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Research Article

Intercalation of Aceclofenac/Sulfobutyl Ether-β-cyclodextrin Complex into Layered Double Hydroxides through Swelling/Restoration Reaction and Its Controlled-Release Properties

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Aceclofenac (AC)/sulfobutyl ether-β-cyclodextrin (SBE-β-CD) inclusion complex intercalated layered double hydroxides (LDHs) composite were prepared by swelling/restoration method. After swelling/restoration, the d-spacing of LDHs is expanded to 2.23 nm, which clearly demonstrates the successful intercalation of AC/SBE-β-CD into LDHs layer. AC/SBE-β-CD inclusion complex in the interlayer has monolayer arrangement based on the d-spacing of LDHs and torus thickness of SBE-β-CD. The AC release performances were also studied in buffer solutions with different pH values. The results show AC/SBE-β-CD intercalated LDHs not only enhance the dissolution profile of AC but also exhibit a controlled-release process, which indicates that the AC/SBE-β-CD-LDHs have a potential application in drug delivery agent.

1. Introduction

The organic/inorganic nanocomposites are promising hybrid materials, which exhibit many unique properties due to the synergies of the inorganic and organic components [1]. Layered double hydroxides (LDHs) are a large class of anionic clays consisting of positively charged brucite-like layers and exchangeable interlayer anions [2, 3]. By intercalation, organic molecules/LDHs composite materials have been widely studied due to the characteristic of tunable composition and exchangeable anion in fields of catalysis, adsorption, controlled-release of drug molecules, UV/IR absorption materials, and so forth [4–10]. Macrocyclic compounds, one important group of organic compounds in host-guest chemistry with excellent applications on structural assembly and molecule/ion recognition, on the other hand, can act as guest components for the composites [11]. In the recent decade, macrocyclic compounds such as cyclodextrins [12–16], calixarenes [1, 17–19], and crown ethers [11, 20] intercalated into LDHs have attracted intensive attention because of their potential novel properties. For the preparation of these composites, most traditional methods are coprecipitation, ion-exchange, calcination/rehydration, and delamination/restoration which usually needed long time or heating/refluxing treatment [1]. Recently, a new swelling/restoration method reported by Ma's group [1, 19, 20] showed similar advantage as delamination for facile entrance of bulk guests, while it can give better morphology. However, to the best of our knowledge, there is no report on the synthesis and applications of cyclodextrins (CDs) or their derivatives intercalated LDHs composite materials through swelling/restoration reaction.

Aceclofenac (AC) is a nonsteroidal anti-inflammatory drug (NSAID) which has shown marked therapeutic effects in rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis [21, 22]. However, the side effects of gastrointestinal irritation and sparingly aqueous solubility limit practical use of AC [23]. Therefore, it seems a good option for

intercalation of AC/(CDs) inclusion complex into LDHs to reduce side effects and provide an effective therapy for arthritis with lose dose and duration of therapy.

In this work, a swelling/restoration approach for intercalation of AC/sulfobutyl ether-β-cyclodextrin (SBE-β-CD) complex into LDHs was proposed. The structure and controlled-release property of AC/SBE-β-CD intercalated LDH composite were investigated.

2. Materials and Methods

2.1. Materials. $Mg(NO_3)_2{\cdot}6H_2O$, $Al(NO_3)_3{\cdot}9H_2O$, NaOH, $NaNO_3$, and formamide were purchased from Sinopharm Chemical Reagent Co., Ltd. (China). Aceclofenac (AC) was obtained from Wuhan Xinjialing Biotechnology CO., Ltd. (China). SBE-β-CD (average degree of sulfobutyl ether substitution of 6.5) was purchased from Shandong Binzhou Zhiyuan Biological Technology Co., Ltd. (China). All reagents were used as raw materials without further purification. CO_2-free deionized water was used throughout the experimental processes.

2.2. Synthesis of Inclusion Complex of AC with SBE-β-CD. The inclusion complex of AC with SBE-β-CD with 1 : 2 molar ratios was prepared using similar kneading method [24]. Accurately weighed quantities of SBE-β-CD and AC were taken in a mortar; a minimum volume of ethanol/water (1 : 1, by volume) mixture was added slowly and kneaded thoroughly with a pestle to obtain a paste. To remove the AC adsorbed on the surface of SBE-β-CD, the inclusion complex was washed with ethanol solution for several times. The obtained solid mass was further dried under vacuum at room temperature.

2.3. Synthesis of MgAl-NO_3-LDHs. The MgAl-NO_3-LDHs was prepared by a procedure of typical coprecipitation methods [2, 3]. Firstly, 50 mL mixture solution containing 0.6 Mol $Mg(NO_3)_2{\cdot}6H_2O$ and 0.3 Mol $Al(NO_3)_3{\cdot}9H_2O$ (Mg/Al molar ratio = 2 : 1) was slowly added to a solution of 4.25 g $NaNO_3$ (0.05 Mol) in 100 mL of water at room temperature with vigorously stirring under N_2 atmosphere to prevent the formation of carbonate intercalated LDHs. The pH of the reaction mixture was adjusted 10.0 ± 0.2 by dropwise addition of 1 Mol NaOH solution. Then the resulting slurry was crystallized at 70°C for 48 h. The white precipitate was isolated by filtration, washed with hot decarbonated water several times, and dried at 80°C for 24 h.

2.4. Synthesis of AC/SBE-β-CD Inclusion Complex Intercalated LDHs by Swelling/Restoration Method. AC/SBE-β-CD inclusion complex intercalated LDHs were prepared by a procedure similar to the methods of Huang et al. [1]. 0.5 g MgAl-NO_3-LDHs was added to 200 mL of formamide, and then the mixture was allowed to stand for 24 h without stirring or shaking, and then a translucent colloidal suspension was obtained. Weighted 2.3 g AC/SBE-β-CD inclusion complex was put into the prepared colloidal suspension of the LDHs in formamide and stirred slowly for 24 h. After having been centrifuged at 18000 rpm, the precipitate was washed with hot decarbonated water several times and dried at 80°C for 24 h. The schematic representation for the formation of AC/SBE-β-CD-LDHs by swelling/restoration method is shown in Scheme 2.

2.5. Characterization. X-ray diffraction (XRD) patterns of the samples were collected using a Bruker D8 Advance XRD diffractometer at Cu Kα radiation and a fixed power source (40 kV and 40 mA, = 1.5406 Å). Fourier-transform infrared spectroscopy (FT-IR) were recorded in the range 400–4000 cm^{-1} on a Nicolet NEXUS 470 Fourier-transform infrared spectrophotometer using KBr pellet technique. Thermogravimetry and differential thermal analysis (TG-DTA) curves were obtained on a NETZSCH STA 449C instrument in the temperature range of 30–680°C with a heating rate of 10°C min^{-1} in air atmosphere. A field emission scanning electron microscope (FSEM) (HITACHI S4800) and transmission electron microscope (TEM) (FEI Tecnai G20) were used to study the surface morphology of sample.

2.6. Release Performances of AC from AC/SBE-β-CD-LDHs. The release performances of AC from AC/SBE-β-CD-LDHs composite were determined essentially following our previous method [22]. 0.1 g of AC/SBE-β-CD-LDHs powder was added to 300 mL of phosphate citrate buffer solutions (pH 4.8 and pH 7.5, resp.) and was stirred at 37°C. At specified time intervals, 2 mL of solution was removed and filtered through 0.45 μm microfiltration membrane. The accumulated amount of AC released into buffer solutions was measured momentarily using a UV-Vis spectrophotometer at λ_{max} = 273 nm of AC. Runs were performed in triplicate. The release profiles were plotted as the relative release percentages of AC against time.

3. Results and Discussion

3.1. X-Ray Diffraction. Figure 1 shows the XRD patterns for AC/SBE-β-CD inclusion complex with ethanol washing (a), without ethanol washing (b), SBE-β-CD (c), and AC (d), respectively. As we can see, SBE-β-CD is amorphous, but AC is in crystalline form. The XRD patterns of AC/SBE-β-CD inclusion complex without ethanol washing show aceclofenac crystalline signals, which could be derived from adsorbed AC on the surface of AC/SBE-β-CD inclusion complex. In contrast, after washing with ethanol, the XRD pattern of Figure 1(a) shows only the amorphous bread peak of SBE-β-CD, suggesting the formation of inclusion with AC. So at the last step of the synthesis of AC/SBE-β-CD inclusion complex, ethanol was used to remove AC adsorbed on the complex.

Figure 2 shows the XRD pattern of MgAl-NO_3-LDHs (a) and AC/SBE-β-CD-LDHs composite prepared by swelling/restoration method (b). As compared to the MgAl-NO_3-LDHs (Figure 2(a), 2θ = 10.20°, d_{003} = 0.87 nm), the basal reflection (003) of AC/SBE-β-CD-LDHs (Figure 2(a), 2θ = 3.96°, d_{003} = 2.23 nm) shifts to a lower 2θ angle. Therefore, the XRD result indicates that restoration of AC/SBE-β-CD-LDHs is formed when AC/SBE-β-CD inclusion

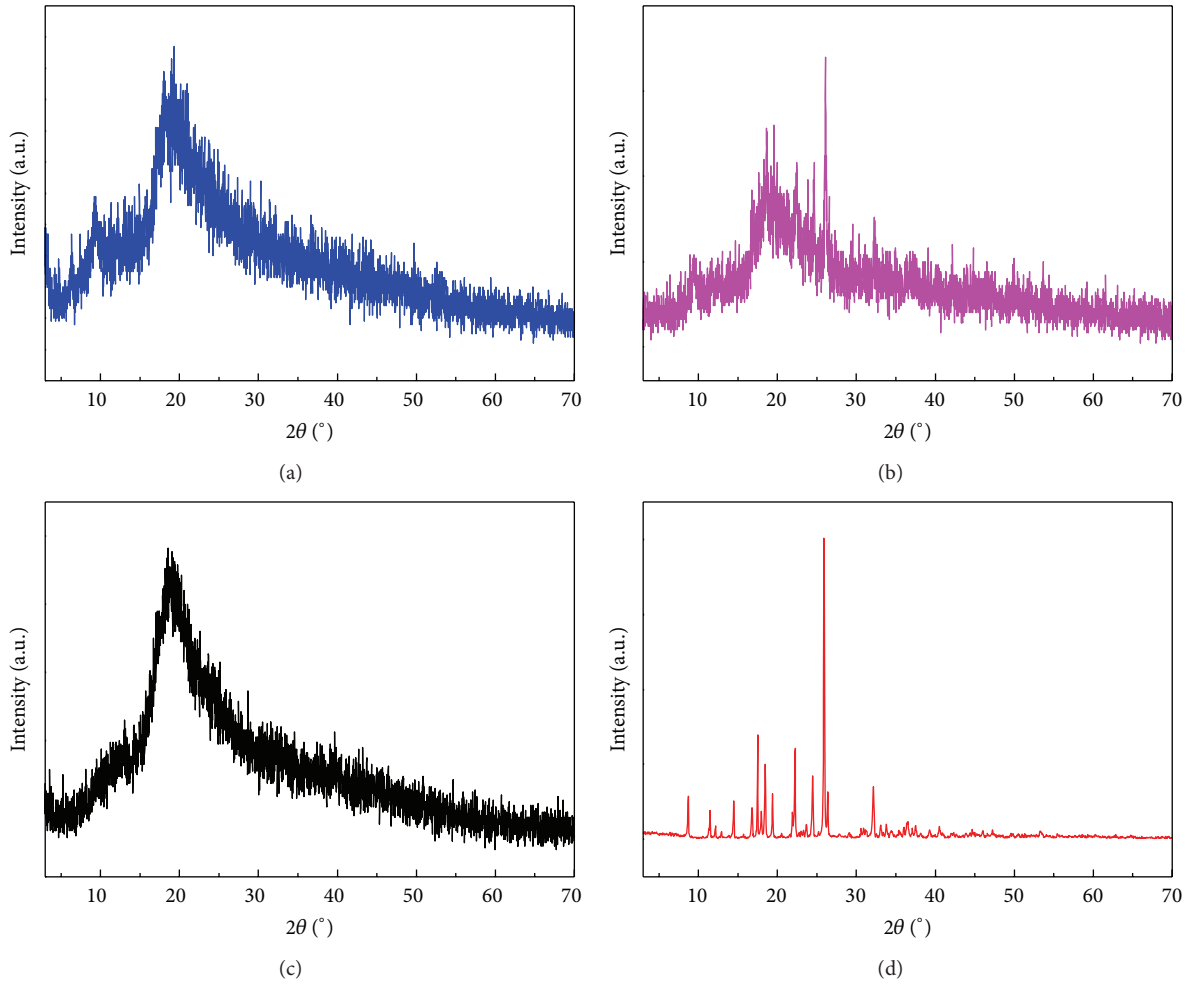


Figure 1: XRD patterns for AC/SBE-β-CD inclusion complex (a) with ethanol washing, (b) without ethanol washing, SBE-β-CD (c), and AC (d).

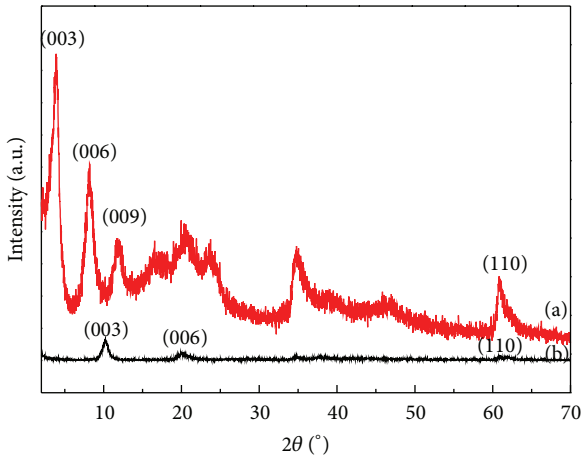
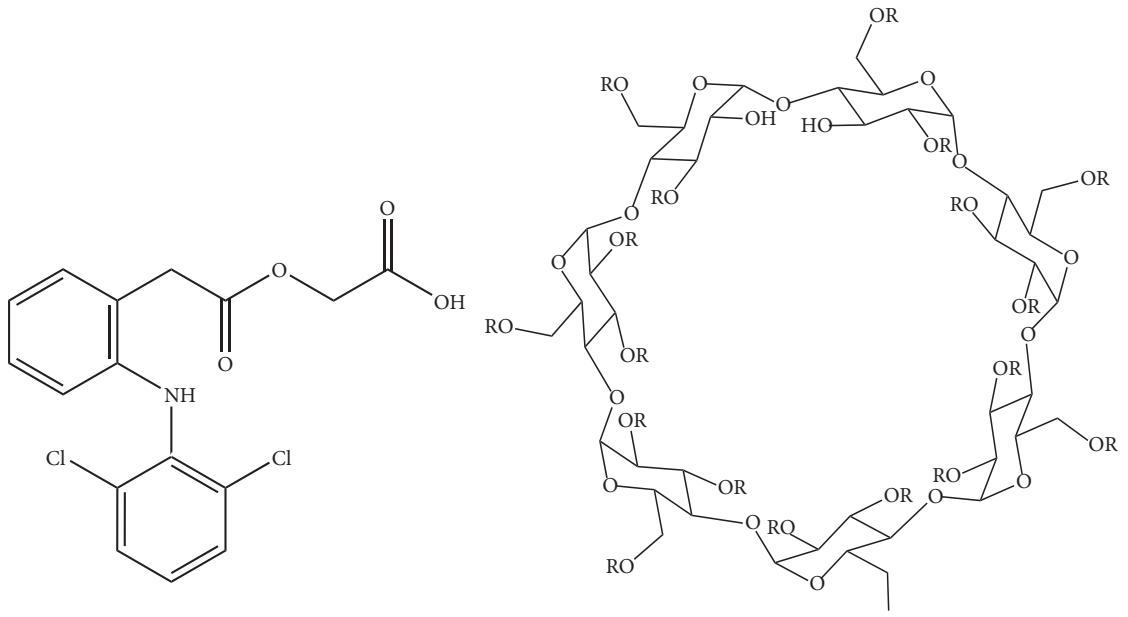
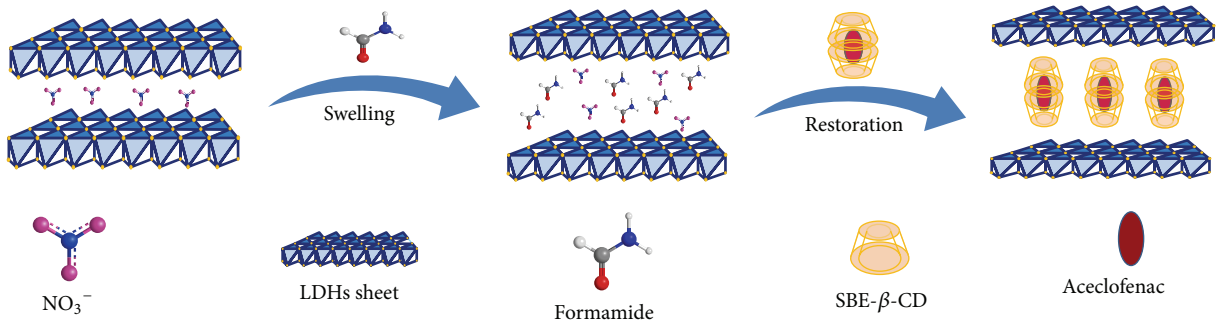


Figure 2: XRD patterns of MgAl-NO_3-LDHs (a) and AC/SBE-β-CD-LDHs (b).



(a) Aceclofenac (AC) (b) Sulfobutyl ether-β-cyclodextrin (SBE-β-CD)

Scheme 1: Structures of aceclofenac (a) and sulfobutyl ether-β-cyclodextrin (b).



Scheme 2: Schematic formation of the AC/SBE-β-CD intercalated LDHs composite.

complex is placed in contact with colloidal suspension of the MgAl-NO_3-LDHs in formamide. Based on the basal spacing d_{003} of 2.23 nm for AC/SBE-β-CD-LDHs observed by XRD and subtracting the thickness of brucite layer (0.48 nm), the gallery height is calculated to be 1.75 nm, which is about double the size of that torus thickness of SBE-β-CD (0.78 nm) [25]. Therefore, as shown in Scheme 1, it is suspected that AC/SBE-β-CD inclusion complex located in the form of monolayer arrangement.

3.2. Fourier-Transform Infrared Spectroscopy. Figure 3 shows the FT-IR spectra of MgAl-NO_3-LDHs (a), AC (b), SBE-β-CD (c), and AC/SBE-β-CD-LDHs composite (d), respectively. The FT-IR spectra of AC (Figure 3(b)) consisted of the sharp absorption bonds of –NH group (3319 cm^{-1}) and of a carbonyl stretching band at 1716 cm^{-1} and 1717 cm^{-1} for –C=O stretching of COO and –COOH group, respectively. The peaks at 1589, 1257, 1149, and 750 cm^{-1} are assigned to other major peaks for AC. In the spectrum of SBE-β-CD (Figure 3(c)), the absorption bands at 3442 cm^{-1} and 2940 cm^{-1} are due to the stretching vibration of O–H and $-CH_2$, respectively. The strong absorption bands at 1206 and 1044 cm^{-1} are the characteristic of stretching vibration of C–H and C–O–C of glucose units [22]. As shown in Figure 3(d), the spectra of AC and SBE-β-CD-LDHs are partially overlapped, and AC/SBE-β-CD-LDHs composite exhibited the main characteristic peaks of AC, SBE-β-CD, and metal-O stretching vibrations. These results indicate that AC/SBE-β-CD have been intercalated into composite by swelling/restoration method.

3.3. Surface Morphology. Figure 4 shows the scanning electron microscope morphology and transmission electron microscope image of AC/SBE-β-CD-LDHs. As we can see

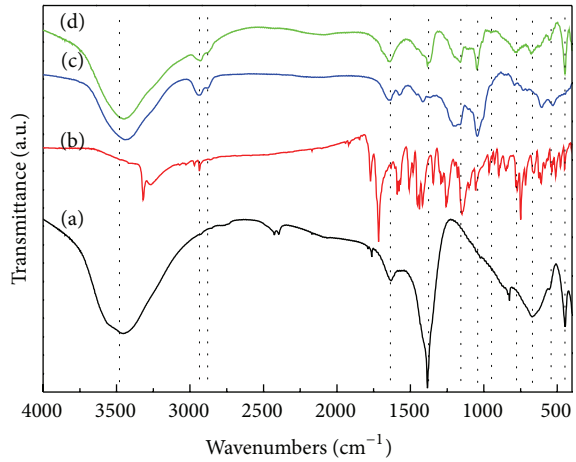


FIGURE 3: FT-IR spectra of MgAl-NO_3-LDHs (a), AC (b), SBE-β-CD (c), and AC/SBE-β-CD-LDHs (d).

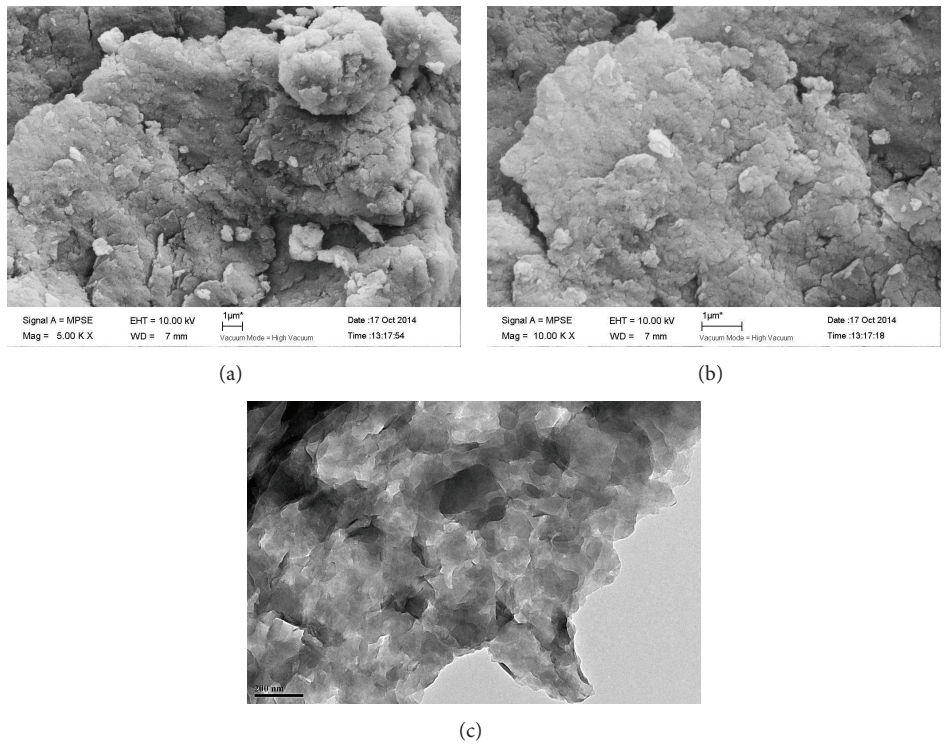


FIGURE 4: Scanning electron micrographs at low (a) and high (b) magnifications and transmission electron microscope image (c) for AC/SBE-β-CD-LDHs.

the AC/SBE-β-CD-LDHs particles are of plate-like shape with slight agglomerates, which is typical morphology of intercalated LDHs.

3.4. Thermal Stability. The TG and DTA curves for the AC/SBE-β-CD-LDHs are shown in Figure 5. The thermal decomposition of AC/SBE-β-CD-LDHs was characterized by four weight loss steps (Figure 5): the first (50–130°C) is due to loss of both adsorbed water and interlayer water molecules; the second (130–260°C) is due to both the decomposition of the SBE-β-CD and the elimination of interlayer water, which has a weak exothermic peak in the DTA curve; the third (260–570°C) is a consequence of dehydroxylation and decomposition of SBE-β-CD. The last stage (590–630°C) can be attributed to the combustion of SBE-β-CD, which has a strong exothermic peak at 625°C in the DTA curve.

3.5. Controlled-Release Properties. The release of AC from AC/SBE-β-CD-LDHs composite was monitored via UV-Vis spectrophotometer. Figure 6 shows AC release performance of the composite in buffer solution at pH 4.8 and pH 7.5, respectively. As we can see, the AC release was rapid at the

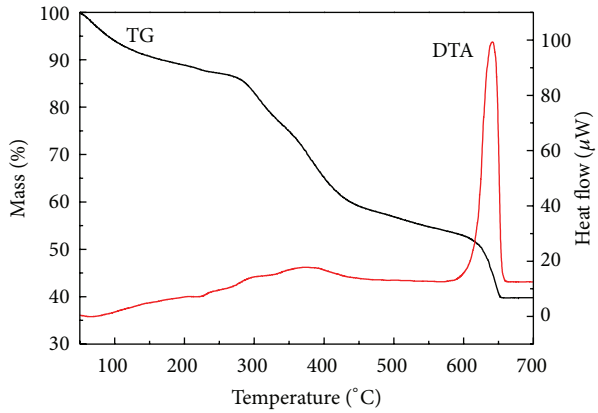


Figure 5: TG-DTA profiles of AC/SBE-β-CD-LDHs.

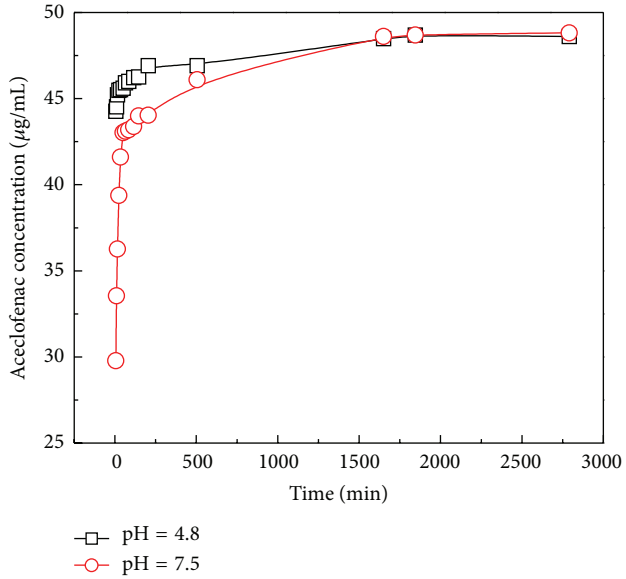


Figure 6: Release curves of AC/SBE-β-CD-LDHs composite in buffer solution at pH 7.5 and pH 4.8.

first 100 minutes and then slowed until it reached equilibrium at pH 4.8. However, a rapid release of AC occurred at the first 40 min, which was followed by a slower release of AC until about 2000 min. It was also found that the AC accumulative concentration at pH of 7.5 (48.8 μg/mL) was nearly the same as that at pH of 4.8 (48.6 μg/mL). Considering the poor solubility of AC [22], thus we can conclude that the present SBE-β-CD intercalated LDHs not only enhanced the dissolution profile of AC but also exhibited a controlled-release process.

4. Conclusion

AC/SBE-β-CD-LDHs nanocomposite with larger AC/SBE-β-CD inclusion complex in the LDHs interlayer can be easily prepared by swelling/restoration method. As compared to MgAl-NO_3-LDHs, the basal reflection (003) of AC/SBE-β-CD-LDHs shifts to a lower 2θ angle (3.96°), and the AC/SBE-β-CD inclusion complex in the LDHs interlayer has monolayer arrangement. The AC/SBE-β-CD-LDHs prepared by swelling/restoration reaction exhibits a controlled-release property with higher concentration of AC.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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