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Solubility behavior and biopharmaceutical classification of novel high-solubility ciprofloxacin and norfloxacin pharmaceutical derivatives

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ABSTRACT

The hydrochlorides of the 1:3 aluminum:norfloxacin and aluminum:ciprofloxacin complexes were characterized according to the Biopharmaceutics Classification System (BCS) premises in comparison with their parent compounds. The pH–solubility profiles of the complexes were experimentally determined at 25 and 37 °C in the range of pH 1–8 and compared to that of uncomplexed norfloxacin and ciprofloxacin. Both complexes are clearly more soluble than the antibiotics themselves, even at the lowest solubility pHs. The increase in solubility was ascribed to the species controlling solubility, which were analyzed in the solid phases at equilibrium at selected pHs. Additionally, permeability was set as low, based on data reported in the scientific literature regarding oral bioavailability, intestinal and cell cultures permeabilities and also considering the influence of stoichiometric amounts of aluminum. The complexes fulfill the BCS criterion to be classified as class 3 compounds (high solubility/low permeability). Instead, the active pharmaceutical ingredients (APIs) currently used in solid dosage forms, norfloxacin and ciprofloxacin hydrochloride, proved to be BCS class 4 (low solubility/low permeability). The solubility improvement turns the complexes as potential biowaiver candidates from the scientific point of view and may be a good way for developing more dose-efficient formulations. An immediate release tablet showing very rapid dissolution was obtained. Its dissolution profile was compared to that of the commercial ciprofloxacin hydrochloride tablets allowing to dissolution of the complete dose at a critical pH such as 6.8.

1. Introduction

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based upon their aqueous solubilities related to dose at three relevant pHs and intestinal permeability (Amidon et al., 1995). According to the BCS, drug substances are classified as follows: class 1 (high solubility–high permeability), class 2 (low solubility–high permeability), class 3 (high solubility–low permeability) and class 4 (low solubility–low permeability). In addition, immediate release oral dosage forms are categorized in accordance with their rates of dissolution. So, when combined with dissolution of a product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from immediate release solid oral dosage forms: dissolution rate, solubility and permeability.

In the last years, the BCS has been applied not only to immediate release solid dosage forms, but also to extended release ones, and is considered a tool in drug development (Lennernas and Abrahamsson, 2005; Wei et al., 2008; Ku, 2008; Grudzień et al., 2008).

To obtain the relevant data to classify an active pharmaceutical ingredient (API), literature review is recommended (FIP, 2008).

Fluoroquinolone antibiotics are widely prescribed drugs because of their safety with good tolerance and broad antibacterial spectrum (Appelbaum and Hunter, 2000). Norfloxacin and ciprofloxacin are representative members of the family (Fig. 1), being the last considered by WHO as an essential drug. No definitive classification has been obtained for these APIs.

It is well known that fluoroquinolones form complexes with certain multicharged cations toward the C-3a and C-4 system (Kmetec et al., 1999; Drakopoulos and Ioannou, 1997; Wallis et al., 1996; Issopoulos, 1989; Sakai et al., 1999; Behrens and Mendoza Diaz, 1986; Mendoza Diaz and Ireta Moreno, 1994). The binding to metals such as Al^{3+}, Mg^{2+}, Ca^{2+} and Fe^{3+} has demonstrated a substantial increase in solubility of fluoroquinolones following complexation (Žakelj et al., 2007), paralleled by a decrease in the partition coefficient (Ross et al., 1992). Also, the binding to Al^{3+} is stronger than to the other metals (Okabayashi et al., 1992; Ross and Riley, 1992; Shimada et al., 1992).

In our laboratory, the hydrochlorides of the aluminum complexes of norfloxacin and ciprofloxacin, named I and II, were previously obtained as stable solids and characterized as new pharmaceutical derivatives of norfloxacin and ciprofloxacin (Olivera et al., 2000b; Manzo et al., 2005; Chattah et al., 2007). Such

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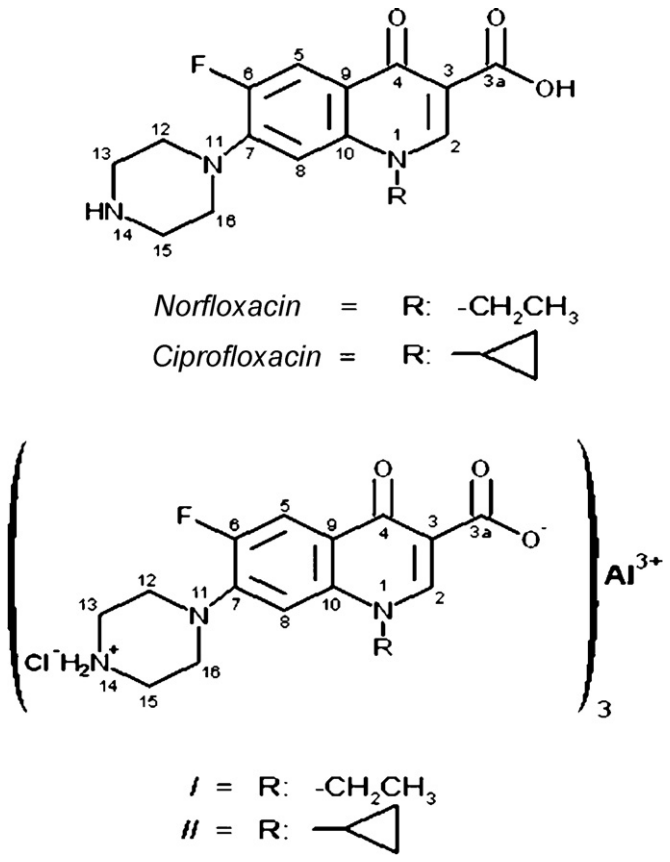

Fig. 1. Structural formulae of norfloxacin and ciprofloxacin and the hydrochlorides of their aluminum complexes I and II, respectively.

complexes have a definite stoichiometric composition of 3:1 fluoroquinolone:aluminum (Fig. 1). Both compounds are hydrates at room conditions.

According to FDA, products containing these complexes would be regarded as pharmaceutical alternatives to the parent APIs.

Previous results on antibiotic potency of both complexes showed no differences with the uncomplexed forms (Alovero et al., 2003). Taking advantage of the raising in aqueous solubility due to Al^{3+} complexation, an ophthalmic formulation from II was developed and tested in rabbits (Allemandi et al., 1999). Also, complexation provided an improvement in glycerin compatibility and then an optimized ototopic formulation of II was successfully tested in a clinical trial for the treatment of acute external otitis (Olivera et al., 2004).

Drug solubility is one of the core factors, which affect the movement of a drug from the site of administration into the bloodstream. It is widely acknowledged that insufficient drug solubility can lead to poor oral absorption (Zhao et al., 2002). Also, it has been shown that orally administered drugs are well absorbed if they have a minimum solubility of 10 μg/ml and log $P \geq 2$ (Wakita et al., 1986).

Owing to the improvement in the biopharmaceutical-related properties, we present in this work, the solubility behavior and the BCS classification of the new derivatives I and II together with that of the parent APIs norfloxacin and ciprofloxacin. Also, a convenient formulation to be used in the subsequent *in vivo* studies is reported.

2. Materials and methods

2.1. Complexes I and II

Complexes I and II were obtained according to the procedure of AR007762B1 patent by starting from norfloxacin (USP) or ciprofloxacin (obtained by neutralization of ciprofloxacin hydrochloride, PA), aluminum chloride hexahydrate (PA) and ethyl alcohol 96°.

2.2. Excipients used in tablets preparation

PH 200 microcrystalline cellulose (NF), sodium carboxymethyl cellulose (NF), talc (NF) and magnesium stearate (NF).

2.3. Buffers

Potassium chloride (PA), sodium acetate trihydrate (PA), potassium dihydrogen phosphate (PA) and 1N sodium hydroxide were used to obtain the buffer solutions: pH 1.2 (HCl/KCl), pH 4.5 (acetic acid/sodium acetate) and pH 6.8 (KH_2PO_4/NaOH), according to USP-XXX.

2.4. Solubility determinations

Aqueous solubility of the complexes was measured as a function of pH. An excess of each derivative was placed into suitable stoppered containers. Seven of these containers (in triplicate) were added with variable volumes of 5 M HCl or 5 M NaOH to obtain pH values between 2 and 8. The samples were immersed in a water bath thermostatized at 37 °C and periodically shaken. Preliminary experiments indicated that after 48 h all solutions were saturated. Once the equilibrium was reached, the pH of the supernatant was regarded. Aliquots of the filtrate properly diluted with acetic acid 0.02 M (pH ≈ 3) were analyzed by UV spectrophotometry (Shimadzu *UV A-160)* at the maximum wavelengths ($\lambda_{máx}$ 277 nm). The whole procedure was repeated at 25 °C. The stability of the compounds in solution was tested by running a sample at the beginning and the end of the experiment by the stability indicating HPLC method described in USP-XXX for norfloxacin and ciprofloxacin. Also, the solid phases at equilibrium at selected points along the pH profile were subjected to the following tests: (a) aluminum content (Eriochromcyanin 0.1% solution; sodium acetate 1.36% solution) according to the procedures described in the Farmacopea Nacional Argentina (FNA, 2000), (b) molar ratio between chloride (titration with $AgNO_3$ 0.079 N; pH meter ORION Model 420A, electrode Metrohm Ag 9100 HERISAU) and norfloxacin or ciprofloxacin (UV spectrophotometry), (c) DSC (A2920 MDSC, TA instruments) and TG (2950 TGA HR thermogravimetric analyzer, TA Instruments) runs.

2.5. Literature data of solubility and permeability

A search in the PubMed Central and Scirus was conducted using the keyword ciprofloxacin or norfloxacin, both combined with absolute, absorption, bioavailability, permeability, pharmacokinetics, solubility, aluminum, metals, dissolution and oral.

2.6. Preparation of tablets

The complex II was selected to prepare a solid formulation containing an amount of II equivalent to 250 mg of ciprofloxacin. Composition and procedure of the selected formula were as follows: dry granules were obtained by compressing II in a single punch-tableting machine. The obtained discs were milled with mortar and pestle and subsequently sieved. The fraction of particle size range 600–425 μm was mixed with sodium carboxymethyl cellulose (8%), microcrystalline cellulose (21%). After 35 min of mixing, the lubricants (0.5% magnesium stearate and 0.5% talc) were added and mixed for 2 more minutes. A double-cone mixer was used. Compression force of the tableting machine was regulated to a final hardness of 6 kg/cm^2. The tablets were tested for hardness ($n = 10$),

friability (6.5 g, $n = 12$, Equipos Farmacéuticos, Argentina, tablets friability tester), uniformity of weight ($n = 10$) and disintegration time ($n = 6$, Hanson Research tablets disintegrator, 37 °C) in 1000 ml of buffers pH 1.2, 4.5 and 6.8.

2.7. Dissolution rate of the tablets of II and commercial ciprofloxacin hydrochloride

The dissolution tests were carried out in a SR Dissolution Test Station, Hanson Research, using the dissolution Apparatus 2 (paddle) of the USP-XXX at 50 rpm and 37 °C. Testing was conducted on 12 dosage units of II or commercial ciprofloxacin hydrochloride (Cipro®, 250 mg) in 900 ml of each of the following dissolution media: pH 1.2, 4.5 and 6.8. Samples were withdrawn and filtered at 5, 10, 15, 20, 60, 90 and 120 min. The concentrations of ciprofloxacin dissolved were determined by UV spectrophotometry at $\lambda_{máx}$ 277 nm. The pH was regarded at the end of the assay and no variations were observed. The tablets were considered "very rapidly dissolving" if no less than 85% of the amount of ciprofloxacin contained in the tablets dissolved in 15 min or less at the three pHs.

3. Results and discussion

3.1. Permeability classification

According to the present FDA Guidance, an API is classified as "highly permeable" if the fraction absorbed is 90% or higher (FDA, 2000). The WHO Guideline (WHO, 2005) sets a lower limit of 85% absorbed, whereas the European Medicines Agency (EMEA) (CPMP, 2001) requires high permeability but does not define a limit for the fraction of drug absorbed. Literature clearly describes ciprofloxacin and norfloxacin as low permeability drugs. Although Lindenberg et al. (2004) provisionally classified ciprofloxacin hydrochloride as class 2/4 drug, LeBel (1988) has reported oral bioavailability of ciprofloxacin as erratic and low (65–85%). Recent studies based on cellular or *in situ* models have shown involvement of intestinal transporters, including efflux proteins in the oral absorption of ciprofloxacin (Rodríguez-Ibañez et al., 2003; Žakelj et al., 2006). In line, there is an apparent lack of dose proportionality of area under the concentration-time curve (AUC) in humans (Cipro®, 1989; Ciprofloxacin, 2007).

Accordingly, Volpe (2004) has previously classified ciprofloxacin permeability as low based in a Caco-2 cell culture. Žakelj et al. (2006) reported that intestinal permeability of ciprofloxacin is comparable to that of fluorescein (a low permeability paracellular marker) in all regions of the rat small intestine and classified it as a low permeability drug. Still others authors classified ciprofloxacin as a class 4 drug on the bases of the Biopharmaceutics Drug Disposition Classification System (Wu and Benet, 2005).

Norfloxacin is absorbed by passive diffusion and there is a dose proportionality of AUC in humans from 200 to 800 mg (Noroxin®, 2007). Human pharmacokinetic data for norfloxacin show a fraction absorbed of only 30–40%, indicative of a poorly permeable compound (Adhami et al., 1984; Zhu et al., 2002). Apparent permeability of norfloxacin either in non-everted intestinal sacs or Caco-2 cells was also described as low (Ruana et al., 2006; Balimane et al., 2005) confirming it is a BCS low permeability drug.

In presence of Al^{3+}, fluoroquinolones could exist as aluminum complexes in physiological conditions. The optimum pH range for the formation of these complexes has been reported as 3.5–4.5 (Drakopoulos and Ioannou, 1997). However, the complexation is pH and temperature dependant, as well as reversible and dynamic. So the uncomplexed drug coexists in solution with different stoichiometry complexes (Kmetec et al., 1999; Drakopoulos and Ioannou, 1997; Issopoulos, 1989; Okabayashi et al., 1992; Ross and Riley, 1992).

There are several reports regarding a reduction in oral bioavailability when a dose of a fluoroquinolone is given concomitantly with metallic antacid containing aluminum and/or magnesium. However, two aspects should be noted here. First, a high molar excess of aluminum with respect to ciprofloxacin or norfloxacin is present (Lehto and Kivisto, 1994). Second, the adsorption of quinolones by aluminum hydroxide reprecipitated in the small intestine, which is strong for norfloxacin and ciprofloxacin and weak for ofloxacin, was suggested to play an important role in the reduced bioavailability of these APIs (Tanaka et al., 1993). As a matter of fact, the oral bioavailability of ofloxacin was not reduced by coadministration with these products (Sanchez Navarro et al., 1994).

It has been reported that limited amounts of Al^{3+} (1:1, fluoroquinolone:Al^{3+}) do not affect the ability of fluoroquinolones to pass through a biological membrane (Tanaka et al., 1993). In the same line, it was previously determined in our laboratory that norfloxacin and ciprofloxacin go across everted rat intestinal membrane sacs at nonsignificantly different rates when permeability from solutions of I and II and their respective uncomplexed forms were compared (Olivera et al., 2000a, b). Besides, their antimicrobial activity was not affected by stoichiometric concentrations of aluminum (Alovero et al., 2003; Allemandi et al., 1999).

Similar results were obtained by other authors with fluoroquinolones and stoichiometric concentrations of other metals such as Ca^{2+}, Mg^{2+} and Bi^{3+} (Žakelj et al., 2006; Shaikh et al., 2007).

All this evidence taken together let us to conclude that stoichiometric complexes between norfloxacin (or ciprofloxacin) and Al^{3+} have intestinal permeabilities comparable to those of uncomplexed forms. Hence, available data indicate that permeability of both complexes is low and will be the rate-limiting step in the absorption process for immediate release solid oral products.

3.2. Solubility and BCS classification

Solubility of I and II and their parent compounds norfloxacin and ciprofloxacin was determined considering the BCS framework outlined in current guideline recommendations. The FDA defines "highly soluble" over the pH range 1–7.5 (FDA, 2000), whereas the EMEA (CPMP, 2001) and the WHO Guidelines (WHO, 2005) limit the requirements to the pH range 1.2–6.8.

As other fluoroquinolones norfloxacin and ciprofloxacin are zwitterionic compounds that in aqueous solution speciate as described in Fig. 2. Speciation yields the pH independent constant $K_5 = [(+-)]/[(00)]$. Both compounds exhibit a "U"-shaped pH–solubility profile with high solubility at pHs below 5 and above 10, and minimum solubility near neutrality at isoelectric pH. The low solubility domain is controlled by the saturation of the neutral species whose concentrations remain constant along such pH range, Eq. (1), in parenthesis fluoroquinolones species as expressed in Fig. 2:

$$\text{Apparent solubility} = [(00)]_{\text{const.}} + [(+-)]_{\text{const.}} + [(0+)] + [(0-)] \quad (1)$$

Therefore, although ciprofloxacin hydrochloride is the salt currently used in immediate release oral dosage forms, its solubility in a wide range of pH is determined by the neutral species (00) and (+−). Notice that pHs close to neutrality are critical to classify these compounds and their new derivatives.

Yu et al. (1994) reported pH–solubility profile of norfloxacin and ciprofloxacin and their intrinsic solubilities as a function of tem-

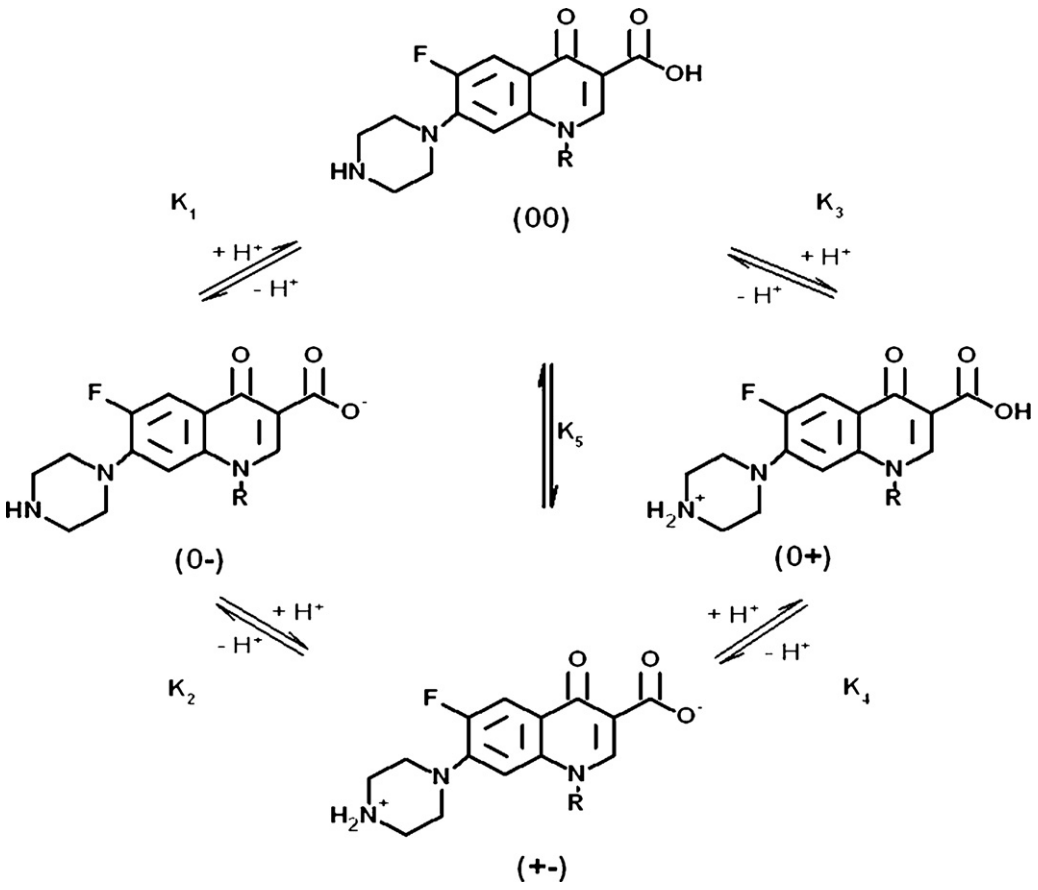

Fig. 2. Ionization equilibria of fluoroquinolones in aqueous solutions. K_1–K_5 are microionization constants.

perature showing that both have an endothermic heat of solution with minimum solubility at pH ~ 7. Values of intrinsic solubility were ciprofloxacin: 0.037 mg/ml (6 °C), 0.086 mg/ml (25 °C), 0.14 mg/ml (30 °C) and 0.17 mg/ml (40 °C); norfloxacin: 0.27 mg/ml (6 °C), 0.37 mg/ml (25 °C) and 0.85 mg/ml (40 °C).

The pH–solubility profile of norfloxacin at 25 °C was also reported by Ahumada et al. (1993) with minimum solubility of 0.31 mg/ml at pH 7. Fallati et al. (1994) informed pH–solubility profile of ciprofloxacin at 25 °C with a minimum of 0.088 mg/ml at pH 6.84. In agreement, Ross and Riley (1990) also found that the intrinsic solubility of fluoroquinolones at 25 °C ranged from 0.0297 to 2.75 mg/ml.

The WHO (WHO, 2007) recommended dose of ciprofloxacin is 250 mg (as hydrochloride). Immediate release solid dosage forms with marketing authorization in Argentina, and USA have strengths of 250, 500 and 750 mg. Doses of 500 and 1000 mg are available in modified release formulations (ANMAT, 2008; Ciprofloxacin, 2007, 2008). Norfloxacin is not a WHO essential drug. Marketing authorizations have been given to tablet strengths of 100, 200, 400, 500, 600 and 800 mg in Argentina and USA (Noroxin®, 2007;Norfloxacin, 2008). Only the tablets with 400 mg are actually available. Hence, norfloxacin and ciprofloxacin are clearly classified as low solubility drugs at pH 6.8 and 7.5, since they do not satisfy the criteria of dose:solubility ratio < 250 ml (Table 1). Kasim et al. (2002) classified ciprofloxacin hydrochloride as a high solubility drug, reporting a solubility value of 10 mg/ml. However, this value would correspond to the aqueous acidic solution obtained from ciprofloxacin hydrochloride.

Fig. 3(A) and (B) show pH–solubility profiles obtained at 37 °C for I and II compared to uncomplexed drugs reported data. At the end of study, degradation products were not observed, which confirm their chemical stability.

The pH–solubility profiles show a clear increase in the solubility upon aluminum complexation. Although solubility of the complexes also decreases as pH rises, it is still higher than that of their parent compounds at pHs near neutrality, including those suggested by BCS guidances (pH 6.8 and 7.5) (Table 1).

Aqueous saturated solutions of I and II have a pH of 5.80 and 5.56, respectively. The analysis of the composition of the solid phases at equilibrium at these pHs (Table 2) shows the stoichiometric composition 3:3:1 for both Cl^-:norfloxacin:Al^{3+} and Cl^-:ciprofloxacin:Al^{3+}. This means that the solubility product (*K*sp) between [Cl^-] and [$(+-)_3Al^{3+}$] species was reached.

Aluminum complexes are subjected to several equilibria along the range of pH of BCS concern yielding a higher number of species than their parent fluoroquinolones.

Table 1
Solubility at 37 °C and dose:solubility ratio of I and II compared to uncomplexed norfloxacin and ciprofloxacin.

Compound	pH	Solubility (mg/ml)	Dose (mg)	Dose:solubility ratio[a]
I	7.0	116.3	800[b]	**6.9**
	8.3	21.1	800[b]	**38.0**
Norfloxacin	6.9	1.2[c]	800[d]	666.7
	7.5	1.0[c]	800[d]	800.0
II	6.9	3.1	250[b]; 750[b]	**79.9; 239.6**
	7.6	2.4	250[b]; 750[b]	**103.7**; 311.2
Ciprofloxacin	6.9	0.22[c]	250[e]; 750[d]	1136.4; 3409.1
	7.8	0.20[c]	250[e]; 750[d]	1250.0; 3750.0

[a] Dose:solubility ratio ≤ 250, indicating high solubility related to dose (in bold numbers).
[b] Expressed as mg of norfloxacin or ciprofloxacin.
[c] From Yu et al., 1994.
[d] Maximum dose marketing authorization.
[e] Maximum dose recommended by WHO.

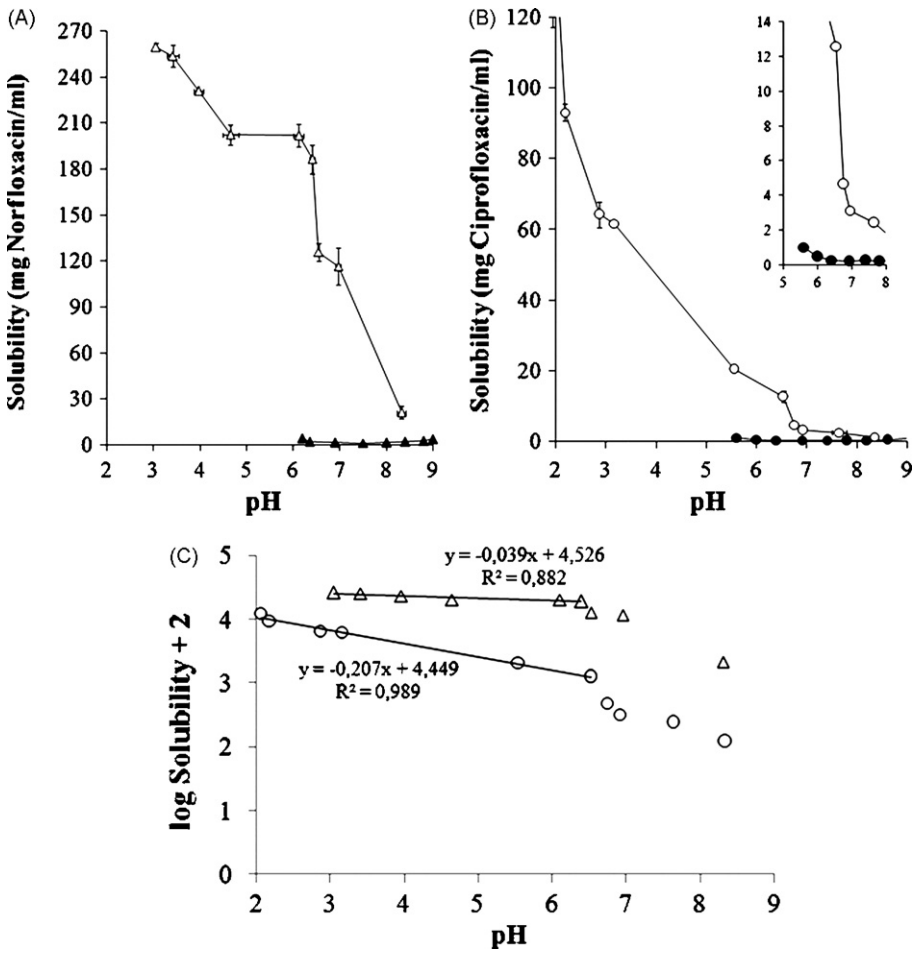

Fig. 3. (A) and (B) pH–solubility profiles of (-△-) I and (-○-) II at 37 °C compared to (-▲-) norfloxacin and (-●-) ciprofloxacin (at 40 °C taken fromYu et al., 1994). (C) pH–log solubility profiles of I and II.

In fact, on one hand, dissociation of the 3:1 complex yields 2:1 and 1:1 species together with free fluoroquinolone molecules according to Eqs. (2–4), where K_{ass} are the association constants:

$$(+-)_2Al^{+3} \quad +)(+-) \overset{K_{ass}3}{\rightleftharpoons} (+-)_3Al^{+3} \tag{2}$$

$$(+-)Al^{+3} \quad (+-) \quad \overset{K_{ass}2}{\rightleftharpoons} (+-)_2Al^{+3} \tag{3}$$

$$Al^{+3} + (+-) \quad \overset{K_{ass}1}{\rightleftharpoons} (+-)Al^{+3} \tag{4}$$

Association constants between Al^{3+} and norfloxacin at 25 °C have been reported as $pK_{ass\,1} = 7.03$, $pK_{ass\,2} = 5.44$ and $pK_{ass\,3} = 5.45$ (Okabayashi et al., 1992). Therefore, the molar solubility in acidic media is given by Eq. (5), where the species that reaches saturation crystallizes and domines the solubility since its concentration is constant under such conditions:

$$\text{Molar solubility} = [(+-)_3Al^{+3}] + [(+-)_2Al^{+3}] + [(+-)Al^{+3}] + [Al^{+3}] \tag{5}$$

A competition between Al^{3+} and H^+ to bind the fluoroquinolone arises from the overlapping among the equilibria depicted in Fig. 2 and Eqs. (2–4). Therefore, a pH effect on solubility is expected. In fact, it can be seen in Fig. 3 (C) that the increase of log solubility of I upon H^+ increasing is almost linear in the pH range 6.5 to 3.0 with a slope of $3.9*10^{-2}$ at 37 °C. Similar results were obtained at 25 °C for both compounds and are available as supporting information. Slopes close to unity are currently found in systems in which the apparent solubility is raised upon protonation of the solubility-determining specie in the pH range in which $[H^+] > K_a$. Then, the

Table 2
Solid phase analysis at selected pH in the solubility study.

Test analysis	pH									
	1.2		4.5		5.8	5.6	6.8		7.5	
	I	II	I	II	I	II	I	II	I	II
Cl^-:fluoroquinolone ratio	–	–	–	–	1	1	–	0.67	0.95	0.72
Aluminum	(+)	(–)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Uncomplexed fluoroquinolone[a]	(–)	(+)[b]	(–)	(–)	(–)	(–)	(–)	(–)	(–)	(–)
Cl^-:fluoroquinolone:Al^{3+} ratio	3:3:1	1:1:0	3:3:1	3:3:1	3:3:1	3:3:1	3:3:1	2:3:1	3:3:1	2:3:1

[a] Absence of fusion in DSC.
[b] DSC melting point 322 °C, assigned to ciprofloxacin hydrochloride fusion.

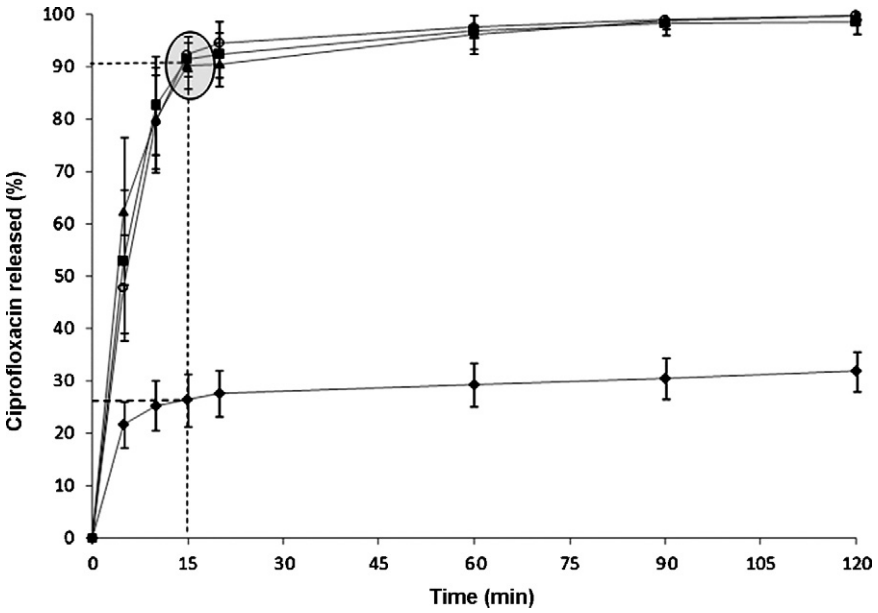

Fig. 4. Dissolution rate profiles (average of 12 units and their ± SD) of the batch of immediate release tablets of II at the three pH tested: 1.2 (-▲-), 4.5 (-■-) and 6.8 (-◯-) and commercial ciprofloxacin hydrochloride pH 6.8 (-♦-). Dashed lines indicate the percentage of ciprofloxacin dissolved in 15 min.

modest pH effect on solubility of I is clearly associated to the competition between Al^{+3} and H^+ to bind the fluoroquinolone. A similar behavior is observed with II. There, a higher slope was observed (0.21 at 37 °C) revealing a higher sensitivity of log solubility of II towards pH effects, which would be associated to its lower solubility and therefore lower Al^{+3}/H^+ ratio.

In addition, as the pH of the solutions of I and II is raised, deprotonation of complexed fluoroquinolone molecules originates species with lower water affinity and, at higher pHs, HO^- ions begin to compete with fluoroquinolones to bind aluminum.

The analysis of the composition of solid phases at equilibrium with saturated solutions of I and II at selected pHs is presented in Table 2. According to these results the stoichiometric form 3:3:1 Cl^-:norfloxacin:Al^{3+} is the species that reaches saturation and domains solubility in the whole pH range, as can be inferred from the presence of aluminum in the solid phases, the Cl^-:norfloxacin ratio and the absence of a melting endotherm in the DSC profile ascribable to uncomplexed norfloxacin, as previously reported (Olivera et al., 2000b).

A different pattern was observed with II, in which case the composition and stoichiometry of the solid phase is not constant along the pH interval. In fact, although the stoichiometric form 3:3:1 Cl^-:ciprofloxacin:Al^{3+} is the species that determines solubility at intermediate acidic pHs, the uncomplexed form ciprofloxacin hydrochloride determines solubility at pH 2. This means that the rise of (0+) and Cl^- changed the solubility control. Besides, at pHs 6.8 and 7.5 the molar ratio Cl^-:ciprofloxacin was near 0.7 for II, suggesting that one of the three ciprofloxacin molecules of the complex in the solid phase is in its unprotonated form (theoretical ratio Cl^-:ciprofloxacin = 0.666), giving a stoichiometric composition 2:3:1 Cl^-:ciprofloxacin:Al^{3+} at that pHs.

As a result of the solubility increase observed, both complexes fulfill the criterion of dose:solubility < 250 ml and then, from the BCS point of view, they can be classified as "high solubility" APIs. The only exception is for the ciprofloxacin dose strength of 750 mg at upper pH limit to the FDA criteria (pH 7.5) since it allows dissolution of only 600 mg of ciprofloxacin contained in II. It was recently suggested that the FDA should also redefine the solubility boundaries for BCS high solubility to pH 1.2–6.8 (Yu et al., 2002) and recent publications have used this interval for solubility classification (Manzo et al., 2006; Kalantzi et al., 2006).

The increase in solubility upon complexation set the complexes as class 3 drugs, different from the APIs currently used in solid dosage forms norfloxacin and ciprofloxacin hydrochloride, which are class 4 drugs.

3.3. Development of a very rapidly dissolving formulation

The solubility improvement could allow to the development of more efficient formulations, with high solubility in the entire intestinal pH.

Complex II was selected to develop a formulation to be evaluated according to the BCS premises, since it was more challenging owing its more critical solubility.

Uniformity of content (0.516 ± 0.01 g) and friability (0.12%) of the batch surpass USP requirements for infrared solid dosage forms.

In Fig. 4, the percentage release (pH 1.2, 4.5 and 6.8) of II formulation tablet is provided. As can be seen there, 90% of the ciprofloxacin content dissolves in 15 min proving its very rapid dissolution at the three pHs tested. However, a noticeable variation is observed at the beginning. Additionally, disintegration times of tablets of II as a function of pH (Table 3) are in agreement with solubility profile of II and may account for the differences observed suggesting that disintegration would be the limiting step of drug release from tablets of II. In contrast, commercial ciprofloxacin hydrochloride tablet shows that its low solubility restricts dissolution of the complete dose (Fig. 4 and Table 3).

Table 3
Disintegration times and ciprofloxacin release (%) at 5, 10 and 15 min of immediate release tablets of II at the three pH tested: 1.2, 4.5 and 6.8 and commercial ciprofloxacin hydrochloride at pH 6.8.

Tablets	pH	Disintegration time (min)	Ciprofloxacin release (%)		
			5 min	10 min	15 min
II	1.2	4.68	62.5	79.9	90.2
	4.5	5.60	52.8	82.6	91.4
	6.8	5.73	47.9	79.6	92.5
Cipro® 250 mg	6.8	–	21.6	25.3	26.4

The very rapidly dissolving tablet developed can be regarded as a pharmaceutical alternative to ciprofloxacin hydrochloride tablets and would be a good way to develop more dose-efficient formulations. The pharmacokinetics, bioavailability and safety of the novel complexes are currently been studied in our laboratory.

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Appendix A. Supplementary data

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