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New hybrid nanostructures based on oxacillin–hydrotalcite-like anionic clays and their textural properties

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Abstract

New hybrid nanostructures based on inorganic matrices of hydrotalcite-like anionic clays (HT) incorporated with oxacillin are obtained by using calcinations-restructure method. XRD and TEM analyses are used to study the structural and textural characteristics of the clay containing hybrids. When nanoparticles of iron oxides are loaded on the layered anionic clay matrix a more effective delivery system of the drug is obtained. The results can be used to reduce the toxic side effects of oxacillin (e.g. upset stomach, diarrhea, cholestastic hepatitis), its aggregation process in aqueous solutions and also can open new perspectives for targeted the drug delivery.

Keywords: Oxacillin; Layered double hydroxides; Hydrotalcite; Drug delivery; TEM

1. Introduction

The biohybrid materials, formed by host inorganic matrices and drug guests, have attracted considerable attention nowadays (Choy et al., 2007; Tammaro et al., 2007). The inorganic matrix is able to act as a deliver carrier, to provide a controlled/targeted delivery of the drug or to improve the drug long-term stability and storage by isolating it from an unfriendly environment (Tronto et al., 2004; Carja et al., 2007a, b, c). Among a variety of inorganic materials layered double hydroxides (LDHs) or hydrotalcite (HT)-like anionic clays are endowed with great potential as a biocompatible layered matrix for this purpose. Represented by the general formula $[M^{II}_{1-x}M^{III}_{x}(OH_2)]^{x+}[A^{m-x/m} \cdot nH_2O]^{x-}$, LDHs, are porous materials whose structure is built by positively charged brucite-like layers and interlamellar exchangeable anions A^{m-} located, as water molecules, in the interlayer space (Cavani et al., 1991). Their textural characteristics can be designed to control not only the shape, size and distribution of the anionic clay particles but also the features of particles organisation and interconnection patterns (Okamoto et al., 2007; Carja et al., 2007a, b, c). Further, recently reported results show the possibility to develop a targeted drug delivery by using LDHs matrices with magnetic properties (Trujillano et al., 2006; Carja et al., 2007a, b, c). Oxacillin sodium (5 methyl-3 phenyl-4-isoxazolyl penicillin sodium) is a beta-lactam antibiotic in the penicillin class widely used in the treatment of infections such as osteomyelitis and septicemia. The toxic side effects of oxacillin (e.g. cholestatic hepatitis, upset stomach, diarrhea, acute interstitial nephritis), its aggregation process in aqueous solution and the low stability are some no desirable characteristics of the drug therapy (Homaidhi et al., 2002). The use of hydrotalcite-like anionic clay as a host matrix for oxacillin is an attempt to obtain a novel therapeutic delivery system able to overcome the drug problems. Using this information, to our knowledge for the first time, we report the synthesis and characterization of oxacillin–hydrotalcite-like anionic clays. The textural properties of the obtained hybrids are studied by TEM. The drug release profile when the clay matrix is loaded with nanoparticles of iron oxides will be also discussed.

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2. Methods and materials

2.1. Characterization of the samples

Powder X-ray diffraction (XRD) patterns were recorded using a Philips PW 1840 diffractometer under the following conditions: 40 kV, 30 mA, monochromatic Cu Kα radiation ($\lambda = 0.15418$ nm) over a 2θ range from 2° to 70°. TEM analysis was performed on a Hitachi instrument operating at 200 kV. The samples were prepared by dispersing them in ethanol. The release behavior of the encapsulated oxacillin from the hybrid samples was profiled in a dilute solution of sodium chloride, which is very similar to the body fluid conditions. 0.5 g of the Ox–LDH or the Ox–FeOx/LDH samples were dispersed in a mixed solution containing 500 ml of 0.1% NaCl aqueous solution and 70 ml of ethanol and stirred at 35 °C with a rate of 100 rpm. The procedure for quantitative determination of oxacillin was based on the capacity of penicillin to transform on heating in penicillenic acids having specific adsorption in the UV-spectrum region (Korobkin and Korchagin, 1978). The amount of the released antibiotic was determined periodically by a Jasco UV–vis spectrophotometer, periodically monitoring the optical density of the solution at a wave length of 335 nm by using the optimal conditions previously reported in (Korobkin and Korchagin, 1978) The amount of immobilized oxacillin was determined from the concentration change of penicillenic acid of oxacillin in solution before and after immobilization by measuring the absorbance at 335 nm. The immobilized drug was calculated by interpolation from a standard curve.

2.2. Preparation of the samples

The inorganic host matrix was synthesized by using the direct coprecipitation method following the procedure by Reichle et al. (1986). The FeOx/LDH sample was obtained by using a similar procedure to that we previously reported (Carja et al., 2007a, b, c), while for obtain the oxacillin–clay formulations the calcination-restructure method based on the clay ''memory effect'' was used (Cavani et al., 1991). More precisely:

- LDH: $Mg(NO_3)_2{\cdot}6H_2O/Al(NO_3)_3{\cdot}9H_2O$ (molar ratio 2/1) and an aqueous solution (1 M) of $NaOH/Na_2CO_3$ were added dropwise together, in such a way that the pH of the synthesis medium remained at a constant value of 9.5. The resulting white precipitate was aged at 45 °C, for 24 h under stirring. The sample, denoted as LDH, was calcined in air, at 550 °C for 12 h with a heating rate of 7 K min^{-1}.
- Ox/LDH: 1 g of ''freshly'' calcined LDH was added to an ethanol–aqueous solutions (1/2, vol.%) of oxacillin sodium (Fluka regent) at a constant pH of 7.7, under nitrogen atmosphere and vigorous stirring (calcination and restructure of LDH); the volumes of the drug solution was calculated such that the drug concentration has exceeded two times the exchange capacity of the clay. The obtained sample was aged at 40 °C for 1 h and denoted Ox/LDH.
- Ox–FeOx/LDH: 1 g of ''freshly'' calcined LDH was added to 250 ml of aqueous solution (0.5 M) of $FeSO_4$ under vigorous stirring and nitrogen atmosphere; after an ageing step at room temperature this sample is denoted as FeOx/FeLDH. After its calcination at 450 °C, 10 h the same experimental procedure described for Ox/LDH is used as next step; the final sample is denoted as Ox–FeOx/LDH.

3. Discussion

Fig. 1(a) illustrates the XRD patterns of the studied samples. All the diffraction peaks are typical of the layered double hydroxides structure (Cavani et al., 1991) with sharp and symmetric reflections of the basal (0 0 3), (0 0 6), and (0 0 9) planes and broad, less intense and asymmetric reflections for the nonbasal (0 1 2), (0 1 5) and (0 1 8) planes. For FeOx/LDH and Ox–FeOx/LDH the two reflections of (1 1 0) and (1 1 3) around 60° cannot be clearly distinguished pointing out that, in this case, the disorder of the layered structure increases. The XRD features of LDH and FeOx/LDH, with a first recorded peak around 11 Å, are characteristic for a nonintercalated hydrotalcite-layered structure. For Ox–FeOx/LDH the splitting of (0 0 3) plane is appeared and the first peak is shifted around 8.9 Å pointing out to a partial expanded structure of the layered clay. This result may indicate a partial intercalation of the drug between the LDH layers. Assuming a 3R polytypism for the hydrotalcite and from the positions of the XRD peaks the lattice parameters a and c can be calculated. The refined cell parameter a is a function of the metal–metal distance within the layers pointing out the cations stacking in the 0 0 3 planes while the c parameter is related to the distance from the centre of one layer to the centre of another (Cavani et al., 1991). For all the samples the parameter a has almost the same value equal to 3.06 Å; this result is due the unaltered layer composition of the host clay. The calculated interlayer free spacing (IFS = $d_{003} - 4.8$ Å, Cavani et al., 1991) increases from 2.89 Å for LDH to 2.91 Å for FeOx/LDH and reaches 8.72 Å for Ox–FeOx/LDH indicating a hybrid formulation in which the layers of the LDH are expanded by the organic guest. TEM analysis is

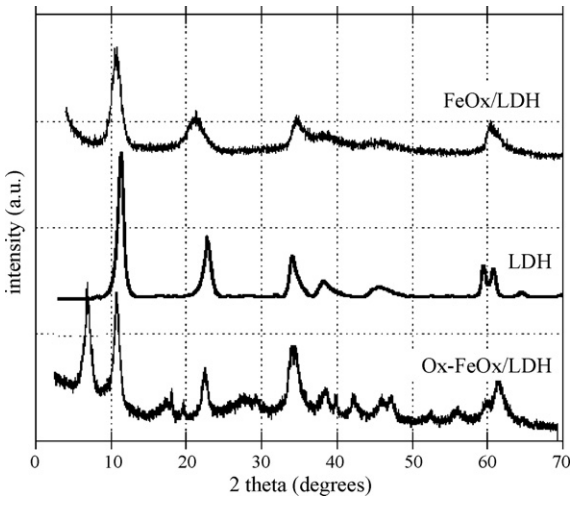

Fig. 1. XRD patterns of the studied hybrid samples.