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ORIGINAL CONTRIBUTION

Synthesis and characterization of Naproxen intercalated Zn–Al layered double hydroxides

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Abstract In this paper, naproxen was intercalated into Zn–Al layered double hydroxides (LDHs) by ion exchange method to obtain naproxen/LDHs nanohybrids. The effects of the contact time, the composition, and the structural charge density ($\sigma_{S,T}$) and the specific surface area of LDHs, and pH value on the uptake of naproxen on LDHs, and the release of naproxen from the naproxen/LDHs nanohybrids were investigated. The adsorption isotherm curves of naproxen on the LDHs obey the Langmuir equation, and apparent monolayer capacity (A_m) in units of mmol m^{-2} increases with the increase of the $\sigma_{S,T}$ value of the LDHs samples. The release rate of naproxen from the naproxen/LDHs nanohybrids decreases with the increase of the $\sigma_{S,T}$ value of the LDHs samples and is much lower than that of naproxen troche, indicating that the naproxen/LDHs nanohybrid is an efficient drug-controlled release system. In the pH range of 6~11.5, the uptake amount (A_{eq}) of naproxen on the LDHs decreases with the increase of pH value. The A_m values of LDHs(Cl^-) are much higher than that of LDHs$\left(CO_3^{2-}\right)$, which may contribute to that LDHs(Cl^-), which has a stronger anion exchange ability than LDHs$\left(CO_3^{2-}\right)$. The naproxen molecules are possibly adsorbed on each surface of the basal layer of LDHs. In other words, a bilayer is formed in the gallery of LDHs.

Keywords Naproxen · Layered double hydroxide · Nanohybrids · Controlled release

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Introduction

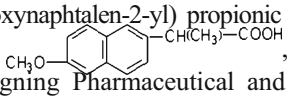
Layered double hydroxides (LDHs), or the so-called hydrotalcite-like compounds, are the only known family of layered solids with structural positive charged layers and interlayer balancing anions [1, 2]. LDHs may be represented by the general formula $\left[M^{II}_{1-x}M^{III}_{x}(OH)_2\right]^{x+}\left[A^{n-}_{x/n}\right]^{x-}\cdot mH_2O$, where M^{II} and M^{III} are di- and trivalent metal cations, 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 structural charged layers, and the structural positive charge density ($\sigma_{S,T}$) 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 physicochemical properties, LDHs have widespread applications in many areas such as anion adsorbents, medicine carriers, ion exchangers, catalyst supports, catalysts and membranes [6–13].

More recently, LDHs are attracting much attention in drug delivery and gene therapy because of their biocompatibility, anion-exchange property, and nontoxicity, etc. [14–17]. Choy et al. [14] 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 [18, 19], 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, which are extremely significant factors for the preparation of drug/LDHs nanohybrids, drug-controlled release, and delivery efficiency, are still far to be fully understood. In this paper, naproxen/Zn–Al LDHs nanohybrids were prepared, and the aims are to investigate the adsorption of naproxen on LDHs, the release behavior of naproxen from the nanohybrids, and the mechanism of naproxen–LDHs interaction.

Experimental

Materials

Naproxen, (+)-(*S*)-2-(6-methoxynaphtalen-2-yl) propionic acid, with the following structure,  , was purchased from Jinan Yongning Pharmaceutical and was used without further purification. It is a nonsteroidal anti-inflammatory drug frequently used in the treatment of rheumatic diseases.

All other chemical reagents used were A.R. grade.

Preparation and Characterization of LDHs and naproxen/LDHs nanohybrids

The Zn–Al LDHs samples were synthesized by the coprecipitation method according to literature [2]. Under a N_2 atmosphere, the mixed solutions of $ZnCl_2{\cdot}6H_2O$/$AlCl_3{\cdot}6H_2O$ at different molar ratios were prepared with a total metal ion concentration of ~0.5 mol l^{-1}. Then the coprecipitation agent, diluted ammonia water (6 wt%), was added to the mixed solutions under stirring at a speed of 25 ml/min till the final pH value reached 9.5. The precipitate was aged for 1.5 h in the mother solution at room temperature and then filtered and washed with deionized water to remove NH_4Cl and the excess ammonia. The filter cakes held in a glass bottle were peptized at a constant temperature of 80 °C in an oven for about 24 h, to obtain Zn–Al LDHs (Cl^-) sol samples.

A similar procedure was used to prepare Zn–Al LDHs$\left(CO_3^{2-}\right)$ sol sample, except that NaOH and Na_2CO_3 were used as coprecipitation agent.

A desired amount of naproxen solution was mixed under stirring with a desired amount of LDHs sol to form a series of naproxen–LDHs suspensions with a series of initial concentrations (C_{in}) of naproxen and a constant LDHs concentration of 1 g l^{-1}. The pH values of the suspensions were adjusted by 1 mol l^{-1} NaOH and HCl solutions, respectively. The suspensions were kept for a desired time interval (t) in THZ-82 model constant-temperature shaker at 25 °C under a nitrogen atmosphere to obtain naproxen/LDHs nanohybrids. Then, the suspensions were centrifuged, and supernatants were taken for measurements of remaining naproxen concentrations, whereas precipitates, naproxen/LDHs nanohybrids, were used for release experiments.

The chemical compositions of the LDHs samples were determined by elemental analysis using a S/max3080E2 model X-ray fluorescent spectrometer. The average platelet diameters of the various LDHs samples were determined to be in the range of 50~70 nm using a JEM-100cxII model transmission electron microscope. The specific surface areas (S) of the LDHs samples were determined by an Omnisorp 100-CX model automatic gas adsorption apparatus using the nitrogen adsorption isotherms at 77 K treated according to the BET method. Power X-ray diffraction (PXRD) data were obtained on a D/max-rA model diffractometer with Cu Kα radiation (40 kV and 80 mA). The theoretical structural charge density ($\sigma_{S,T}$) was calculated [2, 4]. The chemical compositions and characteristic parameters of the Zn–Al LDHs samples are listed in Table 1.

Measurement of uptake amount and release amount of naproxen

The naproxen concentration was determined by a HP-8453 model UV–Vis absorption spectroscopy. The uptake amount (A) of naproxen on LDHs was obtained according to the change between the initial naproxen concentration (C_{in}) and the remaining naproxen concentration.

Table 1 Chemical compositions and characteristic parameters of Zn–Al LDHs samples

LDHs sample	Chemical formula	S/(m^2 g^{-1})	$\sigma_{S,T}$	
			mmol g^{-1}	mmol m^{-2}
$Zn_{0.48}Al_{0.52}$–Cl LDH	$[Zn_{0.48}Al_{0.52}(OH)_2]$ $(OH)_{0.34}Cl_{0.18}$	12.45	5.704	0.458
$Zn_{0.59}Al_{0.41}$–Cl LDH	$[Zn_{0.59}Al_{0.41}(OH)_2]$ $(OH)_{0.24}Cl_{0.17}$	40.90	4.381	0.107
$Zn_{0.63}Al_{0.37}$–Cl LDH	$[Zn_{0.63}Al_{0.37}(OH)_2]$ $(OH)_{0.21}Cl_{0.16}$	51.30	3.910	0.076
$Zn_{0.68}Al_{0.32}$–CO_3 LDH	$[Zn_{0.68}Al_{0.32}(OH)_2]$ $(CO_3)_{0.16}$	33.53	3.352	0.100

To measure the amount of naproxen released from naproxen/LDHs nanohybrids, 0.01 g of naproxen/LDHs nanohybrids prepared at C_{in} of 15 mmol l^{-1} and pH 8.5 was added to 1 l of the Na_2HPO_4–NaH_2PO_4 buffer solution (pH 6.86), and the mixture was kept for a desired time interval (t) in a constant-temperature shaker at 37 °C, and then was centrifuged. The supernatant was used for measuring the naproxen concentration to obtain the released amount of naproxen.

Results and discussion

Morphology of naproxen in naproxen/LDHs nanohybrids

Figure 1 shows the XRD patterns of LDHs and naproxen/LDHs nanohybrids samples. It can be seen from Fig. 1 that the interlayer distance values of LDHs samples are in the range of 7.55~7.66 Å and that of naproxen/LDHs nanohybrids are in the range of 23.30~23.86 Å. The higher interlayer distance values of naproxen/LDHs nanohybrids than LDHs indicate the successful preparation of naproxen/LDHs nanohybrids, and the naproxen is indeed intercalated into the gallery of the LDHs.

As the thickness of the LDHs hydroxide basal layer is 4.8 Å [19], the gallery height of the LDHs samples intercalated by naproxen is in the range of 18.5~19.06 Å (the mean gallery height of naproxen/LDHs nanohybrids is about 18.78 Å) [11], whereas the length of naproxen anion calculated by the method of molecular mechanics [20] is 12.20 Å. Therefore, it is proposed that naproxen molecules probably formed an overlapped bilayer in the LDHs gallery, as illustrated in Fig. 2. Naproxen molecules are adsorbed on each surface of the LDHs hydroxide basal layer with the carboxyl of naproxen anion attaching to the positively charged surface by electrostatic interaction to form a monolayer. Two neighboring naproxen monolayers have an overlapping part and eventually form a bilayer, and the mean height of the overlapping part is about 5.62 Å.

Another probably morphology of naproxen in naproxen/LDHs nanohybrids is the oblique arrangement to form a monolayer on each surface of the LDHs hydroxide basal layer, and two neighboring naproxen monolayers do not have an overlapping part [18]. According to our available information, we cannot yet distinguish which morphology of the above two morphologies really exists in the galley of LDHs.

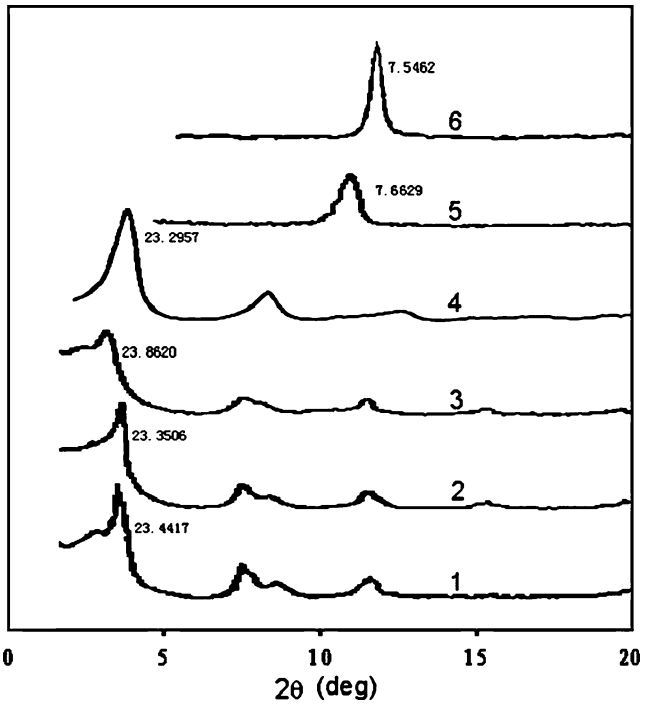


Fig. 1 XRD patterns of LDHs and naproxen/LDHs nanohybrids. *1* Naproxen/ $Zn_{0.48}Al_{0.52}$–Cl LDH; *2* naproxen/ $Zn_{0.59}Al_{0.41}$–Cl LDH; *3* naproxen/$Zn_{0.63}Al_{0.37}$–Cl LDH, *4* naproxen/ $Zn_{0.68}Al_{0.32}$–CO_3 LDH; *5* $Zn_{0.63}Al_{0.37}$–Cl LDH; *6* $Zn_{0.68}Al_{0.32}$–CO_3 LDH. The initial naproxen concentration is 15 mmol l^{-1}, pH 8.5

The uptake of naproxen on LDHs

Typical uptake (or adsorption) kinetic curves of naproxen with C_{in}=15 mmol l^{-1} on the LDHs samples are shown in Fig. 3. Similar uptake curves were obtained for the other naproxen initial concentrations. It can be seen from Fig. 3 that the equilibrium values of the naproxen-uptake amount (A) are attained after about 160 min, which is almost independent of the LDHs types. The contact time interval (t) was fixed at 24 h in the equilibrium adsorption experiments.

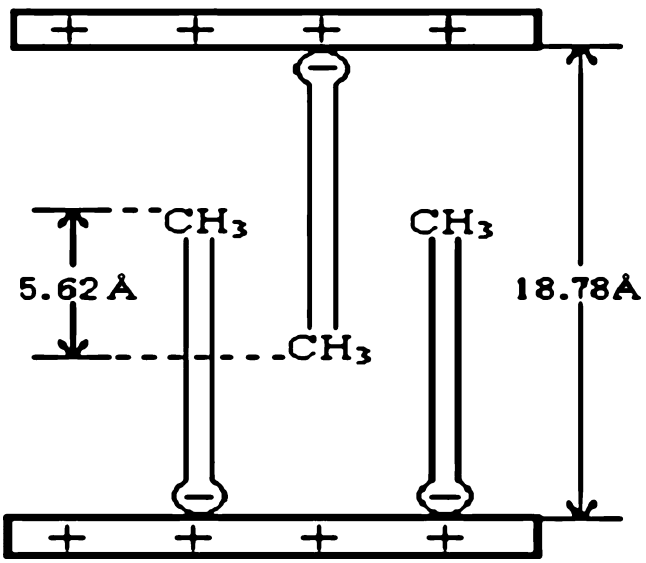


Fig. 2 Schematic structure representation of naproxen/LDHs nanohybrid

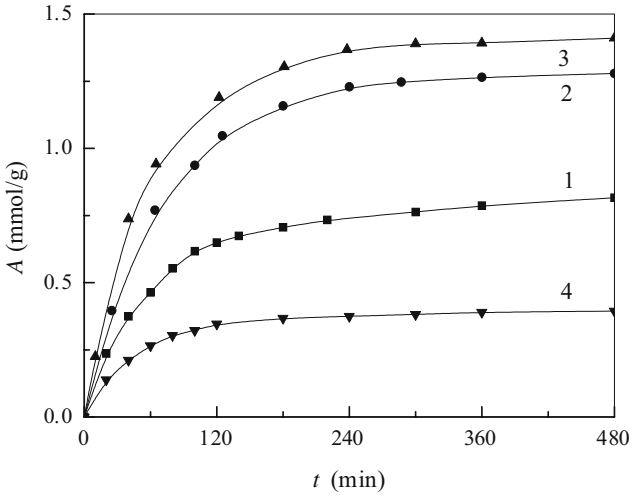


Fig. 3 Adsorption kinetics of naproxen on various LDHs samples. *1* $Zn_{0.48}Al_{0.52}$–Cl LDH; *2* $Zn_{0.59}Al_{0.41}$–Cl LDH; *3* $Zn_{0.63}Al_{0.37}$–Cl LDH; *4* $Zn_{0.68}Al_{0.32}$–CO_3 LDH. The initial naproxen concentration is 15 mmol l^{-1}, pH 8.5

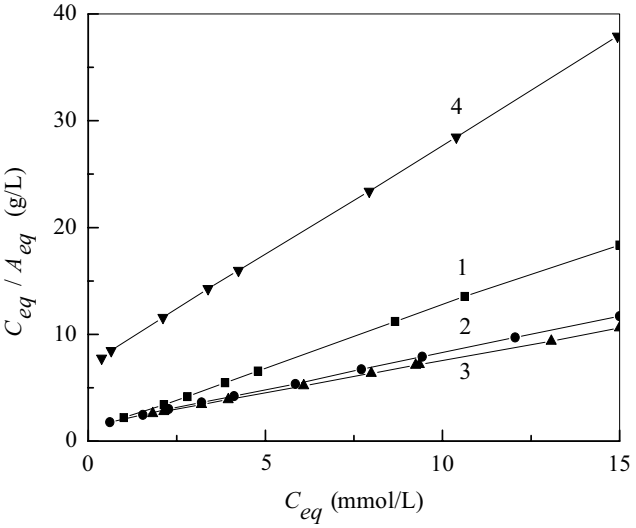


Fig. 5 Langmuir plots for adsorption of naproxen on various LDHs samples. *1* $Zn_{0.48}Al_{0.52}$–Cl LDH; *2* $Zn_{0.59}Al_{0.41}$–Cl LDH; *3* $Zn_{0.63}Al_{0.37}$–Cl LDH; *4* $Zn_{0.68}Al_{0.32}$–CO_3 LDH

The isotherm curves of the equilibrium naproxen-uptake amount (A_{eq}) vs the equilibrium naproxen concentration (C_{eq}) are shown in Fig. 4 for various LDHs samples. It can be seen from Fig. 4 that the A_{eq} values increase initially with C_{eq} and then reach a plateau. As we know, these types of adsorption isotherms may obey the Langmuir equation expressed by the following:

$$C_{eq}/A_{eq} = C_{eq}/A_m + 1/(KA_m)$$

where A_m and K are apparent monolayer capacity and adsorption coefficient, respectively. The plots of C_{eq} / A_{eq} vs C_{eq} are shown in Fig. 5, and all curves are fair straight lines, indicating that the isotherm curves of naproxen on the LDHs indeed obey the Langmuir equation, and the naproxen ions adsorb onto each LDHs basal layer surface with a monolayer, which is well consistent with the XRD result. A bilayer is formed between two neighboring surfaces of LDHs hydroxide basal layers.

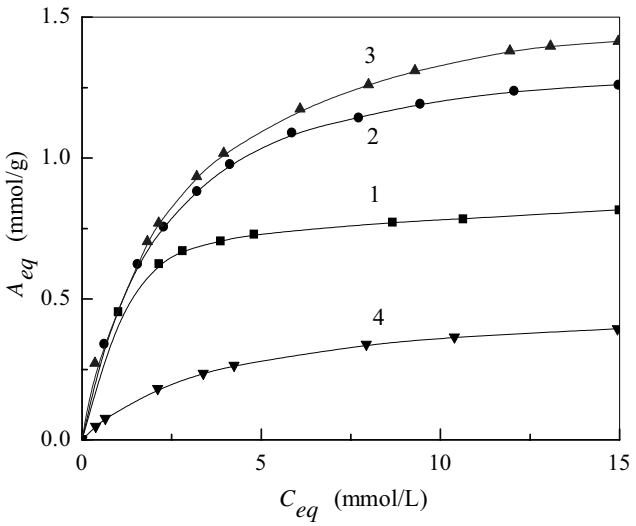


Fig. 4 Adsorption isotherm of naproxen on various LDHs samples at pH 8.5. *1* $Zn_{0.48}Al_{0.52}$–Cl LDH; *2* $Zn_{0.59}Al_{0.41}$–Cl LDH; *3* $Zn_{0.63}Al_{0.37}$–Cl LDH; *4* $Zn_{0.68}Al_{0.32}$–CO_3 LDH

The results of A_m and K obtained from Fig. 5 and the adsorption Gibbs energy change (ΔG) calculated using the equation $\Delta G = -RT\ln K$ are listed in Table 2. It can be seen from Tables 1 and 2 that for the LDHs(Cl^-) samples ($Zn_{0.48}Al_{0.52}$–Cl, $Zn_{0.59}Al_{0.41}$–Cl, and $Zn_{0.63}Al_{0.37}$–Cl LDHs) with the increase of the $\sigma_{S,T}$ value, the A_m value in units of mmol g^{-1} decreases, whereas that in units of mmol m^{-2} increases. The increase of the A_m value in units of mmol m^{-2} with the increase of the $\sigma_{S,T}$ value is not surprising because in the view of the electrostatic interaction, the increase of the $\sigma_{S,T}$ value should enhance the adsorption of naproxen on the LDHs, the increase of the absolute value of ΔG with the increase of the $\sigma_{S,T}$ (see Table 2) is a positive evidence. The decrease of the A_m value in units of mmol g^{-1} with the increase of the $\sigma_{S,T}$ is because the S value of the LDHs(Cl^-) samples decreases.

Comparison of the results of LDHs(Cl^-) ($Zn_{0.48}Al_{0.52}$–Cl, $Zn_{0.59}Al_{0.41}$–Cl, and $Zn_{0.63}Al_{0.37}$–Cl LDHs) and LDHs (CO_3^{2-}) ($Zn_{0.68}Al_{0.32}$–CO_3 LDH) shows that the A_m value of the LDHs(CO_3^{2-}) sample is much lower than that of the LDHs(Cl^-) samples (see Fig. 3 and Table 2). This is because the anion exchange ability of CO_3^{2-} ions is much lower than that of Cl^- ions [2].

The contact times needed for 90% of the maximum naproxen-uptake amount, t_{90}(ad), for various LDHs samples can be obtained from Fig. 3 and are listed in Table 2. The t_{90}(ad) value increases with the increase of the A_m value in units of mmol m^{-2}, which is because the relatively

Table 2 Uptake and release parameters of naproxen/LDHs nanohybrids

LDHs sample	A_m		K (mmol $l^{-1})^{-1}$	ΔG kJ mol^{-1}	t_{90}(ad) min	t_{90}(rel) min
	mmol g^{-1}	mmol m^{-2}				
$Zn_{0.48}Al_{0.52}$–Cl LDH	0.8527	0.0685	1.2220	−17.61	220	490
$Zn_{0.59}Al_{0.41}$–Cl LDH	1.4431	0.0353	0.4993	−15.39	180	390
$Zn_{0.63}Al_{0.37}$–Cl LDH	1.6451	0.0321	0.4104	−14.91	165	250
$Zn_{0.68}Al_{0.32}$–CO_3 LDH	0.4862	0.0145	0.2870	−14.02	145	130

higher density of the naproxen on the gallery space may hinder the later intercalation process of the naproxen.

pH effect on the uptake of naproxen

The effect of pH value of suspension on the uptake of naproxen is shown in Fig. 6. In the studied range of pH, the A_{eq} value decreases with the increase of pH. With the increase of pH, the total net positive charge density decreases, and the electrostatic attraction between naproxen anions and LDHs hydroxide basal layer decreases; therefore, the uptake of naproxen decreases. The point of zero net charge (PZNC) of the LDHs samples is about 11 [21], which might be used to explain why the uptake of naproxen is infinitely small at the pH of around 11. At a lower pH (<6), the uptake amounts of naproxen are higher and have little difference among various LDHs samples, which may be related to slight dissolution of LDHs. After pH reaches below 5, the structure of LDHs can be broken up due to the obvious dissolution of LDHs; therefore, the attempts to determine the uptake amount of naproxen is not possible.

The naproxen release of naproxen/LDHs nanohybrids

The release kinetic curves of naproxen from naproxen/LDHs nanohybrids in 0.025 mol l^{-1} Na_2HPO_4–NaH_2PO_4 buffer solution (pH 6.86) are shown in Fig. 7. It can be seen from Fig. 7 that the release rate of naproxen decreases with the increase of the $\sigma_{S,T}$ value of LDHs samples, which may be attributed to the increase of the electrostatic attraction between naproxen anions and LDHs hydroxide basal layer. The increase of the affinity of LDHs layers for naproxen anions will inhibit the exchange process of naproxen anions by HPO_4^{2-} and $H_2PO_4^-$ in bulk solution.

The contact times needed for 90% of the maximum naproxen-release amount, t_{90}(rel), can be obtained from Fig. 7 and are listed in Table 2. It can be seen from Table 2 that the t_{90}(rel) value increases with the increase of the $\sigma_{S,T}$ value of the LDHs samples, which has the same trend as that of the t_{90}(ad) value in the adsorption process. According to the above results, it can be concluded that a

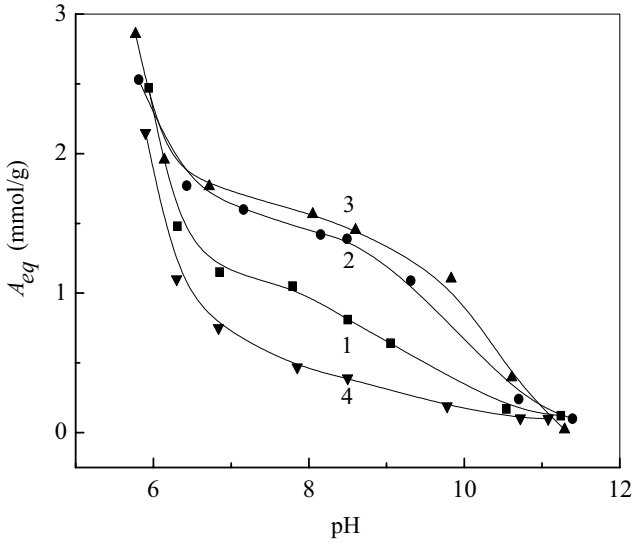


Fig. 6 Effects of pH on the adsorption of naproxen on various LDHs samples. *1* $Zn_{0.48}Al_{0.52}$–Cl LDH; *2* $Zn_{0.59}Al_{0.41}$–Cl LDH; *3* $Zn_{0.63}Al_{0.37}$–Cl LDH; *4* $Zn_{0.68}Al_{0.32}$–CO_3 LDH. The initial naproxen concentration is 15 mmol l^{-1}

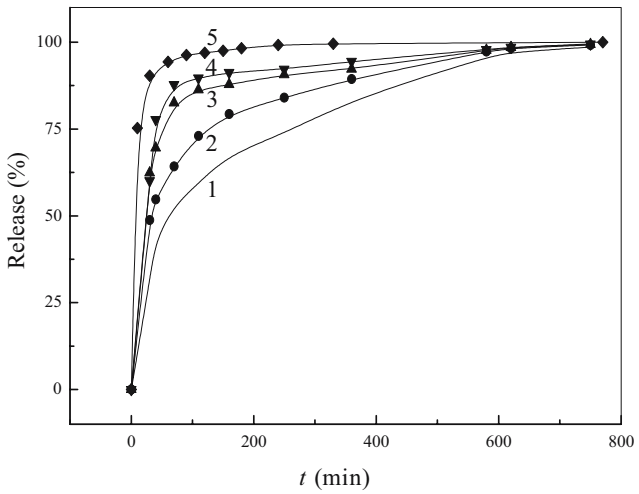


Fig. 7 Release kinetics of naproxen from naproxen/LDHs nanohybrids at pH 6.86 and 37 °C. *1* Naproxen/$Zn_{0.48}Al_{0.52}$–Cl LDH; *2* naproxen/$Zn_{0.59}Al_{0.41}$–Cl LDH; *3* naproxen/$Zn_{0.63}Al_{0.37}$–Cl LDH; *4* naproxen/$Zn_{0.68}Al_{0.32}$–CO_3 LDH; *5* naproxen troche

LDHs sample with a higher $\sigma_{S,T}$ value will lead to a higher A_m value in units of mmol m^{-2}, and a longer contact time needed for reaching the equilibrium adsorption simultaneously will lead to a lower release rate of naproxen from naproxen/LDHs nanohybrids.

In addition, it can be seen from Fig. 7 that the t_{90}(rel) value of naproxen/LDHs nanohybrids is much higher than that of naproxen troche (about 30 min), indicating that the naproxen/LDHs nanohybrid is indeed a potential drug delivery system, which may be attributed to the restricted motion of naproxen anions arising from steric effect of LDHs and the electrostatic interaction between naproxen anions and positively charged LDHs layers.

Conclusions

The XRD and adsorption experimental results indicate that the naproxen/LDHs nanohybrids are successfully prepared and suggest that the naproxen molecules are adsorbed with a monolayer onto each surface of LDHs hydroxide basal layer, In other words, a bilayer is formed in the LDHs gallery. With the increase of the $\sigma_{S,T}$ value of the LDHs samples, the A_m value in units of mmol m^{-2} of naproxen on the LDHs samples increases, and the release rate of naproxen from the naproxen/LDHs nanohybrids decreases. The t_{90}(rel) value of naproxen/LDHs nanohybrids is much higher than that of naproxen troche, indicating that the naproxen/LDHs nanohybrid is indeed an efficient drug-controlled release system. In the pH range of 6~11.5, the A_{eq} values of naproxen on the LDHs samples decrease with the increase of pH value, and above the PZNC (around pH 11) of the LDHs samples, the uptake of naproxen is small. The A_m values for LDHs(Cl^-) samples are much higher than that of LDHs$\left(CO_3^{2-}\right)$ samples, which may be contribute to that LDHs(Cl^-), which has a stronger anion exchange ability than LDHs$\left(CO_3^{2-}\right)$.

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