



## Intercalation Compounds of Hydrotalcite-like Anionic Clays With Anti-inflammatory Agents, II: Uptake of Diclofenac for a Controlled Release Formulation

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**ABSTRACT** The purpose of this study was to investigate whether hydrotalcite is able to intercalate diclofenac, a nonsteroidal anti-inflammatory drug, and release it in a controlled manner. Layered Mg-Al hydrotalcite in the chloride form was used as a host, and the intercalation compound was prepared by Cl<sup>-</sup>/diclofenac anionic exchange. Drug release from the intercalation compound was performed in vitro in simulated intestinal fluid at pH 7.5 according to USP 24 and in a pH 7.0 solution designed to mimic the ionic conditions of the small intestine. Results from the intercalation process show that hydrotalcite is able to intercalate diclofenac with a simple procedure and with a good drug loading (55% wt/wt). The in vitro drug release was remarkably lower than that from the corresponding physical mixture at both pH 7.5 and pH 7.0. In the latter case, the release was not complete at 24 hours. The kinetic analysis shows the importance of the diffusion through the particle in controlling the drug release rate. The obtained results show that hydrotalcite may be used to prepare modified release formulations.

### KEYWORDS:

**Introduction** Considerable research efforts have been focused on oral sustained- and controlled-release drug delivery systems [1]. Special attention has been given to finding a way to regulate the rate of drug release by means of monolithic devices where the drug is dispersed or included in an inert matrix [2,3]. A way to produce inclusion compounds with drugs is given by their intercalation in a lamellar host lattice. In a previous paper [4], we reported on our investigations of whether Mg-Al-hydrotalcite (HTlc), an inorganic and biocompatible anionic layered solid [5], could intercalate drugs and modify their release. Ibuprofen was chosen as a model drug. The promising results obtained prompted

us to extend these studies to other anti-inflammatory drugs; the aim of this work is to prepare the intercalation compound of diclofenac (DIK) in HTlc in order to modify the drug's release. DIK is a good candidate for this study because of both its short biological half-life [6] and the presence, in the molecular formula, of a carboxylic group that allows DIK's intercalation between the layers of hydrotalcite via anionic exchange (**Figure 1**).

The synthetic hydrotalcite used in the present study, prepared as described under Materials and Methods, has a composition of Mg<sub>0.67</sub>Al<sub>0.33</sub>(OH)<sub>2</sub>Cl<sub>0.33</sub> • 0.6H<sub>2</sub>O. The net positive charge arising from the isomorphous substitution of Mg<sup>2+</sup> by Al<sup>3+</sup> is compensated by exchangeable Cl<sup>-</sup> ions accommodated in the interlayer. The ion exchange capacity is 3.9 meq/g, and the interlayer distance 0.78 nm [7].

Since hydrotalcites are dissolved in strong acidic media and thus the drug is immediately released in the stomach, the intercalation compounds needed to be prepared as an enteric coating formulation. (While this work was in progress, a communication [8] appeared dealing with intercalation and deintercalation of diclofenac in a different layered double hydroxide [Li-Al-hydrotalcite].)

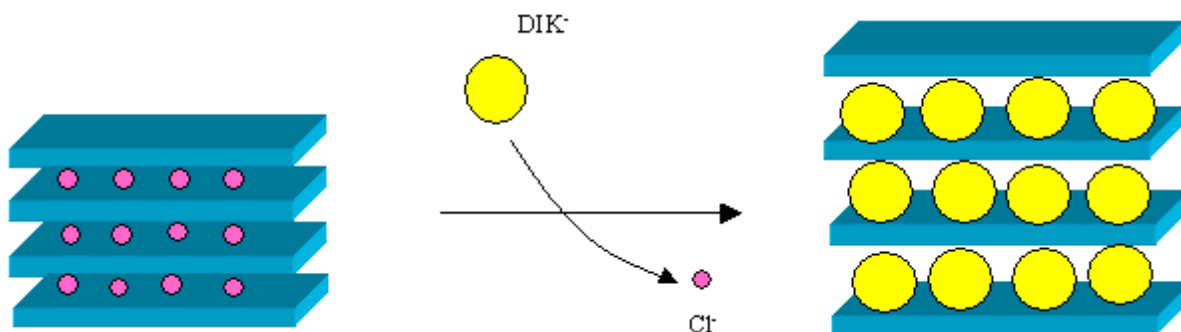
The purpose of this work is to investigate whether HTlc is able to intercalate DIK and to release it in a controlled way in order to obtain a formulation in which the release of the drug is prolonged with the aim of maintaining therapeutic activity, reducing toxic effects, and improving patient compliance. Another aim is to choose the best-fitting mathematical model of the drug release from this matrix from among those usually used in dissolution analysis.

### Materials and Methods Materials

Well-crystallized Mg<sub>0.67</sub>Al<sub>0.33</sub>(OH)<sub>2</sub>Cl<sub>0.33</sub> • 0.4H<sub>2</sub>O (after indicated HTlc-Cl) was obtained as described [9,10]. Diclofenac sodium salt (DIK Na) was purchased from Sigma Chemical Company (St Louis, MO). Other chemicals and solvents were of reagent grade and were used without further purification.

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**Figure 1.** Schematic representation of intercalation of  $\text{DIK}^-$  via anionic exchange.

### ***Intercalation of DIK into HTlc***

Intercalation reactions were performed by equilibrating 1 g of HTlc-Cl with 78 mL of a hydroalcoholic (50% vol/vol) solution  $10^{-1}\text{M}$  of DIK Na ( $\text{Cl}^-/\text{DIK}^-$  molar ratio 1:2), at  $60^\circ\text{C}$  for 3 days in an orbital incubator (Gallenkamp incubator type INR 2000, Leicestershire, UK). After cooling, the mixture was centrifuged with an ALC centrifuge (model 4236A, Milan, Italy) at 5000 rpm for 5 minutes and the residue was washed 3 times with degassed water and finally dried at room temperature.

### ***Analytical procedures and instrumentation***

The powder x-ray diffraction patterns (XRDP) were taken with a PW 1710 Philips diffractometer (Lelyweg, The Netherlands), using the Ni-filtered Cu  $\text{K}\alpha$  radiation.

C, H, and N elemental microanalyses were obtained on a Carlo Erba Elemental Analyzer (model 1106, Milan, Italy). A Stanton-Redcroft STA 780 thermoanalyzer at a heating rate of  $5^\circ\text{C min}^{-1}$  in air flow was used to determine the DIK content by detecting the weight loss of water and DIK as a function of increasing temperature.

DIK content was also determined with UV absorption at  $\lambda_{\text{max}} = 276 \text{ nm}$  (spectrophotometer Jasco-V-520, Tokyo, Japan) after dissolution of a known amount of HTlc-DIK in 6M HCl solution and successive dilution with phosphate buffer at pH 7.5.

Differential scanning calorimetry (DSC) analysis was performed using an automatic thermal analyzer (Mettler Toledo DSC821e, Novate Milanese, Italy). Temperature calibrations were performed with indium as a standard. Sealed and holed aluminum pans were used in the experiments for all the samples, and an empty pan prepared in the same way was used as a reference. Samples of 3 to 6 mg were weighted directly into the aluminum pans, and the thermal analyses were conducted at a scanning rate of  $10^\circ\text{C}/\text{min}$  from 20 to  $500^\circ\text{C}$ . Fourier Transformed-Infrared (FT-IR) spectra were recorded in KBr dispersion on a Jasco model FT/IR-410, 420 Herschel series (Jasco Corporation) using the EasiDiff Diffuse Reflectance Accessory.

### ***Preparation of physical mixture of HTlc-Cl and DIK Na***

A physical mixture was prepared by lightly triturating appropriate quantities of DIK Na (108 mg) corresponding to 100 mg of  $\text{DIK}^-$  and HTlc-Cl (79 mg) ( $\text{Cl}^-/\text{DIK}^-$  molar ratio 1:1) using a small mortar and pestle.

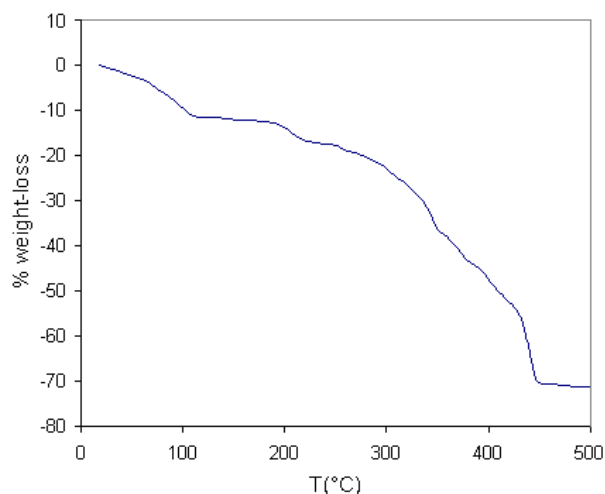
### ***Dissolution of DIK- from HTlc-DIK***

The drug release was performed in the dissolution apparatus USP XX paddle type (Steroglass, Perugia, Italy). The paddle rotation speed was 100 rpm, and the flasks were kept in a thermostatically controlled circulation water bath at  $37 \pm 0.5^\circ\text{C}$ . The dissolution media were the simulated intestinal fluid at  $\text{pH } 7.5 \pm 0.1$  without pancreatine according to USP 24 and a solution designed to mimic the ionic condition present in the small intestine [11] (20 mM disodium hydrogen phosphate, 80 mM sodium chloride, and 30 mM sodium carbonate,  $\text{pH } 7.0 \pm 0.1$ ). The dissolution studies were done by placing 182 mg of HTlc-DIK (containing 100 mg of  $\text{DIK}^-$ ) in 1000 mL of medium under sink conditions. Samples of 4 mL were withdrawn at predetermined intervals, followed by replenishment after each withdrawal with the same volume of fresh medium equilibrated at  $37 \pm 0.5^\circ\text{C}$ . Samples were appropriately filtered (13-mm filter UNIT 0.45 mm NY PP, Lida, Kenosha, WI), diluted when necessary, and analyzed by UV spectrophotometry at  $\lambda_{\text{max}} = 276 \text{ nm}$  after we had verified that  $\text{DIK}^-$  was recovered intact. The HTlc-DIK release was compared with that obtained from the physical mixture (HTlc-Cl/DIK Na). The tests were made in triplicate, and the results were recorded as an average.

## **RESULTS AND DISCUSSION**

### ***Preparation and characterization of the intercalate (HTlc-DIK)***

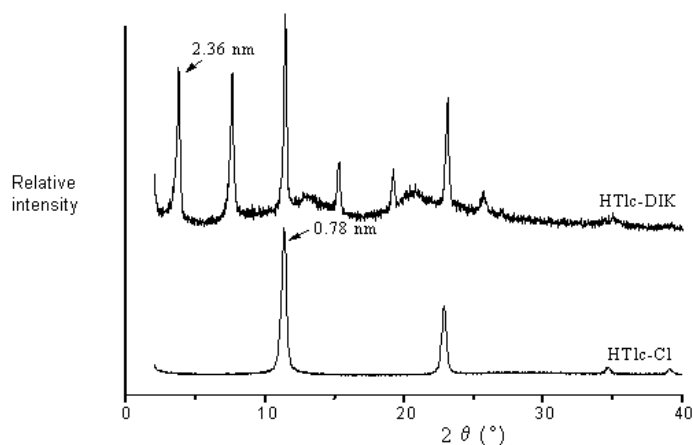
Preliminary experiments showed that this HTlc-Cl possesses a great affinity toward DIK anions since almost complete replacement of chloride by diclofenac anions can be simply obtained by equilibrating the solid



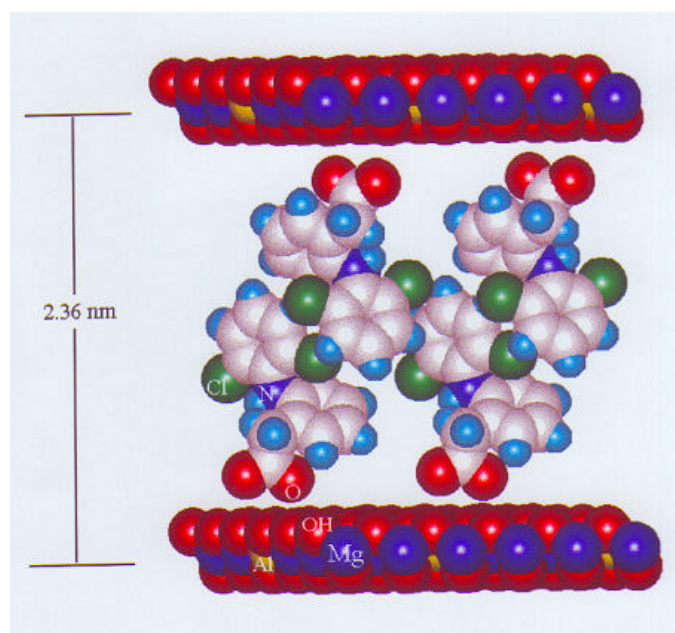
**Figure 2.** Weight-loss curve of HTlc-DIK as a function of temperature.

host with volumes of diluted DIK Na solutions ( $10^{-1}$  to  $10^{-3}$  M) that contain a slight excess of  $\text{DIK}^-$  in comparison with the amount of  $\text{Cl}^-$  ions in the HTlc. The conditions chosen and described under Materials and Methods ensure the complete exchange of  $\text{Cl}^-$  by  $\text{DIK}^-$ , as confirmed by the determination of the 2 anions in solution after equilibration. In every case, a full characterization of the intercalation compound was undertaken to obtain the empirical formula, thermal behavior, and structural information. **Figure 2** shows the weight-loss curve as a function of temperature. Three well-differentiated weight-loss steps are observed. The first step, from 25 to 120°C, can be attributed to the loss of cointercalated water. The second step occurs between 200 and 250°C and is probably associated with the thermal desorption of DIK anions taken up on the surface of the microcrystals. The thermal decomposition of intercalated DIK occurs at temperatures higher than 300°C and overlaps with the dehydroxylation of the HTlc. The XRDP of the sample heated at 1000°C reveal the presence of MgO and  $\text{MgAl}_2\text{O}_4$ . On the basis of these observations, the intercalation compound can be formulated as  $\text{Mg}_{0.67}\text{Al}_{0.33}(\text{OH})_2\text{DIK}_{0.33} \cdot 1.1\text{H}_2\text{O}$ . C, H, and N elemental analysis of the intercalation compound gave experimental data that agreed with those calculated on the basis of the above formula: H found was 4.23% (calculated 4.27%), C found was 31.12% (calculated 31.42%), and N found was 2.57% (calculated 2.62%). The drug loading was 55% — that is, 0.55 g of drug per gram of HTlc-DIK.

**Figure 3** shows the XRDP of the original hydrotalcite and of the intercalation compound. Because of the replacement of  $\text{Cl}^-$  by  $\text{DIK}^-$ , the interlayer distance increases from 0.78 nm to 2.36 nm. Since the thickness of the HTlc layer [12] is 0.48 nm, the gallery height is 1.88 nm (ie,  $2.36 - 0.48$ ). This value accounts for the presence in the interlayer region of a bilayer of DIK anions, partially interdigitated, with their principal axis almost perpendicular to the layer plane. **Figure 4** shows

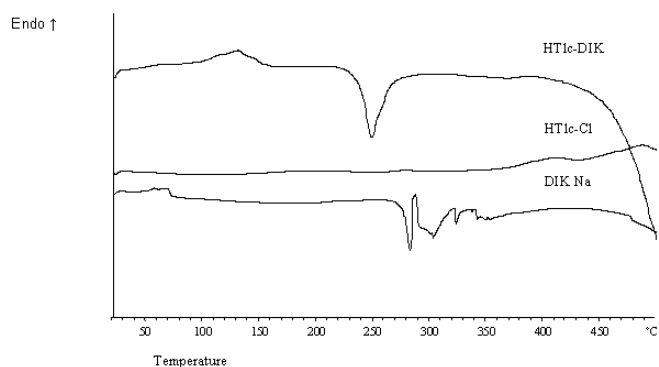


**Figure 3.** Comparison between XRDP of the original hydrotalcite and its intercalation compound with diclofenac.

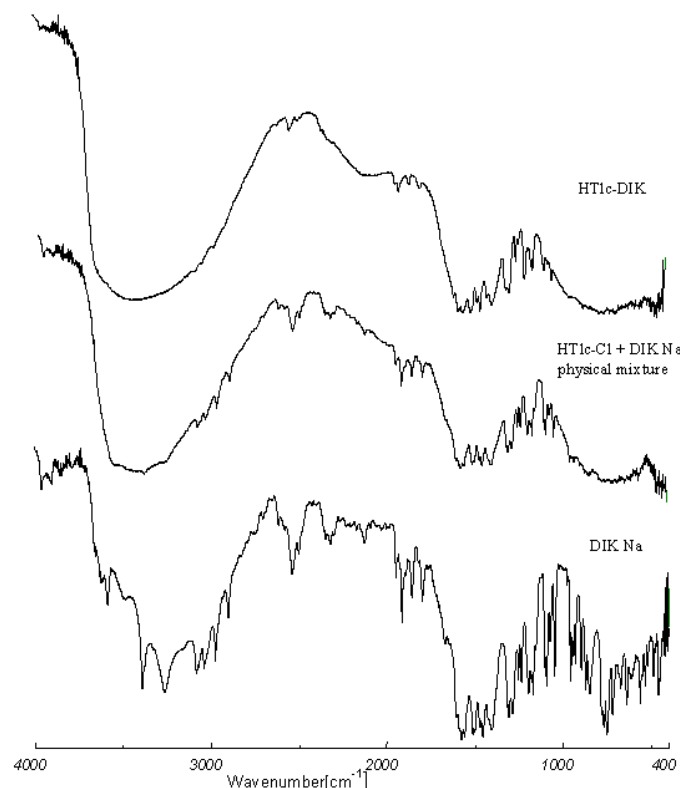


**Figure 4.** Computer-generated representation of 2 layers of Mg-Al hydrotalcite showing a probable arrangement of the intercalated DIK anions.

the computer simulated model, obtained with the Hyperchem program, of the probable arrangement of DIK anions in the intercalation compound, on the basis of the structural data of the host and the composition and interlayer distance of the intercalation compound. The DSC thermograms of DIK Na, HTlc-Cl, and HTlc-DIK are shown in **Figure 5**. The DIK Na thermogram shows peaks from 270°C to 350°C due to the melting and the oxidative degradation of the drug. HTlc-Cl shows 2 endothermic peaks at 400°C and 480°C attributed to the dehydroxylation of the layer hydroxyl group and the loss of the intercalated anion [5]. HTlc-DIK exhibits an endothermic peak at 120°C due to the loss of water and an exothermic peak at 250°C probably corresponding to oxidative degradation of the drug. This process happens at a lower temperature in comparison to DIK Na because of the drug molecular dispersion in HTlc-DIK.



**Figure 5.** DSC thermograms of DIK Na, HTlc-Cl, and HTlc-DIK.

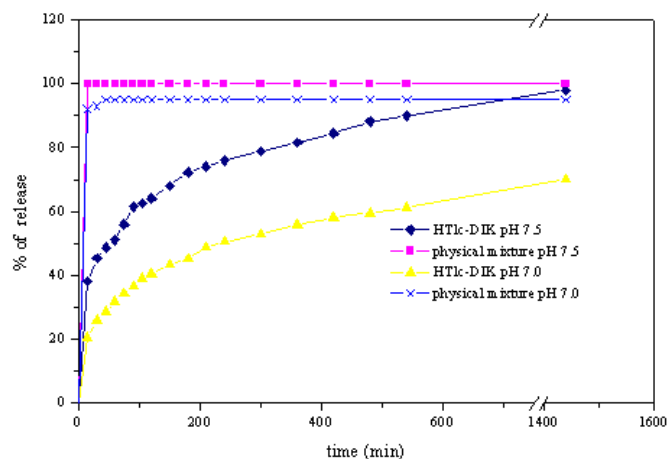


**Figure 6.** FT-IR spectra: DIK Na, DIK Na and HTlc-Cl physical mixture, HTlc-DIK.

**Figure 6** shows the FT-IR spectra of DIK Na, of the physical mixture of the drug and the HTlc-Cl, and of HTlc-DIK. The spectra of the physical mixture and of HTlc-DIK were less resolved than that of DIK Na and showed a broad absorption between  $3700$  and  $3000\text{ cm}^{-1}$  due to the stretching of hydrogen-bound hydroxy groups of the layers and the interlayer water. In all 3 spectra, the peaks at about  $1575$  and  $1390\text{ cm}^{-1}$  relative to the carboxylate group appeared.

### *In vitro drug release*

In vitro drug release was performed in simulated intestinal fluid at  $\text{pH } 7.5 \pm 0.1$  and in a solution designed to mimic the ionic condition of the small intestine ( $\text{pH}$

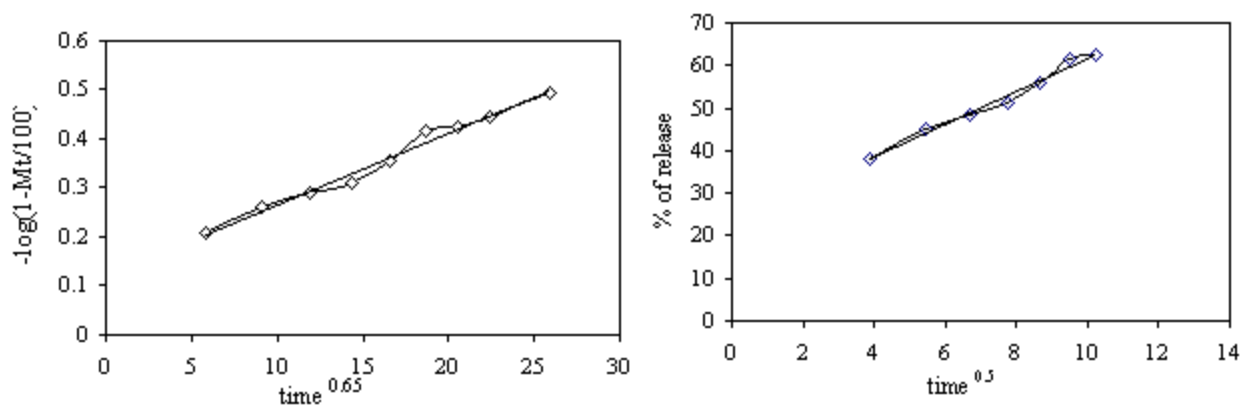


**Figure 7.** Release of DIK from HTlc-DIK and the physical mixture at  $\text{pH } 7.5$  and  $\text{pH } 7.0$ .

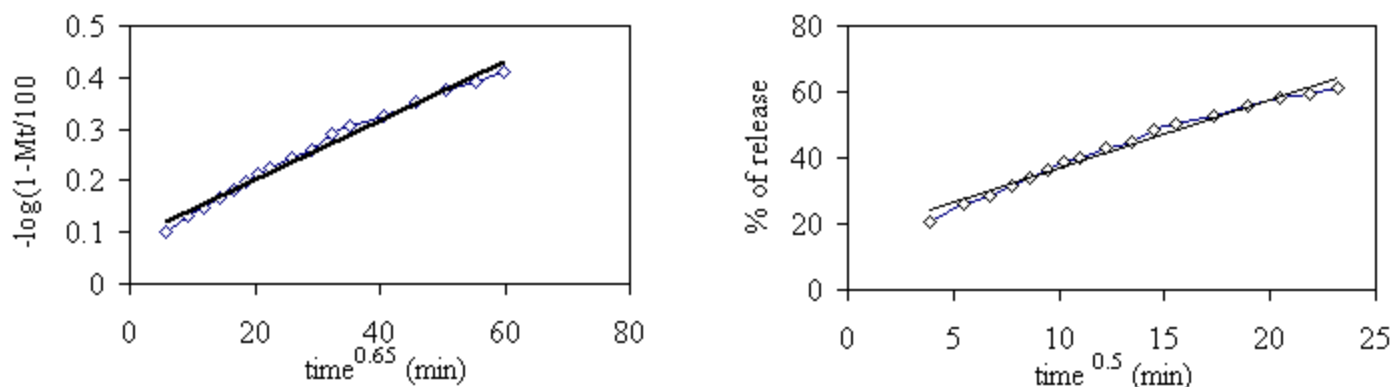
$7.0$ ) [11]. In vitro drug release profiles are reported in **Figure 7**.

At  $\text{pH } 7.5$  the dissolution rate of DIK from HTlc-DIK was slower than that from the physical mixture. The release of DIK from the physical mixture was already complete after 15 minutes, whereas the release of DIK from HTlc-DIK was 38% after 15 minutes, 60% after 90 minutes, and 90% after 9 hours. The burst effect can be explained with the release of DIK anions taken up on the surface of the microcrystals and those intercalated in the external part of the lamellar structure [4]. At the end of the test (24 hours), the residue was recovered from the vessel, centrifuged, washed 3 times with degassed water, dried, and submitted to x-ray powder diffraction. The interlayer distance of this residue was 1.07 nm. This value is relative to HTlc containing phosphates as intercalated ions [13]. The disappearance of the peak at 2.36 nm relative to HTlc-DIK was also observed. This result suggests that the release of the drug from HTlc-DIK is due to exchange of DIK ions with the phosphates of the medium.

As the drug release is due to the exchange of drug anions with the anions of the dissolution medium, once exchanged the drug anions diffuse through the hydrotalcite particle and then through the diffusion layer. Thus the drug release could be controlled by the diffusion through the hydrotalcite particle, or by the diffusion through the solution layer surrounding the particle. The rate of the exchange of drug ions between the hydrotalcite and the dissolution medium would be ultimately determined by the slower of these 2 processes. In the case of ionic resins, when the rate-limiting step is the diffusion through the particle, assuming that resin particles are uniform spheres and that sink conditions are maintained, the fraction of drug released as a function of time is described by the equation of Boyd et al [14]. When the drug release fraction is lower than 0.85, a simplified approximation for this equation has been obtained by Reichenberg [15].



**Figure 8.** Release of DIK from HTIc-DIK as a function of  $time^{0.65}$  and as a function of  $time^{0.5}$  at pH 7.5.



**Figure 9.** Release of DIK from HTIc-DIK as a function of  $time^{0.65}$  and as a function of  $time^{0.5}$  at pH 7.0.

Finally, Bhaskar et al [16] developed a simpler procedure, according to which, in order to establish whether the diffusion through the particle is the rate limiting step, it is enough to check the direct proportionality between  $\log(1 - \text{released fraction})$  and  $time^{0.65}$ . This method was applied to the experimental data, and from this plot a good linearity ( $r = 0.99257$ ) was obtained (**Figure 8**).

Other kinetic analyses were done on the basis of the matrix diffusion control model [17] and first-order kinetic. Only in the case of the Higuchi model was a good linearity obtained ( $r = 0.99243$ ) (**Figure 8**). This result confirmed the importance of the diffusion through the particle in controlling the drug release rate.

The DIK release from the physical mixture in the small intestine medium at pH 7.0 was almost complete after 15 minutes, whereas the drug release from HTIc-DIK was 20% after 15 minutes, 40% after 2 hours, and 50% after 4 hours, up to a maximum of 70% at the end of the experiment (24 hours). It is noteworthy that after 24 hours the DIK ions were not completely exchanged by the medium ions. XRDP of the residue, recovered as described above, displayed 3 peaks at 2.36, 1.07, and 0.78 nm relative to the contemporaneous presence of DIK and of dissolution medium anions between the layers. The slower release of DIK at pH 7.0 in comparison to that at pH 7.5 can be explained with the

higher concentration of phosphates in this latter medium. There are several ways to explain why at pH 7.0 DIK was not completely released. According to the pH value, the dissociation of  $Na_2HPO_4$  generates both  $H_2PO_4^-$  and  $HPO_4^{2-}$  anions that are able to intercalate into HTIc. At pH 7.0, both anions are present, but  $H_2PO_4^-$  is the prevalent form. In the case of another hydroxylapatite containing Zn and Al (Zn-Al-HTIc), the acidic  $H_2PO_4^-$  anions, once exchanged, react with the hydroxyls of the layer to form a layered Zn and Al hydroxyphosphate [13] (grafting reaction). In this strongly bound form, phosphates are no longer movable and can obstruct the exit of the intercalated anions. In this case, the grafting reaction could be so frequent that intercalated anions could be entrapped inside the layers.

The same kinetic models applied at pH 7.5 release were considered **Figure 9** contains plots according to the Higuchi and Bhaskar equation. Linear regression coefficients were 0.9889 and 0.9932, respectively. In this case, as in the previous case, the diffusion through the particle is the limiting step of the drug release.

In a previous work the release of ibuprofen from hydroxylapatite [4] was studied. From the comparison of results obtained in this paper and those previously reported for ibuprofen, 2 conclusions can be drawn. First, diclofenac is released more slowly; second, the release of diclofenac depends on the diffusion through

the particle and not on the drug concentration (first order kinetic), as in the case of ibuprofen. This different behavior can be explained by both the greater affinity of diclofenac for hydrotalcite [18] and its bigger molecular size in comparison to ibuprofen. As already described in our previous paper, the exchange of anions begins from the external part of the particle and proceeds toward the inside, with the consequent formation of an external phase with smaller distance. Diclofenac release, because of its bigger size, may be slowed down more than ibuprofen by the reduction of the interlayer distance in the external part of the layers. Moreover, the greater the distance that the drug has to travel until the exit and as a consequence the number of exchange sites, the greater the influence of the affinity of the drug for the matrix on the release rate.

**Conclusion** In this study the possibility of modifying the release of diclofenac thanks to the intercalating and deintercalating properties of hydrotalcite was explored. The interlayer region of this matrix can be considered a microvessel in which the drug may be stored and from which it is released by a deintercalation process due to the ions present in the small intestine.

From the obtained results the following conclusions can be drawn. The HTlc can intercalate DIK, the intercalation procedure is simple, and the final product has a high drug load. The in vitro dissolution studies show that the drug is released by a deintercalation process due to the exchange of the drug with the ions present in the dissolution medium. At pH 7.5 the drug release from HTlc-DIK is slower than that from the physical mixture and is complete after 9 hours. The kinetic analysis shows the importance of the diffusion through the particle in controlling the drug release rate. In the small intestine medium at pH 7.0 the DIK release is slower than the physical mixture and was not completed. In this case too the diffusion through the particle is the limiting step of the drug release.

On the basis of these results and those obtained in our previous work on ibuprofen [4], HTlc may be used to prepare modified release formulations.

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