



Review article

Intercalation of drugs in layered double hydroxides and their controlled release: A review

Vicente Rives*, Margarita del Arco, Cristina Martín

GIR-QUESCAT, Departamento de Química Inorgánica, Universidad de Salamanca, 37008 Salamanca, Spain

ARTICLE INFO

Article history:

Received 16 August 2013

Received in revised form 28 November 2013

Accepted 2 December 2013

Available online 28 December 2013

Keywords:

Layered double hydroxide

Drug intercalation

Controlled delivery

Organic–inorganic intercalation compounds

Hydrotalcite

ABSTRACT

The intercalation of different drugs in layered double hydroxides with the hydrotalcite-like structure is reviewed. The intercalation processes are carried out following different routes (direct synthesis, coprecipitation, anion exchange) and the advantages and disadvantages of these methods are described for the specific drug/LDH system studied. Characterisation of the intercalation compounds is also studied, to determine the way the guest molecules are intercalated between the layers of the layered double hydroxide. The controlled release (in some cases also the kinetics analysis) is also studied. We conclude that layered double hydroxides are very suitable materials to host different families of drugs and in the controlled release they show beneficial properties, on comparing with the effect of the bulk drug. It should be also stressed that these are almost the unique materials (in addition to layered hydroxy salts) able to host drugs in the anionic form, so nicely completing the studies carried out so far on the suitability of cationic clays to host cationic or neutral drugs.

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1. Introduction

Among the few families of layered compounds with positively charge layers, the so-called layered double hydroxides (LDHs), also known very often as hydrotalcite-like systems, have deserved a lot of attention. Hydrotalcite is a natural occurring hydroxycarbonate of Mg and Al discovered in Sweden in 1842. The structure of hydrotalcite is similar to that of brucite, $\text{Mg}(\text{OH})_2$, an hexagonal close packing of hydroxyl groups, where magnesium cations fill all octahedral holes every two layers. Isomorphous, partial, Mg/Al substitution gives rise to development of a positive charge in the layers, which is balanced by hydrated carbonate anions located in the interlayers which originally were empty in brucite. A scheme is depicted in Fig. 1. The brucite-like layers can be stacked in different ways leading to different structures (Drits and Bookin, 2001; Evans and Slade, 2006), the most common ones being rhombohedral (3R symmetry) and hexagonal (2H symmetry). Probably, one proof of the increasing interest in these solids can be the continuous publication of reviews and monographs on their preparation, characterisation, properties and applications (Costantino et al., 2013; Duan and Evans, 2006; Forano et al., 2013; Rives, 2001; Wypych and Satyanarayana, 2004; Zumreoglu-Karan and Ay, 2012).

The cations in the layers can be substituted by many others, such as Zn, Co, Ni, Mn, Fe (divalents), and Cr, Co, Fe, V, Y, Mn, Ga, lanthanides (trivalents) and also the interlayer anion can be substituted by a great variety of simple or complex anions, e.g., simple inorganic anions (Constantino and Pinnavaia, 1995), organic anions (Jaubertie et al.,

2006; Newman and Jones, 1998; San Román et al., 2006), coordination compounds (Bhattacharjee and Anderson, 2006; Del Arco et al., 2003; Rives and Ulibarri, 1999), polyoxometalates (Carriazo et al., 2006a,b; Del Arco et al., 2004a,b; Hu and Li, 2004; Rives and Ulibarri, 1999), biomolecules or even DNA (Choy et al., 1999, 2001; Desigaux et al., 2006), etc.

Concerning the layer cations, their ionic radii are always close to that of Mg^{2+} (0.72 Å), except that of Al^{3+} (0.50 Å), as distortions arise for larger cations. Regarding the anions, their size/charge ratio is important, as large anions with low charge are unable to balance homogeneously the positive charge of the layers. A compromise should be reached between the layer charge density and the dimensions of guests species in the interlayer. For non-spherical anions, and very specially when the anions contain long chains (e.g., carboxylates or sulfonates with long alkyl chains), several arrangements in the interlayer are possible, namely, a monolayer parallel to the layers, a parallel bilayer or tilted monolayers or bilayers.

This versatility in the chemical composition leads to many and different potential applications. The current interest in LDHs is founded on several properties: They are *basic materials* and the mixed oxides formed upon thermal decomposition show even a larger basicity, related to the oxide anions; intercalation of acidic anions provides systems with unique acid–base properties. They show the so-called *memory effect* (Chibwe and Jones, 1989; Kwon and Pinnavaia, 1989), i.e., the ability to recover their original layered structure when mixed oxides (previously prepared by calcination of some LDHs at moderate temperatures) are put in contact with solutions containing anions. They also show *anion exchange capacity* (AEC), usually larger than that shown by cationic clays, ranging between 2 and 4 meq/g.

* Corresponding author. Tel.: +34 923 294489; fax: +34 923 294574.
E-mail address: vrives@usal.es (V. Rives).

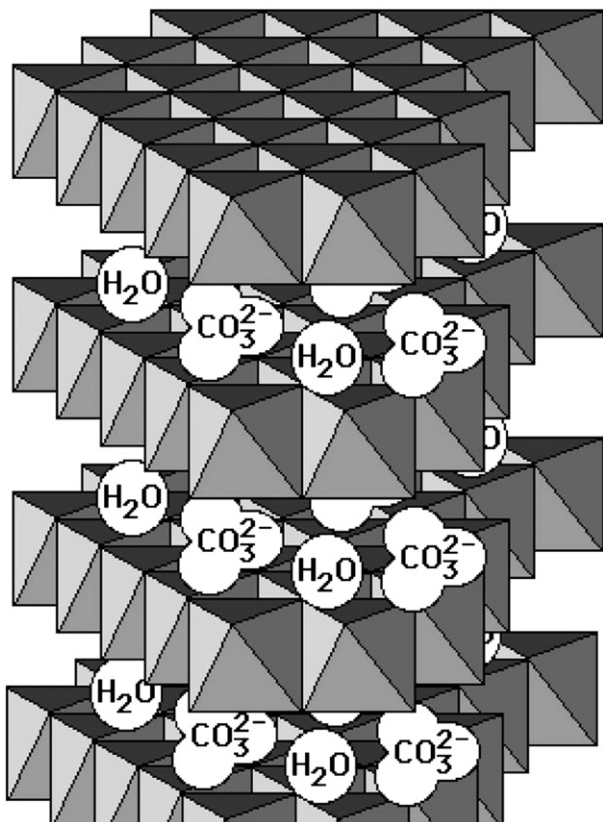


Fig. 1. Idealised structure of a layered double hydroxide, with interlayer carbonate anions. Reprinted from Coordination Chemistry Reviews, Vol. 181. Vicente Rives and Maria Angeles Ulibarri, Layered double hydroxides (LDH) intercalated with metal coordination compounds and oxometalates, pp. 61–120. Copyright (1999), with permission from Elsevier.

Among the many ways proposed to prepare these solids (De Roy et al., 2001; Forano et al., 2013; He et al., 2006; Kanazaki, 2004), the main routes most frequently followed are:

- *Coprecipitation*, consisting of the slow addition of a solution of the metal cations into a reactor containing the anion to be intercalated; increasing the pH by addition of a base or urea hydrolysis that leads to precipitation of the LDH.
- *Anionic exchange* of anions originally existing in the interlayer of a LDH prepared usually by coprecipitation. Chloride or nitrate is preferred as the original anions, as the exchange is easier than for multicharged anions. The reaction is usually carried out by stirring the LDH precursor in a solution containing an excess of the anion to be intercalated; application of ultrasounds speeds up the exchange process (Kooli et al., 1997).
- The *reconstruction* method is based on the memory effect (Chibwe and Jones, 1989; Kwon and Pinnavaia, 1989) shown by the product formed upon mild calcination (ca. 500 °C under dynamic inert gas atmosphere (Del Arco et al., 1994; Rocha et al., 1999)) of a LDH (usually in the nitrate or carbonate form), i.e., the ability to recover a layered structure when the mixed oxide is immersed in a solution of the anions to be intercalated.
- *Hydrothermal* and *microwave* treatments are often applied to improve the crystallinity and other properties of the LDHs (Benito et al., 2006a,b,c, 2008a,b, 2009; Herrero et al., 2007a,b, 2009).

Layered double hydroxides or the homogeneously dispersed mixed oxides formed upon their calcination find applications in different fields:

- Water decontamination; based on the large AEC, hydrotalcites can be used to adsorb polluting anions from aqueous solutions, while the

mixed oxides formed upon calcination can be used to scavenge anions from solutions on recovering the layered structure (Forano, 2004; Goh et al., 2008; Ulibarri and Hermosín, 2001). The intercalation of sodium alginate in ZnAl and MgAl LDHs gave rise to an increase in the adsorption capacity of the intercalated systems – above those shown by alginate or the clay used individually – for water treatment, such as removal of fluorine ions or Orange II dye (Mandal et al., 2012).

- Materials science mainly as additives to organic polymers; the composite formed exhibits enhanced mechanical properties, mainly related to the aspect ratio of the lamellar particles of the hydrotalcite (Kaluskova et al., 2004; Leroux and Besse, 2004; Wang and Zhang, 2004); they also act as flame retardants (Chen and Qu, 2003; Pereira et al., 2009) and possess barrier effects (Sorrentino et al., 2005).
- Catalysis. Original LDHs exhibit strong basic properties and can be used as heterogeneous catalysts, to avoid environmental problems when using soluble basic catalysts (Jinesh et al., 2010; Rives et al., 2003). They can be also used as catalyst supports or catalyst precursors. Several reviews have reported on the catalytic properties of different families of LDHs (Albertazzi et al., 2004; Basile and Vaccari, 2001; Cavani et al., 1991; Centi and Perathoner, 2008; Costantino et al., 2013; Figueras, 2004; Monzón et al., 2001; Rives et al., 2010; Seis et al., 2001; Tichit and Coq, 2003).
- Medicine. Biologically-active molecules are also among the different sorts of molecules which can be intercalated between the brucite-like layers of LDHs, a property which has opened their applications in Medicine and Pharmacy. One of the first reviews on this subject was published in 2001 by Costantino and Nocchetti (2001), which has been followed by the works by Xu and Lu (2006), Choy et al. (2007), Ladewig et al. (2009), Jakubiková and Kovanda (2010), Chakraborty et al. (2010a,b), Cunha et al. (2010), Wang and O'Hare (2012) and Costantino et al. (2009, 2013).

The applicability of LDHs in this field is based mainly on three properties: increased solubility of the drug, basicity of the LDH matrix, and ability for drug controlled release. The addition of LDHs usually improves the solubility of the drugs (Perioli and Pagano, 2012; Perioli et al., 2013) without modifying their chemical structure and thus their pharmacological activity. On the other hand, the intrinsic basicity of the LDH structure provides these materials with antacid properties (Parashar et al., 2012.), which are dependent on the route followed to prepare the Mg,Al hydrotalcite. Finally, it is generally observed that on suspending a drug-LDH intercalation compound in aqueous solutions, release of the drug follows a two step process. First a rapid release, and secondly a maintained, slow release, usually related to anionic exchange with anions of the medium.

In this scenario, our aim in this work has been to provide a broad description of the interactions between several drugs and layered double hydroxides. We have excluded the interaction of LDHs with non-steroidal antiinflammatory drugs, which has been recently reviewed elsewhere (Rives et al., 2013). Our work summarises the information published roughly from 2000 and we have organised the work attending to the pharmacological properties shown by the different drugs. We have given priority importance to the preparation procedures, as many of the papers reviewed have undoubtedly demonstrated that the ability for drug insertion and the release process is dependent on the preparation method followed, probably because of the different physicochemical properties (particle size, crystallinity, etc.) shown by the same compound, when prepared following different routes. Where available, data on the release of the drug are also included.

2. Antibiotics

Encapsulation of penicillin in an inorganic host and the use of such encapsulation composites as sustained-release medications have been scarcely studied in the literature. Li et al. (2006) have reported the intercalation of phenoxymethylpenicillin (PMP), a member of the penicillin

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