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Release kinetics from LDH-drug hybrids: Effect of layers stacking and drug solubility and polarity

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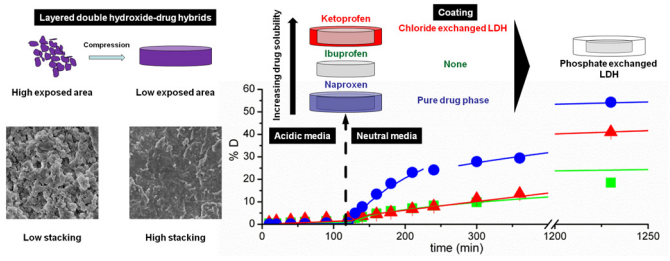
HIGHLIGHTS

- High drug loading, even exceeding anion exchange capacity, due to lateral interactions.
- Compact disposition of LDH-D hybrids when compressed, slowed surface reactions and diffusion.
- Faster release by anion exchange in neutral media, rate dependent on the apolar tail of the drug.
- Slow matrix weathering in acidic media, release rate and mechanism dependent on drug solubility.

GRAPHICAL ABSTRACT



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ABSTRACT

This work highlights the effect of drug solubility and polarity and solid layer stacking on the release rate and mechanism of layered double hydroxides-drug (LDH-D) hybrids. With such a purpose, LDH-D hybrids containing three structural related non-steroidal anti-inflammatory drugs (ibuprofen, naproxen or ketoprofen) were synthesized by a simple co-precipitation method. LDH matrixes exhibited a high drug loading capacity, even exceeding the anion exchange capacity of the solid especially with the more apolar drugs. The structure and interfacial properties of the particulate LDH-D hybrids were also dependent on the polarity of the loaded drug. Finally, the release mechanisms in neutral and acidic media were studied with compressed LDH-D hybrids. The hybrids compression leaded to highly stacked platelets that caused a slower and steadier drug release rate than particulate LDH-D hybrids in all cases. In neutral medium, the drugs were exclusively released by anion exchange with HPO_4^{2-} ions and the release rate was determined by the drug polarity. In acidic medium, weathering was the main release mechanism. However, additional processes (anion exchange, drug solubilization) were concurrent in the latter media, the overall mechanism and release rate being dependent on the drug solubility.

1. Introduction

Magnesium and aluminum layered double hydroxides (LDH) are biocompatible inorganic solids with brucite ($Mg(OH)_2$)-like structure. Isomorphic substitution of Mg^{2+} by Al^{3+} in the layers leads to a charge excess compensated by the introduction of anions in the interlayer space. They are able to incorporate organic anions, such as pharmaceutically active drugs [1,2], biomolecules [3–5], agrochemicals [6], plant growth regulators, food additives and dyes [7,8] by intercalation and/or adsorption, to prepare organic–inorganic hybrids. Anion release from these hybrids is produced by three mechanisms [9]: ion exchange (highly

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dependent on the anion nature and concentration of the release media), desorption and weathering (both processes depend on the pH of the release media).

Among the organic–inorganic hybrids, special attention has been paid to those including pharmaceutically active drugs (LDH-D); the main alleged advantages of LDH-D hybrids being drug preservation, release rate modification and, in some cases, bioavailability increment [10–12]. Particulate LDH-D hybrids prepared with non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen or ketoprofen [13], show a slower release rate compared to the pure drug in intestinal media and an increased solubility of the acidic form of the drug in gastric media [9,14,15]. A great disadvantage of particulate LDH-D is the fast and complete release produced from the hybrids. However, the release rate from LDH-D can be reduced by increasing either the layers stacking or the particle size of the matrix. Guwanan and Xu [16] showed that the release rate of ibuprofen from LDH hybrids was determined by the aggregation of the LDH platelets. Similarly, Zhang et al. [17] showed that bigger particles leaded to longer release times from methotrexate-loaded LDHs. Surprisingly, there have been only a few comparative studies analyzing the incidence of the physicochemical properties of the drugs and the morphology of the solid on the release behavior from LDH-D hybrids [8].

In this work, the release rate from LDH-D hybrids was reduced by compressing the particulate solids into discs, which allowed studying the drugs release mechanisms and the effect of the drug physicochemical properties on the kinetic profiles in different media. Ibuprofen (Ibu), naproxen (Nap) or ketoprofen (Ket) were selected as interlayer anions, as they are structurally related NSAIDs. Biocompatible LDHs of Mg and Al, loaded with Ibu, Nap or Ket, were synthesized and characterized to determine the structure and interfacial properties of the hybrids. Particulate LDH-D was then compressed to obtain discs of densely packed hybrid particles. One- and two-steps kinetic experiments with compressed LDH-D hybrids were performed in acidic (0.05 mol L^{-1} phosphate buffer pH = 6.8) and/or in neutral (HCl pH = 1.2 + 0.05 mol L^{-1} NaCl) media and modeled to determine the drugs release mechanisms.

2. Materials and methods

Pharmaceutical grade Ibu, Ket and Nap (Parapharm®, Buenos Aires, Argentina) and reagent grade chemicals were used without further purification. Deionized water with a resistance of 18.2 MΩ was obtained using a Millipore ultrapurification system. The experiments were carried out at room temperature (25 °C) unless otherwise stated.

2.1. Synthesis

LDH-D hybrids (containing either Ibu, Nap or Ket) were synthesized by the coprecipitation method at constant pH [9,18]. A 0.1 L solution containing the metal ions (0.4 mol L^{-1} $AlCl_3$; 0.8 mol L^{-1} $MgCl_2$) was added drop wise to a 0.1 L solution containing 0.08 mol of the corresponding drug under vigorous stirring at pH = 9, controlled by addition of a 2 mol L^{-1} NaOH solution. The obtained slurries were centrifuged, washed and finally dried at 50 °C until constant weight. The hybrids were named LDH-Ibu, LDH-Ket and LDH-Nap according to the intercalated drug.

2.2. Structural and morphological characterization

Mg and Al content were determined by atomic absorption spectrometry in a Varian AA240 instrument. The samples were dissolved in HNO_3 and afterwards diluted to meet the calibration range. Dispersions of the hybrids in neutral medium (0.1 g L^{-1}, 0.05 M buffer phosphate, pH = 6.8) were prepared to determine their drug content using UV–vis spectrophotometry (Shimadzu UV1601, Japan). Water content was estimated by thermogravimetric analysis between 25 and 200 °C, carried out in a SETARAM Setsys Evolution 16/18 instrument at a 5 °C min^{-1} heating rate.

Powder X-ray diffraction (PXRD) patterns were recorded in a Phillips X'pert Pro instrument using a CuKα lamp (λ = 1.5408 Å) at 40 kV and 40 mA between 3° and 60° (2θ) in step mode (0.05°, 1.2 s). FT-IR spectra were measured in a FT-IR Bruker IFS28 instrument using KBr pellets (1:100 sample:KBr ratio). Scanning electron microscopy (SEM) images were obtained in a FE-SEM Σigma instrument on samples covered with a Cr layer.

The hydrodynamic apparent diameter (d) and zeta potential (ζ) of the samples were determined by dynamic light scattering (DLS) and electrophoretic light scattering (ELS) measurements, respectively, using a Delsa Nano C instrument (Beckman Coulter). Aqueous dispersions of the hybrids (0.1 g L^{-1} in $5{\cdot}10^{-2}$ mol L^{-1} NaCl) were prepared and sonicated for 30 min. Their d and ζ values were determined at different pH values, adjusted by addition of a NaOH solution. d and polydispersity values were calculated from the autocorrelation function ($g^{(2)}$) using the cumulants method, while electrophoretic mobilities were converted to ζ using the Smoluchowski equation. Contact angle (θ) measurements were performed by the sessile drop method using a homemade goniometer and deionized water drops over compressed LDH-D hybrids prepared at 2 tons with a 11 mm die. The experiments were performed in triplicate.

2.3. Drug release kinetics

Compressed LDH-D hybrids were prepared by compression of the corresponding sample (400 mg) in an 11 mm die at 2 tons. Two different degassed and thermostatized (37.0 ± 0.5 °C) release media were selected: acidic (HCl pH = 1.2 ± 0.1 in 0.05 mol L^{-1} NaCl) and neutral (0.05 mol L^{-1} phosphate buffer pH = 6.8 ± 0.1). SEM images of the compressed LDH-D hybrids before the different release experiments were also taken.

Drug release from compressed LDH-D hybrids in each release medium (one-step experiments) was studied in a dissolution test station (AT-7 smart, Sotax, Switzerland), using USP-method 2 (paddle, US Pharmacopeia, 2009 [19]) at 100 ± 1 rpm with 900 mL of dissolution media at 37.0 ± 0.5 °C. 4 mL of the samples were taken and filtered at defined time intervals up to 24 h, and replaced with an equivalent volume of fresh medium. The drug concentration was measured by UV–vis spectrophotometry at the corresponding absorbance maximum (λ = 264 nm, 271 nm and 260 nm for Ibu, Nap and Ket, respectively). Finally, a two-step release study was performed according to USP-method B (delayed-release dosage form, US Pharmacopeia, 2009 [19]). Namely, compressed LDH-D hybrids were tested for 2 h in acidic medium and then removed, rinsed with water and introduced in neutral medium, up to 24 h. All the experiments were conducted in triplicate to calculate the mean values and standard deviations included in the release profiles.

Separately, PXRD patterns, FTIR spectra and SEM images of the hybrids after the release experiments in acidic medium were also obtained. Compressed LDH-D hybrids were previously milled until a homogeneous powder was obtained.

Higuchi, zero order and Peppas kinetic models [20] were employed to fit the drug release behavior of the compressed LDH-D hybrids. However, Peppas model is the most general one and includes the other two models. The equation that describes Peppas model is:

$$\%D = \frac{M_t}{M_0} \cdot 100 = k_P t^n; \quad \log \%D = \log k_P + n \log t \tag{1}$$

where M_t is the amount of drug released at time t, M_0 is the initial drug content of LDH-D hybrid and k_P is the kinetic release constant.