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# Improving the Carprofen Solubility: Synthesis of the $Zn_2Al$-LDH Hybrid Compound

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ABSTRACT

The development of efficient strategies for drug delivery is considerably desired. Indeed, often several issues such as the drug solubility, the control of the drug release rate, the targeted delivery of drugs, the drug bioavailability, and the minimization of secondary effects still present great obstacles. Different methodologies have been proposed, but the use of nano-hybrids compounds that combine organic and inorganic substances seems particularly promising. An interesting inorganic host is the layered double hydroxide (LDH) with a sheets structure and formula $[M^{2+}_{1-x}\ M^{3+}_{x}\ (OH)_2](A^{n-})_{x/n}\ yH_2O$ ($M^{2+}$ = Zn, Mg; $M^{3+}$ = Al; $A^{n-}$ = nitrates, carbonates, chlorides). The possibility to exchange these counterions with drug molecules makes these systems ideal candidates for the drug delivery. In this article, we synthesize by co-precipitation method the hybrid compound Carprofen-$Zn_2$Al-LDH. Carprofen, a poorly soluble anti-inflammatory drug, could also benefit of the association with a natural antacid such as LDH, to reduce the gastric irritation after its administration. Through X-ray diffraction and Fourier-transformed infrared spectroscopy (FT-IR), we could verify the effective drug intercalation into LDH. The dissolution tests clearly demonstrate a significant improvement of the drug release rate when carprofen is in the form of hybrid compound.



## Introduction

In the pharmaceutical science, the design of effective strategies of drug delivery is a particularly desired issue.[1] In fact, more than one-third of currently available drugs are poorly soluble in body fluids. Therefore, it is particularly important to improve drug solubility and bioavailability, to control the drug release rate, the targeted delivery of drugs, and to minimize the secondary effects. The forefront methodologies make use of nanohybrids, substances that combine organic and inorganic materials and are now particularly appealing for nanomedicine.[2] They may offer many advantages, including drug release at a predetermined time, decrease of undesired fluctuation in the drug blood levels, less frequent drug administration, decreased adverse effects and enhanced therapeutic response. The layered double hydroxides (LDHs), also named hydrotalcites, are very promising inorganic hosts, whose structural features are well known in the literature.[3,4] They are a class of anionic clays derived from brucite, $Mg(OH)_2$, with 2-dimensional nano-sheets structure and chemical formula $[M^{2+}_{1-x}\ M^{3+}_{x}\ (OH)_2](A^{n-})_{x/n}\ yH_2O$. In general, $M^{2+}$ is a divalent cation such as Mg, Zn, or Cu, $M^{3+}$ is a trivalent cation such as Al, Cr, or Fe, and $A^{n-}$ is an anion such as $CO_3^{2-}$, $NO_3^-$, and $Cl^-$ that balances the positive fixed charges of hydrotalcite layers.[2,5] These counterions are located in the interlayer regions and can be exchanged with other inorganic, organic, and metallo-organic molecules but, interestingly, also with drugs. The drug intercalation does not destroy the layered structure, and the hybrid system maintains the original LDH properties. However, the exchange process could be especially hard, in particular when carbonate groups are involved. To this aim, different methodologies have been proposed, chiefly depending on the drug water affinity: simple ion exchange, reconstruction, coprecipitation, and secondary intercalation.[6-9] In the current pharmaceutical market, hydrotalcite is yet present in commercial antacid formulation (e.g., Talcid®), due to its natural basic behavior. In addition, at a research level, LDH has been also intercalated with antibiotics, antihypertensives, anticarcinogens, and anti-inflammatory.[6,10-14] In this regard, it is well known that the prolonged use

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of anti-inflammatories can produce important side effects, such as gastrointestinal lesions. So, the design of host-guest systems that combine the enhanced drug solubility and the reduction of gastric irritation is considered a new interesting approach.

Carprofen [(*RS*)-2-(6-chloro-9*H*-carbazol-2-yl) propanoic acid] is a nonsteroidal anti-inflammatory drug used in veterinary medicine in the treatment of patients with rheumatoid arthritis, osteoarthritis, and acute gouty arthritis. It exists into 2 polymorphic forms I and II in enantiotropic relationship.[15] Polymorph I is stable at room temperature, then it transforms on heating into polymorph II, which holds as a metastable form after cooling. In the pharmaceutical market, it is commercialized as pure API (e.g., Rimadyl®), but, since carprofen is essentially insoluble in water at 25°C, it could be interesting to try new formulation. In the literature, to this aim, its successful association in a co-crystal with 4,4′-dipyridyl was tried[16] as well as with hydroxypropyl-$\beta$-cyclodextrin.[17]

In this work, we report the synthesis of Carprofen intercalated into the $Zn_2Al$ LDH structure by using the co-precipitation method. The use of XRD and fourier-transformed infrared spectroscopy (FT-IR) allowed us to characterize the hybrid system and to demonstrate the effective drug intercalation between the hydrotalcite layers. The solubility of the new compound was determined at 20°C and the *in vitro* dissolution tests, performed in water and in phosphate buffer at pH = 4.5 (simulating fed state), at 37°C, were used as a proof of the effectiveness of the proposed strategy for the improvement of the drug solubility and dissolution rate. A reference commercial product (Rimadyl®) was tested in the same condition for comparison.

## Materials and Methods

### *Synthesis*

Carprofen was obtained from the Sigma-Aldrich Company (Milan, Italy).

The carprofen intercalation into the Zn/Al LDH has been obtained by using the co-precipitation method.[10] All the synthesis steps were performed at room temperature by using decarbonated water. First of all, 1.239 g of $Zn(NO_3)_2$ $6H_2O$ (Sigma-Aldrich) and 0.78 g of $Al(NO_3)_3$ $9H_2O$ (Sigma-Aldrich) were dissolved into 5 mL of water, in a molar ratio Zn:Al 2:1. Then, 1.14 g of carprofen (the same mol amount of Zn) was dissolved in a mixture of water and ethanol (3:2 ratio) under magnetic stirring and NaOH solution was added until pH = 9 was reached. The salts solution was slowly added to that of drug, paying attention to add at the same time soda to maintain the pH close to 9. The obtained suspension was vigorously stirred under nitrogen for 24 h at room temperature. The suspension was then centrifuged to collect the solid product that was washed many times with decarbonated water and finally was maintained in a dessicator ($P_2O_5$) until it was completely dried. This sample will be named LDH-C.

A sample of pure $Zn_2Al$ LDH was also prepared for comparison, by following the same procedure. The mixture of salts was added to 10 mL of decarbonated water and yielded to pH = 9 by NaOH addition. In the following, this sample will be named LDH.

### *Techniques*

X-ray powder diffraction (XRD) measurements were performed by using a Bruker D5005 diffractometer with the CuK$\alpha$ radiation, graphite monochromator, and scintillation detector. The patterns were collected in air with a step size of 0.03° and counting time of 2 s per step in the angular range 3-70°, by using a low background silicon sample holder.

Calorimetric measurements were carried out using a DSC Q2000 apparatus interfaced with a TA 5000 data station (TA Instruments, NewCastle, DE). The DSC instrument was calibrated using ultrapure (99.999%) indium (m.p. = 156.6°C; $\Delta H = 28.54$ J $g^{-1}$) as standard. The calorimetric measurements were conducted in open standard aluminum pans under nitrogen flow (45 mL/min) at 10°C $min^{-1}$ ($n = 6$ repetitions).

FT-IR spectra were obtained with a Nicolet FT-IR iS10 Spectrometer (Nicolet, Madison, WI) equipped with attenuated total reflectance sampling accessory (Smart iTR with ZnSe plate) by co-adding 256 scans in the 4000-400 $cm^{-1}$ range at 4 $cm^{-1}$ resolution.

LDH-C solubility was determined using the shake-flask method, at 20°C, in deionized water, the drug dissolved was measured after 4 h and after 24 h: an aliquot of the liquid was filtered (0.45 μm, Millipore), properly diluted and finally the carprofen concentration was determined by spectrophotometric detection at 300 nm (Lambda 25 UV; Perkin-Elmer, Monza, Italy).

For the tablets production, 8 mm in diameter and coded Tab20, LDH-C was mixed with the other excipients in a Turbula apparatus (Turbula T2A; Bachofen, Basel, Switzerland) for 10 min and then tableted using a single-punch machine (Korsh EK0; Berlin, Germany). The formulation is reported in Table 1.

The dissolution tests were performed using the USP Apparatus 2 (paddle, Erweka DT-D6; Erweka, Dusseldorf, Germany), at 100 rpm, the powder as such was poured in 1000 mL of deionized water (pH = 6.9), phosphate buffer pH = 4.5 (to simulate fed state), or HCl 0.1N water solution, pH = 1 (to simulate fasted state), at 37°C. The amount of drug released was determined by UV detection at 300 nm with a spectrophotometer equipped with an automated sampler (fitted with 0.45 μm Millipore filters) and connected to a PC for data processing (Winlab V6 software; Perkin-Elmer). Rimadyl® 20 mg (Zoetis Belgium NV, Louvain-La-Neuve, Belgium) was used as reference. The pure drug, LDH-C, Tab20, and the commercial tablets were tested in the same conditions, and all samples contain a drug dose of 20 mg of carprofen ($n = 6$ repetitions).

## Results and Discussion

### *DSC Analysis*

The calorimetric measurements could represent a first proof of the formation of a new chemical entity because of drug intercalation.

The DSC curves of pure drug, LDH, and the hybrid composite are shown in Figure 1. Carprofen shows only a sharp endothermic peak, due to the drug melting at 209.1°C and with an enthalpy change of $\Delta H = 112.8$ J/g.[15] The LDH curve shows a broad endothermic peak with an onset temperature of 129.5°C and an enthalpy change of $\Delta H = 177.5$ J/g. This peak can be attributed to an initial LDH dehydroxylation of the metal hydroxide layers.[18] In the LDH-C curve, a small endothermic event at about 90 °C, combined to mass changes measured by TGA is probably due to the loss of adsorbed surface water and structured water.[12,19] In addition, a stabilizing effect of the

**Table 1**
Tablets Formulation Tab20, Single Unit Composition

| | |
|---|---|
| LDH-C (Corresponding to 20 mg of Carprofen) | 65.9 mg |
| Microcrystalline cellulose NF, Avicel® (FMC, Philadelphia, PA) | 250.0 mg |
| Polyvinylpyrrolidone cross-linked, Polyplasdone® (GAF, New York, NY) | 30.0 mg |
| Talc (Carlo Erba, Milan, Italy) | 5.0 mg |
| Colloidal silicon dioxide, Syloid® 244 (Grace GmbH, Worms, Germany) | 1.0 mg |
| Magnesium stearate (Carlo Erba, Milan, Italy) | 1.0 mg |
| Total weight | 352.9 mg |