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IN VITRO AVAILABILITY OF LOMEFLOXACIN HYDROCHLORIDE IN PRESENCE OF ESSENTIAL AND TRACE ELEMENTS

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Lomefloxacin hydrochloride is a third generation fluoroquinolone antibacterial agent having a broad spectrum of action against a wide range of Gram-positive and Gram-negative organisms. The *in vitro* availability studies of lomefloxacin were carried out in presence of essential and trace elements such as magnesium, calcium, chromium, ferric, ferrous, cobalt, nickel, copper, zinc and cadmium in simulated gastric juice, simulated intestinal juice and blood pH at 37^{o}C using B.P 2003 dissolution test apparatus. It was observed that availability of lomefloxacin was depressed in presence of nickel and zinc in simulated gastric juice and in presence of Fe^{2+} in simulated intestinal juice, while many metals like magnesium, chromium, iron (both Fe^{2+} and Fe^{3+}), cobalt, nickel, copper and cadmium depressed the availability of lomefloxacin at blood pH. Furthermore, the availability of lomefloxacin alone in simulated intestinal juice and at blood pH was reduced as compared to simulated gastric juice. The antibacterial activities of lomefloxacin in presence of these metal ions were observed and compared to control against six different microorganisms i.e., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Bacillus fragilis* and *Streptococcus pneumonia* by disc diffusion method to measure the inhibitory zone and MIC were determined by tube dilution method.

Keywords: Lomefloxacin, hydrochloride, *in vitro* availability, antibacterial activity.

INTRODUCTION

Lomefloxacin hydrochloride is 1- ethyl 6,8-difluoro-1,4-dihydro 7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid monohydrochloride (Colin., 1999) shows the attachment of C-6 fluorine atom contributes to the antibacterial activity and its binding to DNA gyrase (topoisomerase II) (Domagala *et al*., 1986, Koga *et al*., 1980). It exert its antibacterial action by antagonism of the enzyme DNA gyrase also known as topoisomerase II, causing inhibition of DNA synthesis, antagonism of RNA and protein synthesis and ultimately cell death (Wolfson *et al*., 1989).

Lomefloxacin hydrochloride is a difluorinated quinolone antimicrobial possess broad spectrum of antibacterial activity against aerobic Gram negative bacteria, approved only for treatment of urinary tract infections and bronchitis caused by *Haemophilis influenzae* or *Moraxella catarrhalis* (Colin., 1999). It is bactericidal against most strains of *Enterobacteriaceae* causing urinary tract infections. Respiratory pathogens such as *Moraxella catarrhalis*, *Haemophilis influenzae* and *Legionella pneumophilia* are highly susceptible to lomefloxacin, having good activity against *Neisseria gonorrhea* and *Haemophilis ducreyi* but less activity against other genital pathogens such as *Gardnerella vaginalis*, *Chlamydia trachomatis*, *Mycoplasma homonis* or *Ureplasma spp* (Mayer *et al*., 1992).

Lomefloxacin is normally administered orally, followed by rapid and complete absorption from the gastrointestinal tract (>98%) (Mant 1992; Morse 1990). The absorption rate constant is $3.8h^{-1}$. In the formation of metal chelate complexes, non- metallic antacids have no effect on the absorption of the lomefloxacin. It was observed that bioavailability of lomefloxacin decreased to 40% with aluminium and magnesium containing antacids.

The effect of antacid on the absorption of lomefloxacin in human was studied. Lomefloxacin was administered concomitantly with aluminum and magnesium containing antacids under fasting condition, its plasma level decreased by one-half, AUC was reduced by 40% and urinary recovery value also decreased by 40%. This study confirmed the existence of chelate complexes of lomefloxcin with Al^{3+} and Mg^{2+} and it was found that lomefloxacin bind more strongly with Al^{3+} than with Mg^{2+}. Therefore the decrease of lomefloxacin level in plasma could be due to reduce absorption of Al^{3+} and Mg^{2+}-lomefloxacin chelate complexes (Shimada *et al*., 1992).

The concurrent use of aminophylline or theophylline or caffeine with lomefloxacin has not been found to be significantly altered the theophylline clearance or caffeine metabolism (USPDI., 1999, Healy *et al*., 1991). On the contrary, lomefloxacin administered with NSAID as fenbufen or biphenylacetic acid, strongly bind to GABA receptor and is most potent inducer of seizure in rat and mouse model (Christ *et al*., 1989).

Due to the reported interactions of lomefloxacin hydrochloride with other drugs and more particularly with di- and trivalent metal cations, present paper deals with the *in vitro* availability studies of lomefloxacin in presence of essential and trace elements such as magnesium, calcium, chromium, manganese, ferric, ferrous, cobalt, nickel, copper, zinc and cadmium in different dissolution mediums in order to simulate gastric juice, intestinal juice and blood pH at 37°C using B.P 2002 dissolution technique.

MATERIALS AND METHODS

Materials and equipment

Lomefloxacin reference was gift from Searle Pakistan Ltd. The essential and trace elements were used in the form of their hydrated salts and were of pharmaceutical grade. The details of dissolution test equipment have been described earlier (Abid. *et al*., 2005). The absorbance of various samples of lomefloxacin, withdrawn after metal interaction at periodic intervals was measured after appropriate dilutions on a double beam UV-visible spectrophotometer model Shimadzu UV-1601 coupled with a pentium PC.

Procedure for drug interaction studies

The *in vitro* availability of lomefloxacin reference standard and its interaction with metals was studied individually in simulated gastric juice, buffers of pH 7.4 and 9 at 37°C on dissolution test equipment as described earlier. At the start of each experiment 194 mg of lomefloxacin (0.5 mMole) with metal 1 mMole was introduced in one liter dissolution medium previously maintained at 37°C. Aliquots of 2 ml were with drawn intermittently at interval of 15 minutes for 180 minutes and the volume of dissolution fluid was maintained by adding an equivalent amount of dissolution fluid with drawn. The sample was scanned in the region 200-360 nm against reagent blank and the absorbances were recorded at 321 & 288 nm for simulated gastric juice and at 326 & 281 nm for buffers of pH 7.4 and pH 9, which were the λmax, determined previously under these conditions and molar absorptivities calculated accordingly.

Antibacterial studies

The antibacterial studies were carried on lomefloxacin (raw material) and in presence of essential and trace elements mentioned above against six different microorganisms as *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Bacillus fragilis* and *Streptococcus pneumonia*.

Preparation of solutions

Potassium dihydrogen orthophosphate (0.6 Gm), disodium hydrogen orthophosphate (6.4 Gm) and sodium chloride (5.85 Gm) were dissolved in sufficient deionized water to produce 1000 ml of phosphate buffer having pH 7.4. This buffer was sterilized by autoclaving at 121°C and at 15 psi pressure for 15 minutes. Solutions of lomefloxacin and the essential and trace elements were made in this buffer having concentration of 1000 μg/ml. For lomefloxacin in presence of essential and trace elements solution of drug and each metal was mixed in equal volumes and heated with stirring at 60°C for thirty minutes, cooled and used for antibacterial studies.

Preparation and inoculation of antimicrobial plates

The agar medium was prepared in conical flasks and allowed to cool to 50°C on a water bath. Petri dishes were

sterilized by placing in an oven at 150°C for one and a half hour and then 6 to 7 ml of agar media was poured on each plate, dried at room temperature for one day (Ericson *et al*., 1971).

Sterile cotton buds were separately dipped in the inoculum (up to 0.1 ml) of each organism grown in broth media; cultures of organisms were individually streaked on every side of agar plates. Then agar plates were inverted and incubated at 37°C for 16 to 24 hours to obtain the growth of the test organisms (National Committee For Clinical Laboratory Standards., 1990).

Paper disc diffusion method

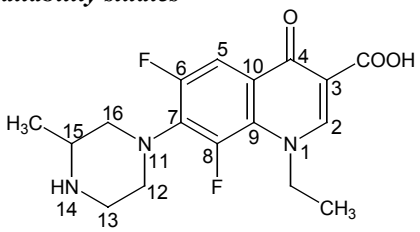
Sterilized Whatmann filter paper discs of 5 mm diameter were dipped in already prepared 1000 μg/ml concentration of stock solutions of lomefloxacin (reference) and lomefloxacin-metal salts solutions and then were placed on the surface of agar; up to four discs on each plate were used. The plates were incubated at 37°C for 24 hours, and the results of zone of inhibition values were noted for 24 hours (Shivankar *et al*., 2003).

Tube dilution method

In seven test tubes 1 ml of nutrient broth was pipetted and these were then autoclaved. By serial dilution method 1ml of a stock sample solution was added in the first test tube, shaken thoroughly, from the first test tube again 1 ml of solution was added in second test tube and from this in third test tube, the procedure was repeated up to the last seventh test tube with thorough shaking. Different serial dilutions of samples ranging in the concentration from 500 to 7.81 μg/ml were prepared. 0.1 ml of single colony of bacterial culture were poured in each test tube separately with shaking, plugged with cotton wool and incubated at 37°C for 24 hours.

RESULTS AND DISCUSSION

In vitro availability studies



The modification of C-7 position of the quinolone molecule has being extensively investigated and it has been found that substitution at C-7 position has great impact on potency, spectrum, solubility and pharmacokinetics. Quinolones with small or linear C-7 substituents such as H, Cl, CH_3, $NHCH_2CH_2NH_2$, $NHCH_3$, $NHNH_2$ posses moderate to weak antibacterial activity while substituted or un substituted 5- or 6-membered heterocycles (pyrrolidinyl, pyrrolyl, thiomorpholinyl, morpholinyl and piperazinyl) produce quinolones with good antibacterial activity. Furthermore, the addition of a basic substituent on 6-membered ring analogues substantially increased antibacterical activities while causing little change in DNA gyrase inhibitory activities. In general quinolones having a methyl group on the piperazinyl ring are more active against Gram-positive bacteria while showing relatively decreased activity against Gram-negative bacteria. In lomefloxacin this methyl group is on position 3 while in case of ciprofloxacin it is on position 4 at heterocyclic nitrogen. Such quinolones are well absorbed, have high serum levels and long serum half-lives than the corresponding C-7 piperazinyl quinolones. In lomefloxacin the piperazinyl group absorbs at 288 and 281 nm, while the heterocyclic ring containing β-keto carboxylic group absorb at 321 and 326 nm depending upon pH of the medium. Unexpected depression and elevation in molar absorptivities at these positions are indicative of drug metal complexation. During these lomefloxacin metal interaction studies, the absorbances were measured at both wavelengths in order to access the extent of complexation at both sites. Lomefloxacin in presence of various metals followed first order dissolution rate constant. The dissolution time $T_{100\%}$, value of K, $T_{50\%}$ and $T_{90\%}$ of lomefloxacin in presence of these metals are given in tables 1. Graphs were plotted as percent drug available versus time at different pH and wave lengths (figures 1-6).

The *in vitro* availability study of lomefloxacin in presence of metals, in simulated gastric juice at 321 and 288 nm inferred that the percent availability of drug reduced most prominently in nickel, is maximum available at 89% and in lomefloxacin zinc interaction the available drug was 75.46% and 77.54% at the end of experiment as given in table 1 and figure 1 and 2. The values of dissolution rate constant (K), $T_{50\%}$ and $T_{90\%}$ at 321 and 288 nm in presence of drug nickel interaction were found to be same as 0.0126, 54.92 and 182.46 respectively and in case of zinc complex it was 0.0078, 88.76 and 294.86 at 321 nm and 0.0082, 83.51 and 277.40 at 288 nm, whereas the percent drug availability decreased slightly when lomefloxacin interacted with other metals.

In the similar manner lomefloxacin interaction studies with copper in pH 7.4 at 326 nm, showed that the drug availability to be slightly reduced to 81.01% at the end; the values of rate constant (K), $T_{50\%}$ and $T_{90\%}$ observed as 0.0092, 75.07 and 249.37. Similarly, lomefloxacin chromium and ferric interaction studies in pH 7.4 at 281 nm showed a significant decline in drug availability after half an hour (67.82%) and the complex so formed was stable even after 2.5 hour (availability 69.99%). The rate constant (K), $T_{50\%}$ and $T_{90\%}$ for chromium and ferric ions were found to be 0.0125, 55.00 and 182.72 and 0.0080, 86.35 and 286.86 respectively. Other metals also decreased the

availability of drug initially, but later considerable amount of drug was present in the medium although not equivalent to reference. This is evident from the dissolution rate constants in table 1 and figures 3-4.

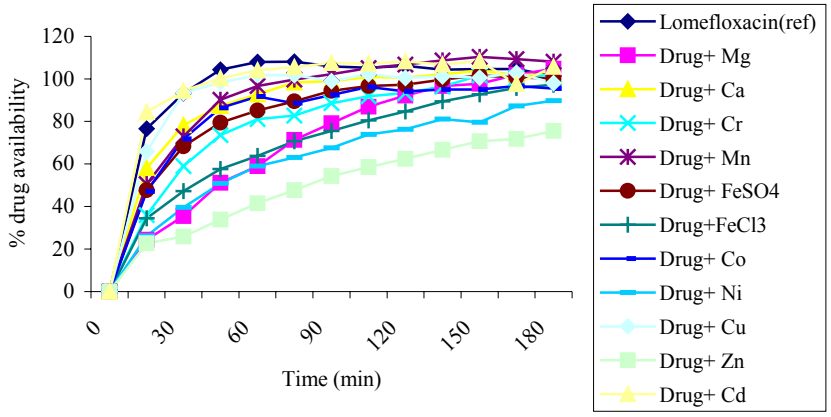


Figure 1: Availability of lomefloxacin in presence of various metals in simulated gastric juice at 321 nm.

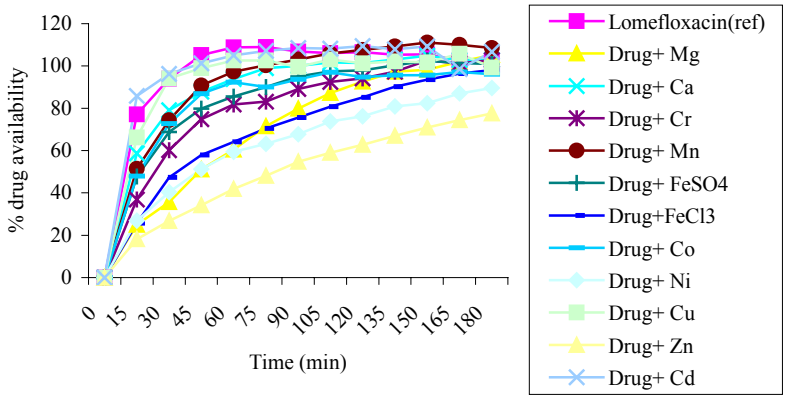


Figure 2: Availability of lomefloxacin in presence of various metals in simulated gastric juice at 288 nm.

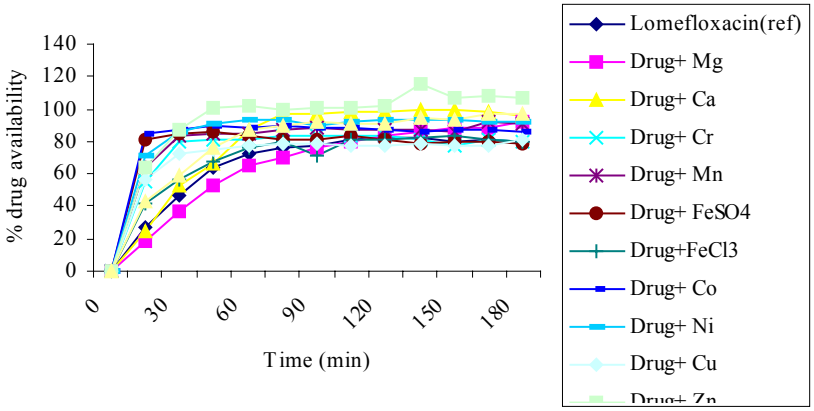


Figure 3: Availability of lomefloxacin in presence of various metals in buffer of pH 7.4 at 326 nm.

There was no decrease in drug availability in presence of metals in buffer of pH 9. On the contrary, the drug metal complexation was shown by increase in absorbance at 326 and 281 nm, resulting in increase (> 100%) in drug availability. These results show that complexation is favored at this pH which is found in intestine.

On the bases of these results, it is evident that availability of lomefloxacin was greatly affected by interactions of

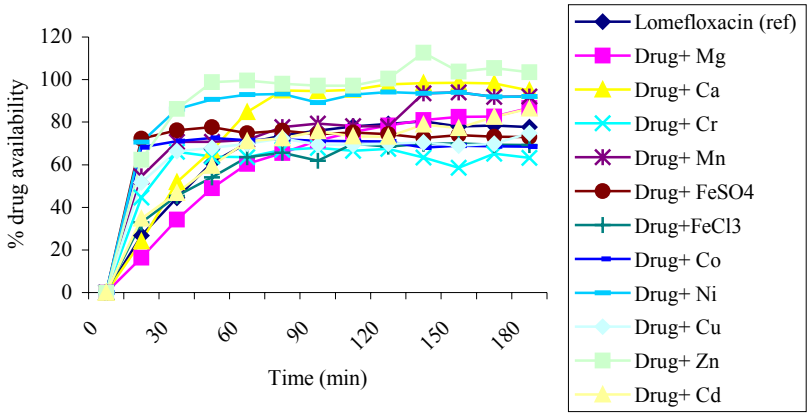


Figure 4: Availability of lomefloxacin in presence of various metals in buffer of pH 7.4 at 281 nm.

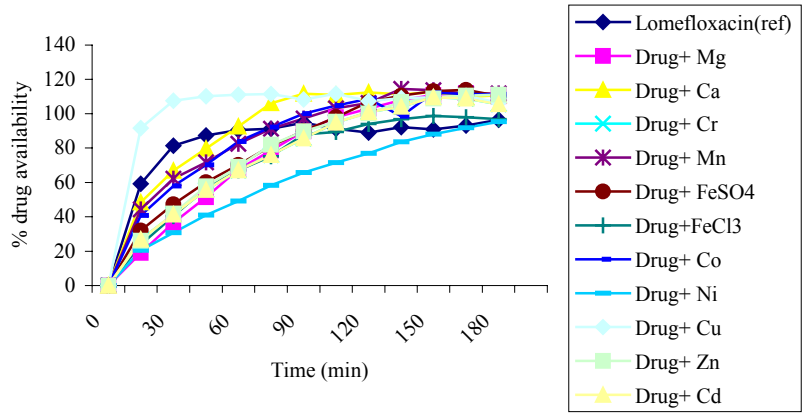


Figure 5: Availability of lomefloxacin in presence of various metals in buffer of pH 9 at 326 nm.

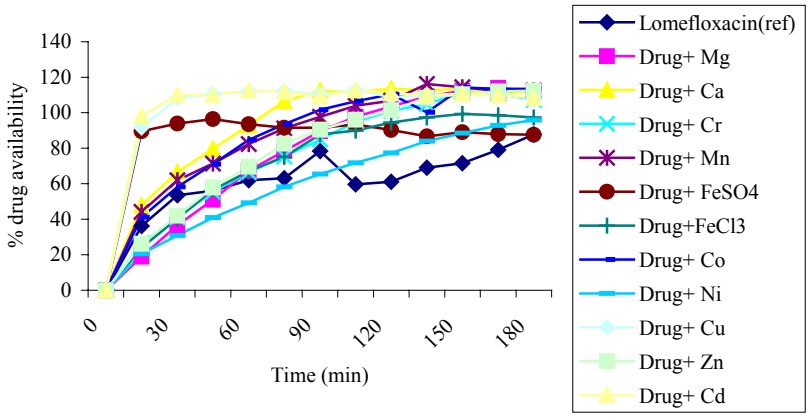


Figure 6: Availability of lomefloxacin in presence of various metals in buffer of pH 9 at 281 nm.

essential and trace elements particularly in pH 9 which has profound effect on drug metal interaction. These interactions results in the formation drug- metal chelates. The effect of antacid and certain mineral supplements in decreasing absorption and bioavailability of fluoroquinolones can be traced to the β-keto-carboxylic acid group (Lomaestro *et al*., 1995). From infrared spectroscopy and ^{19}F and ^{13}C nuclear magnetic resonance spectroscopy these β-keto carboxylic acid groups have been shown to chelate divalent and trivalent metal ions (Lecomte *et al*., 1994, Shimada *et al*., 1992). The strength of chelation to a quinolone varies with the metal ion with affinity constant rising in the order $Ca^{+2} < Mg^{+2} < Fe^{+3} < Al^{+3}$ (Ross *et al*., 1994). The complexation of lomefloxacin with Al^{3+} is much

stronger while the binding with Ca^{2+} and $Mg^{2+}$is much weaker.

concentrations (MICs) of lomefloxacin hydrochloride reference drug and in presence of essential and trace

Table 1

Various dissolution times and first-order dissolution constants in the presence of essential and trace elements

S. No	Drug	<—Simulated gastric juice —>				<—Buffer of pH 7.4 —>				<— Buffer of pH 9 —>			
		$T_{100\%}$	K_{288nm}	$T_{50\%}$	$T_{90\%}$	$T_{100\%}$	K_{281nm}	$T_{50\%}$	$T_{90\%}$	$T_{100\%}$	K_{281nm}	$T_{50\%}$	$T_{90\%}$
1	Lome	31.9	0.094	7.37	24.49	168.0	0.012	57.49	190.9	205.1	0.011	59.36	197.18
2	Lome+Mg	152.7	0.026	25.74	85.52	207.8	0.011	62.03	206.1	107.6	0.035	19.58	65.04
3	Lome+Ca	75.74	0.061	11.26	37.41	152.3	0.027	24.83	82.48	64.66	0.044	15.81	52.53
4	Lome+Cr	138.7	0.026	25.84	85.85	132.7	0.012	55.01	182.7	110.8	0.028	24.64	81.84
5	Lome+Mn	61.64	0.060	11.47	38.11	159.5	0.018	36.85	122.4	92.23	0.041	16.75	55.65
6	Lome+Fe^{2+}	122.5	0.032	21.32	70.81	57.92	0.033	20.78	69.04	46.71	0.073	9.44	31.35
7	Lome+Fe^{3+}	183.5	0.022	31.44	104.4	214.3	0.008	86.36	286.9	151.1	0.032	21.36	70.95
8	Lome+Co	169.7	0.021	31.85	105.8	62.09	0.028	24.17	80.31	80.26	0.036	19.08	63.37
9	Lome+Ni	200.7	0.012	54.93	182.5	127.5	0.023	29.36	97.54	187.8	0.017	39.29	130.52
10	Lome+Cu	90.31	0.062	11.00	36.55	240.5	0.007	90.41	300.3	16.35	0.165	4.18	13.88
11	Lome+Zn	232.1	0.008	83.51	277.4	108.0	0.034	20.35	67.58	109.4	0.030	22.64	75.21
12	Lome+Cd	31.17	0.109	6.34	21.06	208.3	0.011	62.53	207.7	15.3	0.260	2.66	8.84

Lome = Lomefloxacin; T = Dissolution time (min)

Table 2

Zone of inhibition and susceptibility ( ) of lomefloxacin in presence of essential and trace elements at 37°C

Drug	*Staphylococcus Aureus*	*Salmonella typhi*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Streptococcus pneumonia*	*Bacillus fragilis*
Lome (Ref)	9.0 (125)	11.0 (250)	14.8 (125)	10.0 (125)	13.0 (125)	12.0 (62.5)
Lome + Mg	5.0 (125)	11.8 (250)	7.0 (125)	9.5 (250)	11.3 (125)	8.5 (250)
Lome + Ca	8.3 (250)	12.0 (250)	13.0 (125)	6.0 (250)	9.6 (125)	11.0 (250)
Lome + Cr	6.3 (250)	10.0 (250)	9.0 (125)	7.0 (250)	11.0 (125)	12.0 (125)
Lome +Mn	6.0 (125)	7.5 (250)	8.3 (125)	7.0 (250)	12.6 (125)	10.0 (250)
Lome + Fe^{++}	8.8 (250)	10.9 (250)	11.8 (125)	10.01(500)	11.2 (125)	3.5 (125)
Lome + Fe^{+++}	9.0 (250)	11.0 (250)	12.0 (125)	10.0 (500)	11.5 (125)	3.5 (125)
Lome + Co	7.0 (125)	12.0 (250)	13.1 (125)	9.0 (250)	8.5 (125)	10.0 (250)
Lome + Ni	8.5 (250)	11.0 (250)	10.0 (125)	8.6 (250)	12.5 (250)	6.0 (62.5)
Lome + Cu	7.0 (250)	9.5 (250)	14.0 (500)	9.2 (250)	8.0 (125)	9.0 (125)
Lome + Zn	6.0 (125)	9.2 (250)	12.5 (250)	8.0 (125)	7.3 (125)	11.0 (250)
Lome + Cd	5.0 (125)	7.5 (250)	9.5 (125)	9.0 (500)	13.0 (250)	8.0 (125)

Lome = Lomefloxacin; zone of inhibition in mm; susceptibility in μg/ml

Antibacterial studies

Lomefloxacin in presence of eleven essential and trace elements i.e., magnesium, calcium, chromium, manganese, ferrous, ferric, cobalt, nickel, copper, zinc and cadmium were subjected to *in vitro* antimicrobial screening. Paper disc diffusion and tube dilution methods were adopted. Antibacterial activity of quinolones require the presence of the pyridone ring on the right hand side of fluoroquinolone (Mutschler *et al*., 1986). The introduction of a fluorine atom in position 6 and the piperazine ring in position 7 of lomefloxacin are important steps to reach a high level of antibacterial activity (Gootz *et al*., 1996, Asahina *et al*., 1992, Chu *et al*., 1990, Rosen., 1990). The results of antibacterial activity expressed in terms of zone of inhibition (in mm) and the minimum inhibitory elements are given in table 2.

The reference drug, lomefloxacin hydrochloride showed remarkable activity towards the Gram positive bacteria *Bacillus fragilis* at 62.5 μg/ml while *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli* were sensitive at 125 μg/ml whereas, *Salmonella typhi* was sensitive at 250 μg/ml concentrations.

There was no change in antibacterial activity of lomefloxacin in presence of magnesium, manganese, cobalt, zinc and cadmium against *Staphylococcus aureus,* while the MIC was increased in presence of calcium, chromium, iron, nickel and copper. Similarly, there was no effect on the antibacterial activity of lomefloxacin in presence of all metals against *Salmonella typhi*, *Pseudomonas aeruginosa*

and *Streptococcus pneumoniae* except in case of *Pseudomonas aeruginosa* the MIC were increased in case of copper & zinc and in case *Streptococcus pneumoniae,* the MIC were increased in case of nickel and cadmium. Although, lomefloxacin was most sensitive against *Bacillus fragilis,* its MIC was increased in case of all metals except nickel where no change in MIC was observed, whilst the zone of inhibition was decreased than the reference drug.

These results suggest that various essential and trace elements have profound effect on the efficacy if lomefloxacin. On the basis of these studies, it is suggested that multivitamins containing minerals or antacids may not be co-administered with lomefloxacin in order to prevent these types of interactions in the body and in case, any of the later drugs are needed to be given, an intermittent dose regimes should be suggested.

REFERENCES

Abid I, Arayne MS and Sultana N (2005). *In vitro* release of tetracyclines in presence of H_2-receptor antagonists. *Pak. J. Pharm. Sci.,* **18**(2): 55-60.

Analar Hand Book and Green Pages (1998). BDH Chemicals Ltd., England 24 (1994).

Asahina Y, Ishizaki T and Suzue S (1992). Recent advances in structure activity relationship in new quinolones, *Prog. Drug. Res*., **38**: 57-106.

British Pharmacopoeia (2002). Her Majesty's Stationary Office, **2**: A-189.

Christ W, Gindler K, Gruene S, Hecker W, and Jacobson M (1989). Interactions of quinolones with opiods and fenbufen, a non steroidal anti-inflammatory drug involvement of dopamnergic neurotransmission. *Reviews of Infectious Disease*, **11**(suppl 5): 1393-1394.

Colin D (1999). *Therapeutic Drugs*, Churchill Livingston, New York, 2nded (2): 80-85.

Chu DTW and Fernandes PB (1990). Recent developments in the field of quinolone antibacterial agents. *Adv. Drug Res*., **21**: 39-144.

Domagala JM, Hanna ID, Heifetz CL, Hutt MP and Mich TF (1986). New structure activity relationships of the quinolone antibacterials using the target enzyme. Development and application of a DNA gyrase assay, *Journal of Medical Chemistry,* **29:** 394-404.

Drug Information for Health Care Professional (1999). USPDI, 19th ed(1): 1486-1495.

Ericson HM and Sterris JC (1971). Antibiotic Sensitivity Testing: Report of an International Collaborative Study, *Acta. Pathol. Microbiol. Scand.*, Section B, Suppl. Number 217.

Gootz TD and Brightly KE (1996). Fluoroquinolone antibacterials: SAR, mechanism of action, resistance, and clinical aspects, *Med. Res. Rev.*, **16**: 433-486.

Healy DP, Schoenle JR, Stotka J and Polk RE (1991). Lack of interaction between lomefloxacin and caffeine in normal volunteers. *Antimicrob. Agents. Chemother*, **35**(4): 660-664.

Jaffery GH, Bassett J, Mendham J and Dennyr C (1989). Vogel's Text Book of Quantitative Chemical Analysis, English Language Book Society, 5th ed., 832.

Koga J, Itch A, Marimba S, Cease S and Irikura T (1980). Structure-activity relationships of antibacterial 6,7-and 7,8-disubstitiuted 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids. *Journal of Medicinal Chemistry*, **23**: 1358-1363.

Lomaestro BM and Bailie GR (1995). Absorption interactions with fluoroquinolones. *Drug Saf.,* **12**: 314-333.

Lecomte S, Baron MH, Chenon MT, Coupry C and Moreau NJ (1994). Effect of magnesium complexation by fluoroquinolones on their antibacterial properties. *Antimicrob. Agents Chemother.*, **38**: 2810-2816.

Mayer KH and Ellal JA (1992). Lomefloxacin microbiologic assessment and unique properties. *American Journal of Medicine*. **92**(suppl. 4A): 588-628.

Mant TG (1992). Multiple dose pharmacokinetics of lomefloxacin: Rationale for once a day dosing. *American Journal of Medicine*. **92**(Suppl. 4A): 26s- 32s.

Morse IS (1990). Pharmacokinetics and safety of single oral doses of lomefloxacin. *Biopharmaceutics and Drug Disposition*. **11**: 543-551.

Mutschler E and Winterfeldt E (1986). Trends in Medicinal Chemistry, Verlagsgessllschaft mbH, Germany, 1sted., pp.503-512.

National Committee for Clinical Laboratory Standards. Tentative Standard (1990). M7A2. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Villinova, Pa.

Rosen T (1990). The fluoroquinolones antibacterial agents. *Prog. Med. Chem*., **27**: 236-295.

Ross DL and Riley CM (1994). Dissolution and complexation of the fluoroquinolones antimicrobials- an update. *J. Pharm. Biomed. Anal*., **12**: 1325-1331.

Shimada J, Shiba K, Oguma T, Miwa H, Yoshimura Y, Nishikawa T, Okabayashi Y, Kitagawa T and Yamamoto S (1992). Effect of antacid on absorption of quinolone lomefloxacin. *Antimicrob. Agents Chemother*., **36**(6): 1219-1224.

Shivankar VS, Vaidya RB, Dharwadkar SR and Thakkar NV (2003). Synthesis, characterization and biological activity of mixed ligand Co(II) complexes of 8-hydroxyquinoline and some amino acids. Inorganic Chemistry Division, The Institute of Science, Mumbai 400032, India, Marcel Dekker Incorporation, pp.1597-1621.

Wolfson JS, Hooper DC and Swartz MN (1989). Mechanisms of action and resistance to quinolone antimicrobials agents. In: Quinolone. Antimicrobial. Agents. American Society for Microbiology, Washington DC, pp.5-34.