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Research paper

Structural and physicochemical aspects of drug release from layered double hydroxides and layered hydroxide salts

Ricardo Rojas [a,*], Yamila Garro Linck [b], Silvia L. Cuffini [c], Gustavo A. Monti [b,d], Carla E. Giacomelli [a]

[a] INFIQC-CONICET, Departamento de Fisicoquímica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Haya de la Torre s/n, 5000 Córdoba, Argentina
[b] IFEG-CONICET, 5000 Córdoba, Argentina
[c] Instituto de Ciência e Tecnologia, Universidade Federal de São Paulo, Campus São Jose dos Campos, Rua Talim, 330 (12.231-280), Villa Nair, Brazil
[d] FAMAF, Universidad Nacional de Córdoba, 5000 Córdoba, Argentina

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ABSTRACT

Layered double hydroxides (LDHs) and Zn layered hydroxide salts (LHSs) present different physicochemical and interfacial properties derived from their dissimilar structure and composition, which affect the release behavior of the intercalated drug. In this work, these aspects are studied using LDHs and LHSs intercalated with ibuprofen (Ibu), naproxen (Nap) or ketoprofen (Ket) to understand the behavior of intercalation compounds as drug carriers. The structure of the solids and the interaction mode between the drugs and the layers were determined by chemical analysis, PXRD, FTIR and NMR. Further, the interfacial properties (potential zeta and hydrophilic/hydrophobic character) of the solids, as well as their drug release profiles were also comparatively studied. The drugs were attached by electrostatic interactions to LDH layers while coordinate bond was produced in the case of LHSs. The different interaction modes, together with the higher drug density between LHS layers produced more crystalline solids with larger basal spacing values than the corresponding LDH. This detailed structural study allowed for establishing the correlations between structure, interactions, morphology, interfacial properties and drug release behavior. Thus, the different interaction modes determined the surface charging behavior, while the solubility of LHS layers led to a fast drug release in neutral media. Finally, the loose drug arrangement in the hybrids caused a solubility increase in acid media. These correlations are helpful to predict and optimize the behavior of drug delivery systems based on both LDHs and Zn–LHSs.

1. Introduction

Layered double hydroxides (LDHs) and layered hydroxide salts (LHSs) are two groups of intercalation compounds with anion exchange capabilities. They hold different layer structure and bonding (Fig. 1), which leads to different physicochemical properties (Rojas and Giacomelli, 2013). LDH layer structure (Fig. 1A) is derived from that of brucite ($Mg(OH)_2$) by isomorphic substitution of divalent (M^{2+}) by trivalent (M^{3+}) ions in octahedral sites (Evans and Slade, 2006), while interlayer anions (A^{n-}) establish electrostatic interactions with the positively charged layers, the overall formula of these solids being $[M^{2+}_{1-x}M^{3+}_x(OH)_2](A^{n-})_{x/n}yH_2O$. On the other hand, LHSs present different structures with different binding modes between the interlayer anions and the layers. Thus, LHSs with formula $[Zn_5(OH)_8]A_{2/n}\cdot mH_2O$ (Fig. 1B) are derived from that of brucite by elimination of a quarter of Zn^{2+} ions in octahedral sites while additional Zn^{2+} ions are placed in tetrahedral sites at the bottom and top of each empty octahedron. Three vertices of each tetrahedron are occupied by hydroxyl anions of the layer, while the fourth is occupied by either water molecules (Arizaga et al., 2007; Biswick et al., 2009, 2012) or the interlayer anion (Poul et al., 2000; Guadalupe et al., 2008; Rojas and Giacomelli, 2013). In the first case, electrostatic interactions are mainly present between the interlayer anions and the layers while, in the latter, the anions are attached through a coordinate bond. The other layer structure ($[Zn(OH)_{2-x}]A_{x/n}$) shown in Fig. 1C, is obtained by replacing hydroxyl groups of the brucite-like structure by an oxygen atom of A^{n-}, which is attached by coordinate bond. Attaining one or another layer structure is dependent on both the synthesis conditions (Miao et al., 2006; Inoue and Fujihara, 2010) and the intercalated anion (Kongshaug and Fjellvåg, 2004).

As stated above, the differences in structure and bonding of these solids are reflected in their physicochemical and interfacial properties. Thus, exchange reactions are produced in both groups, but they are more properly described as ligand exchange reactions when anions are attached by coordinate bond (Meyn et al., 1993; Williams et al., 2012). Further, electrostatic interactions allow detachment of anions from the surface of LDH particles in aqueous dispersions, which results in positively charged particles. On the other hand, coordinate binding does not allow anion detachment from the particle surface and only ligand exchange reactions are possible when the interlayer anion is coordinated to Zn–LHS layers. Consequently, these solids present neutral or

* Corresponding author. Tel.: +54 3515353866; fax: +54 3514334188.
E-mail address: rrojas@fcq.unc.edu.ar (R. Rojas).

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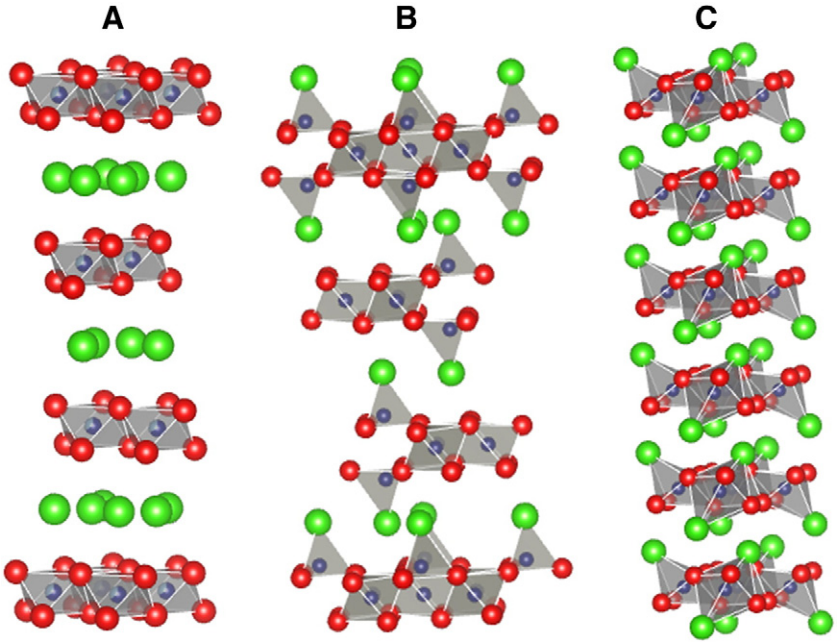

Fig. 1. Structure of LDH (A) and Zn–LHS (B and C) matrixes. Chloride was chosen as interlayer anion while water molecules were excluded from the scheme.

negatively charged particles (Rojas and Giacomelli, 2013). Finally, their dissolution behavior is different, as can be expected from the solubility of the hydroxides of the metal ions that constitute their layers (Parello et al., 2010; Rojas, 2014).

LDHs are extensively studied for pharmaceutical applications: hydrotalcite can be found in commercial antacid formulations such as Almax© and Talcid©, and they have also been proposed for the controlled release of anionic drugs due to their ease of preparation, high drug loading, release mechanism, and drug protection ability. LDHs have been intercalated with anti-inflammatory, antibiotics, antihypertensives, anticarcinogens, among others (Costantino et al., 2008; Choy et al., 2011; Rives et al., 2013, 2014; Rodrigues et al., 2013). Among these drugs, non steroidal anti-inflammatory drugs (NSAIDs) have been the most widely studied. Thus, large loadings of ibuprofen (Ibu), naproxen (Nap) or ketoprofen (Ket) have been incorporated to these solids using coprecipitation, anion exchange and reconstruction methods (Rives et al., 2013; Rojas et al., 2014). The drug content is completely released at either acid or neutral pH by matrix dissolution or anion exchange, respectively (Rojas et al., 2012) at a release rate that depends on factors such as particle size (Gunawan and Xu, 2008) and the solubility and hydrophobic character of the intercalated drug (Rojas et al., 2014). LHSS have also been intercalated with vitamins, antioxidants and NSAIDs, which are released by mechanisms similar to those of LDHs (Bull et al., 2011; Taj et al., 2013). Thus, LHSs have been intercalated with the conjugated bases of diclofenac, ibuprofen, mefenamic acid and 4-biphenylacetic acid, and formulated as tablets and enteric-coated beads (Bull et al., 2011; Richardson-Chong et al., 2012; Taj et al., 2013) in order to prevent matrix dissolution in acid media and produce modified release profiles.

Nevertheless, few comparative studies of these structurally related solids as well as their drug release behavior from LDH-drug (LDH-D) and LHS-drug (LHS-D) hybrids have been published (Yang et al., 2007). In order to explore the differences between these solids as well as the effect of the physicochemical properties of the drug, LDHs and LHSs intercalated with three NSAIDs (ibuprofen, naproxen and ketoprofen, Fig. 2) were obtained. The structure and interaction modes between the drugs and the layered matrix were determined by chemical analysis, powder X-ray diffraction (PXRD), Fourier transform infrared (FTIR) and solid state nuclear magnetic resonance (NMR) and the interfacial properties (potential zeta and hydrophilic/hydrophobic character) of the hybrids, as well as the drug release profiles were comparatively studied.

2. Materials and methods

Ibu, Ket and Nap anhydrous acids (≥98% purity, Parapharm®, Buenos Aires, Argentina), $MgCl_2 \cdot 6H_2O$ (Baker), $AlCl_3 \cdot 6H_2O$ (Anedra), $ZnCl_2$ (Cicarelli), NaOH (Baker), NH_4OH (Merck) and deionized water

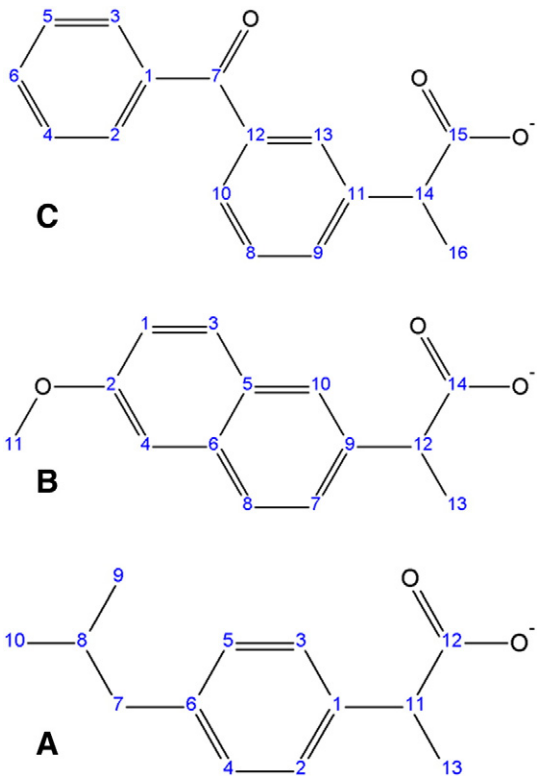

Fig. 2. Structural formulae of the intercalated drugs: A) ibuprofen, B) naproxen, C) ketoprofen.