Synthesis and Controlled Release Properties of Prednisone Intercalated Mg−Al Layered Double Hydroxide Composite

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A drug−inorganic composite involving prednisone−cholate ion micelles intercalated Mg−Al layered double hydroxide (LDH) has been assembled by a coprecipitation method. Powder X-ray diffraction (XRD), Fourier transform infrared (FT-IR), and UV−vis absorption spectroscopy indicate a successful intercalation of prednisone-containing micelles into galleries of the LDH matrix. The in vitro drug release studies show that no burst release phenomenon was observed at the beginning of release tests, and the pH value imposes very little influence on the release performance of prednisone in the studied pH range 4.8−7.6. It is, therefore, concluded that the MgAl-LDH can be used as an excellent inorganic drug carrier for prednisone in a wide range of pH values. Four kinetic models (first-order equation, Higuchi equation, Bhaskas equation, and Ritger−Peppas equation) were chosen to study the release kinetics of prednisone from the LDH carrier, and it was found that this process can be described by the Ritger−Peppas equation satisfactorily based on a directing Excel-based solver (DEBS). Moreover, the mechanism for drug release was also discussed.

1. Introduction

Many drugs have poor water solubility, leading to difficulties in efficient dose delivery and unwanted side effects. An example is prednisone, a drug of adrenocorticotro, which has been investigated as a possible therapeutic treatment for several forms of cancer. However, systemic drug administration results in distribution of the drug throughout the patient's body through blood circulation. This can lead to elevated drug concentrations in undesired parts of the body with severe side effects. Additionally, there are many cases where conventional drug administration methods do not provide satisfactory pharmacokinetic profiles because the drug concentration rapidly falls below desired levels. Therefore, a drug delivery and controlled release system is a more sophisticated drug administration method designed to overcome such problems.[1] These systems utilize carriers that slowly release their contents in order to maintain drug concentrations at the desired levels for a longer period of time. At present, much attention has been paid to polymers or various types of lipid vesicles and liposomes, as drug carriers that form micro- or nanoparticles.[2−5]

Recently, biocompatible inorganic materials, such as layered double hydroxides (LDHs), are being used in drug delivery and controlled release systems. These materials are more stable and less toxic than conventional drug carriers. LDHs consist of layers of magnesium hydroxide, with aluminum isomorphically substituted to give the layers a net positive charge. This charge is balanced by interlayer hydrated anions, resulting in multiple layers of alternating host layers and gallery anions. There has been interest in the preparation of biomolecule−LDH complexes for delivery systems. This approach has been used to successfully deliver pharmaceutically active molecules, such as gramicidin, amphotericin B, ampicillin, and nalidixic acid.[6] Similar systems based on LiAl-LDH have been studied to deliver therapeutics such as ibuprofen in controlled release systems.[7,8] Owing to the intercalation property of LDHs, many LDH compounds with intercalated beneficial organic anions, such as DNA,[9−11] amino acid,[12−16] anti-inflammatory drugs[17,18] and plant growth regulators[19] have also been prepared. Many reports were focused on the study of drug−LDH hybrid materials to increase the bioavailability of poorly water-soluble, negatively charged, anti-inflammatory drugs. These drugs can be directly intercalated into the LDH galleries and then be released in molecular form. The composites have high chemical stability and can be maintained as long as 4 years.[20]

Although this scheme provides an interesting route to deliver negatively charged drugs based on LDH materials, the delivery of nonionic, poorly water-soluble drugs remains a challenge. Tyner et al., who reported a new method, utilized LDHs to control nonionic, poorly water-soluble drug delivery.[21,22] This process involves first encapsulating the hydrophobic molecules in an anionic micelle derived from a biocompatible surfactant, and then the negative charge on the surfactant allows the uptake of the drug-loaded micelle between the sheets of the LDHs by an ion exchange process.

In the present study, prednisone was selected as a model drug for nonionic, poorly water-soluble drugs. It was first encapsulated in cholate ions micelles and then intercalated into MgAl-LDH galleries by the method of coprecipitation. The physiological and biological importance of bile salts (sodium cholate, for instance) lies in their ability in delivery systems for medicines, to solubilize and emulsify cholesterol, dietary lipids, and fatsoluble vitamins in the gastrointestinal tract.[23] In this work, cholate was chosen to form prednisone-containing micelles and then was further intercalated into the LDH matrix as a drug carrier. X-ray diffraction (XRD), Fourier transform infrared (FT-IR), and UV−vis spectroscopy indicate a successful intercalation of this prednisone−cholate micelles. The release behavior of the resulting composite at different pH buffers has been studied, demonstrating that this drug−micelle−LDH composite can be used as an excellent controlled release formulation in a wide range of pH values from 4.8 to 7.6. Moreover, four kinetic models (first-order equation, Higuchi

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equation, Bhaskas equation, and Ritger−Peppas equation) were chosen respectively to study the release kinetics of prednisone from LDH carrier, and it was found that this process can be described by the Ritger−Peppas equation satisfactorily based on a directing Excel-based solver (DEBS). It can be therefore expected that the method in this work provides a potential application in the field of controlled release for nonionic and water-insoluble drugs.

2. Materials and Methods

2.1. Reagents. Prednisone (98% purity) was purchased from J&K Chemical Ltd. and used as received; sodium cholate (98% purity) was purchased from Shanghai Sangon Biological Engineering Technology Co., Ltd. Other inorganic chemicals including $Mg(NO_3)_2 \cdot 6H_2O$, $Al(NO_3)_3 \cdot 9H_2O$, NaOH, etc., were of analytical grade and used without further purification. Phosphate buffer solutions were used at 37 °C.

2.2. Determination of the Critical Micellar Concentration (CMC) Value of Sodium Cholate. The formation of micelles was confirmed by using prednisone as a fluorescence probe. Prednisone and sodium cholate were suspended in distilled water, and the pH of the stock solution was found to be ~8. The fluorescence spectra were measured with the concentration of sodium cholate varying from 8 to 32 mM (the prednisone concentration was 1.06×10^{-6} M). The excitation wavelength (λ_{ex}) is 283 nm.

2.3. Synthesis of LDH−Cholate−Prednisone Composite. Synthesis of LDH−cholate−prednisone by a coprecipitation method was carried out as follows. Prednisone (30 mg, as a 2 mg/mL solution in chloroform) was added to an aqueous solution (200 mL) of sodium cholate (1.72 g, 20 mM) and stirred under N_2 to allow for the evaporation of chloroform. When the cholate micelles containing prednisone molecules have been formed, an aqueous solution (25 mL) containing NaOH (0.32 g) and a solution (25 mL) containing $Mg(NO_3)_2 \cdot 6H_2O$ (0.684 g) and $Al(NO_3)_3 \cdot 9H_2O$ (0.500 g) (initial Mg/Al = 2.0) were simultaneously added dropwise into the micellar solution under N_2 atmosphere with vigorous stirring until the final pH of ca. 10 was obtained. The resulting slurry was aged at 70 °C for 60~70 h. The product was filtered, washed thoroughly with CO_2-free water, and finally dried at 70 °C for 12 h. The product was denoted as LDH−cholate−prednisone.

2.4. Determination of Prednisone Loading. A known weight of the LDH−cholate−prednisone composite (typically 10 mg) was dissolved by 5.0 mL of 1.0 M HCl solution and then diluted to 10.00 mL by alcohol. The concentration of prednisone was measured by UV−vis spectroscopy (λ_{max}: 244 nm) based on a multipoint working curve. Runs were performed in triplicate.

2.5. In Vitro Drug Release Study. To measure the release performances of prednisone from LDH−cholate−prednisone, 0.4 g composite powder was added in 900 mL of phosphate buffer solutions (pH 4.8, 6.8, and 7.6, 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 absorbance of the filtrate, at the λ_{max} of prednisone, was measured and plotted as the relative release percentages of prednisone against time.

2.6. Characterization. Powder X-ray diffraction data were recorded by a Shimadzu XRD-6000 power X-ray diffractometer using Cu Kα radiation (λ = 0.154 nm) at 40 kV, 30 mA, a scanning rate of 10° min^{-1}, and a 2θ angle ranging from 2° to 70°. The sample of LDH−cholate−prednisone was also characterized on a Rigaku D/MAX2500 VB2+/PC X-ray diffractometer under air condition, using Cu Kα radiation (0.154184 nm) at 40 kV and 200 mA with a scanning rate of 5°/min, a step size of 0.02°/s, and a 2θ angle ranging from 1.5° to 10°. UV−vis absorption spectra were performed on a Shimadzu UV-2501PC spectrometer. The Fourier transform infrared (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. Fluorescence measurements were carried out with Shimadzu RF-5301PC spectrofluorimeter. Thermogravimetry and differential thermal analysis (TG-DTA) were carried out on a PCT-1A thermal analysis system under ambient atmosphere with a heating rate of 10 °C/ min. Elemental analyses were performed by inductively coupled plasma (ICP) atomic emission spectroscopy using solutions prepared by dissolving the samples in dilute HCl. Carbon, hydrogen, and nitrogen analyses were carried out using a Perkin-Elmer Elementarvario elemental analysis instrument.

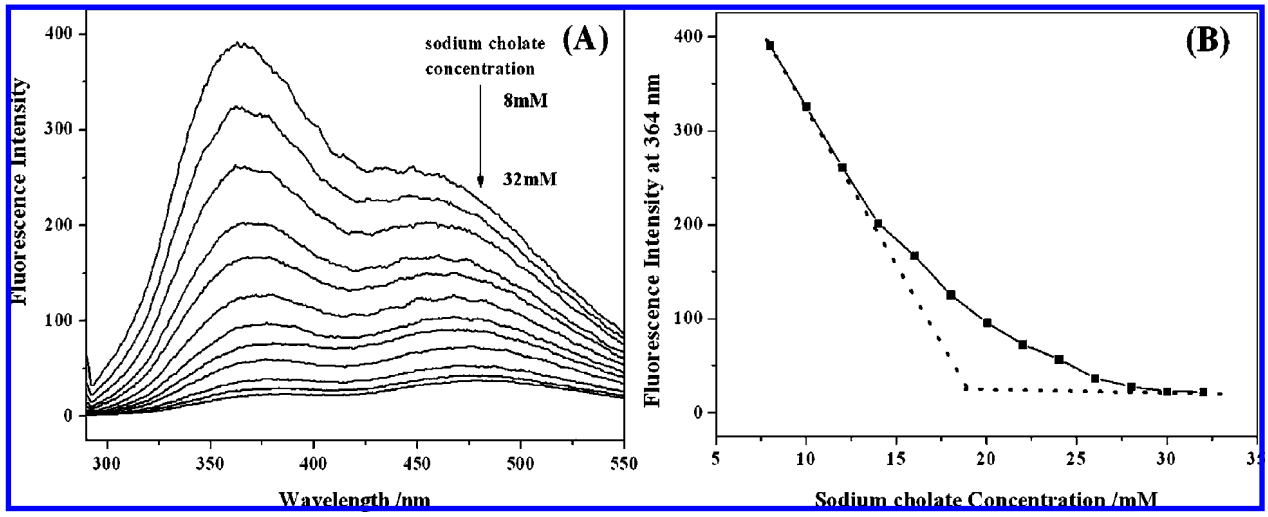


Figure 1. (A) Emission spectra of prednisone with different concentrations of sodium cholate. (B) Intensity of prednisone at emission maximum (364 nm) in the emission spectra as a function of concentration of sodium cholate at room temperature. [prednisone] = 1.06×10^{-6} M; [sodium cholate] = 8−32 mM; λ_{ex} = 283 nm.

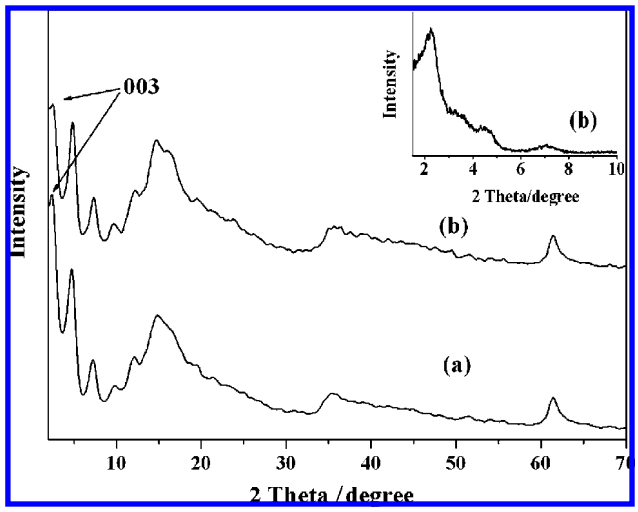


Figure 2. Powder X-ray diffraction patterns for (a) LDH−cholate and (b) LDH−cholate−prednisone (for clarity, the XRD pattern in the 2θ range of 1.5−10° was displayed in the inset).

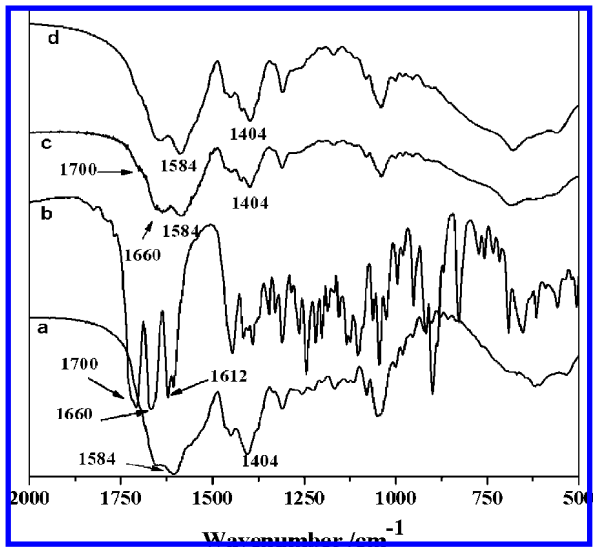


Figure 3. FT-IR spectra of (a) sodium cholate, (b) prednisone, (c) LDH−cholate−prednisone, and (d) LDH−cholate.

3. Results and Discussion

3.1. Determination of CMC Value of Sodium Cholate. The formation of cholate ion micelles was verified by a fluorescence probe technique using prednisone.[24] Although the reported CMC values of sodium cholate range from 10 to 19 mM,[24] it is necessary to determine the CMC value for this system first. The fluorescence emission spectra of prednisone in the presence of sodium cholate at a fixed λ_{ex} of 283 nm are shown in Figure 1A. It can be seen that the peak intensity decreases with the increase of the concentration of sodium cholate, especially at 364 nm. This is due to the fact that prednisone in water has a strong emission peak at 364 nm, which decreases significantly when it transfers into a hydrophobic environment. This phenomenon indicates the formation of micelles, which is in agreement with Small's model of micelle formation.[25] Figure 1B shows the effect of the sodium cholate concentration on the intensity of 364 nm for the emission spectrum. The intersection point of the horizontal line and the bias can be defined as the CMC value, which was found to be 19 mM. As a result it can be concluded that prednisone-containing cholate micelle is formed in aqueous solution with the CMC value of 19 mM.

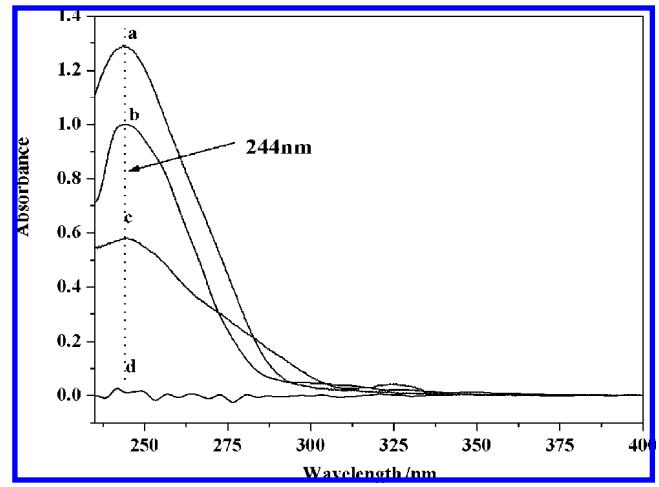


Figure 4. UV−vis spectra of (a) prednisone solution, (b) prednisone−cholate micelle, (c) LDH−cholate−prednisone after dissolution in solution (V_{HCl}: $V_{ethanol}$ = 1:1), and (d) sodium cholate solution.

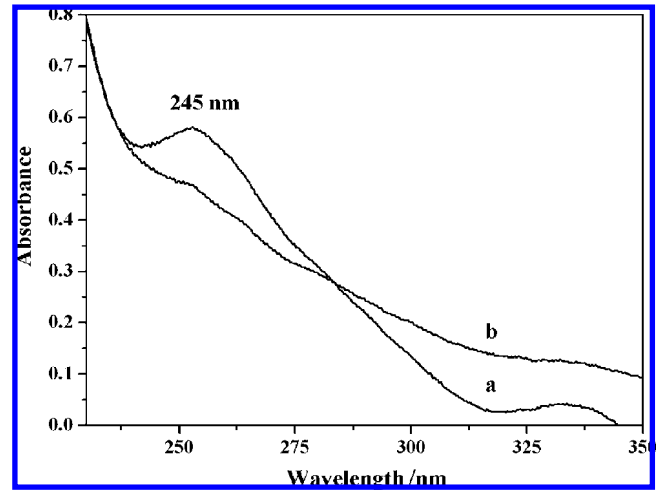
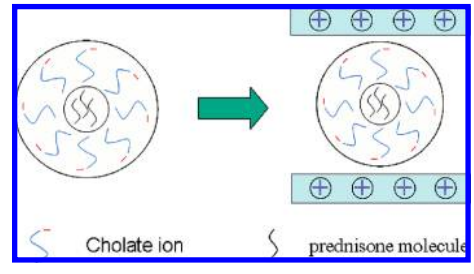


Figure 5. UV−vis spectra of the LDH−cholate−prednisone with the concentration of (a) [cholate] = 20 mM and (b) [cholate] = 10 mM.

3.2. Characterization of the LDH−Cholate−Prednisone Composite. The powder XRD patterns of LDH−cholate and LDH−cholate−prednisone are shown in Figure 2. The interlayer distance d_{003} value, representing the combined thickness of the brucitelike layer (0.48 nm) and the gallery height, is a function of the size and the orientation of intercalated anions.[26] Compared with the LDH−cholate (Figure 2a, $2\theta = 2.299$, $d_{003} = 38.4$ Å), the basal reflection (003) of LDH−cholate−prednisone composite (Figure 2b, $2\theta = 2.236$, $d_{003} = 39.5$ Å) shifts to a lower 2θ angle. This may indicate the intercalation of prednisone−cholate micelle into galleries of LDH, which will be further confirmed in the next section.

Scheme 1. Possible Representation for the Structure of LDH−Cholate−Prednisone Composite



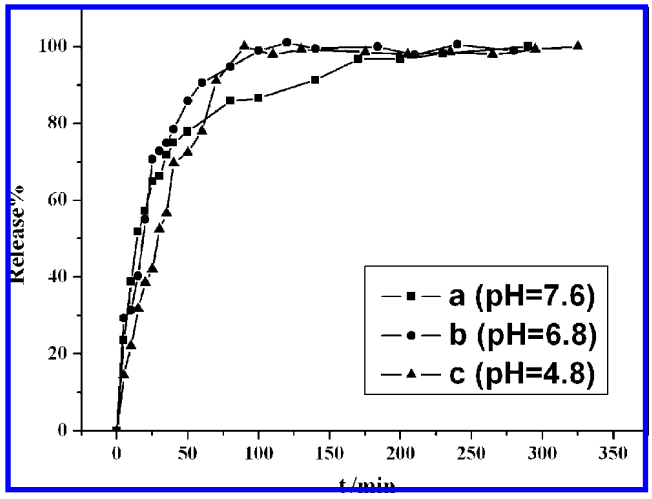


Figure 6. Release profiles of prednisone from the composite in buffer solutions at 37 °C with different pH values.

The FT-IR spectra of pristine sodium cholate, pristine prednisone, LDH−cholate−prednisone, and LDH−cholate are displayed in Figure 3. For the sake of clarity, only the main absorption bands were listed. In the spectrum of sodium cholate (Figure 3a), the strong absorption bands at 1584 and 1404 cm^{-1} are characteristic of the stretching vibrations of C═O and O−H, respectively. The spectrum of prednisone (Figure 3b) shows the stretching vibration of C═O at 1700 cm^{-1} and C═C from cyclohexadiene at 1660 cm^{-1}. The other absorption bands below 1000 cm^{-1} are attributed to δ(C−H) deformation modes. The spectrum of LDH−cholate (Figure 3d) displays characteristic bands of sodium cholate at 1584 and 1404 cm^{-1}, confirming the intercalation of cholate ions. For the spectrum of LDH−cholate−prednisone (Figure 3c), both of the characteristic bands of prednisone at 1700 and 1660 cm^{-1} and those of sodium cholate at 1584 and 1404 cm^{-1} were observed. It was found that the IR absorption of prednisone is weak for the sample of LDH−cholate−prednisone composite, which can be attributed to two possible reasons: (1) According to previous reports,[27,28] the movement of a drug molecule from a micelle core will be slower in comparison to the movement of drug out of core that is more mobile, which could lead to the low IR absorption of prednisone. (2) The actual drug concentration in the LDH−cholate−prednisone composite is low. This will be further discussed below.

UV−vis spectroscopy was used to investigate whether intercalation of prednisone into the LDH host was associated with any change in its chemical composition or environment. Figure 4 shows the UV−vis spectrum of prednisone released from LDH−cholate−prednisone composite after dissolution in HCl−ethanol solution (Figure 4c), with the pristine prednisone (Figure 4a), prednisone/cholate micelle (Figure 4b), and sodium

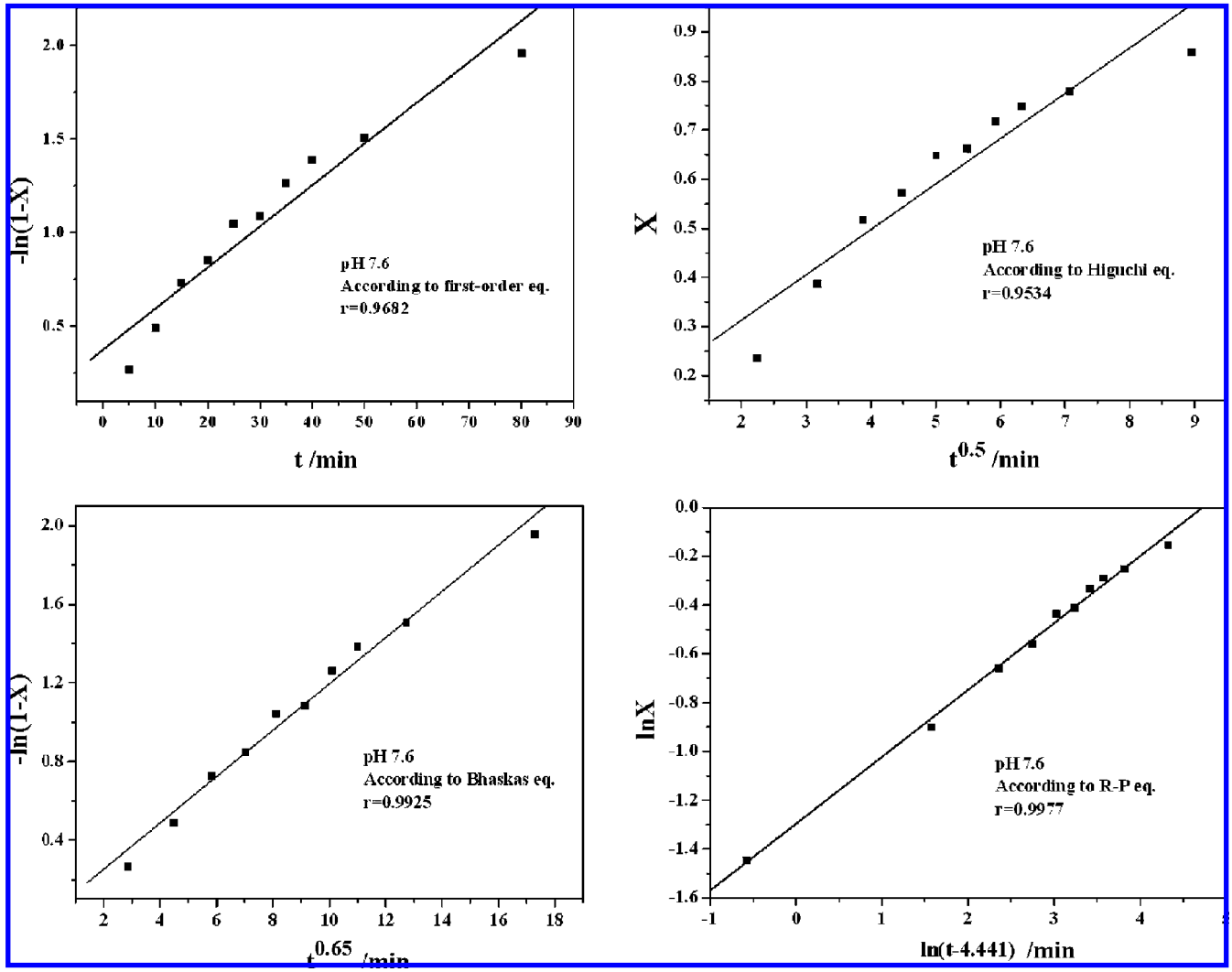


Figure 7. Plots of different kinetic models for the release of prednisone from the composite at pH 7.6.

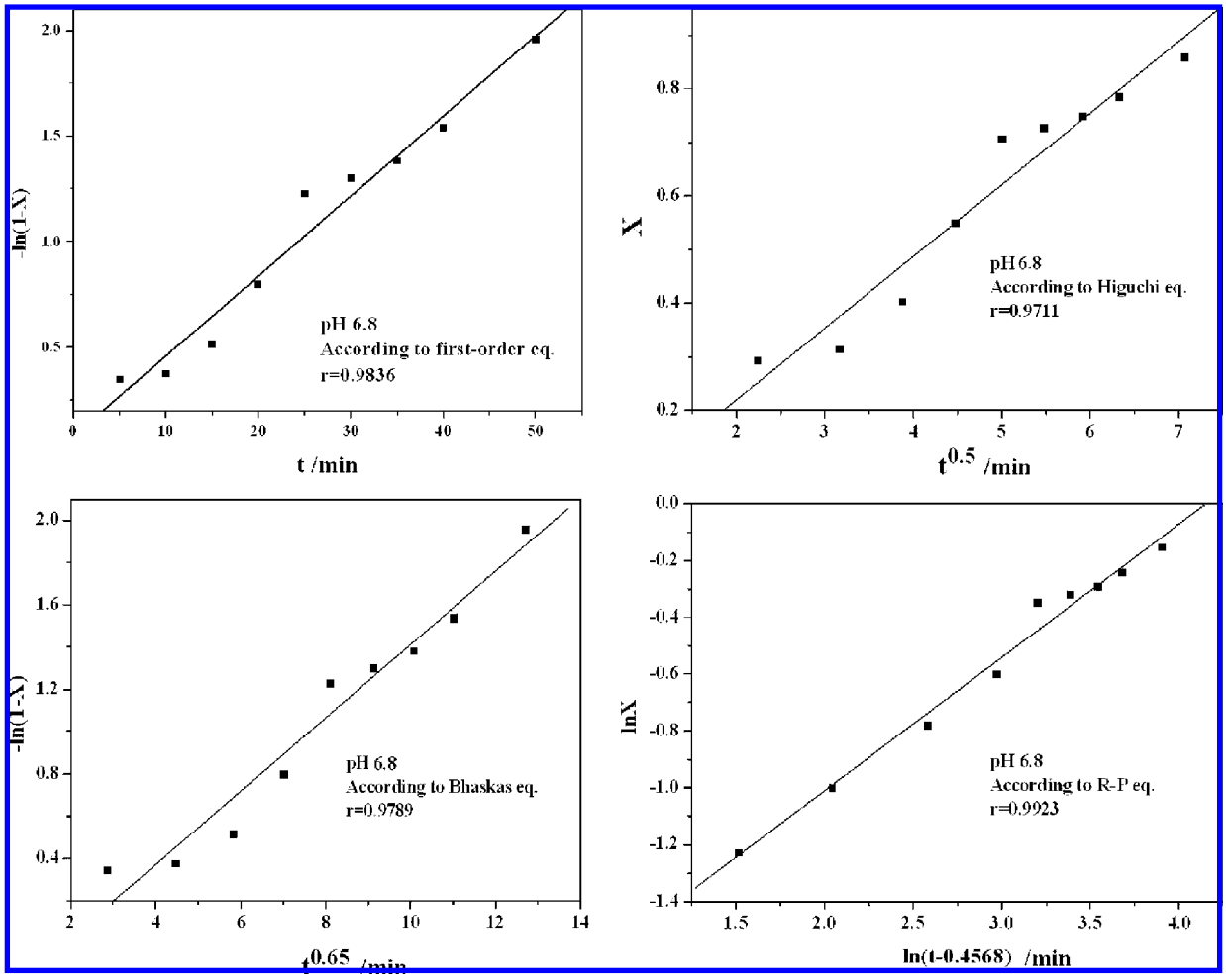


Figure 8. Plots of different kinetic models for the release of prednisone from the composite at pH 6.8.

cholate (Figure 4d) as comparison samples. It can be seen that pristine prednisone exhibits a strong absorption band at 244 nm, while pristine sodium cholate displays no absorption from 200 to 400 nm. A band at 244 nm (Figure 4b) is noted for the prednisone/cholate micelle. In the case of prednisone released from the LDH−cholate−prednisone composite, an absorption band at 245 nm (Figure 4c) was observed. Combined with the results obtained by fluorescence probe technique using prednisone (3.1 part), the XRD and FT-IR results mentioned above, the UV−vis results indicate that the prednisone−cholate micelle was successfully intercalated into the LDH host.

It should be noted that the micellization of cholate is very important for prednisone to intercalate into LDH. The following experiments can verify it. For comparison, two composite samples of LDH−cholate−prednisone were synthesized by the same method with the sodium cholate concentrations of 10 and 20 mM, respectively, i.e., one concentration is lower than the CMC value, and the other is higher than it. Equal weights of two samples were dissolved in solution (V_{HCl}:$V_{ethanol}$ = 1:1) and measured by UV−vis spectrometer, respectively (Figure 5). The spectrum of LDH−cholate−prednisone ([cholate] = 20 mM, Figure 5a) displays a band at 245 nm attributed to prednisone, while it is inconspicuous in the spectrum of LDH−cholate−prednisone ([cholate] = 10 mM, Figure 5b). The comparison study were indicates that the formation of prednisone−cholate micelle is crucial for the preparation of LDH-based drug composite.

The drug loading for the LDH−cholate−prednisone composite was determined to be 3.82% (w/w) by the method of UV−vis spectroscopy based on a multipoint working curve. This result is a little higher than other reports[6,21] on encapsulating hydrophobic drug molecules into LDH. Elemental analysis gave Mg 8.192%, Al 4.339%, C 48.95%, and H 7.684%. The chemical composition for the LDH−cholate−prednisone composite can be obtained: $[Mg_{0.68}Al_{0.32}(OH)_2](C_{21}H_{26}O_5)_{0.022}$-$(C_{24}H_{39}O_5^-)_{0.32}\cdot 0.12H_2O$, based on the results of elemental analysis, ICP, TG-DTA, and UV−vis spectroscopy.

On the basis of the basal spacing d_{003} of 39.5 Å for the LDH−cholate−prednisone composite observed by XRD, the gallery height was calculated to be 34.7 Å by subtracting the thickness of the inorganic layer (4.8 Å). The host−guest interactions for the composite consist of the electrostatic attraction between the positively charged LDH layers and the negatively charged micelles, as well as the hydrogen bonding formed among the host layers, the guest anions and the interlayer water molecules. Taking into account the molecular dimensions of cholate and prednisone (11.66 and 9.93 Å, respectively, determined by the ChemWindow 6.0 software) and the existence of the prednisone−cholate micelle, a schematic supramolecular structure of the LDH−cholate−prednisone composite was tentatively proposed and presented in Scheme 1.

3.3. In Vitro Drug Release Behavior. The drug release properties of prednisone from the LDH−cholate−prednisone composite have been investigated at a constant temperature of 37 °C. Figure 6 shows the release profiles of composite in solution at pH 4.8, 6.8, and 7.6, respectively. It was found that the rapid release during the first 40 min is followed by a slower

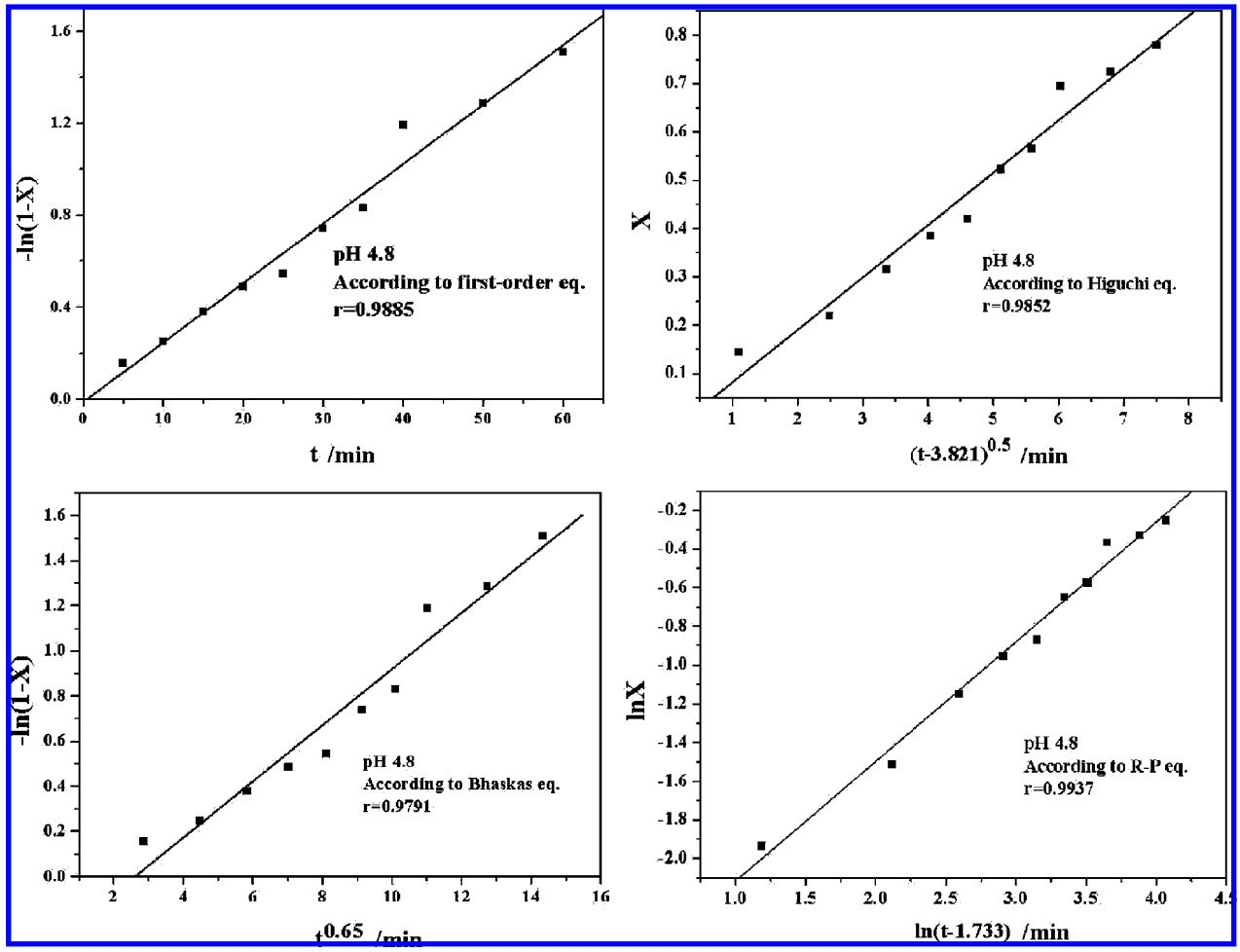


Figure 9. Plots of different kinetic models for the release of prednisone from the composite at pH 4.8.

release of the drug, and equilibrium was achieved after ca. 150 min. In the case of pH 7.6 (Figure 6a), the released percentages of 65% and 90% were obtained after 40 and 140 min, respectively, and prednisone was completely released at ~175 min. For pH 6.8 and 4.8 (Figure 6b and c), the release rates are a little higher than that of pH 7.6, and complete release of prednisone was observed at ~105 min. Compared with the release behavior based on LDH−drug composites reported previously,[21] it is worth noticing that there is no burst phenomenon occurring at the beginning of all the release tests. It was also found that the pH value of the medium imposes very little influence on the release performances of prednisone. This is rather 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.[19] In this work, prednisone is double protected from the physiological environment in the LDH−cholate−prednisone composite, first by the organic environment of the micelles and second by the durability of the LDH. Therefore, the release process of the LDH−cholate−prednisone is controlled by the synergistic effect of both the cholate micelle and LDH host, demonstrating almost 100% release of prednisone and applicability in a wide pH range of 4.8−7.6.

The drug release based on the LDH−cholate−prednisone composite could be controlled by any of the following steps: (1) dissolution of LDH particles;[29,30] (2) ion-exchange reaction between prednisone-containing micelles and phosphate anions in buffer solution;[31] (3) disaggregation of the cholate micelle and release of prednisone. The release mechanism of prednisone from the LDH−cholate−prednisone composite is very complicated and not completely understood. According to the literature, a first-order equation (eq 1),[32] the Higuchi equation (eq 2),[33,34] the Bhaskas equation (eq 3),[32] and the Rigter−Peppas (RP) equation (eq 4)[35,36] with modification were chosen to study the release dynamics of this system:

$$X = 1 - e^{-k(t-\alpha)} \quad (1)$$

$$X = k(t - \alpha)^{1/2} \quad (2)$$

$$X = 1 - e^{-k(t - \alpha)^{0.65}} \quad (3)$$

$$X = k(t - \alpha)^{n} \quad (4)$$

where X, t, k, and α are the release percentage, release time, kinetic constant, and modified parameter, respectively. Here, n is an exponent, which is normally used to describe different release mechanisms. The value of $n < 0.45$ corresponds to the drug diffusion control; $n > 0.89$ is attributed to the dissolution of LDH particles; $0.45 < n < 0.89$ is due to the cooperation of drug diffusion and LDH dissolution. A directing Excel-based solver (DEBS) was used in this work, and the equations were evaluated by residual sum of squares (SUM, SUM = $\Sigma(X - X')^2$) and r (coefficient).

On the basis of the four different kinetic models, the fitting results of drug release profiles at pH 7.6, 6.8, and 4.8 are given in Figures 7, 8, and 9, respectively. The parameters of SUM, α, n, and r are tabulated in Table 1. It can be seen from Table

Table 1. Fitting Parameters of Drug Release Profiles to Different Kinetic Models

pH	parameter	first-order eq	Higuchi eq	Bhaskas eq	RP eq
pH 7.6	SUM	3.35×10^{-2}	4.79×10^{-2}	1.80	5.14×10^{-3}
	α	0	0	0	4.44
	n				0.277
	r	0.9682	0.9534	0.9925	0.9977
pH 6.8	SUM	2.08×10^{-2}	2.13×10^{-2}	1.78	2.11×10^{-2}
	α	0	0	0	0.466
	n				0.528
	r	0.9836	0.9711	0.9789	0.9923
pH 4.8	SUM	7.29×10^{-3}	1.33×10^{-2}	3.06	8.26×10^{-3}
	α	0	3.821	0	1.73
	n				0.631
	r	0.9885	0.9852	0.9791	0.9937

1 that the release of prednisone from LDH−cholate−prednisone follows the RP equation very well at different pH values, with satisfactory coefficients of 0.9977 (pH 7.6), 0.9923 (pH 6.8), and 0.9937 (pH 4.8). The value of n is 0.277 ($n < 0.45$) at pH 7.6, so the release mechanism corresponds to the drug diffusion control. At pH 6.8 and 4.8, the values of n are 0.528 and 0.631 ($0.45 < n < 0.89$), respectively, indicating that the drug release mechanism depends on the combination behavior control, including dissolution of the composite, ion-exchange, and diffusion of prednisone. Because of the noncorrelative relationship between the release behavior and pH value, it can be speculated that the synergistic effect of both cholate micelles and LDH host plays an important role in determining the drug release properties.

4. Conclusion

A new delivery system for prednisone has been demonstrated in this work. The drug was loaded into micelles first and then intercalated into the MgAl-LDH galleries by the method of coprecipitation. XRD, FT-IR, and UV−vis absorption spectroscopy indicate a successful intercalation of prednisone-containing micelles between the LDH layers. The in vitro release studies show that there is no burst phenomenon occurred at the beginning of release tests at different pH buffers. Because of the synergistic effect of both cholate micelle and LDH host, the solution pH imposes very little influence on the release performance of prednisone in the studied pH range 4.8−7.6. Four kinetic models (first-order equation, Higuchi equation, Bhaskas equation, and Ritger−Peppas equation) were used to study the release dynamics of this system. The kinetic studies by a directing Excel-based solver (DEBS) show that the release of prednisone from LDH−cholate−prednisone follows the RP equation satisfactorily. At pH 7.6, the release mechanism corresponds to drug diffusion control. At pH 6.8 and 4.8, the drug release depends on the combination behavior control, including dissolution of the composite, ion-exchange, and diffusion of prednisone. As a result, this drug-containing micelle intercalated LDH composite in this work provides a novel drug release formulation with potential application for nonionic and water-insoluble drugs, taking advantage of applicability in a wide range of solution pH (4.8−7.6) and almost complete release (100%).

Acknowledgment

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