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Physicochemical properties of the fluoroquinolone antimicrobials. III. Complexation of lomefloxacin with various metal ions and the effect of metal ion complexation on aqueous solubility

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Summary

The complexation of lomefloxacin with five metal ions (Al^{3+}, Ca^{2+}, Mg^{2+}, Bi^{3+}, and Fe^{3+}) commonly found in antacid or vitamin preparations has been studied at 25°C. The stability constants and stoichiometries were determined by measuring the change of aqueous solubility of lomefloxacin as a function of metal ion concentration. The concentration of lomefloxacin was determined by liquid chromatography. The stoichiomtery of binding was confirmed independently by FAB-MS analysis of aqueous solutions of the complexes. The binding constants were dependent on the nature of the metal ion and were related to the charge density. The pharmaceutical and biopharmaceutical implications of the effects of metal ion complexation on the aqueous solubility of lomefloxacin are discussed.

Introduction

The fluoroquinolones are an important class of antimicrobials whose potential clinical usefulness continues to expand (Desplaces et al., 1986; Mitscher et al., 1989). One of the most widely quoted and most frequently investigated drug incompatibility of the fluoroquinolones arises from their apparent interactions with antacids and other drugs, such as ranitidine, which modify the intestinal pH (Flor et al., 1985, 1990; Hoffken et al., 1985a,b, 1988; Frank et al., 1986; Lener et al., 1987; Schentag et al., 1988; Frost et al., 1989a,b; Grasela et al., 1989; Nix et al., 1989a,b; Polk, 1989; Polk et al., 1989; Brouwers et al., 1990). Co-administration of the fluoroquinolones with antacids has also been implicated in a reduction in antimicrobial activity in urine (Barbhaiya et al., 1982; Ratcliffe et al., 1983; Pohlod et al., 1984; Kumada et al., 1985; Smith et al., 1985, 1988; Blaser et al., 1988; Gurdal et al., 1990; Perez-Giraldo et al., 1990). This reduction in activity has been attributed to the high concentration of magnesium in urine. This theory is supported by the observations that the quinolones are less ac-

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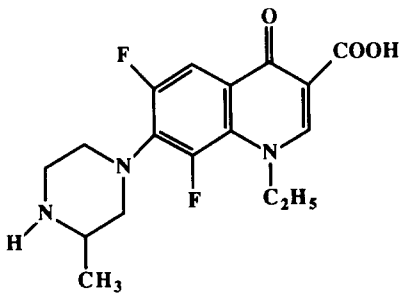

Lomefloxacin
Fig. 1. Structure of lomefloxacin.

tive in urine than in buffer solutions and that addition of magnesium and other cations to urine further reduces their antimicrobial activity (Ratcliffe and Smith, 1983; Blaser et al., 1985; Smith and Ratcliffe, 1985; Blaser and Luthy, 1988; Gurdal et al., 1990; Perez-Giraldo et al., 1990).

It is not clear from the previous studies whether the effects of antacids on the biopharmaceutical properties of the fluoroquinolones are due to the effects of metal ion complexation, shifts in pH of intestinal fluid or urine, or both. Elsewhere, we have reported on the effects of pH on aqueous solubility and 1-octanol-water partition coefficient (Ross et al., 1990, 1992a,b). To understand the physicochemical basis of the clinically important interaction of this class of drug and oral antacids, a systematic, comparative study of the complexation of the fluoroquinolone antimicrobials with the metal cations commonly found in antacid preparation is clearly needed. This paper was concerned with the complexation of a model fluoroquinolone, lomefloxacin (Fig. 1) with Fe^{3+}, Bi^{3+}, Ca^{2+}, Mg^{2+}, or Al^{3+}.

Materials and Methods

Materials

Lomefloxacin mesylate and lomefloxacin HCl were gifts from G.D. Searle and Co., Skokie, IL). The buffer components and metal salts (in their chloride forms) for complexation studies were ACS reagent and all other chemicals were reagent grade. Water was purified in a Milli-Q Water System (Millipore Corp., Bedford, MA) and stored in glass containers until use.

Data analysis and statistical considerations

Statistical analyses were conducted with the software package StatView SE$^{+®}$ (Abacus Concepts, Inc., Berkeley, CA) on a Macintosh® (Apple Computer, Inc., Cupertino, CA) personal computer.

Apparatus

pH measurements pH values were determined on an Orion SA 520 pH meter (Orion Research, Inc., Boston, MA) and a Tiny Combination pH electrode (Microelectrodes, Inc., Londonderry, NH) or a calomel pH combination glass electrode (Markson, Phoenix, AZ).

Liquid chromatography Samples were assayed for fluoroquinolone content by LC using the method described previously (Ross and Riley, 1990, 1992b).

Thermogravimetric analysis (TGA) TGA was performed on a Perkin-Elmer TGS-2 Thermogravimetric Analyser interfaced with a Perkin-Elmer Thermal Analytical Data Station.

Fast atom bombardment mass spectrometry (FAB-MS) FAB-MS spectra of lomefloxacin and Al^{3+}, Mg^{2+}, and Fe^{3+} mixed at a drug:metal ratio of 4:1 were obtained on a ZAB HS mass spectrometer (VG Analytical Ltd, Manchester, U.K.) equipped with a 11/250 data system. Aqueous samples were diluted with a mixture of glycerol/ thioglycerol. Positive ion fast-atom bombardment (FAB) was performed using a xenon gun operated at 8 keV energy and 0.8 mA emission.

Complexation studies

Dithizone test Glassware was washed with nitric acid and rinsed with metal-free water before use to eliminate any trace metal contaminants. All buffers were checked for the presence of heavy metal ions using the dithizone test (Stout et al., 1939).

Determination of binding constants by the solubility method The solubility of lomefloxacin in the presence of Al^{3+}, Ca^{2+}, Mg^{2+}, Bi^{3+}, and

Fe^{3+} was studied at constant pH and ionic strength (with NaCl). Excess drug was added to a series of buffer solutions (Ca^{2+}, 0.5 M acetate buffer, pH 5, $\mu = 1.3$; Mg^{2+}, 0.5 M acetate buffer, pH 5, $\mu = 1.4$; Al^{3+}, 1 M acetate buffer, pH 4, $\mu = 2.5$; Fe^{3+}, 0.1 M HCl, pH 1, $\mu = 1.2$; Bi^{3+}, 1 N HCl, pH 0, $\mu = 1.7$) in which the concentration of metal ion was increased incrementally. The pH was measured at the beginning and at the end of each experiment to ensure that no change in pH had occurred. Numerous preliminary experiments were conducted (data not shown) to determine the molarity of buffers needed to control the pH. Once the appropriate buffer concentration had been determined the final experiments were then performed at constant ionic strength. The solutions were protected from light by wrapping the sample vials in aluminum foil and agitated for at least 24 h in a water bath at 25°C. After equilibrium was achieved, the samples were centrifuged, diluted with mobile phase and assayed by LC. Equilibrium was considered to be acheived when two samples taken at least 1 h apart varied in concentration by less than 10%. All solubility determinations were made at least in triplicate.

Theory

Interactions between a substrate and ligand may result in the formation of one or more thermodynamically stable complexes. The proportions of each complex present will depend on concentration. Higher order complexation may be expressed as a series of bimolecular reactions:

$$L \overset{S,\ K_{11}}{\rightleftharpoons} SL \overset{S,\ K_{21}}{\rightleftharpoons} S_2L \ldots \overset{S,\ K_{m1}}{\rightleftharpoons} S_mL \qquad (1)$$

Eqn 1 assumes that no more than one ligand molecule combines with the substrate molecules. The general formula, Eqn 2, for the binding of m subtrates is:

$$K_{m1} = \frac{[S_mL]}{[S][S_{(m-1)}L]} \qquad (2)$$

The stepwise binding constants (or stability constants) for 1:1 or 2:1 complexes can be defined as follows:

$$K_{11} = \frac{[SL]}{[S][L]} \qquad (3)$$

$$K_{21} = \frac{[S_2L]}{[S][SL]} \qquad (4)$$

The units of the stepwise binding constants are M^{-1}. Often it is impossible to separate the individual binding constants and the apparent binding constant (K_{app}) is used:

$$K_{appmn} = \frac{[S_mL_n]}{[S]^m[L]^n} \qquad (5)$$

The stability product, K_{appmn}, is simply the product of the stepwise stability constants. For example, if $m = 2$ and $n = 1$, $K_{app}21 = K_{11}K_{12}$.

For a series of stepwise equilibrium processes as described above the mass balances of the substrate and the ligand may be expressed by Eqns 6 and 7, respectively:

$$[S]_t = [S] + [SL] \ldots + m[S_mL] \qquad (6)$$

$$[L]_t = [L] + [SL] \ldots + [S_mL] \qquad (7)$$

Results

Analytical methods

Initially analytical investigations (UV spectrophotometry, fluorescence, titrimetry and solubility) were conducted to determine whether one analytical technique could be used to measure the binding of all the metal ions of interest with lomefloxacin. Preliminary studies indicated that the UV absorbance of lomefloxacin was shifted dramatically in the presence of Fe^{3+} and Bi^{3+}; however, no substantial shift in UV absorbance was seen in the presence of Ca^{2+}, Mg^{2+}, or Al^{3+}. The fluorescence intensity of lomefloxacin was found to increase dramatically in the presence of

Ca^{2+} and Mg^{2+}, but not in the presence of Fe^{3+}, Bi^{3+}, or Al^{3+}. Although the potentiometric titration of lomefloxacin with Bi^{3+} was precluded because of limited solubility of bismuth salts, titrations with lomefloxacin in the presence of Ca^{2+}, Mg^{2+}, Fe^{3+}, and Al^{3+} were performed. The pH-titration curves of lomefloxacin in the presence of Fe^{3+} or Al^{3+} were shifted dramatically, while only small shifts were seen in the presence of Ca^{2+} or Mg^{2+}. The change in UV absorbance in the presence of Fe^{3+} and Bi^{3+}, the change in fluorescence in the presence of Ca^{2+} and Mg^{2+}, and the shift in the pH-titration curve in the presence of Fe^{3+} and Al^{3+}, were all taken as evidence that all the metal ions studied here complexed with lomefloxacin. However, none of these analytical techniques provided a single method to study the complexation of lomefloxacin with all the metal ions of interest.

Fortunately, the change in aqueous solubility of lomefloxacin in the presence of Ca^{2+}, Mg^{2+}, Al^{3+}, Bi^{3+}, and Fe^{3+} was found to provide a single method by which to compare the complexation of all the metals ions of interest and to aid in the understanding of the solubility of the metal-ion drug complexes.

Complexation measured by changes in aqueous solubility

The solubility of lomefloxacin was found to increase in the presence of Ca^{2+}, Mg^{2+}, Al^{3+}, or Fe^{3+}. The solubility of lomefloxacin increased to a constant value with increasing Bi^{3+}, followed by a marked decrease in solubility at higher Bi^{3+} concentrations. Although attempts were made to hold the the ionic strength of solutions constant, it should be noted that at metal ion concentrations ≥ 0.05 M the solubility of drug was dramatically higher and this contributed to an increase in the ionic strength. In addition to providing valuable practical information about the relationship between solubility and metal ions, the increase in solubility with increasing metal ion concentration was also used to determine the stability constants. Because excess solid substrate was always present, it was assumed that $[S] = S_0$. Assuming that no more than one ligand molecule (metal ion) will bind to the substrate molecule (lomefloxacin), rearrangement and substitution of the mass balance equation (Eqn 6) and the apparent binding constant equation (Eqn 5) results in:

$$[S]_t = \frac{mK_{appm:1}S_0^m[L]_t}{1 + K_{appm:1}S_0^m} + S_0 \qquad (8)$$

In deriving Eqn 8, the assumption was made that the highest order complex is the predominating species. A plot of $[S]_t$ vs $[L]_t$ gives an intercept of S_0 and a slope (λ):

$$\lambda = \frac{mK_{appm:1}S_0^m}{1 + K_{appm:1}S_0^m} \qquad (9)$$

Rearrangement of Eqn 9 allowed the calculation of $K_{appm:1}$:

$$K_{appm:1} = \frac{\lambda}{mS_0^m - \lambda S_0^m} \qquad (10)$$

For Mg^{2+}, Ca^{2+}, Al^{3+} and Fe^{3+} complexation, the experimental data were plotted according to Eqn 8 (Figs 2 and 3). If the slope was less than unity, the assumption was made that $m = 1$ unless other evidence supported the existence of higher order complexes such as mass spectral data or elemental analysis of the isolated solid complex.

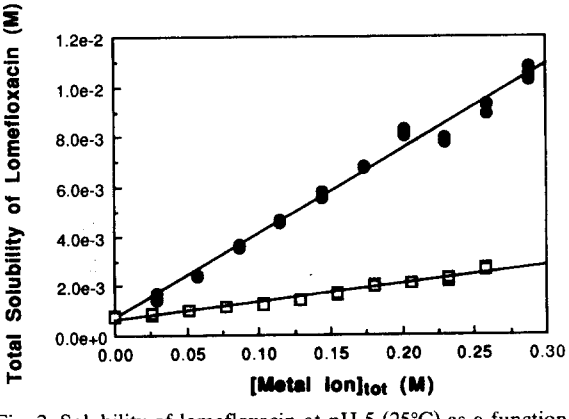

Fig. 2. Solubility of lomefloxacin at pH 5 (25°C) as a function of the total metal ion concentration: Mg^{2+} (●) and Ca^{2+} (□).

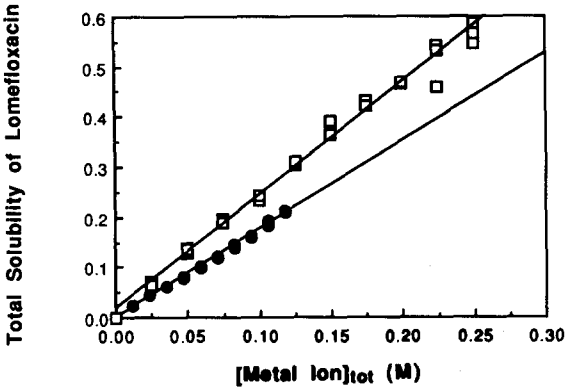

Fig. 3. Solubility of lomefloxacin (25°C) as a function of total metal ion concentration: Fe^{3+} (pH 1) (●) and Al^{3+} (pH 4.35) (□).

Because mass spectrometry indicated the presence of a 2:1 (drug:metal) Mg^{2+} complex (see below), the assumption was made that at high concentrations of drug, such as during the solubility studies, the 2:1 (drug:metal) complex was the predominant species. Therefore, K_{app21} was calculated using Eqn 10 and the assumption that $m = 2$ (Table 1).

Timmers and Sternglanz (1978) reported 1:1 complex formation between nalidixic acid and Mg^{2+} using spectrophotometric methods, however, the drug concentration was only 3×10^{-5} M while concentrations of Mg^{2+} as high as 1.25×10^{-2} M were used. Because the concentration of Mg^{2+} was much greater than that of nalidixic acid in these studies (Timmers and Sternglanz, 1978), formation of higher-order complexes with respect to the drug would be expected to be minimal due to a limited amount of the drug available for complexation.

The plot of $[S]_t$ versus $[Fe^{3+}]$ (Fig. 3) resulted in a line whose slope was greater than 1 indicating the presence of complexes with more than one molecule of lomefloxacin. Therefore, the assumption was made that the 2:1 (drug:metal) complex was the predominant species present ($m = 2$) and a value for K_{app21} was calculated using Eqn 10 (Table 1). The assumption of a 2:1 (drug:metal) complex with Fe^{3+} is consistent with the findings of Issopoulos (1989) who reported 2:1 (drug:metal) complexes formed between norfloxacin and Fe^{3+}. The latter author also reported a log K_{app21} value of 8.60 (Issopoulos, 1989), which is a higher value than that determined here for the lomefloxacin-Fe^{3+} complexes (log $K_{app21} = 7.07$). Ruzicka et al. (1975) also reported that Fe^{3+} formed a 2:1 complex with nalidixic acid at pH 1 with a binding constant (log $K_{app21} = 8.2$–8.34) which was also higher than seen here with lomefloxacin. Vincent et al. (1981) reported that Fe^{2+} formed a 2:1 complex with nalidixic acid with a log K_{app21} value of 6.86. Behrens et al. (1986) synthesized some solid complexes of nalidixic acid and various metals and reported the formation of 3:1 (drug:metal) complexes between nalidixic acid and Fe^{3+}, however, the stoichiometry of these solid complexes may not be indicative of the predominant species in solution.

The plot of $[S]_t$ vs $[Al^{3+}]$ (Fig. 3) resulted in a line whose slope was greater than 2, again indicating the presence of higher order complexes. Therefore, the assumption was made that the 3:1 (drug:metal) complex was the predominant species present ($m = 3$) and a value for K_{app31} was calculated using Eqn 10 (Table 1). Although the binding constant was not evaluated, Nakano et al. (1978) reported the stoichiometry of nalidixic acid-Al^{3+} complexes to be 3:1 which is consistent with that determined here with lomefloxacin and Al^{3+}.

The solubility curves of lomefloxacin with Ca^{2+}, Mg^{2+}, Al^{3+}, and Fe^{3+} were classified as type A systems (Higuchi et al., 1965). The complex was soluble throughout the entire concentration range of the ligand; therefore, pure substrate (S) was

TABLE 1

Apparent binding constants of lomefloxacin with various metal ions at 25°C

Metal ion	Stoichiometry (drug:metal)	log K_{app}	[Complex]/[L] [a]
Ca^{2+}	1:1	1.05 ± 0.03	7.56×10^{-3}
Mg^{2+}	2:1	4.56 ± 0.11	1.55×10^{-2}
Bi^{3+}	2:1	5.29 ± 0.32	1.07×10^{-1}
Fe^{3+}	2:1	7.07 ± 0.07	7.07
Al^{3+}	3:1	10.37 ± 0.09	3.09

[a] $[Complex]/[L] = K_{appm:1}\ S_0^m$ where L is the metal ion.

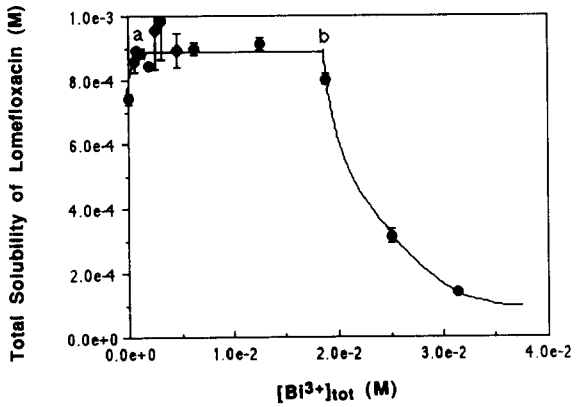

Fig. 4. Solubility of lomefloxacin at pH 0 (25°C) as a function of total Bi^{3+} concentration.

the solid phase in these systems. In contrast, a type B phase diagram was obtained for the Bi^{3+}-lomefloxacin system (Fig. 4). As with the type A system, Higuchi and Connors (1965) have shown that the complex is soluble in the initial portion of the diagram but precipitates after reaching its solubility limit at some critical value of ligand (L) concentration (point a). From points a to b, the concentration of S remains constant due to dissolution of solid S and increasing concentrations of L resulting in the formation of complex which precipitated. Therefore, the solids present in the a–b portion of the diagram are solid complex and solid S (Fig. 4). The length of the plateau is a function of the amount of substrate present initially. When all the solid S has been consumed by complex formation (point b), further addition of L results in formation of complex which precipitates and decreases the total concentration of S in solution (Higuchi and Connors, 1965). To determine the stoichiometry of the complex, the amount of Bi^{3+} present in the solid complex was calculated from the length of the plateau (1.69×10^{-2} M) and the amount of lomefloxacin present in the solid complex was calculated from the difference between the height of the plateau (8.95×10^{-4} M) and the total amount of lomefloxacin added (15 mg $ml^{-1} = 3.35 \times 10^{-2}$ M). The ratio of drug:metal in solid complex was calculated to be 1.93:1 indicating the stoichiometry of the complex was 2:1. The value of the apparent binding constant for Bi^{3+} was obtained by using the slope of the ascending portion of the curve. Table 1 lists the values of log K_{app} for the different metal ions calculated using the experimental S_0 value, the slope of the line, and the assumptions about the various stoichiometries of the complexes as described above.

Because the stoichiometries of the various complexes were different, the ratio of [complex]/[L] has been included to compare the affinity of the different metals to form complexes. At equivalent concentrations of metal ion present, Al^{3+} would bind the largest amount of drug; however, there would be a greater percentage of Fe^{3+} bound as complex.

TABLE 2

Comparison of calculated and observed elemental analyses of the Bi^{3+}-lomefloxacin complexes

Element	Elemental analysis			
	Calculated (%)			Observed (%)
	1:1 ($C_{17}H_{19}O_3N_3Bi$)	2:1 ($C_{34}H_{38}O_6N_6Bi$)	3:1 ($C_{51}H_{57}O_9N_9Bi$)	
C	27.09	33.5	36.36	29.98
H	2.66	3.37	3.62	3.59
N	5.58	6.90	7.49	6.06
Bi	27.76	17.16	12.42	16.75
Cl	23.24 (5) [a]	22.99 (8) [a]	22.88 (11) [a]	22.93
H_2O [b]	2.39 (1) [a]	2.22 (1.5) [a]	2.14 (2) [a]	2.37

[a] Numbers in parentheses indicate the number of atoms estimated to be associated with the complex as calculated from the actual analysis.

[b] Determined by TGA.

Elemental analysis of the solid Bi^{3+} complex (Table 2) was consistent with the 2:1 stoichiometry estimated from the solubility study plateau (Fig. 4). Although the carbon, nitrogen and bismuth contents were slightly lower than predicted by theory for a 2:1 complex, the percentage found was consistently closer to that predicted for a 2:1 complex than for either a 1:1 or 3:1 complex. The solid complex was found to contain chloride which was also apparently complexed with the bismuth and 1.5 molecules of water as determined by TGA.

Stoichiometry of lomefloxacin-metal ion complexes by FAB-MS

For a complete understanding of the complexation of a drug with a metal ion, it is necessary to know the stoichiometry of the formed complex. In general, the greater the number of bonds formed with the metal ion, the greater the stability of the complex; therefore, large coordination numbers are favored between negatively charged ligands and positive metal ions (Demitras et al., 1972). Steric and electrostatic repulsion factors between ligands oppose the tendency toward large coordination numbers, thus causing difficulty when making predictions regarding coordination numbers (Demitras et al., 1972). In the case of ligands which have more than one potential complexation site, such as the tetracyclines, the ability of ligand to bind more than one metal may also influence the stoichiometry of the complexes formed. The quinolones have two potential complexation sites, the 3,4-β-dicarbonyl system and the 4′-piperazinyl nitrogen.

The solubility experiments only estimated the stoichiometry of the lomefloxacin-metal ion complexes. Therefore, it was of interest to verify the presence of complexes with the stoichiometry assumed for the purpose of determining the binding constants. FAB-MS was used to probe the stoichiometry of the Mg^{2+}, Fe^{3+}, Al^{3+}, and Bi^{3+} complexes. In a recent review article, Miller (1989) pointed out some of the problems with using FAB-MS in the study of metal coordination. The two most important problems with the FAB spectra are the reduction which can occur in the radiation-damaged matrix and the insensitivity of the FAB desorption technique toward multiply charged ions. Other drawbacks include matrix compounds reacting with the analyte or analyte reacting with the material from which the probe tip is constructed. Therefore, FAB-induced reactions, such as protonation, dehydrogenation, and reduction, must be taken into account when interpreting FAB-MS data generated to probe solution equilibria (Miller, 1989).

TABLE 3

Peak pattern assignments for the positive-ion FAB-MS of lomefloxacin methane sulfonate complexed with Mg^{2+}, Fe^{3+}, and Al^{3+}

Mg^{2+}		Fe^{3+}		Al^{3+}	
Assignment	AMU	Assignment	AMU	Assignment	AMU
L	352	L	352	L	352
MgL_2	725	L_2	703	AlL_2	727
		FeL_2	757	AlL_2MNa	845
		L_3	1054	L_3	1054
		FeL_3	1108	L_3Na	1078
				L_3Na_2	1100
				AlL_3M	1174

L, lomefloxacin; M, methanesulfonic acid (CH_3SO_3H).

The peak pattern assignments are summarized in Table 3. The presence of a 1:1 complex was not detected for any of the metal ions but this may be an artifact of the FAB desorption technique since the 1:1 complex would be expected to have a 3^+ charge. In the Mg^{2+}-lomefloxacin solutions, only the free drug and 2:1 (drug:metal) complex were observed while the Al^{3+} and Fe^{3+} solutions appear to have 3:1 (drug:metal) complexes present in addition to the free drug and 2:1 (drug:metal) complex. The Al^{3+} and Fe^{3+} solutions also showed the presence of polymeric species of drug.

Discussion

Because there have been many reports in the literature which indicate that different metal ions affect the bioavailability and the antimicrobial activity of the quinolones in different ways, it is important to understand the effects of specific

metal ions on binding. If a particular metal ion did not bind to the quinolones, a product containing this metal ion would represent an attractive alternative in an antacid formulation to one which binds strongly to the quinolones. Therefore, a study of the complexation of lomefloxacin with the metal ions currently contained in antacid products (Ca^{2+}, Mg^{2+}, Al^{2+}, and Bi^{3+}) or iron preparations (Fe^{3+}) was undertaken to evaluate the differences in binding to the various metal ions.

The binding constant and stoichiometry of the lomefloxacin-metal ion complex were found to vary with the metal ion. The divalent cation, Ca^{2+}, was found to form a 1:1 complex with lomefloxacin. The cations, Mg^{2+}, Bi^{3+} and Fe^{3+} were found to form 2:1 (drug:metal) complexes with lomefloxacin, while the other trivalent cation studied, Al^{3+}, formed 3:1 (drug:metal) complexes with lomefloxacin. Antacids containing Ca^{2+} and Mg^{2+} may be preferred to those containing Al^{3+} or Bi^{3+} because the former bound lomefloxacin very weakly. In addition, the Bi^{3+} complex of lomefloxacin was much less soluble in water than lomefloxacin itself.

The order of stability of metal complexes has been studied by inorganic chemists for years. Mellor and Maley (1948) reported that the stability of organo-metallic complexes of divalent cations followed the order $Pd^{2+} > Cu^{2+} > Ni^{2+} > Co^{2+} > Zn^{2+} > Cd^{2+} > Fe^{2+} > Mn^{2+} > Mg^{2+}$ regardless of the nature of the ligands involved and noted that metals forming dsp^2 bonds (Cu^{2+} and Pd^{2+}) resulted in the most stable complexes. Other workers (Irving et al., 1948; Chapman, 1954) suggested that ionization potential or the electronegativity of the metal may be a determinant of the stability of a complex. They proposed that the stability of a complex was determined by the ease of formation of the complex, which was governed by the ionization potential and by the strength of the metal-ligand bonds after complex formation, which, in turn, was governed by the electronegativity differences of the metal and the ligand. Irving and Williams (1953) observed that the stability of a complex increased with the atomic number of the element in the first transition series. They proposed that complex stability

TABLE 4

Ionic radii and charge densities of the metal ions studied

Metal ion	Ionic radius (Å) [a]	Charge density ($Å^{-1}$) [b]
Ca^{2+}	0.99	2.0
Mg^{2+}	0.65	3.1
Bi^{3+}	0.96	3.1
Fe^{3+}	0.64	4.7
Al^{3+}	0.50	6.0

[a] As reported by Demitras et al. (1972).
[b] Charge/ionic radius.

is governed by electrostatic interactions as well as the tendency towards formation of a covalent bond between metal and ligand. The ionization potential of the cation was proposed to provide a measure of the electron-affinity of the cation and the reciprocal of the ionic radius served as a measure of the force of electrostatic interaction (Irving and Williams, 1953).

Although the interaction between the ligand and metal ion is complex, more stable complexes generally are expected from those metals having high charge densities (charge/radius) (Demitras et al., 1972). A smaller, more highly charged ion allows the closer approach of ligands, and the larger charge results in a greater force of attraction which produces a more stable complex (De-

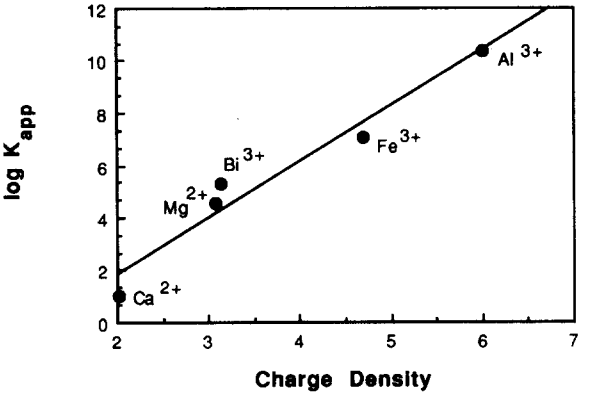

Fig. 5. Results of simple regression analysis correlating the charge density (d) of the metal ion (Table 3) with the log K_{app} value for lomefloxacin (Table 1). The regression line is shown by the solid line and fits the equation: log $K_{app} = 2.1d - 2.4$. The coefficient of correlation (r) is 0.98.

mitras et al., 1972). To determine whether the charge density of the metal ions (Table 4) caused a predictable variation in the binding constants of the lomefloxacin complexes, a linear regression was performed. The general regression equation correlating the log K_{app} with charge density (d) of the metal ion was:

$$\log K_{app} = 2.1(\pm 0.28)d - 2.4(\pm 1.1) \qquad (11)$$

$$r^2 = 0.95,\ p = 0.0045$$

This regression model (Fig. 5) accounts for 95% of the variance associated with the log K_{app} value of lomefloxacin and verifies that the charge density of the metal ion predicts the order of stability for lomefloxacin-metal ion complexes.

Conclusions

The fluoroquinolone antimicrobial drug, lomefloxacin was found to complex with each of the five pharmaceutically relevant metal ions studied. The stoichiometry of binding was dependent on the nature of the metal ion as follows: $L:Ca^{2+} = 1:1$, $L:Mg^{2+} = 2:1$; $L:Bi^{3+} = 2:1$; $L:Fe^{3+} = 2:1$; $L:Al^{3+} = 3:1$. The stability constants, which ranged from 11.2 for $L:Ca^{2+}$ complexes to 2.34×10^{10} for $L:Al^{3+}$ complexes, were directly related to the charge density of the metal ion.

Solubility proved to be a useful method for the determination of the stability constants of the complexes of lomefloxacin with the main metal ions present in antacids and vitamin preparations. This study demonstrated substantial increase in the solubility of lomefloxacin following complexation with polyvalent cations, such as Fe^{3+} and Al^{3+}, suggesting that intravenous formulations could be developed containing a metal-ion salt to increase solubility. The increased solubility of lomefloxacin following complexation with Mg^{2+}, Ca^{2+}, Fe^{3+} and Al^{3+} suggests that the decreased gastric absorption of the quinolones following co-administration of antacid is not due to precipitation of insoluble complexes. A more likely explanation is the decrease in partition coefficient of the fluoroquinolones following complexation with these metal ions. Results of our investigations of the effects of metal-ion complexation on 1-octanol-water partition coefficient will be presented elsewhere.

In contrast to Mg^{2+}, Ca^{2+}, Fe^{3+} and Al^{3+}, complexation with bismuth produced an insoluble species which would presumably not be absorbed from the gastrointestinal tract. There is also the potential for precipitation of the insoluble bismuth complex in the urine following co-administration of lomefloxacin and antacid preparations containing bismuth.

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