第 24 卷第 6 期 无 机 化 学 学 报 Vol.24 No.6
2008 年 6 月 CHINESE JOURNAL OF INORGANIC CHEMISTRY 956~963

药物-无机复合材料姜黄素嵌入镁铝水滑石的合成、表征及缓释性能的研究

曹根庭[1] 邢方方[2] 王 平[3] 倪哲明*,[2]
([1]浙江海洋大学海洋科学学院,舟山 316004)
([2]浙江工业大学化学工程与材料学院,杭州 310014)
([3]浙江工业大学药学院,杭州 310014)

摘要:采用共沉淀和离子交换方法将药物姜黄素(Cur)嵌入到 Mg-Al-LDHs 层间,制备了一种新型的药物-无机复合材料,借助 XRD,FTIR 和 TG-DTA 等手段对样品进行了表征。结果表明,Cur 阴离子以平行或者单层、沿其短轴方向垂直嵌入到层间;与主体层板通过氢键与静电作用形成超分子结构;该超分子结构姜黄素-水滑石复合材料与姜黄素相比,其热稳定性、耐酸性及缓释性能均有大幅度提高,缓释实验数据符合 Bhaskar 方程和一级动力学方程模型。

关键词:水滑石;姜黄素;药物-无机复合材料;热稳定性;缓释
中图分类号:O641.13; O614 **文献标识码**:A **文章编号**:1001-4861(2008)06-0956-08

Synthesis, Characterization and Release of Curcumin-intercalated Mg-Al-Layered Double Hydroxides

CAO Gen-Ting[1] XING Fang-Fang[2] WANG Ping[3] Ni Zhe-Ming*,[2]
([1]*Marine Science and Technology College, Zhejiang Ocean Univesity, Zhoushan, Zhejiang* 316004)
([2]*College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou* 310014)
([3]*College of Pharmacy, Zhejiang University of Technology, Hangzhou* 310014)

Abstract: A drug-inorganic clay composite involving a pharmaceutically active compound curcumin (Cur) intercalated Mg-Al layered double hydroxides (Cur-LDHs) with n_{Mg}/n_{Al}=3.0, has been assembled by co-precipitation and ion exchange methods. XRD and FTIR results indicate a successful intercalation of Cur between the layers with monolayer horizontal(parallel to the layer) and vertical(perpendicular to the layer) orientations of Cur anion. TG-DTA results show that the thermal stability of intercalated organic species is greatly enhanced due to host-guest interaction involving the hydrogen bond compared to pure form before intercalation. The release studies show that release percentages decrease with increasing pH value from 4.0 to 6.5. The kinetic simulation for the release data indicates that the dissolution mechanism is mainly responsible for the release behavior of Cur-LDHs at pH value of 4.0, while the ion-exchange one is responsible for that at pH value of 6.5.

Key words: layered double hydroxides; curcumin; drug-inorganic composite; thermal stability; sustain-release

Organic-inorganic composites have been recognized as one of the most promising research fields in material chemistry [1]. Recently, organo-layered double hydroxides, as an important subject in the area of organic-inorganic composites, have deeply fascinated chemists due to their unique properties[2-4]. Layered double hydroxides (LDHs), also called anionic (anion exchanging) clays or hydrotalicite-like compounds.

收稿日期:2008-02-27。收修改稿日期:2008-04-26。
浙江省自然科学基金(No.Y406069)资助项目。
*通讯联系人。E-mail:jchx@zjut.edu.cn;Tel:0571-88320373
第一作者:曹根庭,男,53 岁,副教授;研究方向:无机功能材料。

These materials are represented by the general formula $[M^{II}_{(1-x)}M^{III}_{x}(OH)_2]\cdot[A^{n-}_{x/n}]\cdot mH_2O$, where M^{II} and M^{III} are di- and tri-valent metal cations, respectively, A^{n-} denotes organic or inorganic anion with negative charge n, and x is defined as the $M^{III}/(M^{II}+M^{III})$ ratio. A wide variety of LDHs can be obtained by the variation of cations M^{II} and M^{III} and the intercalated anion A^{n-} and some LDHs are biocompatible[5~7]. Owing to the intercalation property of LDHs, many LDHs compounds with intercalated beneficial organic anions, such as amino acid [8,9], pesticide[10], and drugs[11~14] have been prepared. Particularly, more attention has been focused on the organic-inorganic LDHs hybrid-containing drug molecules because of its unique properties, such as enhanced dissolution property[15], increased thermal stability[15,16], and controlled release rate [17,18]. Ambrogi et al. [18] studied diclofenac-intercalated Mg-Al-LDHs and its release process. The amount of diclofenac released in phosphate buffer at pH value of 7.0 was less than 70% after 10 h. The kinetic analysis shows the importance of the diffusion through the particle in controlling the drug release rate. Tronto et al. [19] investigated citrate-intercalated 2Mg-Al-LDHs and found that the citrate release is due to the destruction of the layers by acid attack. Wei et al. [16] reported the Mg-Al-LDHs with intercalated naproxen by ion-exchange method and mainly discussed its thermal property, indicating its potential application as the basis of a novel drug reservoir.

Curcumin(Cur), [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] ($C_{21}H_{20}O_6$), is the main constituent of the rhizomes of the plant Curcuma longa. Curcumin has been used for long time in the East as a dye, medicine and flavoring. Curcumin shows a remarkable range of pharmacological activity, including antioxidant, anti-inflammatory and anticancer activity[9,20,21,22]. It also acts as a lypoxygenase substrate, an inhibitor of clooxygenase enzymes [23,24]. It is considered to be a potential chemo-preventive agent and has been clinically tested [25]. Nowadays, Curcumin is becoming more and more popular due to its profound effect on human health.

In the present study, Cur was selected as a model drug and intercalated into Mg-Al-LDHs by co-precipitation and ion exchange techniques. We focus on the structure, thermal property and slow/controlled release property of as-synthesized drug-LDHs composite. In addition, the possible release mechanism is also studied.

1 Experimental

1.1 Synthesis of NO_3-containing Mg-Al-LDHs

An aqueous solution (100 mL) containing NaOH (1.52 g, 0.003 mol) was added dropwise to a solution (160 mL) containing $Mg(NO_3)_2\cdot6H_2O$(1.53 g, 0.006 mol) and $Al(NO_3)_3\cdot9H_2O$(0.75 g, 0.002 mol) (initial n_{Mg}/n_{Al}= 3.0) under nitrogen atmosphere with vigorous stirring until the final pH value of ca 10. The resulting slurry was aged at 25 ℃ for 24 h. Then the resultant was filtered, washed with de-ionized water until the pH value of ca 7 and finally dried in vacuo at room temperature for 12 h giving the product LDHs-NO_3.

1.2 Intercalation Cur into LDHs

1.2.1 Coprecipitation

An aqueous solution(100 mL) NaOH(1.52 g, 0.003 mol) and Cur(1.03 g, 0.003 mol) was added dropwise to a solution(250 mL) containing $Mg(NO_3)_2\cdot6H_2O$(1.53 g, 0.006 mol) and $Al(NO_3)_3\cdot9H_2O$ (0.75 g, 0.002 mol) (initial n_{Mg}/n_{Al} =3.0) under nitrogen atmosphere with vigorous stirring until the final pH value of ca 10. The resulting slurry was aged at 25 ℃ for 48 h. Then the resultant was filtered, washed with de-ionized water until the pH value of ca 7 and finally dried in vacuo at room temperature for 12 h. The product was denoted as Cur-LDHs(cop).

1.2.2 Ion exchange

Under nitrogen atmosphere, 0.5 g of LDHs-NO_3 was added to 50 mL of a 0.06 mol·L^{-1} aqueous drug solution. The pH value of the mixture solution was held constant at 10 by simultaneous addition of 2 mol·L^{-1} NaOH solution. The mixture was stirred vigorously for 24 h at room temperature. The precipitate was washed by de-ionized water, and finally air-dried. The product was denoted as Cur-LDHs(ie).

1.3 Characterization

Powder X-ray diffraction(XRD) patterns were reco-

rded on a Thermo ARL SCINTAG X-ray diffractometer, using Cu $K\alpha$ radiation (λ=0.154 18 nm) with Ni filter at 40 mA and 45 kV, a scanning rate of 5°·min^{-1} and 2θ angle ranging from 5° to 65°.

Fourier-transform infrared(FTIR) spectra were obtained by BRUKER Vector 22 spectrophotometer with the standard KBr disk method.

Elemental analyses were performed by ICP emission spectroscopy using an Ultima instrument on solutions prepared by dissolving the samples in dilute HNO_3.

The TG-DTA measurement was conducted on Zelzsch STA-449C instrument under air with a heating rate 10 ℃·min^{-1} up to 800 ℃.

1.4 Drug release of Cur

A solution-simulated gastrointestinal and intestinal fluid at pH values of 4.0 and 6.5 without pancreatine (phosphate-buffered solution) was employed as release medium, respectively. The release of Cur from Cur-LDHs into the media was performed by adding about 0.05 g Cur-LDHs into 100 mL release medium at 25 ℃. The paddle rotation speed was 100 r·min^{-1}. A sample of 2 mL was withdrawn at predetermined intervals and centrifuged. The accumulated amount of Cur released into the solution was measured momentarily by 722 spectrophotometer at 420 nm. Control experiment: release of Cur from physical mixture (0.1 g LDHs-NO_3 and 0.2 g Cur) in pH=4.0 and 6.5 phosphate-buffered solution was measured momentarily by 722 spectrophotometer at 420 nm.

2 Results and discussion

2.1 Dissociation property of Cur

Quinoid structures play an important role in the tautomeric forms of the Cur in aqueous media. Dissociation of Cur in water involves three steps arising from the presence of two phenolic groups and the acetyl-acetone type group in enol form as illustrated in Fig.1. The values of pK_a are K_{a1}=8.38(-OH), K_{a2}=9.88 (-OH) and K_{a3}=10.51 [26]. According to the pH value of the solution and pK_a values of Cur, the distribution coefficient δ can be calculated. On the basis of the synthesis condition with pH=10, the calculated values

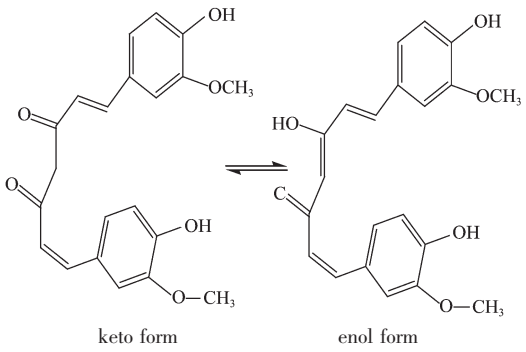

Fig.1 Keto-enol equilibrium of Cur molecule

of δ are δ_0=6.61%(Cur), δ_1=27.55%(Cur^-), δ_2=36.32% (Cur^{2-}) and δ_3=35.44%(Cur^{3-}). It indicates that 94 % Cur exists in alkaline solution in the form of anion.

The water solubility for the Cur is relatively small, though it increases in alkaline solutions: in such conditions the Cur molecule is deprotonated thus giving rise to red solution. A theoretical study, in agreement with the enol form shown in the Fig.1, has suggested[24] the formation of a di-anion in basic media. Fig.2 shows the three-dimensional molecular size of Cur estimated by the software 2004. Molecular size: the long axis length is 1.74 nm; the short axis length is 0.72 nm, the thickness is 0.30 nm. Its structure is almost perfectly planar.

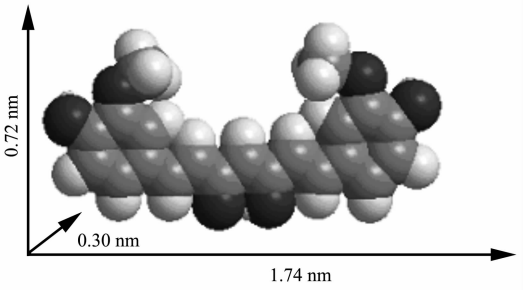

Fig.2 Three-dimensional molecular size of Cur

2.2 Crystal structure

Fig.3 gives the XRD patterns for Mg-Al-LDHs, Cur-LDHs (ie) and Cur-LDHs (cop). It shows that the basal spacing(d_{003}) of Mg-Al-LDHs is 0.77 nm. For Cur-LDHs, the characteristic reflections of LDHs compounds, and the basal reflection (003) shifts to lower 2θ angles (for 003 reflection: 2θ=6.5°, 10.8°) as compared with that of Mg-Al-LDHs (Fig.3a)) indicating the intercalation of Cur in the LDHs layers. It can also be found that the Cur-LDHs show expanded structure. Cur-

LDHs(ie) has a 0.82 nm basal spacing as shown in Fig. 3b. However, Cur-LDHs (cop) has both 0.82 nm and 1.36 nm basal spacings (Fig.3c). The observed basal spacings of Cur-LDHs, 0.82 and 1.36 nm, are resulted from the horizontal (parallel to the layer) or monolayer vertical (perpendicular to the layer) orientation of the incorporated Cur. Given that the thickness of Cur is approximately 0.30 nm (Fig.2), a basal spacing of 0.82 nm could be explained in terms of a horizontal orientation(Fig.4a) by adding the thickness of the LDHs layer(0.48 nm)[7]. The short axis length is about 0.72 nm, the basal spacing would be 1.36 nm for monolayer with vertical-arranged Cur(Fig.4b).

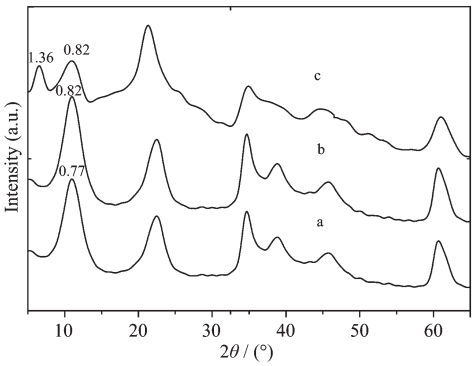

Fig.3　XRD patterns for Mg-Al-LDHs (a), Cur-LDHs (ie)(b) and Cur-LDHs (cop) (c)

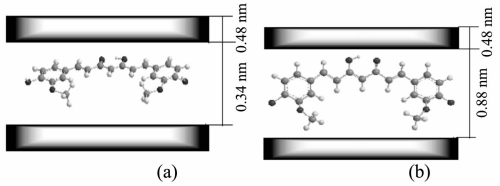

Fig.4　Schematic illustration of the orientation of Cur intercalates

The FTIR spectra of Cur and Cur-LDHs with reference to LDHs-NO_3 are shown in Fig.5. The FTIR spectrum of Cur as reference in Fig.5a can be assigned as follows [28,29]: (1) 3 595 cm^{-1} to phenolic ν (OH) vibrations; (2) 3 075 cm^{-1} to aromatic C-H stretching vibrations; (3) 1 600 cm^{-1} to the stretching vibration of benzene ring skeleton; (4) 1 510 cm^{-1} to the mixed ν(C=O) and ν(C=C) vibration; (5) 1 425 cm^{-1} to the olefinic C-H in-plane bending vibration(δ_{C-H}); (6) 1 280 cm^{-1} to the Ar-O stretching vibration. For Cur-LDHs(Fig.5b,c), indicative of Cur intercalated in LDHs interlayer space,

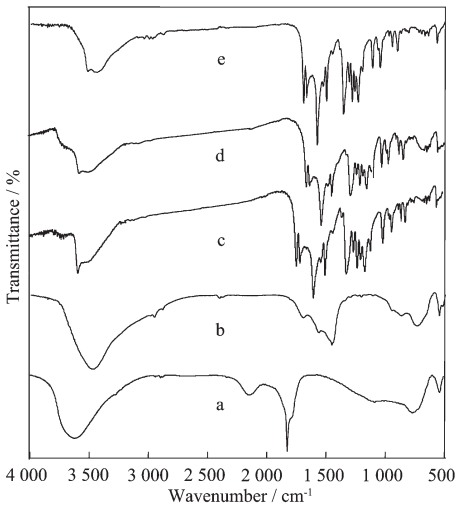

Fig.5　FTIR spectra for LDHs-NO_3 (a); Cur-LDHs (ie) (b); Cur-LDHs (cop) (c) and Cur (d)

are clearly observed. The broad absorption bands at ca 3 410 cm^{-1} arise from the stretching mode of OH groups in the brucite-like layer and physisorbed water. The bands in the range of 3 079~3 000 cm^{-1} are attributed to aromatic C-H stretching vibration of intercalated Cur anions. The band at ca 1 510 cm^{-1} to the mixed ν(C=O) and ν(C=C) vibration, similar to that of Cur (Fig.5a). However, the band at 3 512 cm^{-1} due to phenolic ν(OH) vibrations and shifts to lower wave-number, compared to Cur spectrum, indicating that the intercalation of Cur in the interlayer space involves hydrogen bonding, in addition to the obvious electrostatic attraction between the electropositive cations in layer and organic anions in interlayer. And generally, the band at ca 603 cm^{-1} or 597 cm^{-1} is attributed to M-O and M-O-H stretching vibrations of Cur-LDHs(Fig.5b, c), which locates at ca 69 or 63 cm^{-1} less than that of LDHs-NO_3 (Fig.5a, 676 cm^{-1}), also confirming the existence of host-guest interaction between the interlayer Cur anions and hydroxyl groups of LDHs layers.

2.3　Effect of synthesis methods on the Cur-LDHs

Elemental analyses results of LDHs-NO_3 and Cur-LDHs are shown in Table 1.

The contents of Cur synthesized by ion exchange and co-precipitation methods are 25.0% and 35.6% by mass, respectively. Carbonate ions are also co-intercalated within the gallery spaces to balance the charges. The difference on synthesis mechanism is the

Table 1 Elemental analysis of Cur-LDHs

Sample	Chemical composition	Cur / %
LDHs-NO_3	$[Mg_{0.72}Al_{0.27}(OH)_2](NO_3)_{0.25}\cdot 0.60H_2O$	–
Cur-LDHs(cop)	$[Mg_{0.72}Al_{0.27}(OH)_2](C_{21}H_{18}O_6)_{0.12}(CO_3^{2-})_{0.053}\cdot 0.7H_{20}$	35.6
Cur-LDHs(ie)	$[Mg_{72}Al_{0.27}(OH)_2](C_{21}H_{20}O_6)_{0.08}(CO_3^{2-})_{0.053}\cdot 0.70H_2O$	25.0

result of the marked difference in Cur amount intercalated into LDHs. Firstly, Cur anions are precipitated and crystallized with LDHs in co-precipitation method. Secondly, the guest anions with formal charge of two or higher are intercalated into LDHs layers easily in ion exchange process. This means that it is hard for Cur anion with a formal charge of one to replace for NO_3^- anion and therefore difficult to intercalate into LDHs layers. It is reasonable that the content of Cur in the complex materials synthesized by ion exchange method is much smaller than that by co-precipitation.

2.4 Thermal stability

The TG-DTA profiles of Cur and Cur-LDHs are depicted in Fig.6. In the case of pure Cur(Fig.6a), two main thermal events are observed. The first slow event in the temperature of 200~300 ℃ is attributed to the decomposition and subtle combustion of Cur, which corresponds to a weak broad peak at ca 256 ℃ and a small endothermic one at ca 301 ℃. The last stage (400~600 ℃) is due to the strong combustion of Cur, corresponding to exothermic peak at ca 483 ℃.

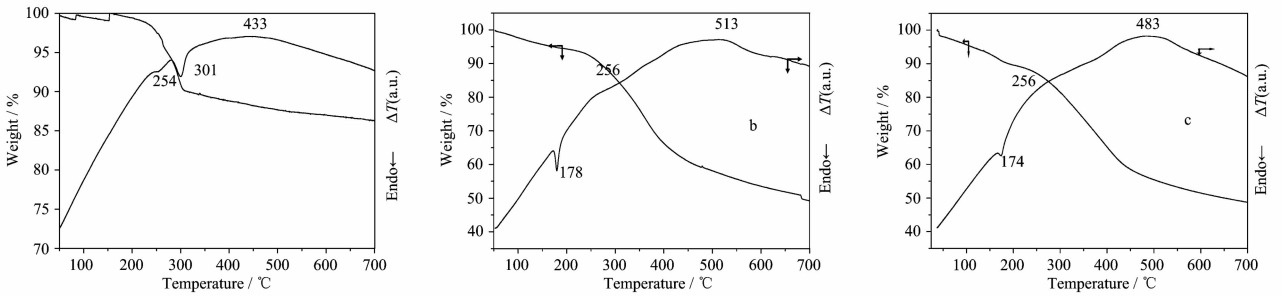

Fig.6 TG-DTA curves for Cur (a), (b) Cur-LDHs (cop) and Cur-LDHs (ie) (c)

However, the TG-DTA curves of Cur-LDHs(Fig.6b, c) reveal three distinguishable weight loss steps. The first steps between 50 and 180 ℃ are attributed to the removal of surface physisorbed water molecules and intercalated structure water, respectively. Correspondingly, the DTA curve shows one endothermic peak at 178 ℃. The followed mass loss(180~300 ℃) corresponds to a weak DTA effect between 200 and 260 ℃ and is due to the removal of residual intercalated water and trace dehydroxylation product of the LDHs layers. The mass loss at 300~600 ℃ corresponds to a broad peak at 513 ℃(Fig.6b) or 483 ℃(Fig.6c) and can be attributed to the major decomposition/combustion of intercalated Cur. Moreover, from TG curve, the mass loss at 300~600 ℃ of Cur-LDHs is 48% which is much higher than elemental analysis(35%). This is because that the dehydroxylation of LDHs layers is incorporated in this temperature region. Compared to the melting vaporization and decomposition temperature of pure Cur, the thermal stability of Cur is greatly improved after intercalation between the LDHs layers, implying that Mg-Al-LDHs can be used as an alternative inorganic matrix for storing organic drug molecule.

2.5 Drug release of Cur

Given the Cur can be released from the layers material without losing its pharmaceutical activity, the pristine LDHs then can be considered as effective drug delivery vehicle and a controlled release system. Hence, we quantitatively monitored the controlled release process of the guest anions under conditions that would resemble physiological conditions through a series of experiments.

The release properties of the drug have been investigated by adding the intercalation compound to the sample of simulated gastrointestinal and intestinal fluid. Fig.7 shows the release profiles of Cur-LDHs in

solutions at pH values of 4.0 and 6.5, respectively. The release behavior at pH=4.0 is very fast during the first 1 h, which can be attributed to the partial dissolution of LDHs layers at weak acidic solution [4,30]. Therefore a slower release step occurs as released percentage of ca. 38.4%, 80.5% and 84.8% after 1, 3.5 and 5 h, respectively. However, this followed slow release step may be due to an ion-exchange process between the intercalated anion in interlayer and phosphate anions in the buffer [11,18,30]. At pH value of 6.5, the release of Cur-LDHs is slow and persistent process, and ca 17.2%, 78.9%, and 83.7% of released percentage is obtained after 1, 3.5 and 4.5 h, respectively.

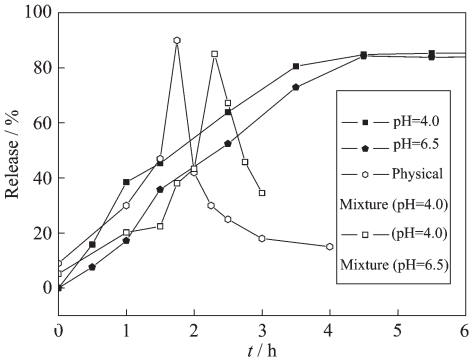

Fig.7　Release profiles of Cur from Cur-LDHs(cop) and Physical mixture in buffer solutions at different pH values

It is worthy of noticing that there is no degradation phenomenon during the course of release test, compared with physical mixture. This sustained release process between the intercalated anion and phosphate anions in the buffer [17,18,30]. On the basis of the release profiles at pH values of 4.0 and 6.5, it is found that the equilibrium percentage of Cur released is not up to 100%. This probably due to the characteristic of ion-exchange reaction [5,31,32]. i.e., this is an equilibrium process and the interlayer anions can not be exchanged completely, but the released organic species is removed continuously.

The drug release based on drug-LDHs system could be controlled either by dissolution of LDHs particles[18,30], or by diffusion through the LDHs particle[18]. According to literature[18] when the drug release fraction is slower than 0.85, Bhaskar equation shown in Eq. (**1**) can be used to evaluate whether the diffusion through the particle is the rate-limiting step. Thus, the release profiles were fitted by Bhaskar equation, together with the first-order equation (in Eq. (**2**)), which is normally used to describe the dissolution phenomena.

$$-\lg(1-X) \sim t^{0.65}, \quad (\mathbf{1})$$

$$-\lg(1-X) \sim t, \quad (\mathbf{2})$$

Where X and t are the release percentage and release time, respectively.

The fitting results are shown in Fig.8. At pH value of 4.0, the release of Cur-LDHs does not follow both equations very well. This phenomenon can be explained by the possibility that the drug release is a co-effect behavior, including dissolution of nano-composites and ion-exchange between the intercalated anions in the lamella host and the phosphate anions in the buffer

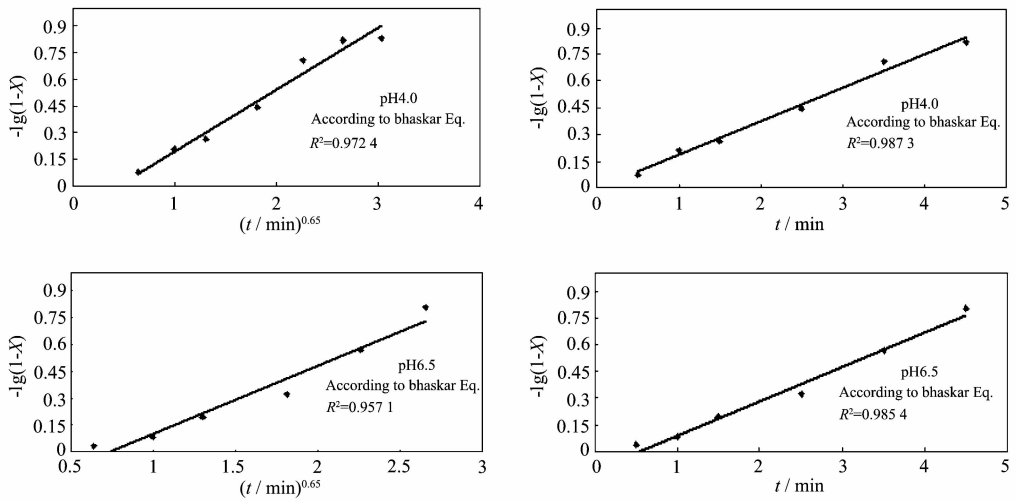

Fig.8　Fitting of the Cur release data to different kinetic equations

solution. In the case of the Bhaskar model linearity is obtained(R^2=0.972 4), compared with that of first-order model(R^2=0.987 3). We can suppose that dissolution of nanocomposites process is the main effect in the co-effect. The same kinetic models applied to release data at pH value of 6.5 are also considered. Fig.8 shows the plots according to the first-order and Bhaskar equations with linear regression coefficients of 0.957 1 and 0.985 4, respectively. In this case, as in the previous one, the dissolution of nanocomposites is the limiting step of the drug release. The fitting data follow the experimental results.

4 Conclusions

Cur-intercalated LDHs-NO_3 with n_{Mg}/n_{Al} =3.0 as drug-inorganic composite has been assembled by co-precipitation and ion-exchange technique. The larger interlayer spacing of 0.88 nm(hihger than the molecular size of Cur (0.72 nm)) for Cur-LDHs as determined by XRD analysis, together with FIIR spectra analysis, suggests a vertical arrangement of Cur anion containing O-O bond between the layers with hydroxyl-benzene anions to both hydroxide layers.

The TG-DTA analysis demonstrates thermal stability of intercalated organic species after intercalating into LDHs interlayer increases greatly.

The release studies of Cur-LDHs show that the release percentages decreases markedly with increasing medium pH value. At pH value of 4.0, the release mechanisms involving dissolution at the beginning of release test followed by an ion-exchange mechanism result in a slower release rate of Cur-LDHs after the first 5 h. At pH value of 6.5, the slower and persistent release process can be interpreted on organic anions and phosphate anion in buffer only.

Acknowledgements: The work was supported by Zhejiang Provincial Department of Science and Technology of China (No. 2003c31023)

References:

[1] Lopes W A, Jaeger H M. *Nature*, **2001**,**414**:735~738

[2] Newman S P, Jones W. *New J. Chem*., **1998**:105~115

[3] Rives V, Ulibarri M A. *Chem. Rev*., **1999**,**181**:61~120

[4] Khan A I, OHare D N. *J. Mater. Chem*., **2002**,**12**:3191~3198

[5] Costantino U, Nocchetti M, in Rives V(Ed.), *Layered Double Hydroxides*: *Present and Future*. New York: Nova Science Publishers, **2001**.383

[6] Choy J H, Kwak S Y, Park J S, et al. *J. Mater. Chem*., **2001**,**11**: 1671~1674

[7] Cavani F, Trifiro F, Vaccari A, et al. *Catal. Today*, **1991**,**11**: 173~301

[8] Whilton N T, Vickers P J, Mann S, J. *Mater. Chem*., **1997**,**7**: 1623~1629

[9] Nakayama H, Wada N, Tsuhako M. *Int. J. Pharm*., **2004**,**269**: 469~478

[10]Meng J H, Zhang H, Evans D G, et al. *Chin. Sci. Bull*., **2005**, **50**:745~751

[11]Li B X, He J, Evans D G, et al. *Appl. Clay Sci.*, **2004**,**27**:199~207

[12]XIA Sheng-Jie(夏盛杰), NI Zhe-Ming(倪哲明), YU Shang-Qin(于尚琴), et al. *Chinese J. Inorg. Chem.*(*Wuji Huaxue Xuebao*), **2007**,**10**:1747~1752

[13]LI Dan(李 丹), NI Zhe-Ming(倪哲明), WANG Li-Geng(王力耕). *Chinese J. Inorg. Chem.*(*Wuji Huaxue Xuebao*), **2006**,**9**:1573~1578

[14]NI Zhe-Ming(倪哲明), XIA Sheng-Jie(夏盛杰), WANG Li-Geng(王力耕). *Chem. J. Chin. Univers.*(*Gaodeng Xuexiao Huaxue Xuebao*), **2007**,**7**:1214~1219

[15]Tyner K M, Schiffman S R, Giannelis E P. *J. Controlled Release*, **2004**,**95**:501~514

[16]Wei M, Yuan Q, Evans D G, et al. *J. Mater.Chem*., **2005**,**15**: 1197~1203

[17]Zhang H, Zou K, Sun H, et al. *J. Solid. State. Chem*., **2005**, **178**:3485~3493

[18]Ambrogi V, Fardella G, Grandolini G. *AAPS Pharm. Sci*., **2002**,Tec.3: article 26

[19]Tronto J, Reis M J D, Silverio F, et al. *J. Phys. Chem. Solids*, **2004**,**65**:75~480

[20]Nurfina A N, Reksoha Diprodjo M S, Timmerman H, et al. *J. Med. Chem*., **1997**,**32**:21~328

[21]Sreejayan N, Priyadarsini K I, Devasagayam A T P, et al. *Int. J. Pharm*., **1997**,**151**:127~130

[22]Venkatesan P, Rao M N A. *J. Pharm., Pharmacol*., **2000**,**52**: 1123~1128

[23]Huang M, Lysz T, Ferraro T, et al. *Cancer. Res*., **1991**,**51**: 813~819

[24]Jankun E, McCabe N, Selman, S J, et al. *Int. J. Mal. Med*., **2000**,**6**:521~526

[25]Ruby A, Kuttan G, Dinesh B, et al. *Cancer. Lett.*, **1995**,**94**: 79~83

[26]Margarita B P, María Teresa R S, et al. *Spectrochim. Acta. Part A*, **2004**,**60**:1091~1097
[27]Balasubramanian K. *Indian J. Chem. Sec. A*, **1991**,**30**:61~65
[28]Tsonko M K, Evelina A V, Bistra A S, et al. *Int. J. Quantum Chem*., **2005**,**102**:1069~1079
[29]Tang B, Ma L, Wang H Y, et al. *J. Agric. Food Chem*., **2002**, **50**:1355~1361
[30]Bin Hussein M Z, Zainal Z, Yahaya A H, et al. *J. Controlled Release*, **2002**,**82**:417~427
[31]Fogg A M, Dunn J S, Shyu D R, et al. *Chem. Mater*., **1998**,**10**: 351~355
[32]Fogg A M, Dunn J S, OHare D. *Chem. Mater*., **1998**,**10**:356~360