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Review

Layered double hydroxides as drug carriers and for controlled release of non-steroidal antiinflammatory drugs (NSAIDs): A review

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ABSTRACT

Non-steroidal anti-inflammatory drugs constitute one of the groups most widely currently used, but show several problems for administration due to low solubility and delivery control. For this reason, several matrices have been tested to support them in order to overcome these drawbacks. Among them, layered double hydroxides have been used in recent years. The aim of this review is to update the current knowledge and findings on this hybrid system, namely, layered double hydroxides intercalated with different NSAIDs. The basic nature of the matrix introduces an additional advantage, i.e., to decrease ulceration damages. We have focused our review mostly on the preparation procedures, as these control, define and determine the performance of the systems *in vitro* and also in living organisms.

Contents

1. Introduction

Layered double hydroxides (LDHs) constitute a broad family of lamellar solids which in the last decades have deserved an increasing interest because of their applications in different fields [1,2]. They are sometimes named as *anionic clays* due to the similarities shared with cationic clays, or *hydrotalcite-like* materials, as derived from the natural hydroxycarbonate of Mg and Al discovered in Sweden in 1842. Their properties have been reviewed in recent years in different books and monographs [2–4].

Their structure is similar to that of brucite, $Mg(OH)_2$, where hydroxyl anions are hexagonally close packed and magnesium cations are filling all octahedral sites every two layers; consequently, edge-sharing octahedra of magnesium cations are surrounded by six hydroxyl groups forming infinite sheets; these layers are stacked on top of each other and held together by weak hydrogen bonds. Some of the cations can be isomorphically substituted by others with similar size, but with higher valence, developing a positive charge in the sheets. Charge balance is recovered by intercalating anions between the layers, Fig. 1, where water molecules also exist. The brucite-like layers can be stacked in different ways, leading to different structures [5], the most typical ones being rhombohedral (3R symmetry) and hexagonal (2H symmetry).

Divalent/divalent isomorphical substitution is also possible, as well as the trivalent/trivalent one; the most commonly found cations in the layers are Mg^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} or Mn^{2+}, and Al^{3+}, Cr^{3+}, Co^{3+}, Fe^{3+}, V^{3+}, Y^{3+} or Mn^{3+}. With the exception of Al^{3+} (0.50 Å), all these elements have similar ionic radii as that of Mg^{2+} (0.86 Å) thus accounting for the isomorphic substitution without a substantial distortion of the structure. Other LDHs containing monovalent and tetravalent metal cations have been also synthetised [6–9], as well as systems containing three or even four different metal cations [10–17].

There are no strict limitations to the nature of the interlayer anions, and systems with many different anionic species are known: simple

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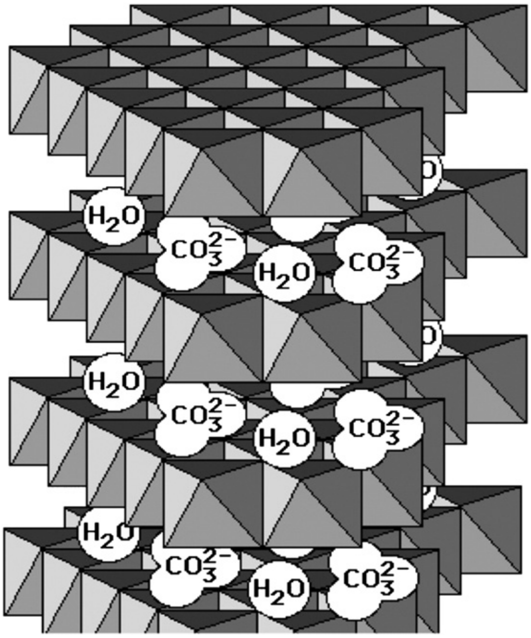

Fig. 1. Idealised structure of a layered double hydroxide, with interlayer carbonate anions.
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inorganic anions (carbonate, nitrate, halides, etc.) [18], organic anions (terephthalate, acrylate, lactate, etc.) [19–21], coordination compounds [22,23], polyoxometalates [24–28], biomolecules such as nucleoside monophosphates (AMP, CMP, GMP or ATP) or even DNA fragments [29–31] have been successfully intercalated.

The only restriction concerning the nature of the anions to be intercalated makes reference to their size/charge ratio, as large anions with low charge are unable to balance properly (homogeneously) the positive charge in the layers. Kwon and Pinnavaia [32] claimed that polyoxometalates (POMs) with the Keggin structure with a charge less than −4 are unable to be intercalated between brucite-like layers with a M^{2+}/M^{3+} molar ratio close to 2, since these molecules are not spatially able to balance the host layer charge.

The M^{2+}/M^{3+} molar ratio usually ranges between 2 and 4, both in all natural occurring LDHs and in most of the synthetic ones. The synthesis of these sorts of solids with molar ratios outside this range has been sometimes claimed [33], although it is difficult to know the accurate layer composition, since for such extreme ratios formation of dispersed amorphous oxides cannot be discarded.

These materials have deserved a great interest in recent decades in different fields because of their specific properties, namely:

- *Acid–base properties*. LDH solids are basic materials with surface basic hydroxyl groups; the basicity of carbonate-intercalated LDHs has been related to the electronegativity of the layer cations [34,35]. The mixed oxides formed upon thermal decomposition of LDHs are more basic than the original LDHs, due to the presence of strong oxide basic sites. Moreover, the intercalation of different species can give rise to the development of acid sites providing systems with unique acid–base properties.
- *Homogeneous mixtures* containing well dispersed elements in layer and interlayer domains in a wide range of composition and ratios can be prepared, allowing to tailor the properties of these solids.
- The so-called *memory effect* [32,36], i.e., the ability to recover their original layered structure when mixed oxides, previously obtained upon calcination of some LDHs at moderate temperatures (usually not exceeding 500 °C) are put in contact with solutions containing anions.
- A good *anion exchange* capacity (AEC), associated to the non-divalent layer cation, usually higher than that shown by cationic clays, and ranging between 2 and 4 mEq/g.

Many different synthetic procedures to prepare LDHs have been described in the literature [37–39]. Selection of one or another greatly depends on the specific material to be prepared. The most widely used are the following:

- *Coprecipitation*, consists of the slow addition of a solution containing salts of the metal cations in the required molar ratio into a reactor containing water; simultaneous addition of an alkaline solution keeps the pH within a selected, narrow range, to precipitate the mixed hydroxide.
- *Anionic exchange* is largely applied to obtain LDHs intercalated with anions of different nature. Strictly speaking this is not a proper synthesis method, but a post-synthesis modification, since it is necessary to have a LDH precursor, usually a carbonate-free LDH. The feasibility of exchanging the anions in LDHs depends on the electrostatic interactions between the layers and the interlayer anions. The equilibrium constants increase as the ionic radius of the anion decreases. The rate-determining step is the diffusion of the in-going anions within the interlayer. Exchange reactions are usually carried out by stirring the LDH precursor in a solution containing an excess of the anion to be intercalated; ultrasounds have been also applied to speed up the exchange process [40].
- The *reconstruction* method is based on the above mentioned *memory effect* [32,36]. First a LDH with the desired metal cations in the brucite-like layer, commonly intercalated with carbonate (which is released as CO_2) is first prepared. Then the solid is calcined at or just below 500 °C (preferable under dynamic inert gas atmosphere to remove CO_2) [41,42]. Finally, the mixed oxide formed is stirred in an aqueous solution of the anions to be intercalated, usually in a concentration several times higher than that required for a stoichiometric reaction.
- *Hydrothermal* and *microwave* treatments have been applied to process LDHs, improving the crystallinity and other properties of the LDHs, especially upon microwave treatment [43–51].

The fields of applications of LDHs are very broad. Only a few of them will be outlined below.

- *Materials Science*. LDHs are used as additives in polyvinyl chloride polymer (PVC), as they improve its strength and retard darkening of the polymer [52,53]. LDHs enhance the mechanical properties of polymer matrices and may provide them with other properties such as colour [54], flame retardant [55,56] or barrier effect [57], and others [58,59]. Hydrotalcite-type materials have been used as electrode surface modifiers. They are more stable under high temperature and oxidizing conditions than organic polymers [60,61].
- *Water decontamination*. The large AEC together with the memory effect exhibited by hydrotalcite-type solids, make them good adsorbents for the removal of harmful species in anionic form; hydrotalcites and their calcined products can be used at pH values close to those at which pollutants are usually found in the environment [62]. Layered double hydroxides were proposed as adsorbents for the capture of inorganic anions such as arsenate, chromate or phosphate from waste water [63–65], and in recent years their use has been extended also for removal of organic toxic species, such as phenolic compounds, pesticides or even nuclear residues. This issue has been recently reviewed [66].
- *Separation processes*. O'Hare and Lotsch [67] have reported the use of these materials for separation or purification of isomeric compounds, due to the differences of affinity shown by the isomers for the LDH. The intercalated isomer can be recovered by treatment