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Influence of metal cations on the solubility of fluoroquinolones

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Although a clinically relevant interaction between a fluoroquinolone and a metal cation was first described more than 20 years ago the biopharmaceutical mechanism of this interaction is still not understood. One of the obvious disagreements in the literature is about the effect of metal cations on the solubility of fluoroquinolones. Namely, metal cations are reported to increase the solubility of fluoroquinolones as well as to decrease it and thus cause the lowered bioavailability. Thus in this work the solubility of ciprofloxacin, norfloxacin and ofloxacin and the effect of metal cations on the solubility of these fluoroquinolones in aqueous media of different pH values were reevaluated. The results clearly show that the metal cations either do not affect or even increase the solubility of fluoroquinolones. Thus they surely do not influence the bioavailability of these drugs by decreasing their solubility. Additionally, possible explanations for the contradictory results reported in the literature are given.

A case of a clinically significant interaction between a fluoroquinolone antimicrobial agent and metal cations present in antacids, mineral supplements and food was first reported in 1985. G. Höffken et al. have observed a decrease of ciprofloxacin bioavailability caused by a coadministration of a magnesium and aluminium containing antacid. The authors of this first report have speculated that the described drug-drug interaction may be related to the formation of complexes (coordination compounds) between the fluoroquinolone and the metal cation (Höffken et al. 1985). Numerous clinical studies in which the authors investigated drug-drug interactions between fluoroquinolones and preparations containing metal cations followed. It was shown repeatedly that the coadministration of fluoroquinolones and preparations containing metal cations generally results in a gross decrease of the fluoroquinolone bioavailability (Lomaestro and Bailie 1995).

Fluoroquinolone coordination chemistry was also intensively studied (Turel 2002). However, these studies could not confirm that the loss of fluoroquinolone bioavailability is a direct consequence of complexation with metal cations. Physico-chemical properties of fluoroquinolones in the presence of metal cations were studied to a lesser

extent. From the biopharmaceutical point of view, the solubility and the possible effect of metal cations on the solubility of fluoroquinolones are highly important because the solubility is one of the parameters, which directly determine drug bioavailability. Ross and Riley discovered that the solubility of lomefloxacin increases due to the presence of Ca^{2+} and Mg^{2+} in an acetate buffer at pH = 5, in the presence of Fe^{3+} in 0.1 M HCl at pH = 1 and in the presence of Al^{3+} in acetate buffer at pH = 4.35. The solubility of the same fluoroquinolone was decreased only by the presence of Bi^{3+} ions at pH = 0. Such extreme experimental conditions were necessary to dissolve the tested metal cations (Ross and Riley 1992). However, solubility determinations at pH = 1 or 0 may lack biopharmaceutical relevance, since the pH value at the site of fluoroquinolone absorption (duodenum and jejunum) is usually not lower than 5 (Barraclough and Taylor 1996). Furthermore the binding constants between metal cations and fluoroquinolones are pH dependent (Ross and Riley 1993). Later, Rodríguez Cruz et al. (1999) reported that the *in vitro* dissolution profile of fluoroquinolones in a phosphate buffer at pH 6 is significantly lowered in the presence of Al^{3+} or Fe^{2+}. Turel also attributed the fluoroquinolone-metal ion interaction to the decrease of the fluoroquinolone solubility (Turel 2002) and even a textbook of medicinal chemistry (Mitscher 2002) states that fluoroquinolones "form less water soluble complexes" with metal ions. On the other hand, some authors have reported the use of Al^{3+} for the solubilisation of ciprofloxacin in liquid dosage forms (Allemandi et al. 1999; Alovero et al. 2003).

It is obvious that the existing literature does not resolve the issue whether the altered solubility in the presence of metal cations causes the decreased bioavailability of fluoroquinolones. The experimental conditions used in some of the above mentioned studies could be either biologically irrelevant, or could change during the experiments (i.e. because of poorly buffered media). We have thus performed a rapid evaluation of the solubility of ciprofloxacin, norfloxacin and ofloxacin (three fluoroquinolones with different intrinsic solubilities (Firestone et al. 1998; pION INC, 2003)) and the effect of metal cations on the solubility of these fluoroquinolones in media buffered to different pH values by different buffers. Aqueous media with pH values 5, 6 and 7 were used and the nominal concentrations of metal cations were 5 mM. We were aware of the fact that this resulted in less defined experimental conditions since the tested metal cations are not sufficiently soluble at these pH values. Thus, the influences of precipitation of metal cations in the form of poorly soluble hydroxides or salts and possibly the adsorption of fluoroquinolones on these precipitates were included in the obtained results. By doing so, we have obtained the results in more biologically relevant experimental conditions since the same processes also occur in the gastrointestinal tract after ingestion of medicines containing metal cations. Namely, nominal concentrations of metal cations in the small intestinal lumen are most likely in the range of 1 to 50 mM, which is also much higher than their solubility.

The results presented in the Table clearly show, that the solubility of fluoroquinolones is either greatly increased or not significantly affected by the presence of metal cations in the medium. According to the theory of the biopharmaceutical classification system (Amidon et al. 1995) minor (although possibly statistically significant) alterations of solubility will not cause detrimental alterations of the drug bioavailability. Thus, only several-fold changes of fluoroquinolone solubility are considered important. As none of the fluoroquinolone – metal cation – buffer combinations yielded an important decrease in solubility, one can conclude, that lowered solubility does not cause the decrease of fluoroquinolone bioavailability after concurrent administration of food or drugs containing metal cations. On the contrary, we have observed that especially Al^{3+} and Fe^{2+} increase the solubility of poorly soluble fluoroquinolones in some buffers to such an extent that Al^{3+}, which is also oxidatively stable, could indeed be used to solubilise poorly soluble fluoroquinolones in liquid pharmaceutical preparations as has been previously suggested (Allemandi et al. 1999; Alovero et al. 2003).

The results in the Table also show that different buffers used to obtain the same pH (7) of the dissolution medium can lead to different effects of metal cations on the fluoroquinolone solubility. Bicarbonate buffer could be seen as a reference since it is roughly mimicking the duodenal and jejunal medium. On the other hand HEPES and especially phosphate buffers are often used in dissolution testing of pharmaceutical preparations. It can also be seen from the results in the Table that the effects of a metal cation on fluoroquinolone solubility in different buffers at the same pH value can be surprisingly different. This observation might explain some of the discrepancies reported in the literature. Furthermore, the great effect of pH on the solubility of most fluoroquinolones could impair the quality of the results obtained in poorly buffered (e.g. phosphate buffer at pH 6 (Rodríguez Cruz et al. 1999)) or even unbuffered (Eboka and Okeri 2005; Córdoba-Díaz et al. 2000) media. Thus, care should be taken when choosing the appropriate dissolution medium for the evaluation of *in vitro* interactions of fluoroquinolone preparations with metal cations. Such evaluations should be performed in several different dissolution media at neutral or slightly acidic pH to avoid improper generalisations of the obtained results. Furthermore, it would also be beneficial to perform such experiments in bicarbonate buffer if possible. Anyhow no *in vitro* – *in vivo* correlation can be ex-

Table: Solubility of three fluoroquinolones in various media containing different metal cations

Metal ion/pH	Acetate 5	MES 6	HEPES 7	Phosph. 7	Bicarb. 7
Ciprofloxacin					
None/blank	2.5	0.8	0.4	0.3	0.3
Mg^{2+}	5.0	2.1	0.9	0.7	0.4
Ca^{2+}	2.5	0.9	0.6	0.2	0.4
Al^{3+}	11.1	8.2	5.9	0.3	2.4
Fe^{3+}	6.1	1.7	1.0	0.2	0.4
Fe^{2+}	10.4	12.6	4.5	3.4	4.5
Norfloxacin					
None/blank	10.6	5.4	2.9	1.8	1.9
Mg^{2+}	15.1	21.4	4.2	5.6	2.1
Ca^{2+}	12.8	8.8	9.4	1.5	3.3
Al^{3+}	21.2	20.8	19.8	5.9	17.0
Fe^{3+}	13.2	5.0	6.6	2.9	4.8
Fe^{2+}	20.2	23.5	13.3	11.5	8.6
Ofloxacin					
None/blank	13.9	14.1	10.9	9.2	9.2
Mg^{2+}	23.1	26.7	23.0	19.9	20.0
Ca^{2+}	20.2	22.7	16.6	9.2	13.9
Al^{3+}	22.2	17.6	23.6	23.2	22.8
Fe^{3+}	24.5	12.8	13.7	19.0	20.4
Fe^{2+}	21.3	24.5	15.9	41.5	17.4

pected for such studies since the effect of metal cations on the solubility of fluoroquinolones is obviously different than their effect on the bioavailability of these drugs.

Experimental

Ciprofloxacin was purchased from Fluka (Deisenhofen, Germany). Norfloxacin and ofloxacin were supplied by Sigma Aldrich Chemie (Steinheim, Germany). The salts of metal cations used in the study ($CaCl_2 \times 2\,H_2O$, $MgCl_2 \times 6\,H_2O$, $AlCl_3 \times 6\,H_2O$, $FeSO_4 \times 7\,H_2O$, $FeCl_3 \times 6\,H_2O$) and all buffer components provided by Merck (Darmstadt, Germany) were of analytical grade.

An excess of fluoroquinolone and 1.5 mL of the appropriate medium (see Table) were placed in pressure resistant plastic vials, which contained the volatile buffer components (acetic acid and carbon dioxide). Ion strength of all media was set to 0.1 by NaCl. The pH value was controlled before and after shaking at 120 rpm for 60 min (a preliminary experiment has shown that the equilibrium solubility is reached after 10–20 min) at 36 °C. Afterwards, the samples were filtered through 0.22 μm pore size filters and diluted 100-fold for analysis. The coefficient of variability (CV) of the results obtained by this procedure was lower than 10%. Concentrations of all fluoroquinolones were measured by HPLC (Agilent 1100 series; UV detection at 278 nm after separation on a 25 mm C18 Chromolith Flash column with 13% of acetonitrile and 87% of phosphate buffer (pH = 3.9) at a flow rate of 3mL/min. The retention times of ciprofloxacin and norfloxacin were 0.6 min while the retention time of ofloxacin was 0.7 min.

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