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*Supplementary material*

SUPPLEMENTARY MATERIAL TO

# Fabrication of bionanocomposite based on LDH using biopolymer of gum arabic and chitosan-coating for sustained drug-release

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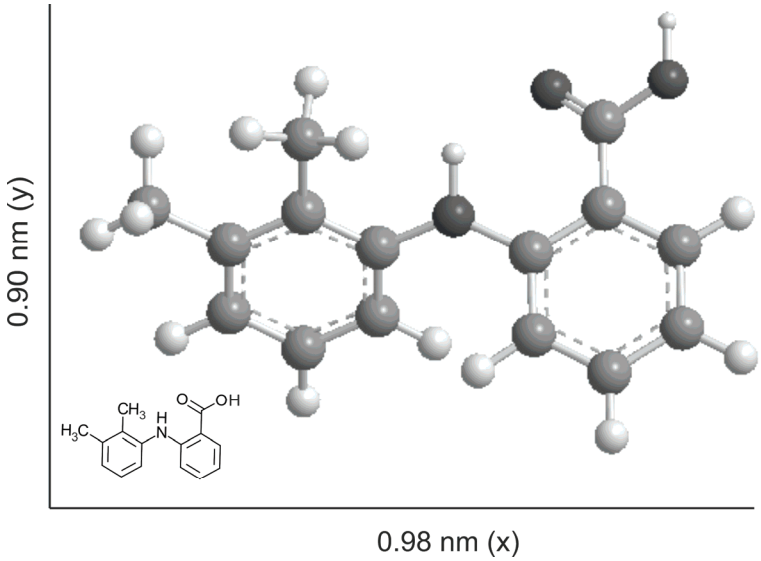


Fig. S-1. Molecular size and structure of MEF.

## DRUG ADSORPTION MECHANISM

In order to evaluate the mechanism of MEF adsorption, 0.02 g of LDH–Cl was placed in an ultrasonic apparatus for 30 min. Beakers containing a solution of the MEF were prepared at different concentrations of 0.5, 1, 2, 3, 4, 5, 7, 8, 9, 10 mg $L^{-1}$ and then 0.02 g of LDH–Cl was added to each beaker. The pH of the mixtures was adjusted to 10 with a buffer solution and stirred for 24 h at 25 °C. The absorbance of the solutions at 285 nm was recorded using a UV device. The

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equilibrium concentration ($q_e$) of MEF adsorbed by LDH–Cl was calculated from the following equation:

$$q_e = V \frac{c_0 - c_e}{m} \quad \text{(S-1)}$$

where $q_e$ is the equilibrium concentration (mg $g^{-1}$), $C_0$ and $C_e$ are the initial concentration and the concentration equilibrium (mg $L^{-1}$) of MEF, respectively. $V$ is the volume of experiment solution (L) and $m$ is the amount of LDH–Cl (g).[1]

*Drug adsorption isotherms*

The adsorption isotherms of MEF by LDH–Cl were investigated based on Langmuir, Freundlich and Temkin models. The Langmuir adsorption isotherm is expressed according to the following equation, in which the adsorption relation is defined as a homogeneous single-layer.

$$\frac{c_e}{q_e} = \frac{c_e}{q_m} + \frac{1}{q_m K_L} \quad \text{(S-2)}$$

where $q_m$ is the maximum sorption of MEF per gram of LDH–Cl (mg $g^{-1}$), and $K_L$ is the Langmuir constant (L $mg^{-1}$).

In addition, to obtain a dimensionless factor, another Langmuir relation was used:

$$R_L = \frac{1}{1 + (K_L c_0)} \quad \text{(S-3)}$$

where $R_L$ is a dimensionless factor. A smaller value of $R_L$ indicates optimal adsorption. $R_L$ can be obtained in four adsorption modes: ($R_L$>1) when the adsorption is undesirable, ($R_L$=1) linearly, (0<$R_L$<1) desirable, and ($R_L$=0) irreversible.

The Freundlich adsorption isotherm is expressed as a heterogeneous and multilayer adsorption and is calculated from the following relation:

$$\ln q_e = \ln K_F + \frac{1}{n} \ln c_e \quad \text{(S-4)}$$

where $q_e$ and $c_e$ are the same as defined in relation (S-1), $K_F$ is the Freundlich constant (L $g^{-1}$), $n$ is adsorption intensity, ($1/n$) is the inhomogeneous factor and expressed in three ways depending on its value: ($1/n$>1) adsorption is undesirable, ($1/n$=0) adsorption is irreversible, (0<$1/n$<1) adsorption is desirable.[2]

The Temkin isotherm suggests the sorption energy decreases linearly with increasing occupation of sites by molecules:

$$q_e = \frac{RT}{b} \ln A + \frac{RT}{b} \ln c_e \quad \text{(S-5)}$$

$$B = \frac{RT}{b} \quad \text{(S-6)}$$

In relation (S-5) $q_e$ and $C_e$ are the same as defined in relation (S-1), $R$ is gas constant (8.314 J mol$^{-1}$ K$^{-1}$), $T$ is temperature (K), $b$ is the Temkin isotherm constant, $A$ is the Temkin binding equilibrium constant (L g$^{-1}$), B is a constant and is an index of sorption heat (J mol$^{-1}$).

*Adsorption isotherms*

In this study, three isotherm models were investigated to explain the relationship between adsorbate (MEF) and adsorbent (LDH). The isotherm curves of MEF adsorption are shown in Fig. S-2.

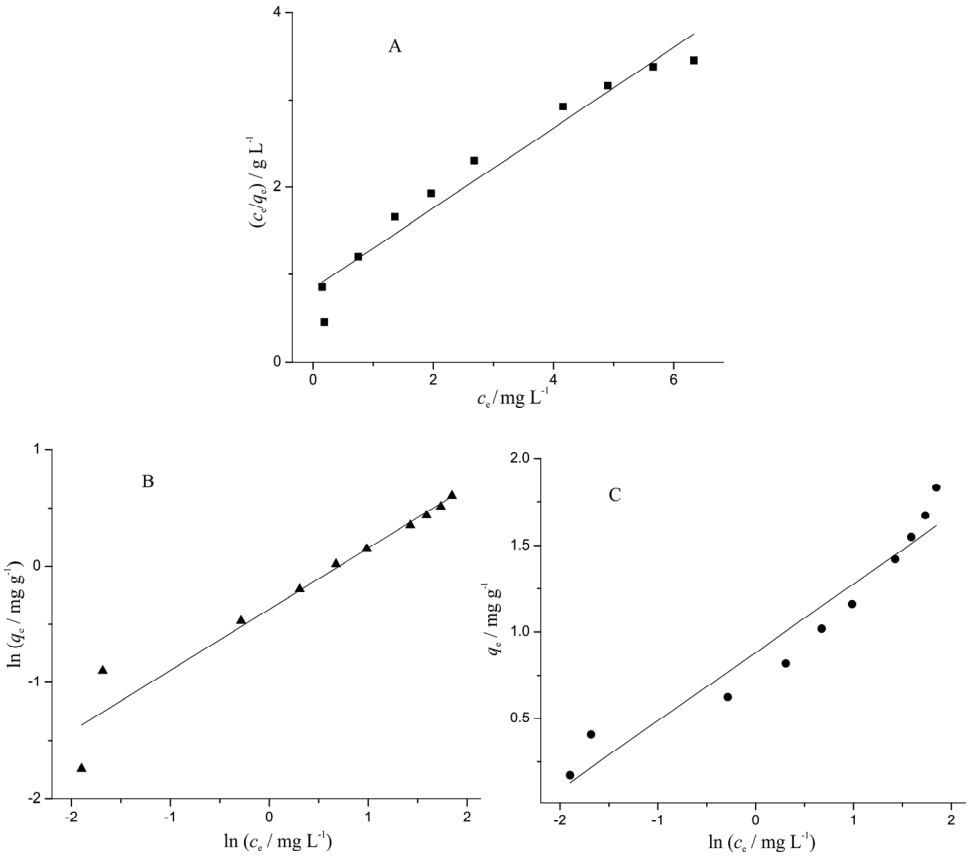


Fig. S-2. The isotherm curves of MEF adsorption by LDH–Cl at 25 ºC (A Langmuir, B Freundlich, and C Temkin).

The results of the adsorption isotherms are listed in Table S-I, indicating that the data fitted well in the Langmuir model with coefficient value of $R^2$ = 0.95. This result for the Langmuir model confirms that MEF molecules are homogeneously intercalated in the interlayer space of LDH. The $q_{max}$ and $K_L$ obtained from the Langmuir model were 2.17 mg $g^{-1}$ and 0.55 L $mg^{-1}$, respectively at 25 °C. These two parameters show the maximum LDH capacity for MEF adsorption.[3] In addition, the separation factor ($R_L$) achieved from Langmuir isotherm was 0.78, indicating that the adsorption of MEF by LDH is favorable.[4] Furthermore, with respect to the value of $R^2$ = 0.94 for the Freundlich isotherm, the next step of MEF adsorption is realized on the surface of LDH.[5]

TABLE S-I. Isotherms parameters of MEF adsorption

| Langmuir isotherm parameters | | Freundlich isotherm parameters | | Temkin isotherm parameters | |
|---|---|---|---|---|---|
| $q_{max}$ / mg $g^{-1}$ | 2.17 | $K_f$ / L $g^{-1}$ | 0.69 | $A$ / L $g^{-1}$ | 9.6 |
| $K_L$ / L $mg^{-1}$ | 0.55 | $n$ | 1.9 | $B$ / J $mol^{-1}$ | 0.39 |
| $R_L$ | 0.78 | $R^2$ | 0.94 | $R^2$ | 0.93 |
| $R^2$ | 0.95 | | | | |

*Investigation of adsorption kinetics*

In this research, the mechanisms of adsorption kinetic of MEF by LDH–Cl were investigated. For this, several beakers containing 100 mL of 5 mg $L^{-1}$ MEF solution at pH=10 were stirred at different intervals and constant speed at 25 °C. The amount of MEF in the solutions after a certain time period was determined by UV-Vis spectrometry at 285 nm. Then, the pseudo-first-order and pseudo-second-order mechanisms were studied for kinetic adsorption of MEF by LDH–Cl.

$$\log(q_e - q_t) = \log q_e - \frac{k_1 t}{2.303} \quad \text{(S-7)}$$

where $q_e$ is the amount of adsorption in equilibrium, $q_t$ is the amount of adsorption at $t$ / min with per unit (mg $g^{-1}$), and $k_1$ is the pseudo-first-order rate constant ($min^{-1}$).[6] The second–order adsorption mechanism is as follows:

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e} \quad \text{(S-8)}$$

where $q_e$ and $q_t$ are the same as defined in relation (S-7), and $k_2$ is the pseudo-second-order rate constant (g $mg^{-1}$ $min^{-1}$).[4]

The curves of the kinetics of MEF sorption are presented in Fig. S-3. According to the results deposited in Table S-II, the sorption of MEF follows from the pseudo-second-order adsorption kinetics corresponds to $R^2$=0.999. A

good accord is seen between the $q_{ex}$ (experimental adsorption capacity) and the $q_e$ (calculated adsorption capacity) attained from the pseudo-second kinetic model. Additionally, the value of the rate constant for pseudo-first-order kinetics achieved a very small amount ($k_1$ = 0.003), which indicates the high rate of MEF adsorption by LDH.

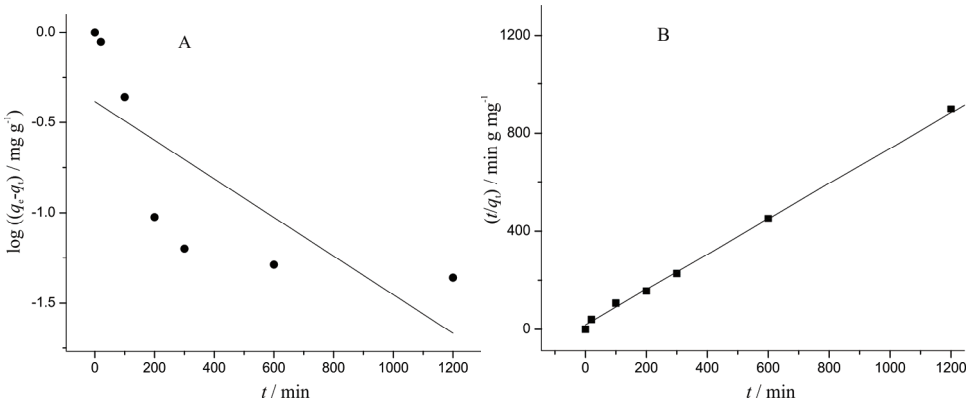


Fig. S-3. The pseudo-first-order adsorption kinetics (A) and pseudo-second-order adsorption kinetics (B) of MEF.

TABLE S-II. The parameters of the pseudo-first-order kinetics and pseudo-second-order kinetics of MEF adsorption

| | | Pseudo-first order kinetics parameters | | Pseudo-second order kinetics parameters | |
|---|---|---|---|---|---|
| $q_{ex}$ / mg g$^{-1}$ | 1.38 | $q_e$ / mg g$^{-1}$ | 0.50 | $q_e$ / mg g$^{-1}$ | 1.39 |
| | | $k_1$ / min$^{-1}$ | 0.003 | $k_2$ / g mg$^{-1}$ min$^{-1}$ | 0.04 |
| | | $R^2$ | 0.85 | $R^2$ | 0.99 |

*Determination of MEF loading*

A quantity of 0.2 g of LDH–MEF, LDH–MEF/CHIT, or LDH–MEF/GUM/ /CHIT was dispersed in 50 mL of phosphate buffer (pH=7.4) and stirred at 100 rpm for 12 h. Thereafter, the pH of the suspension was adjusted to 1.2 using 1 M hydrochloric acid solution and then under the same conditions, the stirring was continued for 12 h. The solution was centrifuged, and its absorption at 285 nm recorded. All steps were repeated three times under identical conditions and the encapsulation efficiency was calculated according to the following equation:[7]

$$\text{Encapsulation Efficiency} = 100\frac{\text{Actual MEF loading}}{\text{Theoretical MEF loading}} \quad \text{(S-9)}$$

*Encapsulation efficiency*

In this study, the amount of drug encapsulation in three carriers was determined and the results are given in Table S-III. As presented in Table S-III,

the encapsulation efficiency of MEF was dependent on the carrier formulation. By co-intercalation of MEF/GUM into the LDH, an increase in the encapsulation efficiency of MEF was observed, which is due to the formation of an amphiphilic emulsion of GUM that allows the retention of more MEF molecules during the hybrid preparation.[8] Therefore, this formulation loaded with co-intercalation of MEF/GUM into the LDH exhibits higher encapsulation efficiency.

TABLE S-III. Encapsulation efficiency of MEF

| Composition | Encapsulation efficiency, % |
|---|---|
| LDH–MEF | 31.23 ±0.57 |
| LDH–MEF/CHIT | 30.01 ±0.61 |
| LDH–MEF/GUM/CHIT | 44.12 ±0.74 |

*In vitro release of MEF*

The release of MEF from LDH–MEF, LDH–MEF/CHIT, and LDH–MEF/ /GUM/CHIT was performed into a simulated environment at pH=1.2 (0.1 M HCl) and pH=7.4 (0.1 M phosphate buffer) at 37 °C. The test environment consisted of a beaker of 50 mL of the desired buffer and 0.2 g carrier, then these suspensions were stirred at 50 rpm for 60 min (pH=1.2) and 660 min for (pH=7.4).[9] The sampling was performed at definite intervals, and then the concentration of MEF released in the medium was analyzed by a UV spectrophotometer at 285 nm.

*Optimization of the pH and loading time*

This research studied the LDH–Cl with a liquid solution of MEF at pH values of 5–12 as shown in Fig. S-4.

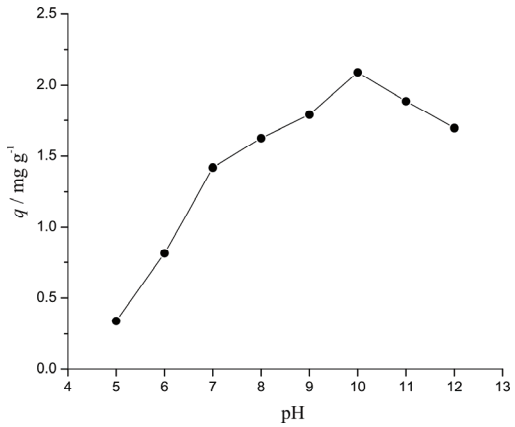


Fig. S-4. Sorption of MEF using LDH–Cl at different pH values. The volume of each solution (10 mL) contained 5 μg $mL^{-1}$ of MEF. The pH values of the solutions were adjusted to 5 to12 by buffer solutions. LDH–Cl (0.02 g) was dispersed in each solution and the suspension was stirred for 24 h.

The optimum pH value for MEF adsorption was 10. This is due to the formation of the mefenamate anion at pH=10 and the structure of the LDH that has a high positive charge of the layers for anionic exchange of chloride anions in the interlayer by MEF anions at pH values higher than 10. The loading time of MEF adsorption at pH=10 was optimized, indicating that the high percentage of MEF was sorbed during time. As shown in Fig. S-5, the LDH–Cl adsorbed 70 % of MEF within the first 100 min, which could be related to surface adsorption and intercalation within the interlayer space.

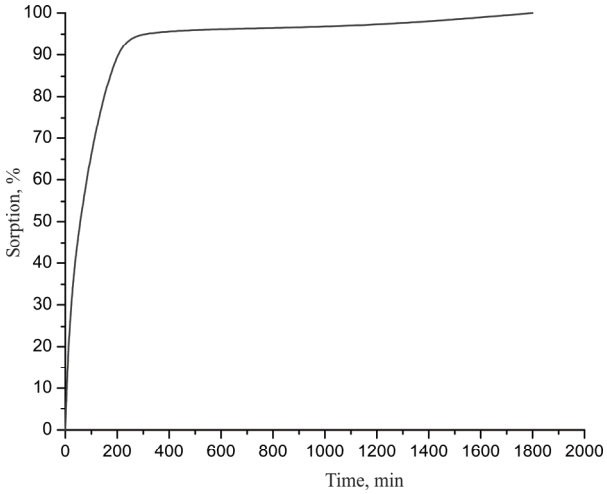


Fig. S-5. Effect of time on the percentage sorption of MEF by LDH–Cl at pH=10. The volume of each solution (10 mL) contained 5 μg $mL^{-1}$ of MEF at pH=10. LDH–Cl (0.02 g) was dispersed to each solution and the suspension was stirred for different times.

*Kinetics of MEF release*

The release data of two buffer solutions (pH 1.2 and 7.4) were fitted by various kinetic models in order to comprehend the dynamics of MEF release from LDH samples. Different kinetic models (Korsmeyer–Peppas, zero and first order models) were applied to fit the MEF release data using KinetDS v3.0 software.[4,10] MEF release from LDH–MEF, LDH–MEF/CHIT, and LDH–MEF/GUM/CHIT at pH values 1.2 and 7.4 follow the Korsmeyer–Peppas pattern with good fitting coefficients (TABLE S-IV). Based on the value of release exponent ($n$) for LDH samples at 1.2 and 7.4, the release of MEF from all samples follows non-Fickian transport mechanism.

TABLE S-IV. Kinetic models of the MEF release from the LDH samples in two buffer solutions

| Buffer solution | Sample | Zero-order | First-order | Korsmeyer–Peppas | |
|---|---|---|---|---|---|
| | | $R^2$ | $R^2$ | $R^2$ | $n$ |
| 1.2 | LDH–MEF | 0.7151 | 0.2457 | 0.9967 | 0.757 |
| | LDH–MEF/CHIT | 0.9227 | 0.2716 | 0.9996 | 0.744 |
| | LDH–MEF/GUM/CHIT | 0.9225 | 0.3027 | 0.9976 | 0.725 |
| 7.4 | LDH–MEF | 0.5716 | 0.2658 | 0.9960 | 0.698 |
| | LDH–MEF/CHIT | 0.6978 | 0.3023 | 0.9985 | 0.687 |
| | LDH–MEF/GUM/CHIT | 0.9006 | 0.3563 | 0.9967 | 0.675 |

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