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International Journal of Pharmaceutics 220 (2001) 23–32

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Intercalation compounds of hydrotalcite-like anionic clays with antiinflammatory agents — I. Intercalation and in vitro release of ibuprofen

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Received 19 November 2000; received in revised form 20 November 2000; accepted 23 February 2001

Abstract

Hydrotalcite-like compounds are layered solids having positively charged layers and interlayer charge-compensating anions. The synthetic $Mg_{0.67}Al_{0.33}(OH)_2\ Cl_{0.33}\cdot 0.6H_2O$, which is biocompatible, has been used to intercalate a model drug, ibuprofen, in order to prepare a modified release formulation. The intercalation compound was prepared via ion-exchange starting from the chloride form of hydrotalcite and its composition, determined both by elemental microanalysis and thermogravimetric analysis, was $Mg_{0.67}Al_{0.33}(OH)_2IBU_{0.33}\cdot 0.47H_2O$, drug content 50% (w/w). As a consequence of the intercalation, the interlayer distance of the host increased from 0.78 nm (interlayer distance of chloride form) to 2.17 nm. The result of dissolution tests at pH 7.5 showed that the in vitro drug release was modified if compared with that obtained with comparative formulations. The mechanism of modified drug release has been interpreted on the basis of the ion exchange process of the ibuprofen anion intercalated in the lamellar host and phosphates contained in the intestinal fluid buffer.

Keywords: Ibuprofen; Mg–Al hydrotalcite; Intercalation; In vitro release; Ion-exchange

1. Introduction

Ibuprofen, α-methyl-4-(2-methylpropyl)benzene-acetic acid, is a non-steroidal antiinflammatory drug used for the relief of symptoms of rheumatoid arthritis and osteoarthritis. It is used both in the treatment of acute flares and in long-term management of these diseases. Its use is often limited by the frequent side effects affecting both the gastrointestinal tract and the central nervous system (Gennaro, 1990). These side effects are also a consequence of high plasma levels following the administration of conventional formulations. These problems could be reduced by a formulation able to control the drug release. Another factor requiring a controlled release formulation is its short half-life (1.8–2.0 h) (Gennaro, 1990).

As matrices to prepare a controlled release formulation, we have taken into account lamellar

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0378-5173/01/$ - see front matter
PII: S0378-5173(01)00629-9

compounds. The idea was to store the drug in the interlayer region of the lamellar host and allow the drug release as a consequence of a de-intercalation process. Among lamellar solids, the natural or synthetic hydrotalcites are of particular interest since they are the only known family of layered host with positively charged layers balanced by exchangeable anions. Moreover they are studied as catalysts, support for catalysts, anion exchangers, adsorbents and additives (Cavani et al., 1991).

Synthetic hydrotalcites are quite easy to prepare in the laboratory and have the general formula $[M(II)_{1-x}M(III)_x(OH)_2]^{x+}[A^{n-}_{x/n}]^{x-}m$ S where M(II) is a divalent metal cation, usually Mg, M(III) is a trivalent metal cation, usually Al, A^{n-} is an exchangeable inorganic or organic anion which compensates for the positive charge of the layer and m are the moles of solvent S, usually water, co-intercalated per mole of compound.

The lamellae of the hydrotalcites are constituted by metal cations occupying the centres of octahedra whose vertices contain hydroxide ions. Each OH group is shared by three octahedral cations and the hydrogen points towards the interlayer region (Allmann, 1970). The interlayer distance depends on the nature of the interlayer anions and on the state of hydration (Cavani et al., 1991).

The Mg Al hydrotalcite (here after indicated HTlc) is biocompatible (Cavani et al., 1991) and has found pharmaceutical applications as an antacid (Goodman-Gilman et al., 1975), as an ingredient in sustained-release pharmaceuticals containing nifedipine (Doi et al., 1985), for stabilizing pharmaceutical compositions (Ueno and Kubota, 1987; Doi et al., 1989) and for preparing aluminium magnesium salts of antipyretic, analgesic and antiinflammatory drugs (Kyowa Hakko Kogyo Co., 1985). In none of these papers has the intercalation property of hydrotalcite been focused upon.

In this paper we report our studies on the intercalation of ibuprofen in HTlc in chloride form (HTlc-Cl) and on in vitro drug release, in order to study a new controlled release formulation.

2. Materials and methods

2.1. Materials

A large batch of well crystallized hydrotalcite in chloride form was obtained by co-precipitation from a 'homogeneous solution' of Mg(II) and Al(III) hydroxycarbonate (Costantino et al., 1998) and successive CO_3^{2-}/Cl^- ion exchange (Reichle, 1986).

Ibuprofen sodium salt was purchased from Sigma (Milano, Italy). Ibuprofen anion will hereafter be called IBU.

Other chemicals and solvents were of reagent grade and used without further purification.

Neo-Mindol® is a Bracco (Milano, Italy) formulation containing ibuprofen sodium salt (200 mg/capsule).

2.2. Intercalation of IBU into HTlc-Cl

The intercalation reaction was performed by equilibrating 1 g of HTlc-Cl with 84 ml of a hydroalcoholic (50% v/v) solution 10^{-1} M of IBU (1.92g) (Cl^-/IBU molar ratio 1/2), at 60°C and 140 rev/min for 3 days in a Gallen Kamp orbital incubator type INR 2000 (Leicestershire, UK).

After cooling, the mixture was centrifuged with an A.L.C. centrifuge (Milano, Italy) mod. 4236A at 5000 rpm for 5 min and the residue was washed three times with degassed water and finally dried in vacuo.

The resulting intercalation product (HTlc-IBU) was characterized by X-ray powder diffraction, C, H elemental microanalysis, thermogravimetric analysis and FT-IR.

2.3. Analytical procedures and instrumentation

The magnesium and aluminium content of the HTlc was determined by standard EDTA titration after dissolution of a weighted amount of the sample (ca. 100 mg) in a few drops of concentrated HCl and dilution with water up to 50 ml.

Elemental microanalysis was obtained on a Carlo Erba (Milano, Italy) Elemental Analyser mod. 1106.

Thermogravimetric analyses (TG) were performed with a Stanton-Redcroft 781 thermoanalyzer at heating rate of 5°C min^{-1} in an airflow.

The X-ray powder diffraction (XRPD) patterns were taken with a computer controlled PW 1710 Philips diffractometer (Lelyweg, Netherland), using the Ni-filtered Cu Kα radiation.

Ibuprofen content was also determined with an UV absorption spectrophotometer Jasco-V-520 (Tokyo, Japan) at $\lambda_{max} = 264$ nm after dissolution of a known amount of HTlc-IBU in 6 M HCl solution and successive dilution with phosphate buffer at pH 7.5.

FT-IR spectra were recorded in KBr dispersion on a Jasco model FT/IR-410, 420 Herschel series (Jasco Corporation Tokyo, Japan) using the Easi-Diff™ Diffuse Reflectance Accessory.

2.4. Powder size

Particle size distribution of HTlc-Cl and HTlc-IBU powder was measured with a single particle optical sizer Accusizer Model 770 (Particle Sizing Systems, Inc. Santa Barbara, CA), Software C770, version 2.1. Before counting, the samples were mixed with Tween 80 and automatically diluted with water under magnetic stirring.

2.5. Scanning electron microscopy

Scanning electron microscopy (SEM) photographs were taken with a Philips SEM 501 (PW 6703) (Holland).

2.6. Preparation of physical mixture of HTlc-Cl and IBU

A physical mixture was prepared by intimate mixing of ibuprofen sodium salt (556 mg) and HTlc-Cl (495 mg) (Cl^-/IBU molar ratio 1/1) in an agate mortar.

2.7. In vitro drug release

The dissolution test was performed in the U.S.P. XX paddle type apparatus by suspending 1 g of HTlc-IBU (equivalent to 500 mg of IBU) in 1000 ml of phosphate buffer at pH 7.5. The mass/volume ratio was chosen in order to simulate sink condition, according to the Na IBU solubility at this pH value (Adeyeye and Price, 1997). Aliquots (4 ml) of dissolution medium were taken at different times, filtered (13 mm Filter UNIT 0.45 μm NY PP, Lida, WI) and their IBU content was determined by UV absorption at 264 nm.

The release profile from our formulation (HTlc-IBU) was compared with those obtained from the physical mixture (HTlc-Cl/IBU) and the commercial formulation Neo-Mindol®.

Tests were made in triplicate and the results were recorded as an average.

3. Results and discussion

3.1. Preparation and characterization of the intercalation compound

The method of preparation based on the precipitation of Mg(II) and Al(III) as hydroxycarbonates, accomplished by the hydrolysis of urea (Costantino et al., 1998), gave a HTlc of empirical formula $Mg_{0.67}Al_{0.33}(OH)_2 \cdot (CO_3)_{0.165} \cdot 0.4H_2O$. It is well known (Miyata, 1983) that the CO_3^{2-} anions are strongly held in the interlayer region and that it is very difficult to replace them with other anions using simple ion exchange procedures. It is also known that the Cl^- anions can be more easily replaced than carbonates. Therefore original hydrotalcite has been converted into the chloride form by titration of the solid with diluted HCl solution, according to the following reaction:

$$Mg_{0.67}Al_{0.33}(OH)_2 \cdot (CO_3)_{0.165} \cdot 0.4H_20 + 0.33\,HCl \rightarrow Mg_{0.67}Al_{0.33}(OH)_2 \cdot Cl_{0.33} \cdot 0.56\quad H_2O + 0.165CO_2.$$

The conversion of HTlc-Cl into the IBU form has been obtained then by an anion exchange process as described in the experimental part. Preliminary analytical determination of Cl^- and IBU in the equilibrating solution, indicated that about all the Cl^- of HTlc were replaced by IBU. Fig. 1 shows the thermogravimetric curve of the intercalation compound, previously stored in a desiccator at r.t. and 75% r.h.. Taking into account that patterns of the sample heated at

1000°C indicate the presence of MgO and $MgAl_2O_4$, the weight loss curve, as a function of temperature, may be interpreted as follows: from room temperature to ca. 200°C the sample looses 0.5 mol of co-intercalated water *per* mol of compound. The weight loss between 200°C and 650°C

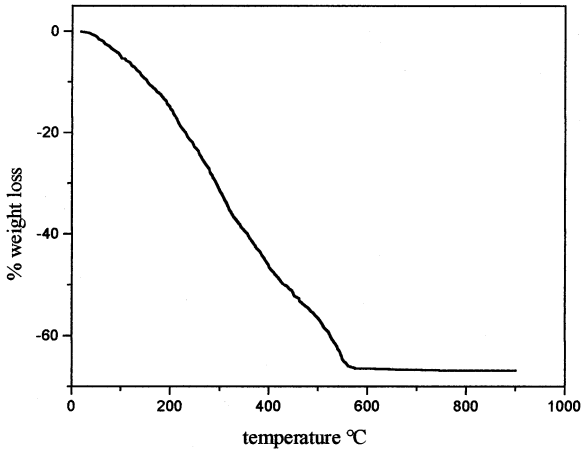

Fig. 1. TG profile for HTlc-IBU.

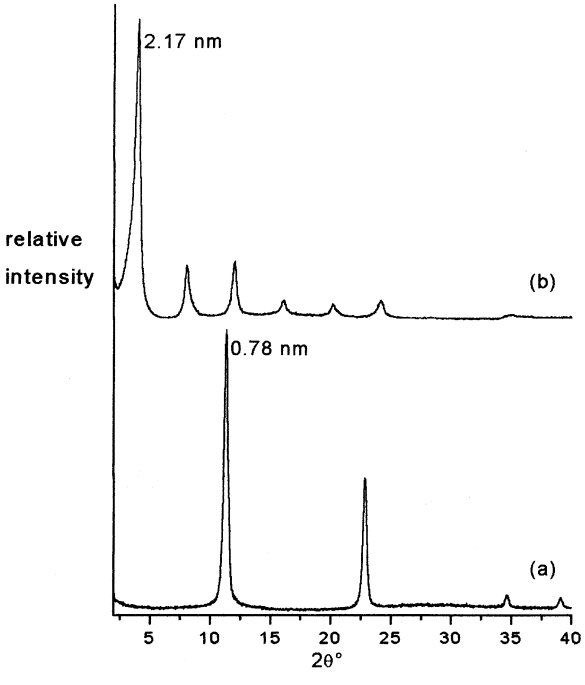

Fig. 2. Powder XRD patterns for HTlc-Cl (a) and HTlc-IBU (b).

is consistent with the loss of 1 mol. of water due to the dehydroxylation of the inorganic layer and to thermal decomposition of 0.33 mol of IBU per mole of compound.

The derived formula is $Mg_{0.67}Al_{0.33}(OH)_2 \cdot IBU_{0.33} \cdot 0.5H_2O$. The H and C elemental analyses were in good agreement with the above formula:

Calculated C = 38.10%; H = 6.38%;

Found C = 38.28%; H = 6.50%.

This composition demonstrates that the amount of organic anions incorporated into HTlc is stoichiometrically related to the net positive charge generated by Al substitution in the inorganic layers and that all hydrotalcite Cl^- ions were exchanged by the IBU ions. The total IBU content of the intercalated product was 0.5 g per 1 g of HTlc-IBU.

Structural information on the arrangement of the IBU anions in the interlayer region were derived from X-ray diffraction and FT-IR analyses.

Fig. 2 shows the XRPD patterns of the original HTlc-Cl and of HTlc-IBU. It can be seen that, as a consequence of the intercalation, the interlayer distance of the host increased from 0.78 nm, that is the interlayer distance of HTlc-Cl, to 2.17 nm. Correspondingly, as the layer thickness is 0.48 nm (Whilton et al., 1997), the gallery height, i.e. the interlayer distance, increased to 1.69 nm. This expanded interlayer separation is consistent with the intercalation of organic anions of size similar to IBU within the gallery spaces of HTlc. Previous studies showed that phthalate, salicylate and anthranilate anions caused an expansion of 1.5–1.55 nm (Meyn et al., 1990).

A gallery height of 1.69 nm suggests that the IBU ions are accommodated in the interlayer region as a monolayer of species partially superimposed with their main axes perpendicular to the layer plane and with the carboxilates of individual anions interacting with the layer surfaces.

Fig. 3 shows the comparison between the FT-IR spectra of ibuprofen sodium salt (a), of physical mixture of drug and HTlc-Cl (b) and of HTlc-IBU (c). No important differences are ob-

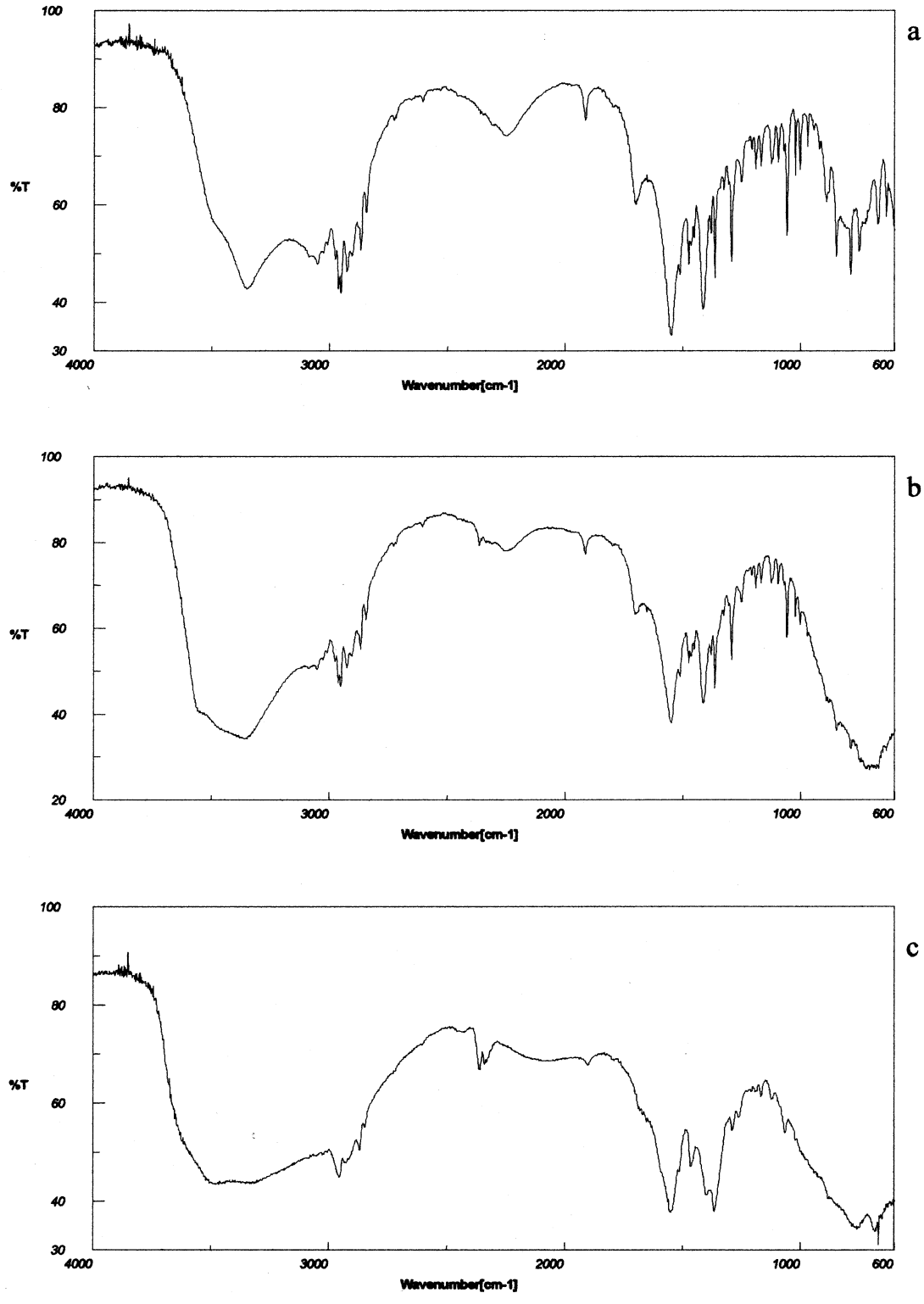

Fig. 3. FT-IR spectra for ibuprofen sodium salt (a), physical mixture (b) and HTlc-IBU (c).

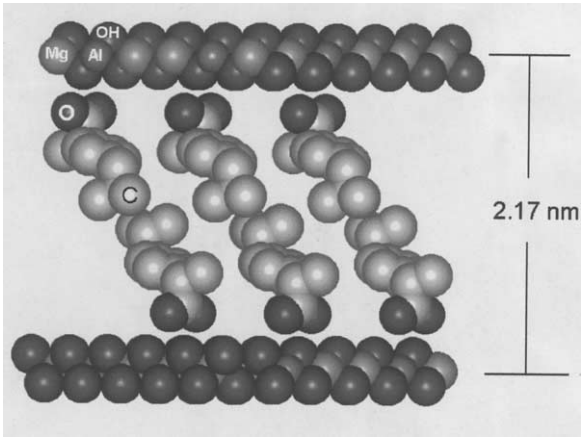

Fig. 4. Computer generated model of HTlc-IBU.

served between the spectrum of the physical mixture and that of ibuprofen salt. However the spectrum of the physical mixture shows a very broad band between 3700 and 3200 cm^{-1} due to the stretchings of OH groups of the layers and interlayer water. The FT-IR spectrum of HTlc-IBU shows the bands corresponding to the intercalated anion. Besides the broad absorption band between 3700–3100 cm^{-1}, which is superimposed to that of the aromatic ring of ibuprofen, other main bands were between 3000 and 2800 cm^{-1} due to the alkyl stretchings of ibuprofen, and at 1552 and 1396 cm^{-1} due to the antisymmetric and symmetric stretchings of $RCOO^-$, respectively. The IR spectra of HTlc-IBU and the physical mixture are of similar shape but some differences can be observed especially in the region between 1550 and 1000 cm^{-1}, probably due to different interactions between ibuprofen and the matrix when the drug is intercalated or when it is physically dispersed.

Fig. 4 shows a computer generated model of the HTlc-IBU, obtained with the Hyperchem program, on the basis of the structural data of the host and the composition and interlayer distance of the intercalation compound.

Finally, in order to have useful information on the mechanism of drug release, the particle size and the shape of the microcrystals were determined.

Powder size distribution curves of the original HTlc-Cl and of HTlc-IBU, in number percentage, are reported in Fig. 5. It may be seen that both the curves show a sufficiently narrow size distribution around 4 μm for the chloride form and 7 μm for the IBU derivative. It may be also noticed that the conversion from the Cl to IBU form does not cause a fragmentation of the microcrystals, on the contrary there is an increase of the mean value of the particle size.

However, the comparison between scanning electron micrographs (Fig. 6a,b) of HTlc-Cl and HTlc-IBU show that HTlc-Cl has well-formed and regular sized microcrystals, while the HTlc-IBU powder appears constituted of non-uniform irregular aggregates. Very likely, the presence of drug molecules taken up on the microcrystal surface can produce a variation of the superficial interactions that influences the aggregation behaviour of the microcrystals. As a consequence of the enlargement of the interlayer region, the layering of HTlc-IBU is also evident and fringes are occasionally observed (Fig. 6c).

3.2. In vitro drug release

The drug release profiles from HTlc-IBU, physical mixture of HTlc-Cl and IBU and the commercial formulation Neo-Mindol® in simulated intestinal fluid are compared in Fig. 7.

The drug release profile from HTlc-IBU is modified if compared with those obtained from physical mixture and Neo-Mindol®. The commercially form and the physical mixture released immediately the total drug content. The release profile of HTlc-IBU showed that 60% of the drug was released after 20 min and the 100% after 100 min from the initial time of the experiment. This difference is probably due to the drug release mechanism from the intercalation compound, because IBU release from HTlc-IBU occurs by exchange between IBU ions and phosphates contained in the buffer.

To confirm this mechanism, after complete release of the drug, the resulting powder was recovered from the phosphate buffer, dried and characterized by XRPD. The relative spectrum showed the absence of the peak at 2.17 nm char-

acteristic of HTlc-IBU and the appearance of a peak at 1.09 nm due to the phosphate intercalation (Costantino et al., 1997).

The rapid release during the first 20 min is followed by a more sustained release of the remaining drug. To explain this gradual decrease of the dissolution rate, some considerations may be drawn. The rate of drug diffusing out of the matrix is controlled by the rigidity of the layers and the diffusion path length. HTlc may be considered a semirigid material and its inter-layer rigidity parameter indicates that this material is stiffer than class II layered solids but not as stiff as class III layered solids (Hines et al., 2000) according to the Solin classification (Solin, 1986). In this kind of matrix, when small species (intestinal phosphate) exchange bigger anions (intercalated drug), a consequent decrease of the interlayer distance occurs. This initial exchange of anions of the external part of the crystals usually causes the formation of an external phase with smaller distance (Alberti and Costantino, 1996) with a consequence decrease of the rate of the drug release.

Where a smaller and larger interlayer distance co-exists in the same crystal, there is the formation of a phase boundary between internal zones containing intercalated IBU and the external in which phosphates have already replaced the drug anions. As the replacement proceeds, the phase boundary moves towards the central part of the crystal and the drug release process progressively declines.

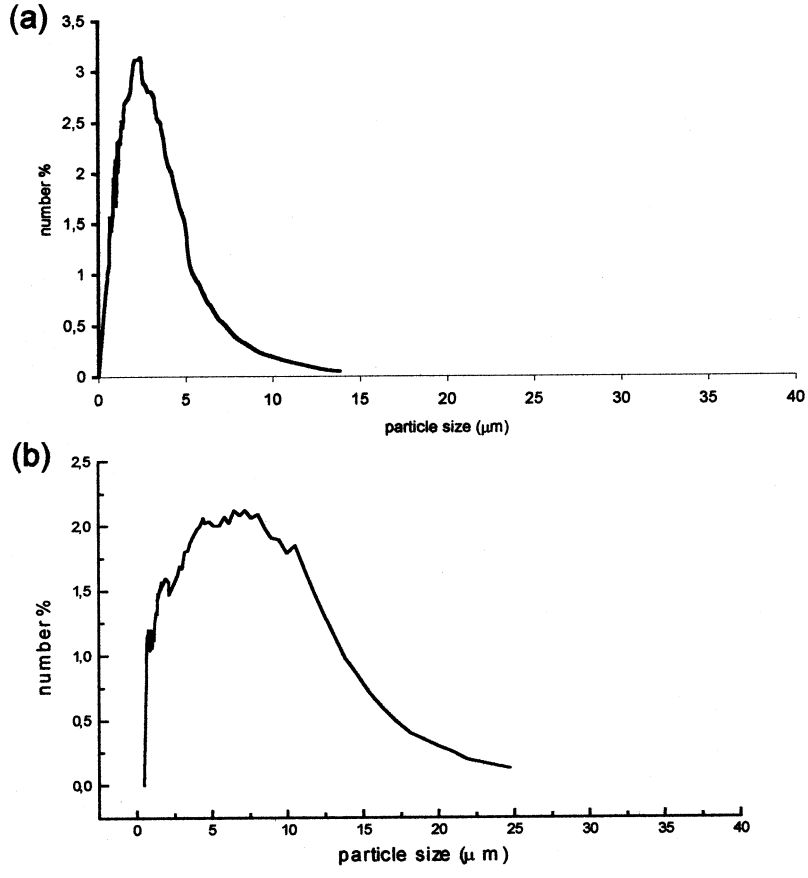

Fig. 5. Powder size distribution of HTlc-Cl (a) and HTlc-IBU (b).

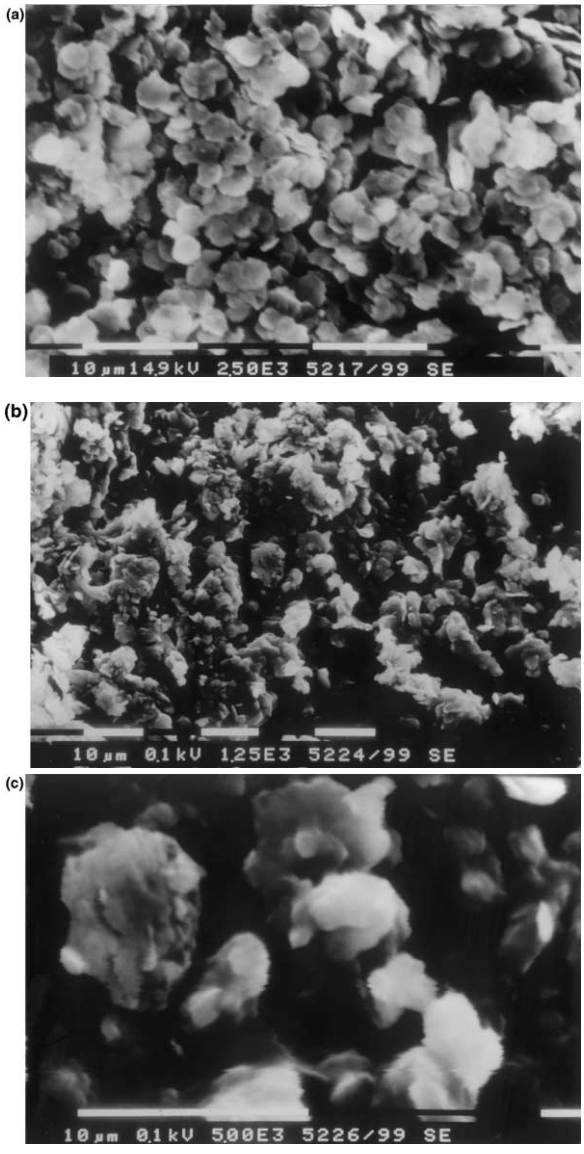

Fig. 6. Scanning electron micrographs of HTlc-Cl (a) and HTlc-IBU (b,c).

Furthermore, at pH 7.5, the H_3PO_4 dissociation generates a mixture of two anions, $H_2PO_4^-$ and HPO_4^{2-}, which both are able to intercalate into HTlc. In the case of Zn–Al–HTlc (Costantino et al., 1997), the acidic $H_2PO_4^-$ anions, once exchanged, react with the hydroxyls of the layer to form a layered Zn and Al hydroxyphosphate (grafting reaction). In this strongly bound form, phosphates are no longer exchangeable and can obstruct the exit of intercalated IBU. HPO_4^{2-} anions too may give grafting reactions, but only when, after HPO_4^{2-} intercalation, the sample is dehydrated over P_4O_{10} or heated at temperatures higher than 40°C. Thus, in our experimental conditions, HPO_4^{2-} anions are available to be exchanged and allow IBU to exit. As IBU anions do not pass through the matrix directly, neither can pass over the grafted anions, they have to find the right pathway with consequent increase of the tortuosity and the length of the diffusion pathway.

In vitro drug release was accomplished in condition approaching those of the intestinal tract. In a gastric environment the release was not performed because HTlc readily dissolved at these low pH values, consequently an enteric formulation would be required.

The IBU release kinetic was described by model functions that normally are used to describe the dissolution phenomena. The release profile suggested that the first order kinetic equation was the most appropriate for describing the release behaviour as shown in Figs. 7 and 8 and as indicated by the linear regression data ($r = 0.9973$).

4. Conclusions

Hydrotalcite-like anionic clays can be used as agents able to intercalate drugs, and de-intercalate them in order to modify their release and to prepare a controlled release formulation.

It is noteworthy to observe that IBU anions exchanged all Cl^- intercalated into HTlc, producing an intercalation compound with a drug loading of 50% w/w.

Dissolution testing showed that the drug release was modified if compared to those of the commercial formulation Neo-Mindol® and of the IBU and HTlc-Cl physical mixture.

Work is in progress to prepare intercalation compounds of hydrotalcite-like anionic clays with other antiinflammatory drugs.

Acknowledgements

This work was supported by grants from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and from the Consiglio Nazionale delle Ricerche (CNR), Rome. The authors thank Dr Morena Nocchetti for her helpful suggestions and Luca Bartolucci for scanning electron microscopy photographs.

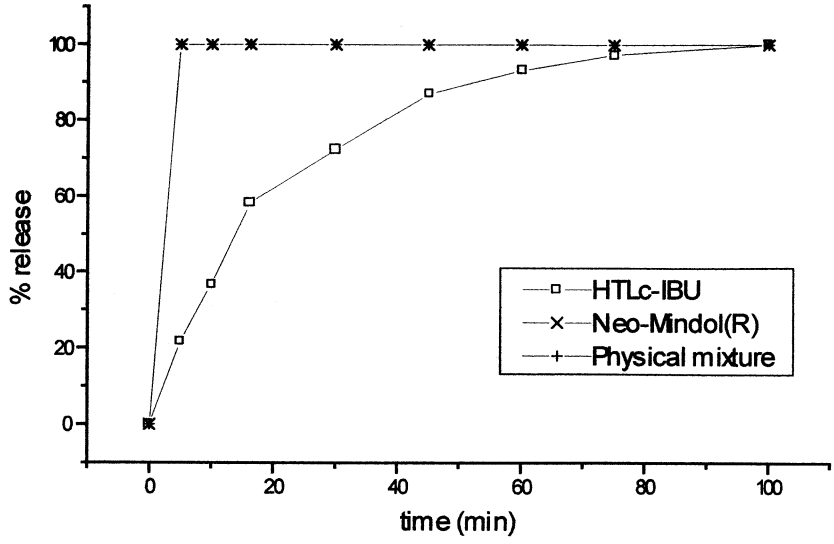

Fig. 7. Release profile of IBU from HTlc-IBU, physical mixture of IBU and HTlc-Cl and Neo-Mindol®.

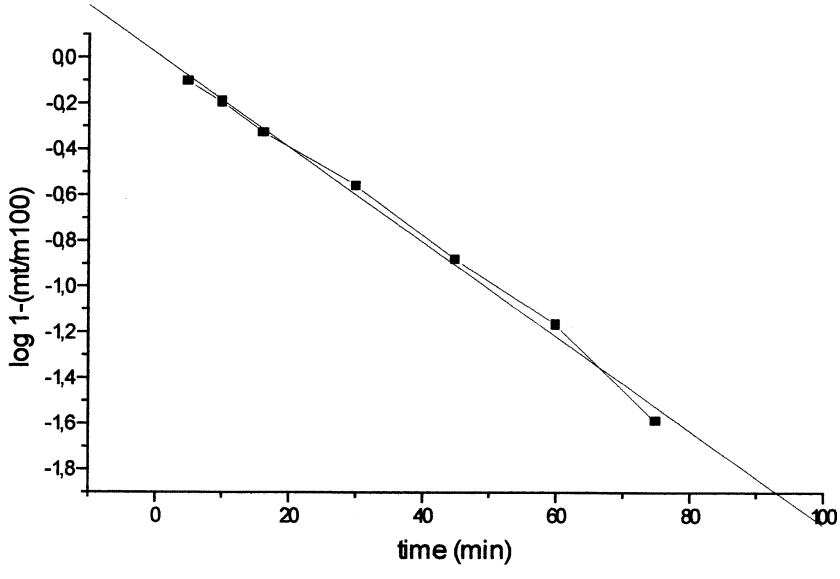

Fig. 8. Fitting of IBU release data with first order kinetics.

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