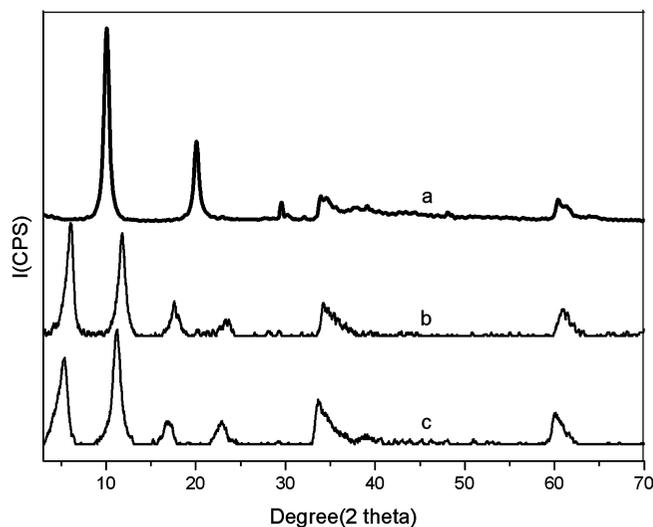


Figure 1. XRD patterns of (a) NO_3 -ZnAl-LDH, (b) CMCD-LDH, and (c) 5-FU/CMCD-LDH.

the product of CMCD intercalated into LDH (denoted as CMCD-LDH, synthesized according to the previous report²⁴) as the comparison samples. In each case, the reflections can be indexed to a hexagonal lattice with $R3\bar{m}$ rhombohedral symmetry, which is often used for the description of LDH structures. As compared to the NO_3 -ZnAl-LDH (Figure 1a, $2\theta = 10.0^\circ$, $d_{003} = 0.88$ nm), the basal reflection (003) of CMCD-LDH (Figure 1b, $2\theta = 6.1^\circ$, $d_{003} = 1.52$ nm) shifts to a lower 2θ angle. This may indicate the intercalation of CMCD into galleries of LDH. Similarly, comparing the CMCD-LDH and 5-FU/CMCD-LDH, the basal reflection (003) of 5-FU/CMCD-LDH composite (Figure 1c, $2\theta = 5.4^\circ$, $d_{003} = 1.79$ nm) shifts to a lower 2θ angle, and the expansion of interlayer distance was observed. These results indicate that 5-FU/CMCD inclusion anions have been intercalated into the LDH lamellar. Moreover, the (110) reflection ($2\theta = 61^\circ$) showed no obvious shift, indicating that no significant change occurred in the LDH host layers along with intercalation of 5-FU/CMCD complex. In addition, the structure of the 5-FU/CMCD inclusion complex is retained even after immobilization into LDH, which will be further confirmed in the next section.

UV-vis spectroscopy was used to investigate whether intercalation of 5-FU/CMCD into the LDH host was associated with any change in its chemical composition or environment. Figure 2 shows the solid state UV-vis spectra of pristine 5-FU, CMCD-LDH, and 5-FU/CMCD-LDH composite, respectively. It can be seen that pristine 5-FU (Figure 2a) exhibits a strong characteristic absorption band at 251 nm, while CMCD-LDH (Figure 2c) displays no absorption at 251 nm. In the case of 5-FU/CMCD-LDH (Figure 2b), the absorption band of 5-FU shifted to 267 nm, with a longer wavelength shifted of 16 nm as compared to pristine 5-FU. This wavelength shift phenomena in UV-vis spectrum may result from the hydrophobic inclusion interaction between 5-FU and CMCD in the interlayer space of LDH.²⁸ The results indicate that CMCD containing 5-FU was successfully intercalated into the LDH host, which is consistent with the XRD result.

Figure 3 shows the FT-IR spectra of pristine NO_3 -ZnAl-LDH, 5-FU, CMCD, and 5-FU/CMCD-LDH composite, respectively. For the sake of clarity, only the main absorption bands were labeled. The spectrum of NO_3 -ZnAl-LDH precursor (Figure 3a) shows a broad absorption band at 3430 cm⁻¹ due to the stretching vibration of the hydroxyl group in the LDH layers and interlayer water molecules. The band at 1384 cm⁻¹

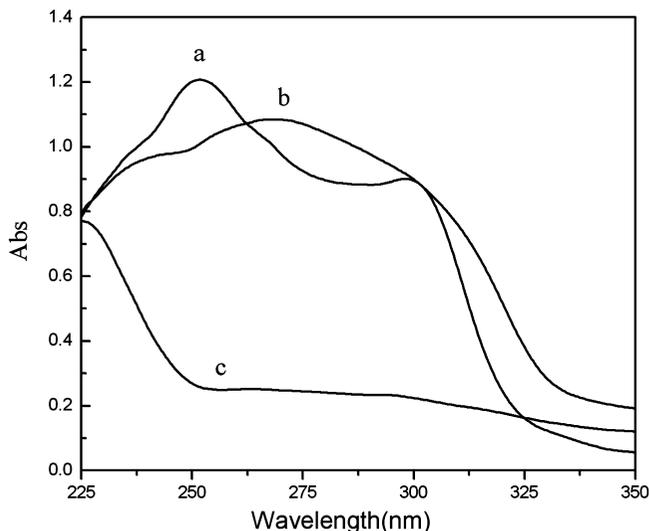


Figure 2. Solid state UV-vis spectra of (a) pristine 5-FU, (b) 5-FU/CMCD-LDH composite, and (c) CMCD-LDH.

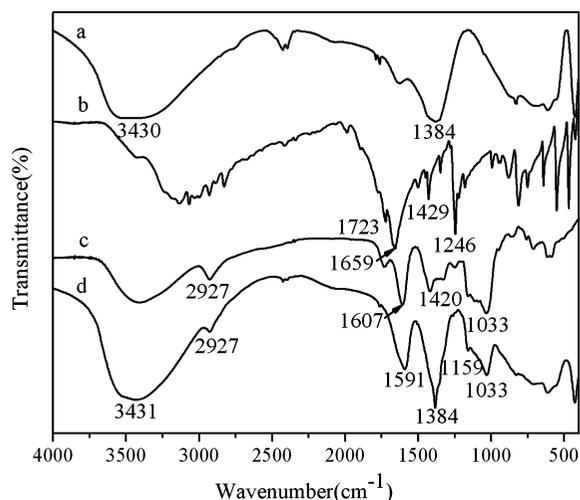
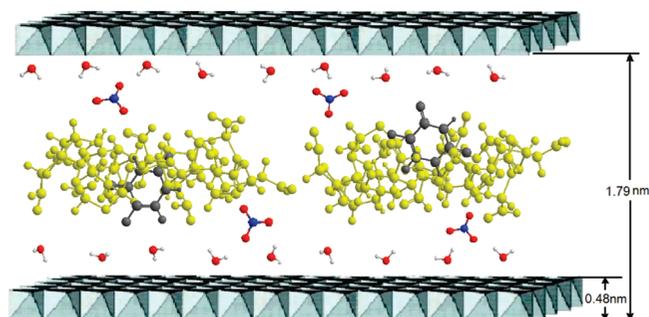


Figure 3. FT-IR spectra for (a) $\text{NO}_3\text{-ZnAl-LDH}$, (b) 5-FU, (c) CMCD, and (d) 5-FU/CMCD-LDH.

is assigned to the stretching vibration of interlayer NO_3^- . For the spectrum of 5-FU (Figure 3b), the broad absorption band around $1659\text{--}1723\text{ cm}^{-1}$ is due to the overlap of peaks ($\text{C}=\text{C}$, $\text{C}=\text{N}$, $\text{C}=\text{O}$). The strong absorption bands at 1429 and 1246 cm^{-1} can be assigned to the vibration of multisubstituted pyrimidine compound and $\text{C}-\text{O}$, respectively. In the spectrum of CMCD (Figure 3c), the absorption at 2927 cm^{-1} is due to the stretching vibration of $-\text{CH}_2$. Two absorption peaks at 1607 and 1420 cm^{-1} are attributed to the antisymmetric and symmetric stretches of carboxylate $-\text{COO}^-$, respectively. The band at 1033 cm^{-1} is assigned to the absorption of glucose units. For the spectrum of 5-FU/CMCD-LDH composite (Figure 3d), it displays a broad band ($3600\text{--}3400\text{ cm}^{-1}$) due to the stretching vibrations of the OH groups in 5-FU, CMCD, and interlayer water. Meanwhile, characteristic bands of CMCD at 2927 and 1033 cm^{-1} were observed, confirming the intercalation of the inclusion complex. Moreover, the antisymmetric stretching band of $-\text{COO}^-$ moves toward to low frequency, at 1591 cm^{-1} . This spectral change may be related to the formation of hydrogen bonding between the carboxylate and the hydroxyl in LDH layer. The band at 1384 cm^{-1} indicates that NO_3^- coexisted with the CMCD anions between the interlayer. However, the characteristic bands of 5-FU at $1659\text{--}1723$, 1429 , and 1246 cm^{-1} were not obvious for the sample of 5-FU/CMCD-LDH; it might be

Scheme 1. A Possible Representation for the Structure of 5-FU/CMCD-LDH Composite



the reason that the actual concentration of 5-FU in the 5-FU/CMCD-LDH composite is too low to be adequately detected using FTIR spectroscopy. The XRD and UV-vis spectra above demonstrate the presence of 5-FU in the composite. This may indicate that the 5-FU molecule was included in the cavity of CMCD.

On the basis of the basal spacing d_{003} of 1.79 nm for 5-FU/CMCD-LDH observed by XRD, and subtracting the thickness of brucite layer (0.48 nm), the gallery height is calculated to be 1.31 nm . Taking into account the dimensions of β -cyclodextrin molecule and the interlayer distance of 5-FU/CMCD-LDH, the 5-FU/CMCD inclusion anions can only adopt a monolayer arrangement with their cavities axis perpendicular to the LDH layer. The interactions in the interlayer region consist of the electrostatic attraction between the positively charged host layers and the negatively charged 5-FU/CMCD, as well as the hydrogen bonding formed among the host layers, the guest anions, and the interlayer water molecules. A schematic supramolecular structure of 5-FU/CMCD-LDH was tentatively proposed and presented in Scheme 1.

3.2. In Vitro Drug Release Behavior. The drug release properties of 5-FU from the 5-FU/CMCD-LDH composite have been investigated in phosphate-citrate buffer solution at a constant temperature of $37\text{ }^\circ\text{C}$. Figure 4 shows the release profiles of the composite in solution at pH 4.8 and 7.2, respectively, exhibiting that the accumulated 5-FU released into the buffer solution increases with the contact time. It was found that the rapid release during the first 50 min is followed by a slower release of the drug. In the case of pH 7.2 (Figure 4a), the released percentages of 60% and 80% were obtained after

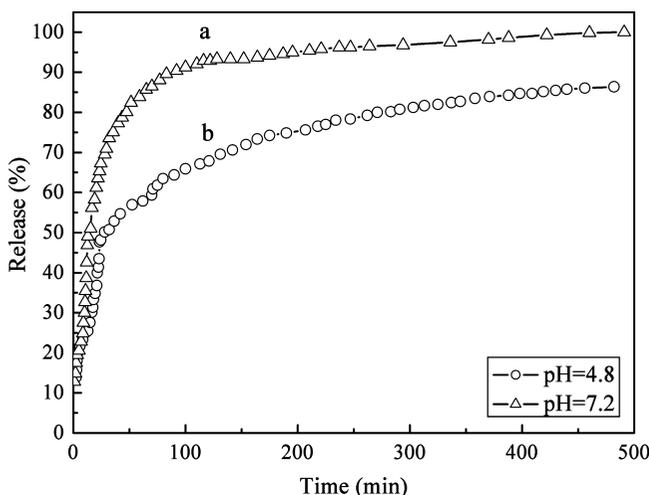


Figure 4. Release profiles of the 5-FU from 5-FU/CMCD-LDH composite in phosphate-citrate buffer solution at different pH values.

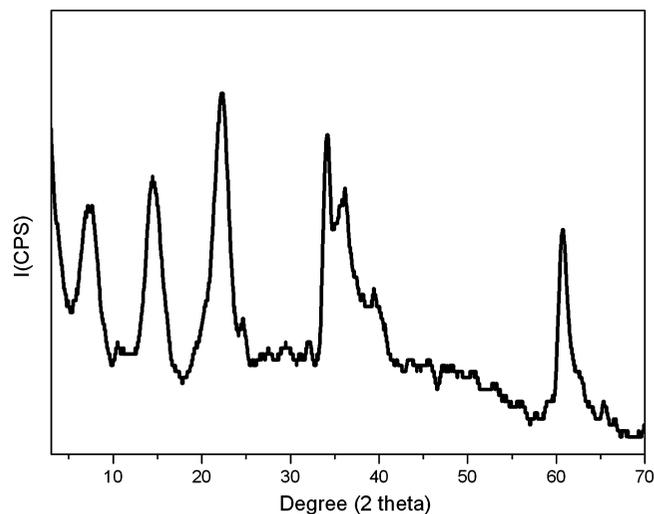


Figure 5. Powder XRD for 5-FU/CMCD-LDH composite after being released in phosphate-citrate buffer (pH 7.2). The d_{003} value accords with that of citrate-intercalated LDH layers.

21 and 50 min, respectively, and 5-FU was completely released at ~ 450 min. For pH 4.8 (Figure 4b), the release rates are a little slower than that of pH 7.2, and the released percentage of 80% was obtained after 300 min. The release behavior at pH 7.2 was demonstrated to be the best: almost 100% of 5-FU could be released from composite into the buffer solution at equilibrium.

As compared to the release behavior based on LDH-drug composites reported previously,²⁹ it is worth noticing that there is no burst phenomenon occurring at the beginning of the release tests. It was also found that the pH value of the medium imposes the influence on the release performances of 5-FU. In pH 7.2, 5-FU was released faster than in that of pH 4.8, and the released amount was higher. This is different from the release behavior of drug intercalated LDHs reported previously, in which lower pH leads to faster release of pharmaceutically active components from LDH.³⁰ In this work, 5-FU is an acidic drug ($pK_a = 7.8$),³¹ and it becomes ionized and cationic charged in pH 4.8. So the inclusion complex between CMCD anion and 5-FU has a much higher affinity in pH 4.8 than in pH 7.4, accounting for a lower release rate at pH 4.8. Meanwhile, the release time of 5-FU from the composite was prolonged in comparison to that from LDH without CMCD,¹⁷ which can be attributed to the incorporation of the drug into the CMCD cavities. Therefore, 5-FU is double protected from the physiological environment in the

5-FU/CMCD-LDH composite, first by the hydrophobic environment of CMCD cavity, and second by the durability of the LDH. Thus, the release behavior of 5-FU from 5-FU/CMCD-LDH composite could be modulated by a change in the environmental pH value.

To better understand the drug/CMCD-LDH composite release behavior, the resultant powder of 5-FU/CMCD-LDH was recovered after release and further characterized by XRD. The XRD pattern was shown in Figure 5. From Figure 5, it is obvious that the sequence of strong (003), (006), (009) reflections at low angle and the (012) reflection at high angle indicates formation of hydrotalcite-like LDH phase. It shows that the layered structure of LDH was still maintained after drug release. The d_{003} value ($2\theta = 7.3^\circ$, 1.21 nm) accords with that of citrate-LDH,³² which suggested the intercalation of citrate anions in the LDH by replacing drug/CMCD inclusion anions. Meanwhile, the absence of 5-FU/CMCD-LDH peak ($2\theta = 5.4^\circ$, Figure 1c) in Figure 5 further confirmed that 5-FU/CMCD anions have been replaced efficiently. It can be concluded that the release of drug from 5-FU/CMCD-LDH composite is mainly via ion exchange with citrate anions.

The drug 5-FU release based on the 5-FU/CMCD-LDH composite could be controlled by either of the following steps: (1) dissolution of LDH particles;³³ (2) ion-exchange reaction between the inclusion complex 5-FU/CMCD and the anions citrate in buffer solution;³⁴ and (3) release of 5-FU from CMCD. The release mechanism of 5-FU from the 5-FU/CMCD-LDH composite is very complicated and not completely understood. According to the literature, the Korsmeyer-Peppas model (shown in eq 1) was chosen to study the release dynamics of this system.³⁵

$$M_t/M_f = kt^n + a \quad (1)$$

where M_t/M_f is the fraction of drug released at time t , and k is a constant related to the properties of the drug delivery system. n is the diffusion exponent, which determines the release mechanism. When $n < 0.5$, the release is dominated by Fickian diffusion; when $0.5 < n < 1$, the release follows non-Fickian diffusion, and when $n = 1$, there is continuous zero-order release. a represents the drug released at zero time and accounts for the initial burst. For the determination of the exponent n , the portion of the release curve where $M_t/M_f < 0.6$ should only be used.

On the basis of the above kinetic model, the fitting results of drug release profiles at pH 4.8 and 7.2 are given in Figure 6,

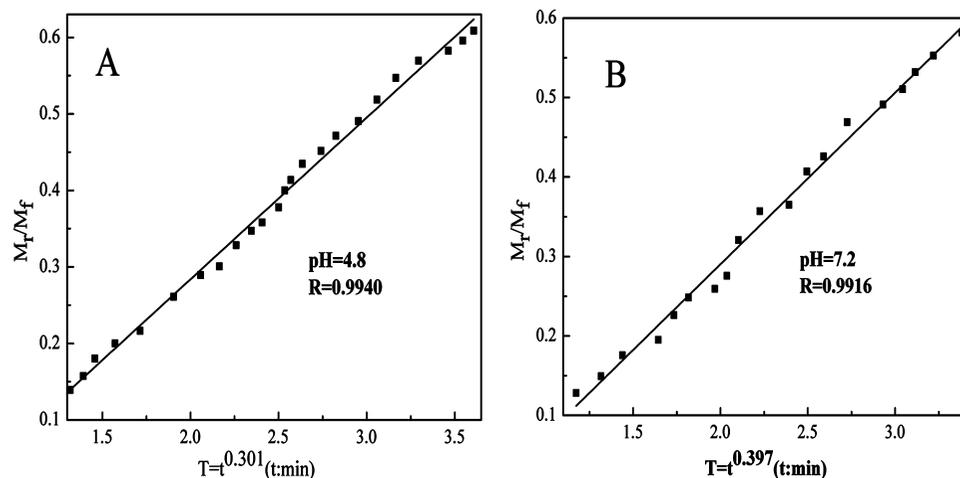


Figure 6. Plots of the Korsmeyer-Peppas model for the release of 5-FU from the 5-FU/CMCD-LDH composite: (A) pH 4.8 and (B) pH 7.2.

Table 1. Fitting Parameters and Equations of Drug Release Data to the Korsmeyer–Peppas Model

pH	equation	n	R^2
4.8	$M_t/M_\infty = 0.21138t^{0.301} - 0.13897$	0.301	0.9940
7.2	$M_t/M_\infty = 0.21596t^{0.397} - 0.14168$	0.397	0.9916

respectively. The equations and parameters of n and R^2 (correlation coefficient) are tabulated in Table 1. From Table 1, it can be seen that the release of 5-FU from 5-FU/CMCD–LDH follows the Korsmeyer–Peppas equation very well at different pH values, with satisfactory coefficients of 0.9940 (pH 4.8) and 0.9816 (pH 7.2). The values of n calculated according to the above method are found to be 0.301 and 0.397 in the medium of pH 4.8 and 7.2, respectively, which implied a Fickian diffusion behavior for 5-FU released from this novel composite in the different environmental pH values.

4. Conclusion

A host–guest supramolecular hybrid material was obtained from the inclusion complex 5-FU/CMCD and ZnAl–LDH via the ion-exchange method. Powder X-ray diffraction, FT-IR, and UV–vis spectroscopy indicate a successful intercalation of 5-FU/CMCD into galleries of LDH. The intercalated structure of this composite was proposed that 5-FU/CMCD anions can only adopt a monolayer arrangement with their cavities axis perpendicular to the LDH layer. Furthermore, the in vitro release studies show that there is no burst phenomenon occurred at the beginning of release tests at the different pH buffers. 5-FU was released faster in pH 7.2 than in the acidic mediums (pH 4.8), and the released amount was higher. The introduction of CMCD into the LDH matrix could prolong the drug release time in comparison to that from LDH without CMCD, which can be attributed to the inclusion 5-FU by the CMCD cavity. The drug release from 5-FU/CMCD–LDH composite involves an ion-exchange process between guest inclusion complex and citrate anions in the buffer and then the release of 5-FU from the CMCD cavity. The Korsmeyer–Peppas equation was used to study the release dynamics of this system. The kinetic study shows that the release of 5-FU from 5-FU/CMCD–LDH composite follows the Korsmeyer–Peppas equation satisfactorily and the release mechanism corresponds to the drug diffusion control. As a result, this drug-including CMCD intercalated LDH composite in this work provides a supramolecular depot for slow and controlled release, with potential application for nonionic and hydrophobic drugs.

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