

Controlled release of organic–inorganic nanohybrid: cefadroxil intercalated Zn–Al-layered double hydroxide

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Background: The intercalation of an antibiotic drug, cefadroxil (CD), into the inter-gallery of Zn, Al nitrate-layered double hydroxide (LDH) was accomplished using a co-precipitation method. This formed a nanostructured organic–inorganic hybrid material that can be exploited for the preparation of a controlled release formulation.

Materials and methods: The drug–LDH nanohybrid was characterized by using field emission scanning electron microscopy (FE-SEM), energy dispersive X-ray spectroscopy (EDS), Fourier transform infrared spectroscopy (FTIR) thermogravimetric (TG) analysis, X-ray powder diffraction (XRD) and UV–visible (UV–vis) absorption spectroscopy, which confirmed the intercalation process. Release tests of nanohybrid in the presence or absence of NaCl or polyacrylamide (PAM) were performed in vitro in gastric (pH 1.2), lysosomal (pH 4.0), intestinal (pH 6.8) and blood (pH 7.4) simulated fluid using UV–vis spectroscopy.

Results: At pH 1.2, LDH was dissolved and intercalated antibiotic released from ZnAl-CD in a molecular form, which led to a significant increase in the antibiotic's solubility. Results showed that the release of drug from nanohybrid at pH 4.0, 6.8 and 7.4 was a sustained process.

Conclusion: This material might reduce side effects by the release of the drug in a controlled manner. However, it was found that the presence of Cl or PAM species in the release media has a negative impact on the release behavior. The weathering mechanism is responsible for the release of CD from the nanocomposite at pH 1.2, while the mechanism of anion exchange may be responsible for the release behavior at pH 4.0, 6.8 and 7.4. A number of kinetic models were chosen to gain more insights into the mechanisms of drug release. At pH 1.2, the zero-order model most satisfactorily explained the release kinetics of CD, while the release data of CD at pH 4.0, 6.8 and 7.4 were governed by Bhaskar kinetics.

Keywords: drug delivery system, ZnAl-CD LDH nanohybrid, hydrotalcite, antibiotic, drug release, kinetics

Introduction

In recent years, drug administration techniques have received extensive attention from pharmaceutical researchers; in particular, controlled release drug delivery systems release the bioactive agent at a specific rate and at the right place to perform its task with efficiency.^{1–3} These systems aim to maintain drug concentration in the blood or in target tissues at the desired levels for a longer period of time, to decrease the administration frequency and also minimize possible side effects.^{4–6}

Recently, new materials, namely, nanohybrids or heterostructured nanocomposites, have been widely used in the drug delivery field. Of the heterostructured nanomaterials, layered nanohybrids can be easily manipulated. These materials are typically prepared

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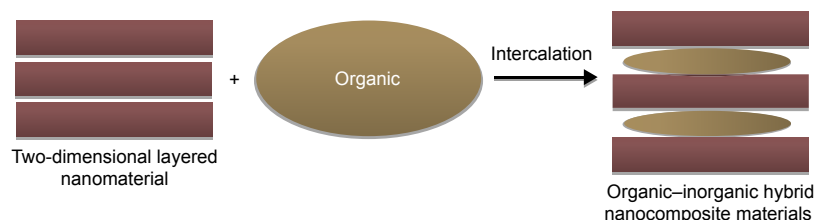


Figure 1 Schematic illustration of organic intercalation into two-dimensional nanomaterials to obtain an organic-inorganic hybrid nano-composite material.

via intercalation reaction, which can be defined as the incorporation of an organic guest into a two-dimensional (2-D) layered inorganic matrix, yielding interesting hybrid organic/inorganic nanocomposite materials that can be used as carriers of drugs and biological active species (Figure 1).^{7,8}

As an important class of inorganic layered nanomaterials, clays have been widely studied as active molecular ion delivery vehicles which can be either cationic with negatively charged aluminosilicate layers or anionic with positively charged hydroxide layers.^{8,9} Layered double hydroxide (LDH) is a synthetic analog of naturally occurring mineral hydroxide¹⁰ and has contributed to the development of drug delivery applications due to its advantages such as anion exchange properties,¹¹ low cytotoxicity, simple preparation,¹² biocompatibility and biodegradability properties,¹³ basicity of the matrix,¹⁴ and low cost.¹⁵ It also leads to the achievement of the following: (i) stabilization of the drugs,¹⁶ (ii) improving both their solubility and cellular uptake,^{15,17} and (iii) controllably releasing them.¹⁸

The chemical composition of LDH can be described by the formula $[M^{II}_{1-x}M^{III}_x(OH)_2]^{x+}(A^{n-})_{x/n} \cdot mH_2O$, where M^{II} , M^{III} , and A^{n-} represent divalent, trivalent metal ions and an interlayer anion of valence n , respectively. The x value is the molar ratio $M^{III}/(M^{II} + M^{III})$ and m is the amount of water in moles.¹⁹ The structure is similar to that of brucite ($Mg(OH)_2$), where a portion of the divalent cations are substituted by trivalent ones, which leads to positively charged sheets.²⁰ These charges are balanced by the interlayer anions.²¹ Thus, LDH structure is composed of M^{II} and M^{III} , which can be accommodated in the octahedral sites in the brucite-like layers and the hydroxyl groups located on the vertices of the octahedral.^{15,19}

Due to the effectiveness and importance of biocompatible Zn, Al LDH, we have chosen this material as nanocapsules for cefadroxil (CD). In its ionic form, it is found that zinc plays a vital role in the human body, where it has the ability to prevent DNA damage, as well as being useful in cancer therapy and controlling the activities of many enzymes.²²

CD is one of the first-generation cephalosporin β -lactam antibiotics and acts against both Gram-positive and

Gram-negative bacteria. Delivery in a nanocapsule may overcome its negative effects and low solubility that lead to poor absorption of drug by living organisms.²³

A series of pharmaceutically active compounds including diclofenac, methotrexate, chloramphenicol, salicylate, cefazolin, ketoprofen, lawsone and chlorogenic acid were intercalated into Zn, Al LDHs, and the feasibility of LDH-based drug delivery systems was demonstrated.^{8,22,24–28} CD has been intercalated into gastroretentive delivery systems (GRDS) in order to analyze its release in acidic pH and to examine the solubility and stability of CD. It was found that the release of CD formulation was sustained for around 14 hours.²⁹ A similar study used hydroxy propyl methyl cellulose as a delivery system for CD to measure the in vitro drug release rate at pH 1.2 and found that the release period was prolonged.³⁰ Conversely, the current study demonstrates that LDH is dissolved rapidly and, consequently, CD is fully released at pH 1.2.

The objectives of this work were to evaluate the ability of LDH to intercalate an antibiotic, and to study the influence of release media pH, and the effect of the presence of exchangeable anions (chloride ions, NaCl) or a macromolecule (polyacrylamide; PAM) in the release medium, on the release rate and the amount of drug released, as well as the effectiveness of the LDH matrix in increasing solubility of the antibiotic and reducing side effects. In order to investigate these objectives, we have intercalated CD in Zn–Al-LDH, containing nitrate as the interlayer anion, by a co-precipitation method. Then, the prepared CD delivery system was characterized by using different physicochemical techniques. After that, we quantitatively monitored the controlled release process of the drug. Finally, the release profile data were fitted by mathematical models in order to evaluate the CD-release mechanisms and kinetics.

Materials and methods

Materials

The metal salts used in the synthesis of the drug-LDH nanohybrid were zinc nitrate hexahydrate ($Zn(NO_3)_2 \cdot 6H_2O$, EMD Millipore, Billerica, MA, USA) and aluminum nitrate nonahydrate ($Al(NO_3)_3 \cdot 9H_2O$, Fluka). CD ($C_{16}H_{17}N_3O_5S$,

MW 363.392 g/mol) and sodium hydroxide pellets (98%) were obtained from Sigma-Aldrich Co. (St Louis, MO, USA) and BDH Chemical Ltd, respectively. Deionized water (ELGA, specific resistivity 18 M Ω) was used for the preparation of the sample and washing the obtained product. All chemicals in this synthesis were used as received without further purification.

Preparation and characterization

Synthesis of LDH-intercalated drugs

Intercalation of the drug into LDH was carried using the co-precipitation method at constant pH.^{18,31} A 200 mL solution containing the metal ions (3.751 g of Al(NO₃)₃·9H₂O (0.01 mol) and 5.949 g of Zn(NO₃)₂·6H₂O (0.02 mol)), was slowly added to the CD solution, which was prepared by dissolving 0.363 g (0.001 mol) of CD in 100 mL of deionized water, Zn²⁺/Al³⁺/guest molar ratio 0.2/0.1/0.01. Then the freshly prepared NaOH solution (0.5 M) was added drop by drop to yield pH = 9; when addition was completed the suspension was vigorously stirred at 60°C for 24 h in order to reach equilibrium. Following this, the product was centrifuged at 2,900 rpm for 10 minutes and washed with deionized water three times to remove the unreacted salt ions, impurities and excess drug. The precipitate was dried at room temperature and the sample was named ZnAl-LDH-CD.

Characterization

X-ray diffraction (XRD)

The samples' crystal structure was recorded by using X-ray diffraction (XRD) with a diffractometer (Thermo Scientific™ ARL™ X'TRA Powder Diffractometer; Thermo Fisher Scientific, Waltham, MA, USA) having $\lambda = 0.154$ nm of Cu K α radiations. The operating current and voltage of the instrument was 50 mA and 40 KV, respectively.

Fourier transform infrared (FTIR)

FTIR spectroscopy was used to obtain direct evidence on the intercalation process as well as the interaction between the drug anions, and LDH and the interlayer water. FTIR spectra of the pristine LDH, and drug-LDH were measured with a Nicolet™ iS™10 FTIR spectrometer (Thermo Fisher Scientific) at 25°C. The spectrum of each sample was collected by cumulating 50 scans, with 32 cm⁻¹ resolution in the mid-infrared (4,000–400 cm⁻¹).

Thermogravimetric (TG) analysis

The TG technique is used to determine the decomposition temperature of the interlayer drug anion, and its content in the ZnAl-CD LDH nanoparticle. Additionally, it can provide information about the thermal stability of drug-LDH.

Thermogravimetric (TG) analysis was performed on a Thermal Analysis Q500 (TA Instruments, New Castle, DE, USA) under a nitrogen atmosphere between 25 and 1,000°C at 5°C/minute heating rate.

Ultraviolet–visible (UV–vis) absorption spectroscopy

The potential interactions between host and guest as well as those between guest and guest, stability of the interlayer drug and release from the nanocomposite were studied by UV–vis absorption spectroscopy (GENESYS 10S UV–vis, Thermo Fisher Scientific) using quartz cuvettes.

Field emission scanning electron microscopy (FE-SEM)

The FE-SEM (JSM-7600F, JEOL, Tokyo, Japan) was used to examine the surface morphology of the organic–inorganic nanohybrid.

Scanning electron microscopy/energy-dispersive X-ray spectroscopy (SEM-EDS)

The elemental composition of the drug-LDH sample was examined using EDS (Oxford) operated at 20 kV attached to the SEM (JSM-7600F, JEOL).

Controlled release study of the anions from the nanohybrids into various media

The release experiments were carried out as follows. The release media included buffer A as a simulated gastric fluid (pH 1.2), buffer B as a simulated lysosomal fluid (pH 4.0), buffer C as a simulated intestinal fluid (pH 6.8), and buffer D as a simulated blood fluid (pH 7.4).

A known amount of nanohybrid (10 mg of drug-LDH) was dispersed in release medium solution (100 mL). The mixture was continuously stirred at a slow speed and kept at 37°C. At specified time intervals, a certain volume of solution (2.0 mL) was withdrawn, centrifuged at 1,300 rpm for 100 s and the resulting supernatant was filtered to remove the insoluble particles, then the absorbance of the CD was determined at 230 nm and further the amount of drug was estimated from absorbance using the calibration curve, through which the percentage of drug liberated was calculated.

Release studies also were performed in the presence of NaCl, by dissolving 10 mg of sodium chloride in the flask containing the nanohybrid sample, and analyzing as previously mentioned.

Additionally, the release processes were studied after adding 1.7 mL of PAM ((C₃H₅NO)_n, Sigma-Aldrich Co.) to 100 mL of release medium that containing 8 mg of bionanocomposite sample (drug-LDH).

Mathematical modeling of drug release

The release kinetics of the drug can be determined through mathematical models.

Zero-order kinetics

The zero-order model that describes the dissolution process related to surface reaction controlled kinetics can be given by Equation 1.^{32,33}

$$M_t - M_0 = -K_0 t \quad (1)$$

where M_t and M_0 are the drug quantity released at release time t and the initial quantity of drug in the nanohybrid, respectively, K_0 is a proportionality constant expressed in concentration per unit time, and t is the time expressed in minutes.³⁴

First-order kinetics

The first-order model (Equation 2) describes the absorption of some drugs, as well as their elimination.³⁵ Unlike the zero-order model, the rate of the release depends on the drug content existing in the LDH matrix.³⁶

$$\ln \left(\frac{M_t}{M_0} \right) = -K_1 t \quad (2)$$

where K_1 is the first-order constant (5).

Bhaskar model

The Bhaskar model is expressed by Equation 3:

$$\ln \left(\frac{M_t}{M_0} \right) = B t^{0.65} \quad (3)$$

where B the corresponding kinetic constant. The Bhaskar equation describes the diffusion of drugs from the resins and insoluble inorganic matrixes.^{37,38}

Higuchi model

The Higuchi model explains that drug diffusion from semi-solid or solid matrixes is a rate-determining step of the release process.³³

$$M_t = K_H (t)^{0.5} \quad (4)$$

where K_H is the diffusion rate constant. The rate of release of the drug is proportional to the reciprocal of the square root of the measurement time.³⁹

Parabolic diffusion model

This model is extensively used to elucidate whether the release process occurs through a surface/edge diffusion process. Equation 5 describes the parabolic model.

$$(M_t/M_\infty)/t = K_p t^{-0.5} + b \quad (5)$$

where M_t and M_∞ are the drug quantities released in time t and infinite time, respectively, K_p is the rate constant for parabolic diffusion model and b is a constant whose chemical significance is not clearly resolved.^{38,40,41}

Korsmeyer–Peppas (K-P) model

In 1984, Korsmeyer and Peppas developed an empirical mathematical equation to confirm the drug mechanism which is represented as:^{42,43}

$$\text{Log of } M_t = K t^n \quad (6)$$

where K is the rate constant for releasing characteristics of the drug/matrix system, while n is a release exponent that distinguish between release mechanisms of drugs; it was estimated from the slopes of a plot of the log fractional drug release vs log time.^{44–46}

For the K-P model, an n value < 0.45 corresponds to quasi-Fickian diffusion. If the value of n is in the range 0.45–0.89, the release of the drug occurs through two processes, dissolution of LDHs and the diffusion of the drug, and the release process is called non-Fickian transport or anomalous diffusion mechanism. When $n > 0.89$, drug release follows dissolution of LDHs and the process is called super case transport II.^{47,48}

Results and discussion

Physicochemical characterization of CD-LDH nanohybrid XRD

The intercalation of CD into LDH was supported by the powder XRD pattern (Figure 2). All characteristic crystalline peaks of pristine LDH were clearly observed in the XRD patterns. However, the nanohybrid did not show any kind of drug crystalline peaks. Generally, LDH exhibited a (003) reflection equivalent to the basal spacing of 8.8–8.0 Å, which reflects the formation of NO_3^- or CO_3^- or Cl^- or SO_4^- intercalated LDH. However, the CD-LDH nanohybrid exhibited a (003) peak at 3.4° , which gives the basal spacing from 8.0 Å to 25.1 Å for CD-LDH, indicating the intercalation of drugs

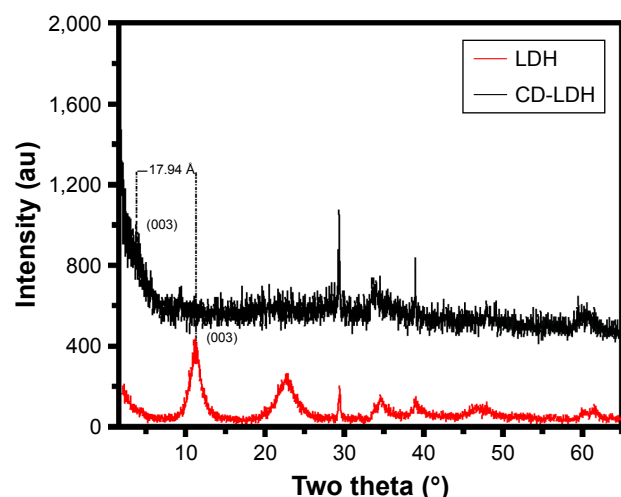


Figure 2 XRD patterns of pristine ZnAl LDH and CD-LDH nanohybrid.
Abbreviations: XRD, X-ray powder diffraction; LDH, layered double hydroxide; CD, cefadroxil.

into LDH. Subtracting the LDH layer thickness (8.0 Å) from the observed basal spacing, the gallery height can be estimated to be 17.1 Å, which is equal to the lateral molecular length of the CD drug. It suggested that intercalated drug molecules are arranged in a lateral manner in the interlayer space.

FTIR

Figure 3 presents the FTIR analysis of the parent Zn–Al LDH-NO₃ and the hybrid of CD-LDH. The pristine LDH spectrum (Figure 3A) shows a broad absorption band at 3,402 cm⁻¹, which can be considered as a common feature for all LDH-like materials, attributable to the –OH stretching vibrations in the Zn/Al-NO₃-LDH layers and physically adsorbed and co-intercalated water.^{49,50} The cause of low-frequency vibration of (OH) group in ZnAl-LDH compared to that of OH-stretching in free water, around 3,600 cm⁻¹, is the hydrogen bonds formed

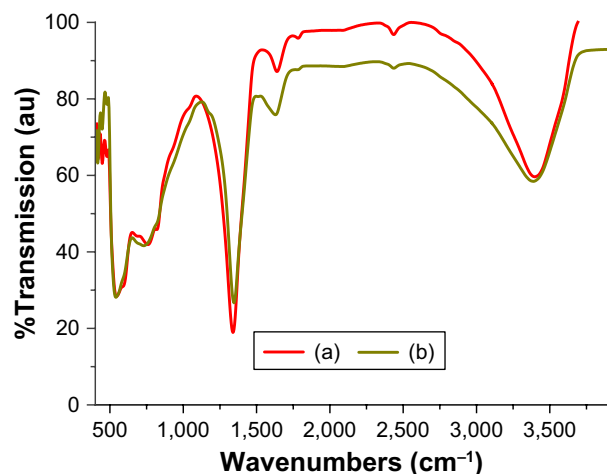


Figure 3 FTIR spectra of (a) pristine ZnAl-NO₃ LDH and (b) nanohybrid CD-LDH.
Abbreviations: FTIR, Fourier transform infrared spectroscopy; LDH, layered double hydroxide; CD, cefadroxil.

between the interlamellar water and hydroxide groups of the Zn/Al inorganic layers.^{50,51} Also, the ZnAl-NO₃ sample shows a strong peak at 1,338.4 cm⁻¹ (due to ν of NO₃⁻),⁵² and a weak band at 1,635.4 cm⁻¹ (δ H₂O).⁵³ Regarding the low wavenumber region of the spectrum (400–800 cm⁻¹), it is expected that bands correspond to metal–oxygen and metal–hydroxyl vibration modes in the LDH sheets.^{54–56} These bands confirm the Zn–Al LDH structure.⁵⁷

In the spectrum of the ZnAl-CD LDH nanohybrid (Figure 3B), the characteristic peak associated with the parent LDH-like hydroxide group, which also arises from the phenolic hydroxides, appears at 3,390.4 cm⁻¹, which, together with the emergence of bands below 1,000 cm⁻¹, indicates that the layers structure of LDH has not changed during the intercalation process.^{58–60} In addition, a pair of absorption bands appears at 1,631.6 and 1,350 cm⁻¹ related to carboxylate asymmetric and symmetric stretching, respectively. Compared to –COO stretching vibration (1,650 and 1,400 cm⁻¹) of pure CD,⁶¹ the shift of the two characteristic peaks to lower frequencies was due to ionization of CD (carboxylic groups)^{62–64} and the strong electrostatic interaction of terminal oxygens of organic anions in interlayer with the electropositive cations in layer as well as the formation of bonding hydrogen between oxygen from carboxylate and the hydroxyl groups in layers or with the interlayer water molecules.^{65–68} Depending on the above results, the CD is intercalated in its anionic form and is stable in the interlayer space of LDH.^{1,69} Of particular note is that the stretching frequency peak of nitrate groups may be overlapped with –COO⁻ symmetric-stretching peak, which may not be completely removed from the interlayers during the intercalation process.⁷⁰ This result is in agreement with the results of Meher⁷¹ and Ghotbi and Bin Hussein.⁵⁸

TG analysis

By analyzing the TG curve of material CD-LDH, it is found that there are seven distinguishable stages of weight loss, which is in agreement with the differential thermogravimetric (DTG) analysis result (Figure 4A and B). In the first and second steps, from 25°C to 160°C, there are about 7.5% and 3.5% losses of the total weight, ascribed to the loss of the physically adsorbed water and water existing within the interlayer galleries, which are attached to the layer of the hydroxide and/or interlayer anion by hydrogen bonds, respectively.^{72,73} Correspondingly, two peaks at ca. 50°C and 125°C are observed in the DTG analysis.⁷² The third mass loss (12% weight loss) occurs in the region of 160°C–250°C and corresponds to a peak in the DTG curve at 225°C, possibly due to the loss of hydroxyl group from the Zn–Al layer, the condensation of which leads to formation of water vapor.^{62,70,74}

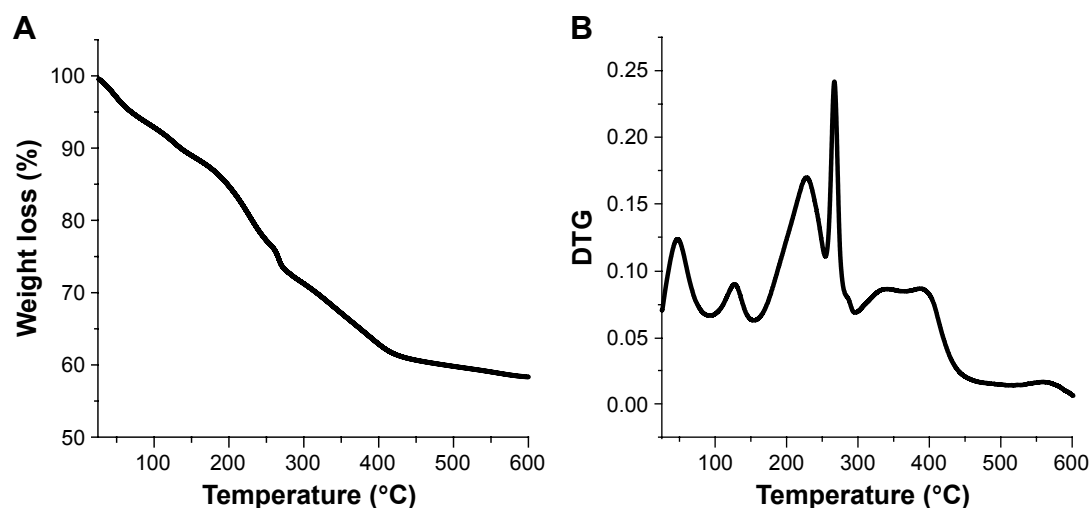


Figure 4 Thermogravimetric (TG) analysis curves: **(A)** TG and **(B)** differential thermogravimetric (DTG) of nanohybrid CD-LDH.
Abbreviations: LDH, layered double hydroxide; CD, cefadroxil.

The DTG diagram shows a sharp peak at 260°C and two weak peaks at 340°C and 390°C associated with combustion of the intercalated CD. According to the TG curve, weight loss should take place in three consecutive steps (250°C–440°C), which leads eventually to the producing CO₂, H₂O and NO_x.^{70,75}

The organic CD ions in CD-LDH have a higher decomposition temperature than pure CD; the DTG curve of pure CD shows three weight losses at 191°C, 240°C and 350°C.⁷⁶ This indicates the improved thermal stability of CD after its intercalation into LDH gallery,^{77,78} due to the host–guest interactions, which involves electrostatic attraction within the LDH layered structure and hydrogen bonding.^{70,72} These results are similar to the results of Lonkar et al⁷⁹ and Wang et al⁸⁰ who studied the intercalation of antioxidant and glutathione into LDH, respectively.

The final stage at 560°C is due to the formation of ZnO and ZnAl₂O₄, where a temperature treatment above 440°C causes a collapse of the layered structure of the sample and leads to full calcification of the solid as well as complete burn of drug component, thus giving rise to oxides of the cations.^{62,81,82}

UV–vis spectroscopy

The UV–vis absorption spectrum of pristine CD (Figure 5A) shows two characteristic absorption bands at 230 and 263 nm, which are ascribed to the phenolic structure (π - π^* transition) and electronic transitions of the enone form (n - π^* transition), respectively.^{83–85}

After intercalation of CD in the ZnAl-LDH host (Figure 5B), it is obvious that the absorption band at 230 nm cannot be identified. This may be attributed to the effect of scattering of LDH particles. Meanwhile, the band at 263 nm shows an apparent red shift with $\Delta\lambda \approx 111$ nm compared to CD.^{78,86}

These results proved that the drug anions are well intercalated between the layers of the LDH.¹² The cause of the occurrence of this shift in the spectrum is the interaction between the host and the guest as indicated by FTIR and TG. It is worth mentioning that electrostatic interaction with the host layer led to the stability of drug anions.^{78,86} Furthermore, the red shift may occur due to guest–guest interaction through π - π^* conjugation of the phenol of interlayer CD ions.^{87,88} Considering the drug–LDH spectrum, the band became broader compared to that in the CD spectrum and this may be due to π -electron delocalization.⁸⁹

FE-SEM

The surface morphology of the ZnAl-LDH-CD nanohybrid is shown in Figure 6. The micrographs were obtained with FE-SEM at 430 \times (Figure 6A), 800 \times (Figure 6B),

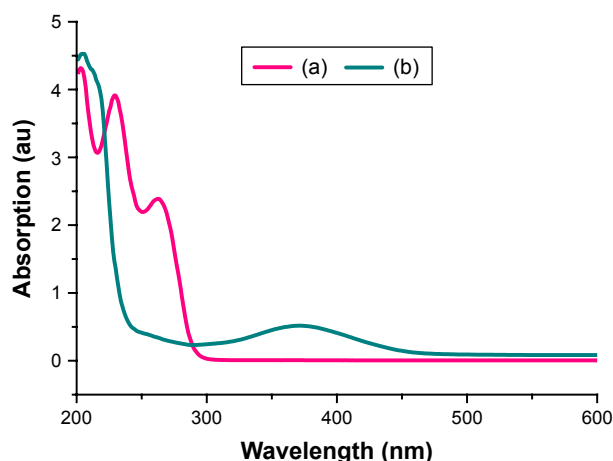


Figure 5 UV–visible absorption of (a) pure cefadroxil and (b) nanohybrid CD-LDH.
Abbreviations: LDH, layered double hydroxide; CD, cefadroxil.

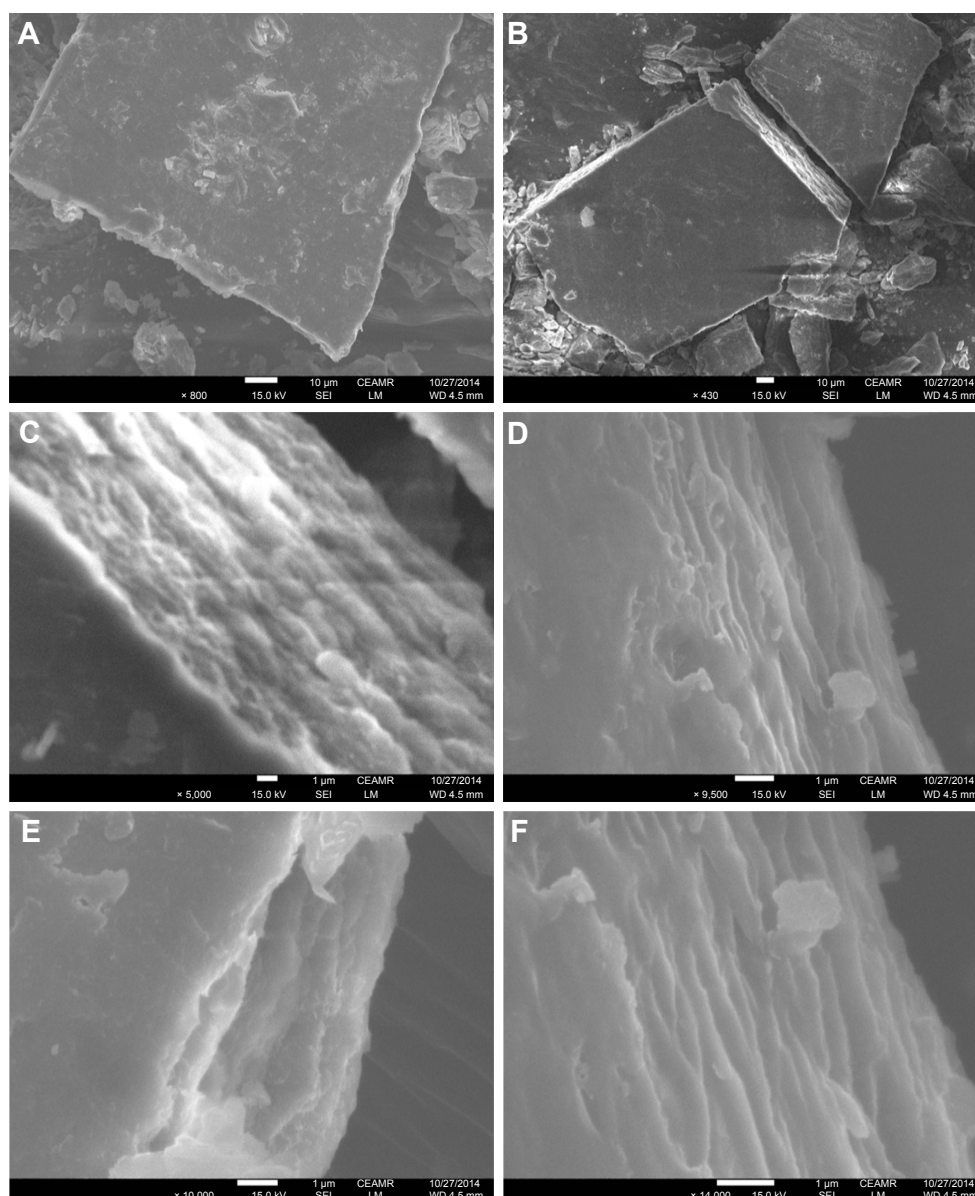


Figure 6 FE-SEM micrographs of nanohybrid CD-LDH. (A) 430× magnification, (B) 800× magnification, (C) 5,000× magnification, (D) 9,500× magnification, (E) 10,000× magnification and (F) 14,000× magnification.

Abbreviations: FE-SEM, field emission scanning electron microscopy; LDH, layered double hydroxide; CD, cefadroxil; CEAMR, Center of Excellence for Advanced Materials Research.

5,000× (Figure 6C), 9,500× (Figure 6D), 10,000× (Figure 6E) and 14,000× (Figure 6F) magnifications.

According to the literature,⁹⁰ FE-SEM micrographs of the synthesized NO_3 -LDH show uniform and regular particles with a hexagonal plate-like shape. In contrast, the photographs of the nanohybrid reveal non-uniform irregular agglomerates of compact.^{91,92} Additionally, the FE-SEM analysis of nanohybrid suggests that the CD-LDH particles have a microblock-like structure.⁹³

SEM-EDS

As illustrated in Figure 7, the EDS pattern of ZnAl-CD confirms the organic and inorganic composition of the CD-LDH

nanohybrid, where it shows common energy lines corresponding to C, O, Zn and Al.⁹⁴ The elemental composition as weight percentages and atomic percentages based on the EDS is shown in Table 1.

In vitro drug release testing

The main part of this work is based on the compared release processes of the drug from the organic–inorganic nanohybrid, Zn-Al CD, in the different solution media, in the presence or absence of chloride anions (sodium chloride salt) or macromolecule (PAM). Since the final quantification of the antibiotic is based on a standard curve, relating the absorbance of the solution with the drug concentration,

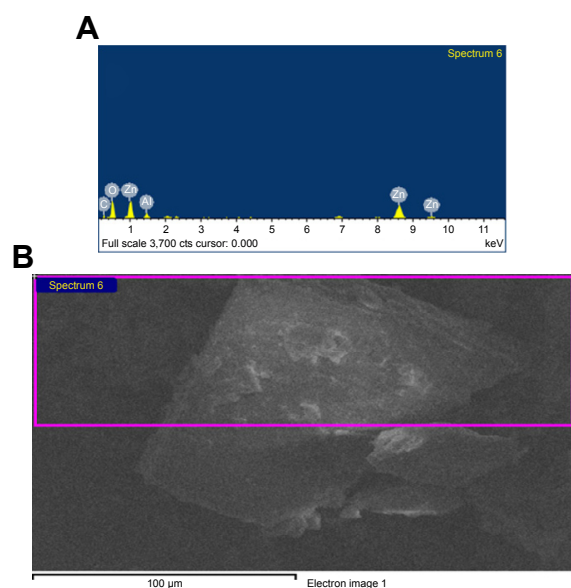


Figure 7 (A) EDS spectrum of nanohybrid CD-LDH; (B) SEM image of the sample used for EDS measurements (inset).

Abbreviations: EDS, energy dispersive X-ray spectroscopy; LDH, layered double hydroxide; CD, cefadroxil; SEM, scanning electron microscopy.

it must build the calibration curve from measurements at 230 nm in all pH medium in the expected concentration range (Figure 8). It is clear that the dependence of the absorbance on the concentration is linear in the investigated range with regression coefficients larger than 0.9 (Table 2).^{4,26,95} According to the literature, there are two main release mechanisms responsible for the rate of release and the amount released: anion-exchange (coupled with diffusion) of the drug molecules through the LDH material in alkaline or neutral media; and weathering/degradation of the LDH inorganic layers by protonation in strong acidic media.^{96–98} In mild acidic media, any of the two mechanisms would determine the drug release rate.³³

CD-Zn/Al-LDH

The drug release profiles, ie, the percentage of CD released into the buffer solution vs time, have been plotted in Figure 9A (strong acidic), 9B (mild acidic), 9C (neutral) and 9D (slightly basic).

Table 1 EDS Analysis of CD-LDH

Element	Weight %	Atomic %
C K	16.45	33.43
O K	28.93	44.15
Al K	3.79	3.43
Zn K	50.84	18.99
Total	100.00	

Abbreviations: EDS, energy dispersive X-ray spectroscopy; LDH, layered double hydroxide; CD, cefadroxil.

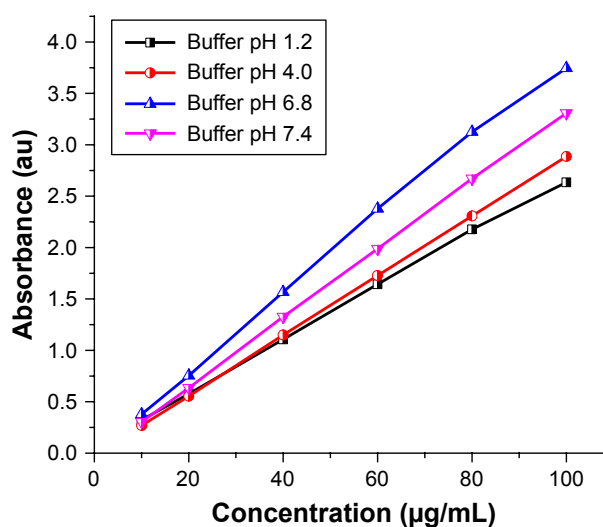


Figure 8 Calibration curve of cefadroxil at the different pH values.

In simulated gastric fluid (Figure 9A), under strong acidic conditions, the LDH is dissolved rapidly and completely and the intercalated CD is fully released, in its molecular form, but not fully dissolved: 71% of CD is dissolved after the end of the experiment from drug-intercalated hydrotalcite.^{33,99,100}

Bin Hussein et al⁹² pointed out that the layered structure of Zn-Al LDH quickly collapses, releasing α -naphthalene acetate (NAA) in strong acidic conditions. The release behavior for the ZnAl-CD nanohybrid does not demonstrate the possibility of the occurrence of ionic exchange between the interlayer CD and the chloride anions of the buffer solution, where the chloride ion affinity to the LDH layers is too low to cause drug replacement. As a result, there is only one mechanism that controls the release of the drug in this media: solid weathering.^{33,96} The intercalation process, as well as the rapid release of CD in the gastric medium, leads to an increase in the solubility of CD and its dissolution rate at the stomach.^{33,101} Ambrogi et al¹⁰² and Del Arco et al¹⁰³ have reported that the presence of inorganic LDH matrix improves the solubility of hardly soluble non-steroidal anti-inflammatory drugs (NSAIDs).

Table 2 Linearity data of CD by UV spectroscopy

Buffer solution	pH 1.2	pH 4.0	pH 6.8	pH 7.4
Equation	$y = 0.0264x + 0.0383$	$y = 0.0289x - 0.0064$	$y = 0.0382x + 0.0162$	$y = 0.0334x - 0.0195$
Slope	0.0264	0.0289	0.0382	0.0334
Intercept	0.0383	-0.0064	0.0162	-0.0195
R ² value	0.9993	0.9999	0.9987	0.9999

Abbreviation: CD, cefadroxil.

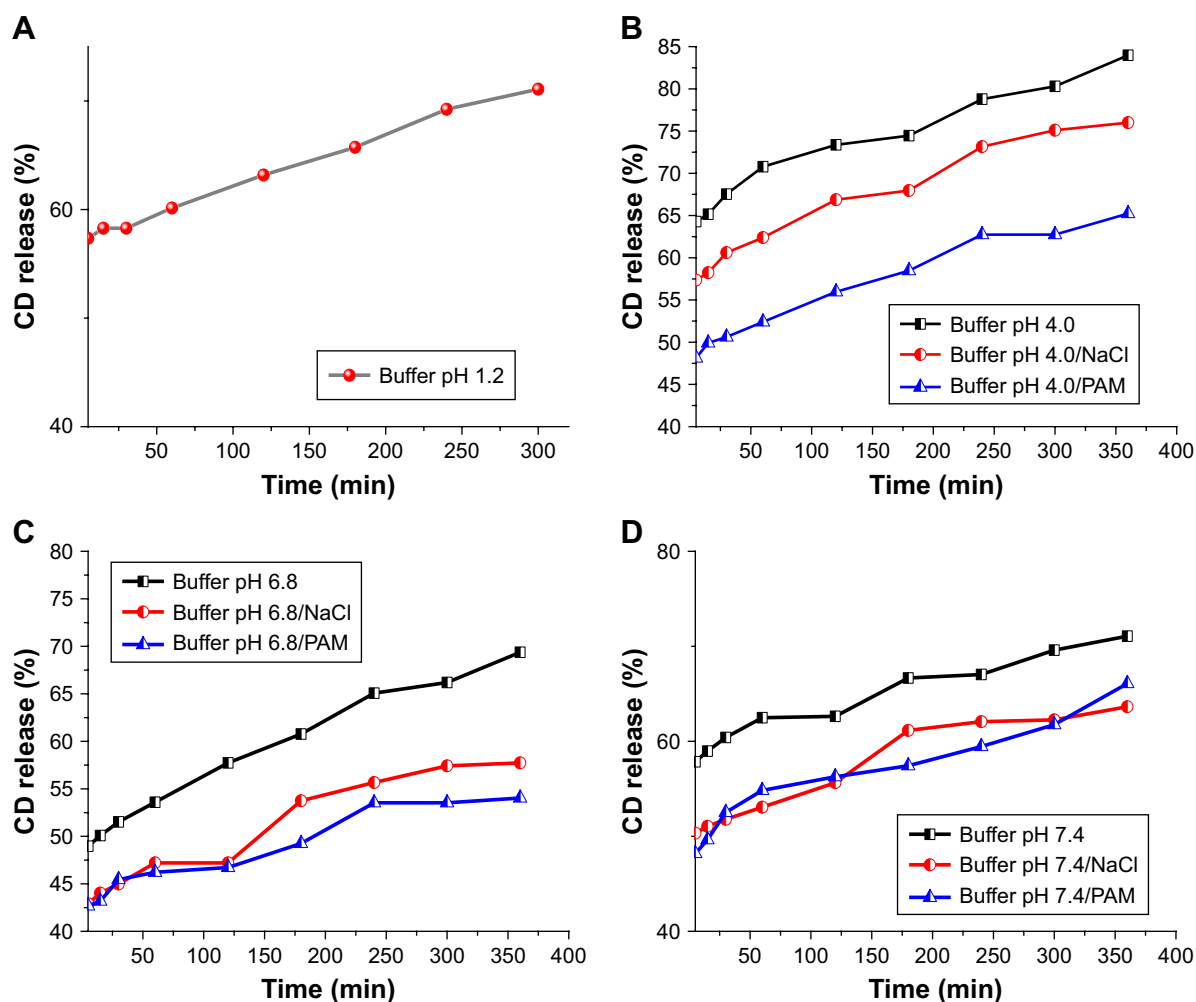


Figure 9 Release profiles of CD from the nanohybrid CD-LDH at pH 1.2 (A), at pH 4.0 (B), at pH 6.8 (C) and at pH 7.4 (D).

Abbreviations: PAM, polyacrylamide; CD, cefadroxil; LDH, layered double hydroxide.

In lysosomal, intestinal and blood simulated fluid, a similar behavior is observed for CD-intercalated LDH in all release media at early stages; about 64%, 49% and 58% of CD is released immediately at pH 4.0, 6.8 and 7.4, respectively.

Subsequently, however, the release of CD-LDH is slow and sustained: after 360 min there is a release amount of 84% at pH 4.0 (Figure 9B); ca. 69% at pH 6.8 (Figure 9C) and ca. 71% at pH 7.4 (Figure 9D).^{33,63,104,105} These findings are consistent with previous research, as reported by Yasin and Ismail²⁷ and Zhang et al¹⁰⁶ for samples containing lawsone and methotrexate intercalated in LDHs, where they studied the release of these drugs at different pH values.

The first stage of the release process can be attributed to the release of organic drug that was weakly adsorbed on the surface of the nanocomposite and that in the external part of the lamellar structure (LDH edges). The slow and sustained release of CD in the later stage may depend on

the slow anion exchange between interlayered CD and the anions in the fluid.^{33,63,69} Unlike CD at the interlayer, the CD at the outside layers will be exposed directly to the medium and will be dissolved immediately.⁹⁹

It is worth mentioning that partial destruction of the lamellar matrix did not happen in simulated lysosomal fluid. This means that the release process is subject to ion exchange mechanism only due to the high crystallinity of the LDH matrix and the great affinity of the intercalated anions for the layers.⁹⁶ With regard to stability of LDH at and above pH 7, this matrix is able to maintain its lamellar structure because it is more stable at those pH values and, consequently, LDH acts like a drug release modulator and the release process was governed by ion exchange mechanism.^{107,108}

From the release profiles in lysosomal, intestinal and blood simulated fluid, it is clear that the percentage of CD liberated does not reach 100%; this may be because of the

characteristics of the ion-exchange reaction. This means that the interlayer anions cannot be exchanged completely.^{59,109,110} Nejati and Rezvani⁷² and Xia et al¹¹¹ have studied the release of olsalazine at pH 7.4 and antihypertensive drugs at pH 4.25; these authors have highlighted that the release of drugs from nanohybrids (drug-LDH) is not complete, for the same reason as above.

The two-step release process can play an active role in therapeutic treatments, where the rapid release in the first stage allows the establishment of a therapeutic dose in a short period of time, while the slow stage allows the maintenance of this dose for long periods, ie, reduces the number of doses that are applied to patients, through the sustained release of drug from the ZnAl-LDH nanohybrid.^{32,112,113}

CD-Zn/Al-LDH/NaCl

As well as the dependence of the CD release rate from the nanohybrid on pH, it is strongly influenced by medium anionic species and their affinity toward the interlayer of the inorganic interlamellar.

Figure 9B–9D show that the release percentages of CD from CD-LDH nanohybrid in the presence of chloride ions are less than those obtained in the absence of exchangeable anion. The release profiles indicated that about 57%, 43% and 50% CD was released immediately at pH 4.0, 6.8 and 7.4, respectively. About 76% of CD is found to be released after 360 min, in lysosomal medium, while a lower release of CD is found in intestinal medium with release of 58% after 6 h. In blood simulated medium, about 64% of the initial CD amount is released during 360 min.

According to the literature,^{114,115} the effect of various medium anionic species on the release of herbicides from the interlayer of ZnAl-LDH (ZAN) follows the following order: i) for single system release media, carbonate anion > phosphate anion > chloride anion; ii) for binary system release media, carbonate and phosphate anions > chloride and phosphate anions > chloride and carbonate anions; iii) for all systems release media, carbonate anion > phosphate anion > carbonate and phosphate anions > chloride and phosphate anions > chloride and carbonate anions > chloride anion.

The reason for the increase of the CD release percentage in single system release media (phosphate ion) compared to the binary anions system of chloride–phosphate is ascribed to the decomposition of potassium phosphate, which leads to the formation of HPO_4^{2-} and H_2PO_4^- , which strongly compete with other anions in the ion exchange process. Phosphate

anions are able to exchange intercalated drugs easily due to their high affinity toward the LDH, thus the release rate of the drug is dominated by phosphate ions.^{107,114} By contrast, when chloride ions are present in the fluid, the rate of the release will be slower, and the amount of drug released will be lower due to the low ion exchange affinity of chloride anion toward the inorganic interlamellar ZnAl-LDH.^{116,117} This result is in good agreement with previous reports of Berber et al¹¹⁸ and Nakayama et al.¹¹⁹ This suggests that it is the affinity of the sacrificial anion for LDH which governs the ion exchange process.⁶⁴

CD-Zn/Al-LDH/PAM

The release studies of CD in the presence of PAM (Figure 9B–9D) show similar release behaviors to those in the presence of chloride anions. It is found that the amount of drug liberated is decreased in the presence of PAM.

The immediate release of CD is 48%, 43% and 48% at pH 4.0, 6.8 and 7.4, respectively. At pH 4.0, CD release from CD-LDH reaches a maximum of about 65% within 360 min. At pH 6.8, the release percentage of CD from the nanohybrid reaches 54% after 360 min. About 66% amount of CD is released from the LDH at pH 7.4 after 360 min.

It is known that PAM is not ionized (it is an uncharged polymer), but when it is added to the buffer solutions, it will hydrolyze partially, ie, a partially hydrolyzed polyacrylamide (HPAM) will be formed. Hydrolysis of PAM in the presence of H^+ as catalyst at pH 4.0 yields a copolymer composed of acrylamide and acrylic acid (Figure 10A), while its hydrolysis in the presence of OH^- as catalyst at pH 7.4 yields a

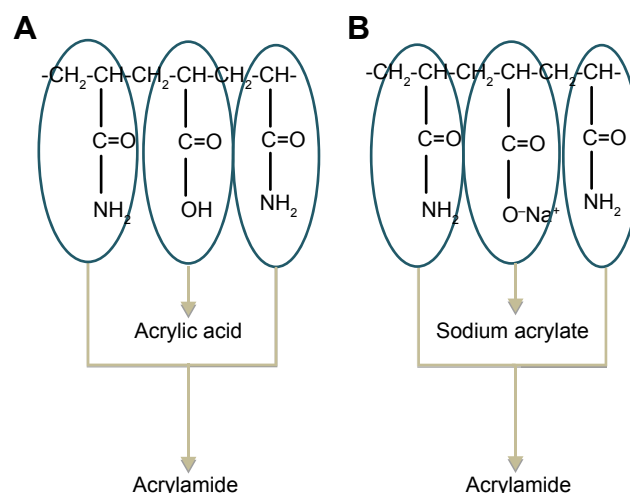


Figure 10 General structure for partially hydrolyzed polyacrylamide resulting from the presence of H^+ (A) and OH^- (B) catalysts in the release media.^{123,125}

copolymer composed of acrylamide and sodium acrylate (Figure 10B).^{120,121} In the case of an intestinal medium, the existence of hydroxide ions in this medium would provide considerable assistance to the hydrolysis.¹²² Since the acrylic acid or sodium acrylate units contain carboxyl groups, they shift such co-polymers to moderately anionic copolymers.

When HPAM COOH or –COONa groups dissociate into –COO[−], the polymer exchanges the CD anions existing on the LDH external sheets and then the carboxylate groups (–COO[−]) of the polymer can interact with the positive surface charge, which leads to inhibition of release of the drug from the nanohybrid. On the other hand, the formation of the negative layer surrounding the LDH particle inhibits the diffusion of CD anions that have the same charge of the diffusion layer.^{122,124}

Release kinetics of drug from CD-LDH nanohybrid

The release can be described as the rate of mass transport from a solid face into the buffer medium at standard conditions.¹²⁶ For drug delivery systems, three steps can be distinguished for drug release from the matrix: the initial step is liquid penetration to the matrix, followed by interaction between the nanohybrid and the buffer solution at the solid–liquid interface, and then diffusion of the drug into the exterior liquid (Figure 11).¹²⁷

In the present work, we used the dissolution-diffusion kinetic models (zero order, first order, Bhaskar, Higuchi, parabolic diffusion and Korsmeyer–Peppas models), in order to describe the overall release process from the drug delivery system, to facilitate quantitative analysis of the data obtained in release study.¹²⁸

Through the values of linear correlation coefficients (r^2), which are shown in Table 3, it is clear that the release mechanisms of the CD from the nanohybrid are the same in

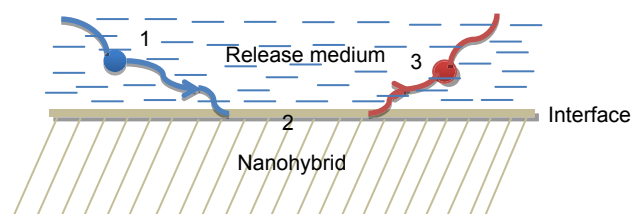


Figure 11 The fundamental steps in the release mechanism of the different drugs. (1) The molecules found in the buffer solution move toward the solid–liquid interface; (2) reaction happening at the interface; (3) the dissolved drug molecules are moving in the direction of the bulk solution.¹²⁶

all release profiles (II = buffer pH 4.0, III = buffer pH 4.0/NaCl, IV = buffer pH 4.0/PAM, V = buffer pH 6.8, VI = buffer pH 6.8/NaCl, VII = buffer pH 6.8/PAM, VIII = buffer pH 7.4, IX = buffer pH 7.4/NaCl and X = buffer pH 7.4/PAM), with the exception of profile I = buffer pH 1.2.

In general, if we look at the values of coefficients related (r^2) obtained from release data fitting analyses based on first-order model (Figure 12B and Table 3); Bhaskar model (Figure 12C and Table 3); Higuchi model (Figure 12D and Table 3); parabolic model (Figure 12E and Table 3); and Korsmeyer–Peppas (Figure 12F and Table 3), it can clearly be seen that CD release at pH 1.2 does not depend on (1) the drug concentration in the matrix, (2) the ion-exchange mechanism, (3) the diffusion through the particle, and (4) an external surface/edge diffusion process.³³

At pH 4.0, 6.8 and 7.4, since the release of the drug occurs by ion exchange with anions existing in the release medium, the following mechanism may be proposed for release of CD from CD-LDH:

- Reaction in the external parts of the particle: ion exchange reaction happens between the drug anions (large ions) existing in the external parts of the LDH

Table 3 Correlation coefficients (r^2) and values of the diffusion exponent (n) obtained from CD release data fitting analyses based on several kinetic equations

Buffer solution	Zero-order r^2	First-order r^2	Bhaskar r^2	Higuchi r^2	Parabolic r^2	Korsmeyer–Peppas	
						r^2	n
pH 1.2 (I)	0.9950	0.9927	0.9863	0.9580	0.9417	0.8052	–
pH 4.0 (II)	0.9629	0.9498	0.9811	0.9794	0.9411	0.8953	0.060
pH 4.0/NaCl (III)	0.9606	0.9483	0.9845	0.9835	0.9425	0.8980	0.069
pH 4.0/PAM (IV)	0.9661	0.9551	0.9874	0.9828	0.9439	0.8877	0.072
pH 6.8 (V)	0.9818	0.9702	0.9961	0.9860	0.9419	0.8818	0.083
pH 6.8/NaCl (VI)	0.9402	0.9325	0.9549	0.9448	0.9401	0.8427	0.070
pH 6.8/PAM (VII)	0.9292	0.9244	0.948	0.9386	0.9434	0.8457	0.057
pH 7.4 (VIII)	0.9568	0.948	0.9733	0.9697	0.9434	0.8814	0.046
pH 7.4/NaCl (X)	0.9239	0.9177	0.9563	0.9539	0.9399	0.8518	0.060
pH 7.4/PAM (IX)	0.9331	0.9187	0.9509	0.9500	0.9465	0.9049	0.066

Abbreviations: CD, cefadroxil; PAM, polyacrylamide.

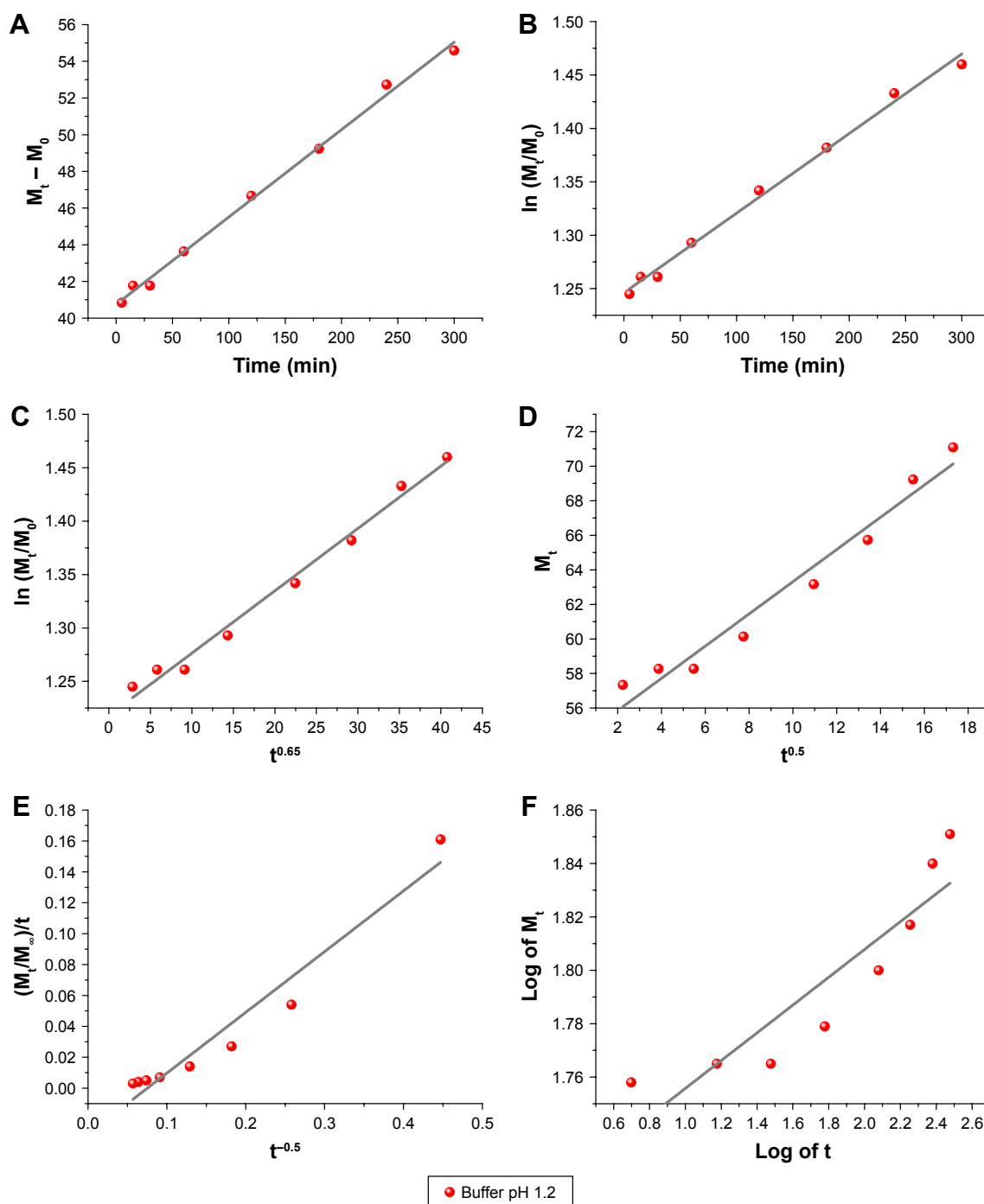


Figure 12 Fitting the nanohybrid CD-LDH release data at pH 1.2 to different kinetic equations. **(A)** zero-order model (description of the dissolution process); **(B)** first-order model (description of the drug absorption); **(C)** Bhaskar model (description of drug diffusion from insoluble inorganic matrixes); **(D)** Higuchi model (description of drug diffusion from semi-solid); **(E)** parabolic model (description of drug diffusion from an external surface); and **(F)** Korsmeyer–Peppas model (confirmation of the drug release mechanism). It is clear that the zero-order model can explain the release behavior kinetic of CD-LDH nanohybrid at pH 1.2 by providing higher linear correlation coefficient, which means that the release process is based on the dissolution of the drug.

Abbreviations: CD, cefadroxil; LDH, layered double hydroxide; M_t , the drug quantity released at release time; M_0 , the initial quantity of drug in the nanohybrid; M_∞ , the drug quantity released in infinite time; t , release time expressed in minutes.

and the anions (small species) of the release media, which leads to the formation of an external phase with smaller interlayer distance (boundary phase) between the external zone in which phosphates have

already replaced the drug anions (small spacing) and the internal zone containing intercalated drug (large spacing). As a result, the ion exchange process will become slow.^{118,129}

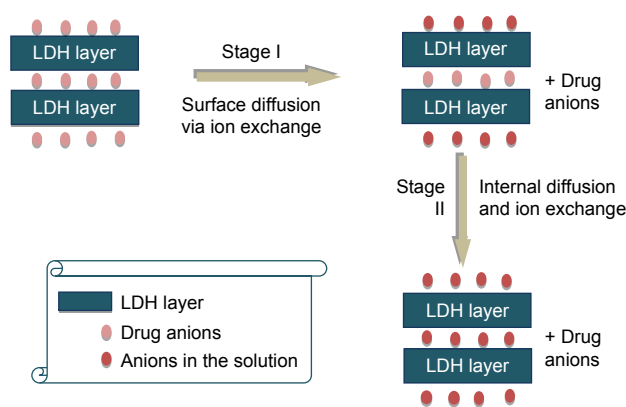


Figure 13 Representation of drug release in buffer solution.¹¹²

Abbreviation: LDH, layered double hydroxide.

- Diffusion through the LDH particle: drug anions diffuse from the LDH interlayer region (Figure 13).
- Diffusion of the drug anions from the bulk solution surrounding the LDH particle (Figure 14).^{15,107}

The slowest of these processes will determine the rate of exchange of drug anions with the solution medium.¹⁰⁷

As an ion-exchange mechanism is involved when using LDH, Bhaskar et al³⁸ created an equation to determine whether the diffusion through the particle is the rate limiting step of the release process. This equation suggests that simply testing for linearity between $\ln(M_t/M_0)$ and $t^{0.65}$ is a possible test of the particle diffusion control.³⁸ When the Bhaskar equation was applied to the measured drug release data, the relationship shown above is perfectly linear (Figures 15A, 16A and 17A), which means that the rate limiting step of the release process is the diffusion out of particles.^{65,124}

Since the Bhaskar model provides excellent r^2 values equal to or more than 0.95 for all media (from II to X; Table 3), it is possible to elucidate the release processes of CD-LDH nanohybrid on the basis of this model. In other words, through this equation, it is clear that the mechanism of the ion exchange is considered fundamental to determine

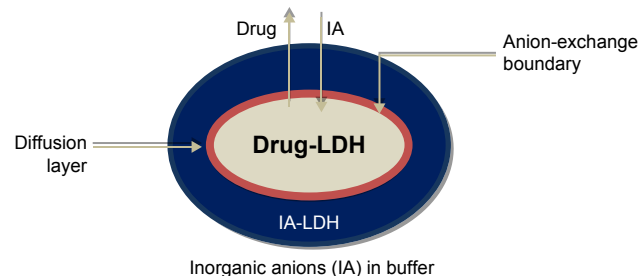


Figure 14 Schematic representation of the diffusion of the drug from the bulk solution surrounding the particle.¹¹³

the overall release rate^{38,130} and the diffusion of the drug from LDH is subject to strict control by the matrix.⁸

Another kinetic analysis using an equation suitable for diffusion from the matrix is the Higuchi model. This model fits the release data very well (Figures 15B, 16B and 17B), confirming the significance of the process of the diffusion in controlling the rate of the release of the drug.¹²⁴

The Korsmeyer–Peppas kinetics mathematical model equation was applied to confirm the diffusion mechanism.¹³¹ The correlation coefficients (r^2) obtained from the fittings were almost acceptable (Figures 15C, 16C and 17C). Overall, the calculated values of diffusional exponent n are lower than 0.45 (Table 3), which means that the drug release rate is controlled by diffusion from the interlayer of the particle via ion exchange; this process is called quasi-Fickian diffusion mechanism.^{43,44}

By comparing correlation coefficients values obtained by the Bhaskar kinetics model with those obtained by parabolic diffusion equation (Figures 15D, 16D and 17D), it is evident that diffusion of the CD anions from the surface of LDH particles into the medium solution via anion exchange, which takes a short time, cannot be a rate determining step of the release process.^{63,106}

The experimental data show a poor fit with the first order kinetics compared to the Bhaskar kinetic model (Figures 15E, 16E and 17E). This means that the release process cannot be based on the amount of the drug in LDH and drug diffusion from LDH is not passive.^{8,106}

The zero-order model fits the experimental data worse than the Bhaskar model (Figures 15F, 16F and 17F), indicating that the release of the drug is not only considered a single dissolution process.¹³²

Conclusion

CD was successfully intercalated into a Zn–Al nitrate LDH by a co-precipitation technique. The intercalation process was confirmed by FTIR for the nanohybrid, which indicated the presence of functional groups for both the drug and the Zn–Al LDH, confirming the success of the intercalation process. Additionally, TG-DTG analysis proved that thermal stability of CD after intercalation was enhanced compared with its free counterpart, due to interactions between host and guest. Characterization by using UV–vis spectroscopy proved that the interlayer antibiotic anions were stabilized by host–guest and guest–guest interactions. FE-SEM analysis indicated that the CD-LDH nanohybrid has a microblock-like structure. EDS results revealed the nanohybrid contained both organic and inorganic

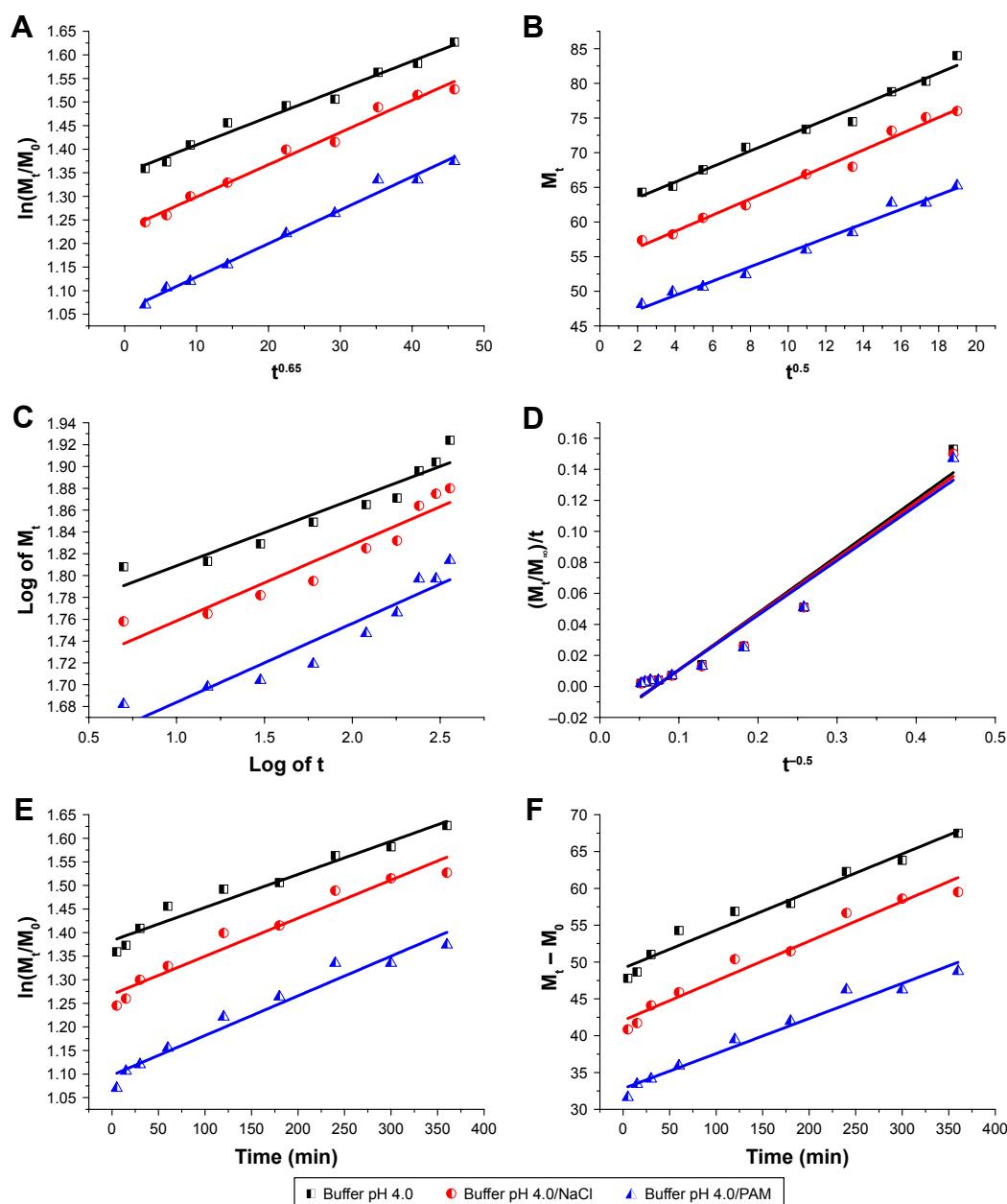


Figure 15 Fitting the nano-hybrid CD-LDH release data at pH 4.0 to different kinetic equations. **(A)** Bhaskar model (description of drug diffusion from insoluble inorganic matrixes); from the Bhaskar model, it is clear that the ion-exchange mechanism is the most responsible for drug liberation; **(B)** Higuchi model (description of drug diffusion from semi-solid); the Higuchi model confirmed the importance of the diffusion through the particle in controlling the drug release rate; **(C)** Korsmeyer–Peppas model (confirmation of the drug release mechanism); from the Korsmeyer–Peppas equation, it turned out that the process is called quasi Fickian diffusion; **(D)** parabolic model (description of drug diffusion from an external surface); R^2 values obtained by parabolic diffusion equation confirmed that CD release did not depend on an external surface/edge diffusion process; **(E)** first-order model (description of the drug absorption); R^2 values obtained by first order kinetics confirmed that CD release did not depend on the drug concentration in the matrix; and **(F)** zero-order model (description of the dissolution process); R^2 values obtained by zero order kinetics confirmed that CD release did not depend on the dissolution process.

Abbreviations: CD, cefadroxil; LDH, layered double hydroxide; PAM, polyacrylamide; M_t , the drug quantity released at release time; M_0 , the initial quantity of drug in the nano-hybrid; M_∞ , the drug quantity released in infinite time; t , release time expressed in minutes.

constituents. Release tests of the CD from its interlamellae of the organic–inorganic nano-hybrid in a strong acid fluid (pH 1.2) indicated that the LDH was dissolved and intercalated antibiotic released from the sample in a molecular form, while at pH 4.0, 6.8 and 7.4 in the presence or absence of Cl ions or PAM there was immediate release of CD anions that occurred at the beginning of release tests, followed by

a slower and sustained release process. So, the ZnAl-CD nano-hybrid can be considered as a sustained drug release system allowing increase of the therapeutic efficacy of the antibiotic by maintaining a dose over a long period of time, thus, this system reduces side effects. In general, the release rate of the anion was found to be dependent on the pH of the release medium. The comparison of the release profiles

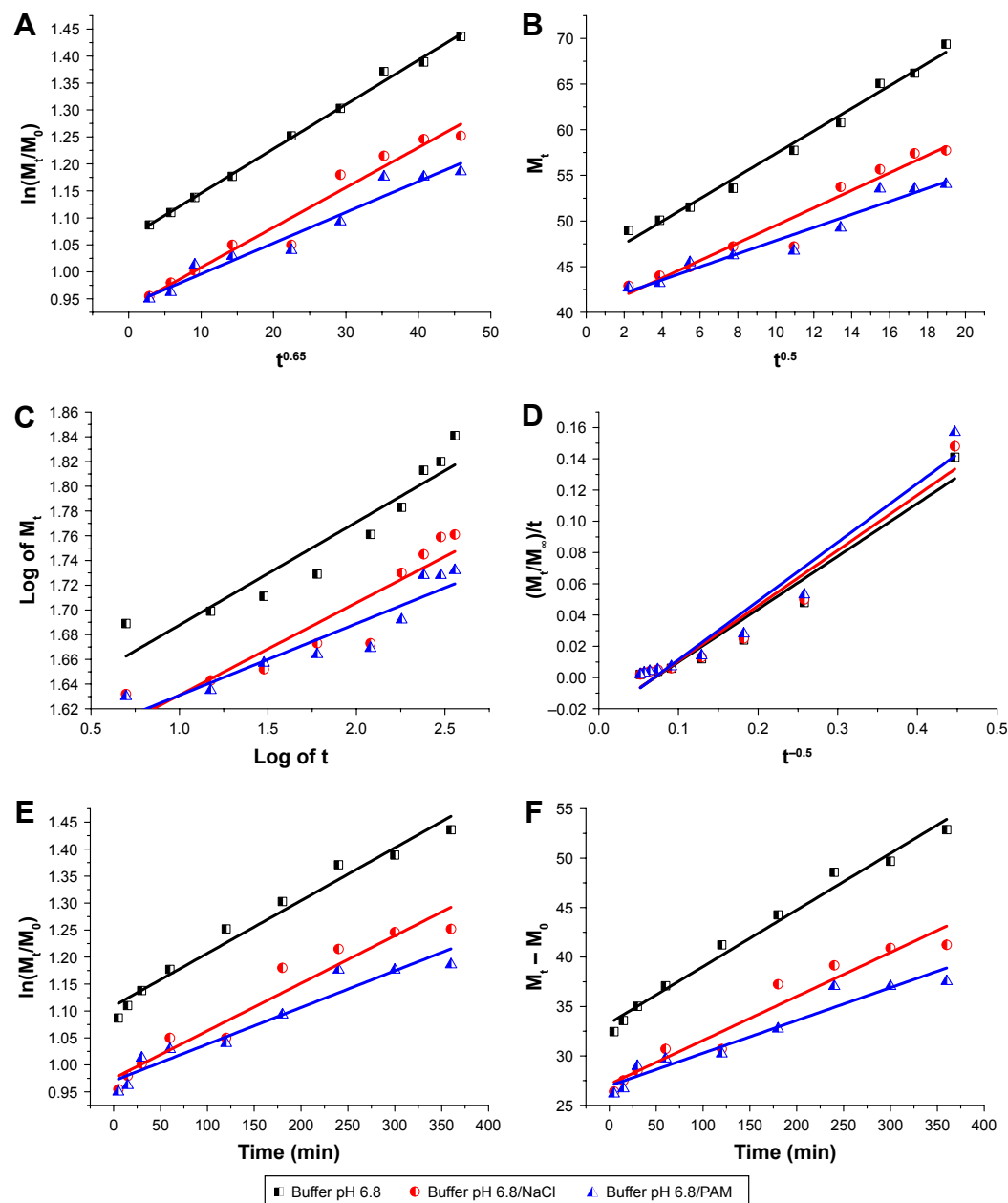


Figure 16 Fitting the nanohybrid CD-LDH release data at pH 6.8 to different kinetic equations. **(A)** Bhaskar model (description of drug diffusion from insoluble inorganic matrixes); from the Bhaskar model, it is clear that the ion-exchange mechanism is the most responsible for drug liberation; **(B)** Higuchi model (description of drug diffusion from semi-solid); the Higuchi model confirmed the importance of the diffusion through the particle in controlling the drug release rate; **(C)** Korsmeyer-Peppas model (confirmation of the drug release mechanism); from the Korsmeyer-Peppas equation, it turned out that the process is called quasi Fickian diffusion; **(D)** parabolic model (description of drug diffusion from an external surface); R^2 values obtained by parabolic diffusion equation confirmed that CD release did not depend on an external surface/edge diffusion process; **(E)** first-order model (description of the drug absorption); R^2 values obtained by first order kinetics confirmed that CD release did not depend on the drug concentration in the matrix; and **(F)** zero-order model (description of the dissolution process); R^2 values obtained by zero order kinetics confirmed that CD release did not depend on the dissolution process.

Abbreviations: CD, cefadroxil; LDH, layered double hydroxide; PAM, polyacrylamide; M_t , the drug quantity released at release time; M_0 , the initial quantity of drug in the nanohybrid; M_∞ , the drug quantity released in infinite time; t , release time expressed in minutes.

revealed that the percentage of drug released in the absence of the NaCl or PAM in the release media was more than that observed with their presence. The release mechanism had been interpreted on the basis of solid weathering at pH 1.2, while anion-exchange (coupled with diffusion) determined drug release at pH 4.0, 6.8 and 7.4. The release of CD into the gastric simulated fluid can be better expressed by the

zero-order model, which means that the release rate of the CD depended on its dissolution. In lysosomal, intestinal, and blood simulated fluid, the Bhaskar model is the best to describe the release behavior kinetic of CD from the CD-LDH nanohybrid. This means that intraparticle diffusion could play a major role in the control of the drug release rate.

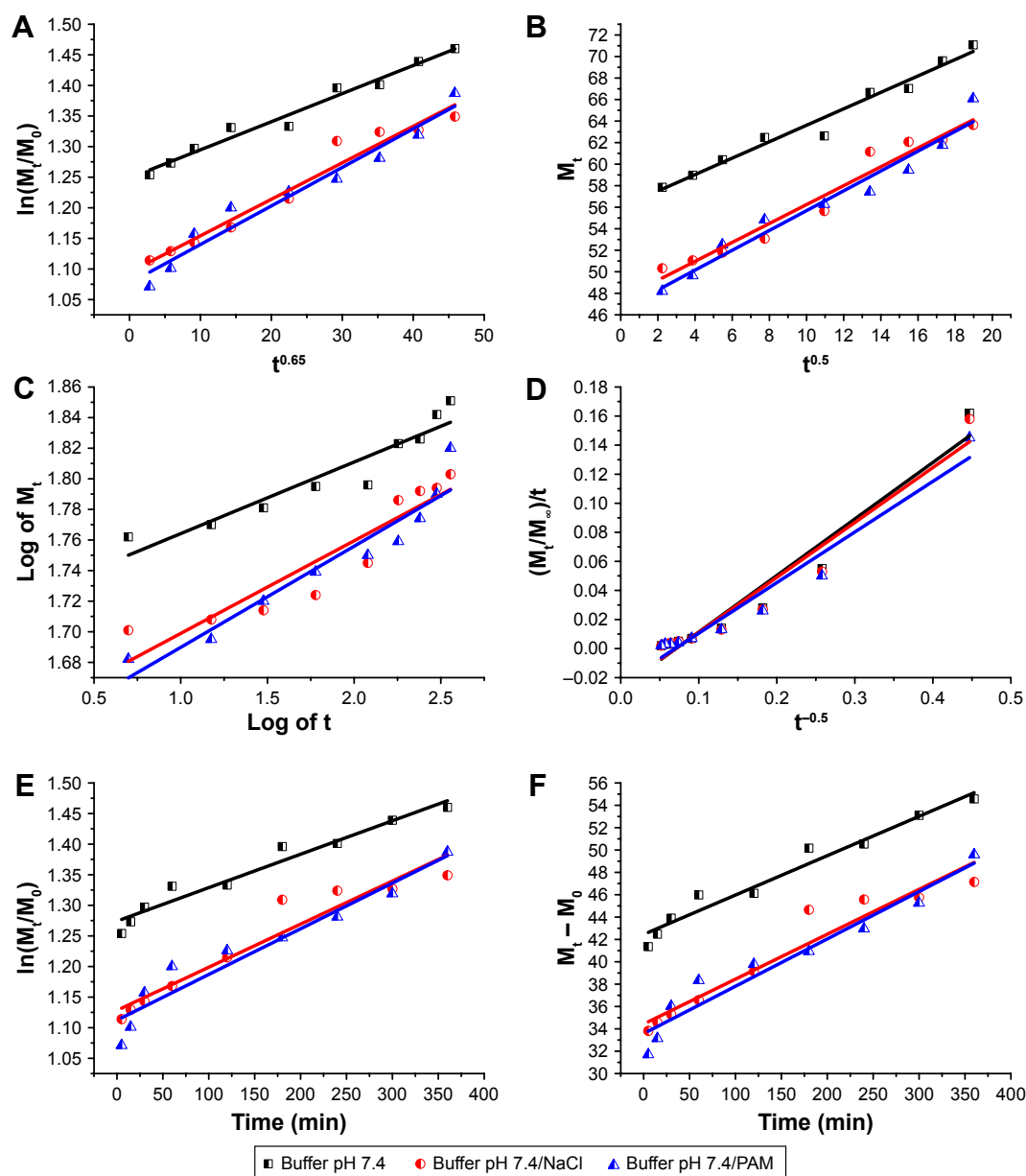


Figure 17 Fitting the nano-hybrid CD-LDH release data at pH 7.4 to different kinetic equations. **(A)** Bhaskar model (description of drug diffusion from insoluble inorganic matrixes); from the Bhaskar model, it is clear that the ion-exchange mechanism is the most responsible for drug liberation; **(B)** Higuchi model (description of drug diffusion from semi-solid); the Higuchi model confirmed the importance of the diffusion through the particle in controlling the drug release rate; **(C)** Korsmeyer–Peppas model (confirmation of the drug release mechanism); from the Korsmeyer–Peppas equation, it turned out that the process is called quasi Fickian diffusion; **(D)** parabolic model (description of drug diffusion from an external surface); R^2 values obtained by parabolic diffusion equation confirmed that CD release did not depend on an external surface/edge diffusion process; **(E)** first-order model (description of the drug absorption); R^2 values obtained by first order kinetics confirmed that CD release did not depend on the drug concentration in the matrix; and **(F)** zero-order model (description of the dissolution process); R^2 values obtained by zero order kinetics confirmed that CD release did not depend on the dissolution process.

Abbreviations: CD, cefadroxil; LDH, layered double hydroxide; PAM, polyacrylamide; M_t , the drug quantity released at release time; M_0 , the initial quantity of drug in the nano-hybrid; M_∞ , the drug quantity released in infinite time; t , release time expressed in minutes.

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Disclosure

The authors report no conflicts of interest in this work.

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