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Formulation of a neutral solution of ciprofloxacin upon complexation with aluminum

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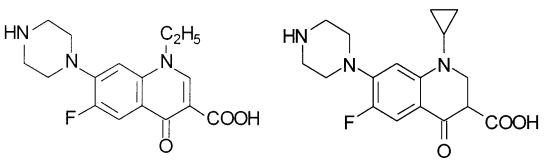
Abstract

Clear solutions of 0.5 and 1.0% ciprofloxacin (CF) of pH 7.2 were prepared by the addition of aluminum chloride hexahydrate ($AlCl_3 \cdot 6H_2O$) in the molar proportion CF:$AlCl_3 \cdot 6H_2O$ (3:1). Minimum inhibitory concentrations (MIC) of these solutions were the same as an equimolar solution of CF · HCl. Solutions exhibited good physical, chemical and microbiological stability and satisfactorily overcame an ocular irritation test on rabbits. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Ciprofloxacin; Solutions; Complexation

1. Introduction

Many of the modern fluoroquinolone antimicrobial agents (AMFQs) in current use in therapy have a piperazine ring attached at position 7. Norfloxacin (NF) and Ciprofloxacin (CF) are currently regarded as model compounds of this series.



NF CF

In aqueous solutions, such compounds exist mainly in their zwitterionic form owing to the acid/base interaction between the basic nitrogen at position 4′ of the piperazine and the 3-carboxylic acid group [1,2] (Scheme 1).

pK_1 and pK_2 data, as well as the microscopic constants of some members of the series, have been estimated and are available in the literature [3].

The acid/base interaction also determines a rather low aqueous solubility of these compounds at pH close to 7 [1–3]. This is the main factor which prevents the design of liquid dosage forms, such as parenteral and ophthalmic solutions, because the aqueous compatibility of these drugs occurs at rather basic or acid pH.

On the other hand, it is well known that fluoroquinolones form coordination complexes with several metal ions [4,5]. Complexes with trivalent cations like Fe^{3+} and Al^{3+} exhibit high affinity constants (CF–Al^{3+}), log k_1: 7.11, log k_2: 5.28, log k_3: 4.66; NF–Al^{3+}, log k_1: 6.94, log k_2: 5.16, log k_3: 4.84 [5]. Then, it was thought to take advantage of this property to improve the aqueous compatibility of these AMFQs at pH values in the neighborhood of the physiological pH. So, the aluminum cation (Al^{3+}) was selected to explore its utility to get soluble complexes with CF. Such complexes may be useful to design ophthalmic solutions.

2. Experimental

2.1. Materials

CF was obtained by precipitation of an aqueous solution of its hydrochloride upon addition of the appropriate amount of sodium hydroxide solution. The precipitate was separated by filtration, washed with

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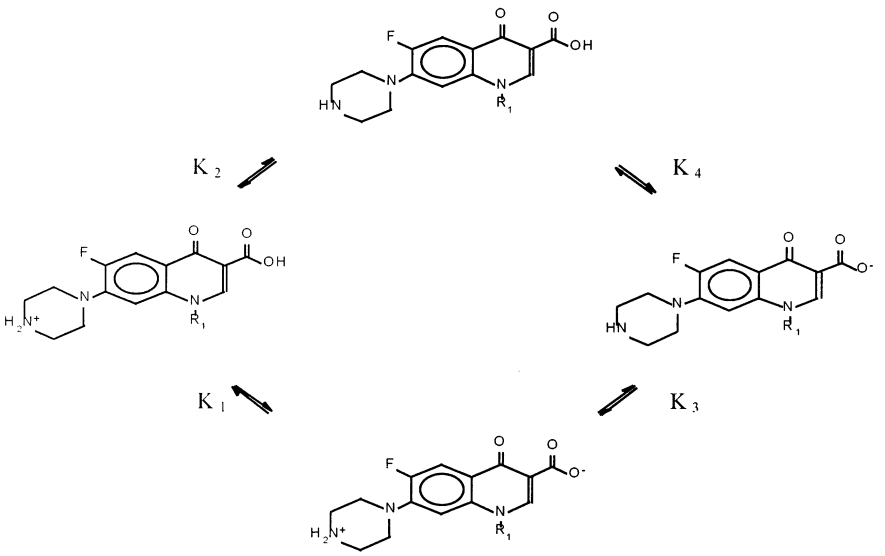

Scheme 1.

distilled water and dried under vacuum to constant weight and then recrystallized. All other reagents used were of analytical grade.

2.2. Formulation design

Solutions of CF (0.5 and 1.0% w/v) were prepared by dissolving the appropriate amounts of CF and aluminum chloride hexahydrate ($AlCl_3 \cdot 6\ H_2O$) in distilled water to keep the molar ratio ($CF:AlCl_3 = 3:1$). The pH of the resulting solutions was adjusted to 7.2 by adding sodium hydroxide solution (0.1 N) and further isotonized with sodium chloride. The bulk solutions were filtered through a 0.22 μm membrane filter and placed into glass containers (15 ml) previously sterilized under aseptic conditions.

2.3. Antimicrobial activity

The antimicrobial activity of the solutions was assayed by determining the minimum inhibitory concentration (MIC) against *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 by the broth macro dilution technique (Mueller–Hinton broth, Merck) according to the procedure outlined by the National Committee for Clinical Laboratory Standards [6].

2.4. Ocular irritability test

The ocular irritability test was performed on rabbits according to a protocol provided by the Instituto Nacional de Medicamentos (INAME) [7].

2.5. Stability of solutions

Solutions placed in the final containers and maintained at room temperature were assayed for potency and physical stability over a 14 month period through MIC assays, ocular inspection and UV spectroscopy.

Table 1
Physical stability of $CF:Al^{3+}$ solutions (0.5 and 1.0% P/V)

Time (months)	Transparency [a]	Particulate matter	UV spectra [a]
0	NC	No	NC
3.5	NC	No	NC
10.5	NC	No	NC
14	NC	No	NC

[a] NC = no change.

Table 2
Antimicrobial activity (MIC, μg/ml) of $CF:Al^{3+}$ (3:1) solution and CF hydrochloride solution against *S. aureus* ATCC 29213 and *E. coli* ATCC 25922

Time (months)	$CF:Al^{3+}$		CF hydrochloride	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*
	(1.0% w/v)		(1.0% w/v)	
0	0.25	<0.03	0.25	<0.015
3.5	0.125		0.125	
10.5	0.25	0.015	0.25	0.015
	(0.5% w/v)		(0.5% w/v)	
0	0.25	<0.03	0.25	<0.015
10.5	0.25	<0.075	0.25	0.015

3. Results and discussion

3.1. Compatibility

The method described under formulation design allows clear 0.5 and 1.0% solutions of CF–Al^{3+} having a pH of 7.2 to be obtained. Such solutions exhibited good physical stability and remained clear during the test period of time (Table 1). Also, their UV spectra did not exhibit any change during that time.

On the other hand, the pH of a solution of CF hydrochloride ranges between 3.0 and 4.5 [8]. As this pH raises with addition of sodium hydroxide solution, a precipitate is immediately formed. Therefore, the use of Al^{3+} as complexing agent appears to be a good way to increase the aqueous compatibility of CF.

3.2. Potency

For the purpose of the present study, MIC assays were considered to be sensitive enough to detect any significant difference among the antimicrobial activity of different solutions of CF.

The determination of MIC against *S. aureus* and *E. coli* indicated that CF–Al^{3+} solutions (test solutions) exhibited the same activity as equimolar solutions of CF hydrochloride (reference solutions). As can be seen in Table 2, the MIC of CF–Al^{3+} remained unchanged over the period of time assayed. Therefore, potency as well as the physical properties of CF–Al^{3+} solutions remained without significant changes during the period of time assayed (10.5 months).

It should be mentioned that in previous reports [9–11] it has been shown that metal cations can reduce the antimicrobial activity of CF. However, these studies were performed using molar ratios Al^{3+}:CF of 10^3 to 10^5, which are far away from the ratio 1:3 used here.

On the other hand, instillation of a drop of CF hydrochloride solution into the eye should shift the pH of the lachrymal fluid towards the acid side. It is well documented that the antimicrobial activity of CF is significantly reduced at acidic pHs [12,13]. Then, although both solutions exhibited the same in vitro activity, it is expected that the in vivo performance of CF–Al^{3+} neutral solution would be better than that of CF.

3.3. Ocular irritability

Both 0.5 and 1.0% solutions of CF–Al^{3+} were assayed in albino rabbit eyes. The results of the test showed that repeated instillation of the solutions does not produce ocular irritation.

4. Conclusions

The results presented show that complexation of CF with Al^{3+} satisfactorily improves its aqueous compatibility, rendering clear, stable solutions. Such solutions keep the original potency of CF and satisfactorily overcome the ocular irritation test in rabbits. Consequently, they are potentially useful in the treatment of ocular eye infections in humans.

Acknowledgements

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