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LEVOFLOXACIN INTERACTIONS WITH ESSENTIAL AND TRACE ELEMENTS

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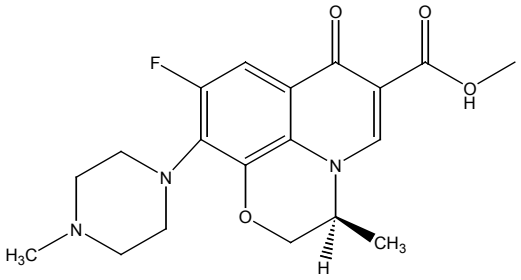
ABSTRACT:

Levofloxacin is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-pipe-razinyl)-7oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate and a fluorinated quinolone antibacterial agent extensively used against both Gram-positive as well as Gram-negative microorganisms. The *in vitro* release of levofloxacin has been studied in presence of metal ions like magnesium, calcium, chromium, manganese, ferric, ferrous, cobalt, nickel, copper, zinc and cadmium in simulated gastric juice, simulated intestinal juice and at blood pH. These studies were carried out using BP 2002 dissolution test apparatus at 37^{o}C. The availability of levofloxacin was found to be markedly retarded in the presence of all the metals studied.

INTRODUCTION

Levofloxacin (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-pipe-razinyl)-7oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate is a Japanese originated synthetic broad spectrum antibacterial agent against Gram-positive and Gram-negative bacteria including *Staphylococcus* species; *Streptococcus pneumoniae* (Craig 1998; Drusano, 2001; Robert *et al.,*1997; Kam *et al.,*1995; Jaime and William, 1998; Critchley *et al.,* 2002 and Fogarty *et al.,* 1998). *Streptococcus pyogenes*, *Streptococcus hemolyticus*, *Entero bacter* species, *Escherichia coli* (Anonymous, 1997), *Salmonella, Klebsiella, Serratia, Enterococcus*, *Pseudomonas aeruginosa* and *Proteus* species (Sparfloxacin and levofloxacin, 1997; Eliopoulos *et al.,* 1996 and Ernst *et al.,* 1997).



Levofloxacin

It inhibits DNA gyrase (Hayakawa *et al.,* 1992; Hoshino *et al.,* 1989 and Neu, 1993) and is two fold stronger than that of its l-isomer ofloxacin (Hammerschlag *et al.,* 1992; Roblin *et al.,* 1994 and Herubin *et al.,* 1992). The activity of levofloxacin is bactericidal in the observation of bacterial morphology; bacterolysis can be seen in the concentration around minimum inhibitory concentration.

In the 1950's and 1960's, clinical work showed that the concurrent ingestion of tetracycline and its derivatives with multivalent cations (i.e. aluminum, magnesium and calcium) could reduce the bioavailability by up to 90%. The most significant of tetracycline-cation interactions occurred between tetracycline and aluminum containing antacids. It was also recognized that divalent or trivalent cations such as Ca^{2+}, Mg^{2+}, or Al^{3+} reduce oral absorption of fluoroquinolones by chelation in the gut (Deppermann and Lode, 1993). Pharmacokinetic studies have described a tremendous scope of interaction between oral levofloxacin and multivalent cations (Fish and Chow, 1997). In many ways, these interactions are as dramatic as those reported with tetracyclines and erythromycin (Arayne *et al.,* 1983, 1984 and 1993).

A number of mechanisms have been reported in the literature based on the changes in the pH of gastric fluid leading to degradation or depressed dissolution and absorption of the antibiotic. Chelation is also considered to be the mechanism responsible for the decreased absorption of the antibiotic in the presence of metals. In present work we describe the effect of various metals ions as magnesium, calcium, chromium, manganese, ferric, ferrous, cobalt, nickel, copper, zinc and cadmium on the *in vitro* availability of levofloxacin. The mechanism of interaction between antibiotic and metals was also studied.

EXPERIMENTAL

Materials

Levofloxacin base and levofloxacin tablets were gifted by Aventis Pharmaceutical Laboratories Ltd., Karachi, Pakistan. The metal salts were of pharmaceutical grade.

Equipment

The dissolution equipment was manufactured according to the B.P. 2002 (British Pharmacopoeia, 2002) standards, which included the dissolution motor and variable speed controller with a stainless steel basket assembly. The top of the basket was modified and replaced by a conical head in order to eliminate air entrapment using dissolution, which is not inconsistent with the present apparatus description. The dissolution container was a flat bottom glass vessel with an internal diameter of 100mm and with a capacity of 1-liter dissolution fluid. The variable speed motor was modified to reduce unwanted vibrations by the incorporation of a suitable capacitor in the speed control circuit and was maintained within ±0.5% of the required speed.

The rotation of the basket assembly was fixed at 100, ±0.5 rpm throughout the experiment. The dissolution assembly was immersed in water bath at 37±0.1^{o}C. The drug in each case was analyzed either by measuring absorbance of aliquots at 288 nm on a UV/VIS (Shimadzu 1601) spectrophotometer.

Preparation of simulated gastric juice

9.1 ml hydrochloric acid of analytical grade (11 N) was taken in a liter volumetric flask. 2.0 g of sodium chloride and 3.2 g of pepsin powder dissolved in water was added to it and the volume was made up to the mark with de-ionized water.

Phosphate Buffers of pH 7.4 & 9.0

These buffers simulated intestinal and blood pH. Potassium dihydrogen orthophosphate 0.6 gm, disodium hydrogen orthophosphate 6.4 gm and sodium chloride 5.85 gm were dissolved in sufficient amount of de-ionized water to produce 1000 ml and adjusted the pH to 7.4 if necessary. For pH 9.0, potassium dihydrogen orthophosphate 1.74 gm were dissolved in 80 ml of water and adjusted the pH if necessary, with 1M potassium hydroxide and diluted to 100 ml with water.

Procedure for interaction studies

In vitro availability was obtained for levofloxacin on the dissolution apparatus as detailed above. The dissolution fluid was 1000 ml of simulated gastric, buffers of pH 7.4 and 9. Samples were withdrawn periodically with an interval of 15 min for 180 min. The volume of dissolution fluid was maintained by adding an equal amount of dissolution fluid withdrawn, which had previously been maintained at the same temperature in the same bath.

In testing the effect of metals on the dissolution behaviour of the antibiotic 1 mole of each metal was individually added to the dissolution medium at the start of the experiment and aliquots were drawn similarly. The absorbance of all the aliquots were measured at the maxima of the drug that showed the drug availability at that particular time. Data is shown in the Tables 1-4 are average of six runs and the results were satisfactorily reproducible.

RESULTS AND DISCUSSION

Levofloxacin is a widely used broad-spectrum oral quinolone antibiotic. In many clinical situations, oral levofloxacin has been used in place of intravenous antibiotics to facilitate the earlier discharge of patients and/or preventing the admission of patients. Like the tetracyclines, the interaction between oral levofloxacin and metals is a chelation reaction. In order for the interaction to occur, the cation must be multivalent. This complex forms an insoluble and non-absorbable compound.

The interactions between these metals and levofloxacin are particularly dramatic when the two agents are given simultaneously. The bioavailability of levofloxacin in simulated gastric juice pH 7.4 and intestinal juices at different time intervals is reduced up to 59% in simulated gastric juice while 35% and 58% in buffer pH 7.4 and pH 9.0 respectively. These decreases in *in vitro* availability of drug are presented in Tables 1-3 and are plotted in Figs.1-3. The variations observed in first-order dissolution constants (K), $T_{50\%}$ and $T_{90\%}$, of levofloxacin in presence of various metals in simulated gastric juice and in buffers of pH 7.4 and 9.0 are given in Table-4.

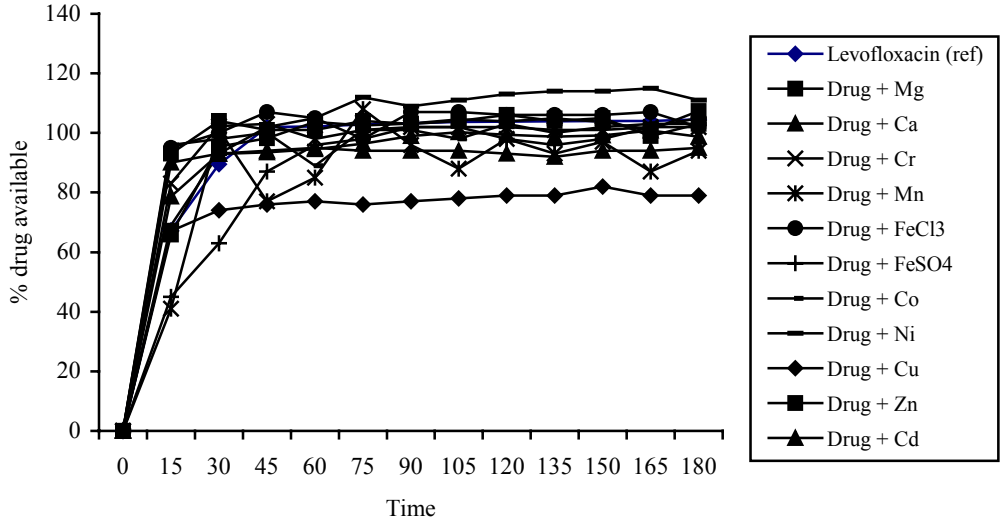


Fig.1: Availability of levofloxacin in presence of various metals in simulated gastric juice.

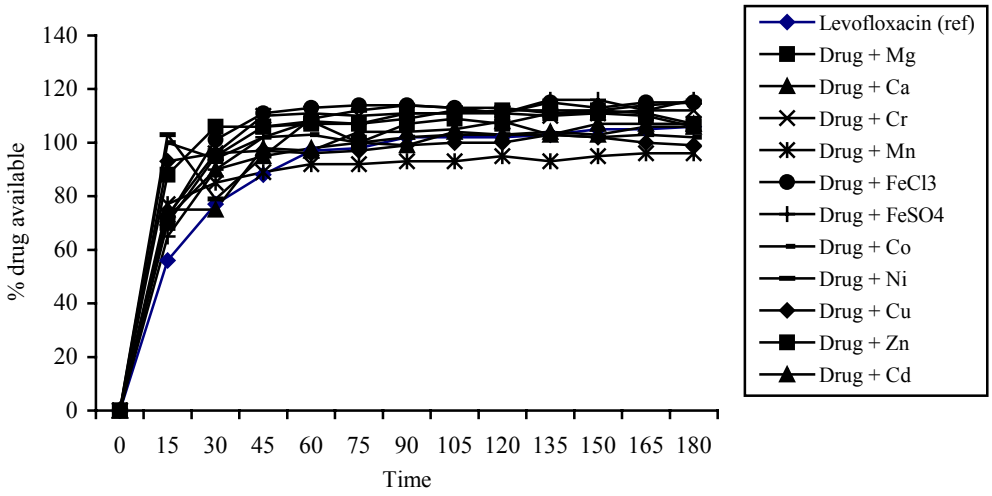


Fig. 2: Availability of levofloxacin in presence of various metals in buffer of pH 7.4.

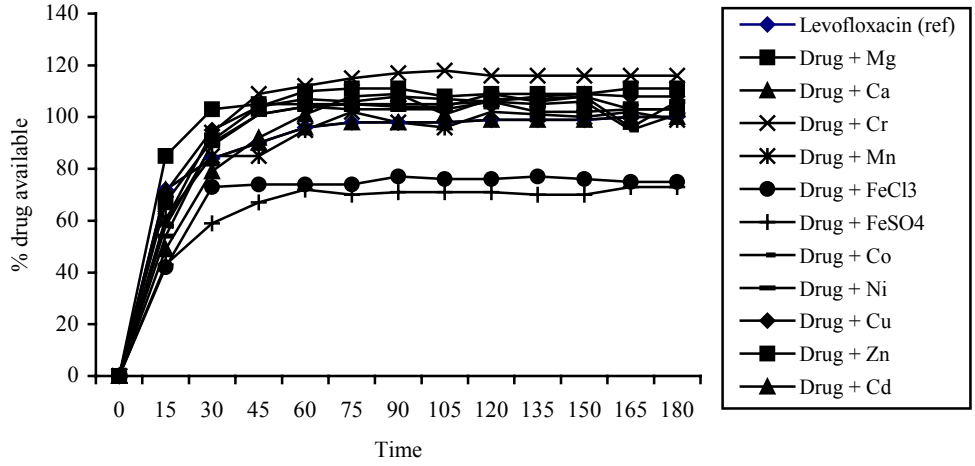


Fig. 3: Availability of levofloxacin in presence of various metals in buffer of pH 9.

As can be seen from these profiles, the availability of levofloxacin decreased in the presence of all metals studied in all the mediums studied. To avoid an interaction between metals and oral levofloxacin, it is inferred that the metals or metal containing preparations must be given at a sufficient interval of levofloxacin dosing. Schellenberg *et al.* (1994) suggested an interval of at least two hours before or two hours after a dose of levofloxacin. In other cases, it has been observed that co-administration of aluminum and magnesium hydroxide, 2 hours before to 6 hours after dosing, consistently reduces bioavailability by 30-90% (Polk *et al.,* 1989).

Table-1

Concentration of levofloxacin (%) in presence of metals at different time intervals in simulated gastric juice

Levofloxacin (Levo) + metal	Time (min)												
	0	15	30	45	60	75	90	105	120	135	150	165	180
Reference (drug)	0.0	67.3	89.5	102.0	102.2	102.8	103.3	103.7	103.8	103.9	104.0	104.0	104.5
Levo + magnesium	0.0	65.9	95.4	98.2	103.7	102.5	103.1	104.5	103.9	104.9	103.7	101.1	107.3
Levo + Calcium	0.0	78.6	92.9	93.5	94.6	96.4	99.0	100.2	99.4	98.7	99.2	100.8	98.7
Levo + chromium	0.0	83.1	102.3	103	98	101	102	102	102	101	101	102	102
Levo +manganese	0.0	41	101	77	85	108	96	88	98	93	97	87	94
Levo + ferrous	0.0	95	100	107	105	98	107	107	106	106	106	107	102
Levo + ferric	0.0	45	63	87	96	98	102	102	98	96	98	102	105
Levo + cobalt	0.0	96	98	100	89	101	101	98	103	100	102	103	103
Levo + nickel	0.0	69	93	102	105	112	109	111	113	114	114	115	111
Levo + copper	0.0	67	74	76	77	76	77	78	79	79	82	79	79
Levo + zinc	0.0	93	104	101	101	104	103	104	106	104	105	99	103
Levo + cadmium	0.0	90	93	94	95	94	94	94	93	92	94	94	95

Table-2

Concentration of levofloxacin (%) in presence of metals at different time intervals in buffer of pH 7.4 at 288 nm

Levofloxacin (Levo) + metal	Time (min)												
	0	15	30	45	60	75	90	105	120	135	150	165	180
Reference (drug)	0.0	56	77	88	97	98	102	102	102	103	105	105	106
Levo + magnesium	0.0	70	95	106	107	107	111	111	112	112	112	111	107
Levo + Calcium	0.0	75	75	98	97	104	104	105	108	103	107	107	107
Levo + Chromium	0.0	73	96	110	111	110	111	111	111	110	111	112	112
Levo + Manganese	0.0	77	85	89	92	92	93	93	95	93	95	96	96
Levo + ferrous	0.0	72	101	111	113	114	114	113	111	115	113	115	115
Levo +ferric	0.0	65	90	102	108	107	109	112	111	116	116	112	116
Levo +cobalt	0.0	100	94	102	103	100	102	103	103	103	102	103	102
Levo + nickel	0.0	103	79	95	109	112	114	113	113	111	112	114	115
Levo + copper	0.0	93	96	97	96	97	99	100	100	103	102	100	99
Levo +zinc	0.0	88	106	106	108	100	107	109	107	111	111	110	106
Levo + cadmium	0.0	72	90	95	98	100	99	104	103	104	103	106	106

Table-3

Concentration of levofloxacin (%) in presence of metals at different time intervals in stimulated intestinal juice at 288 nm

Levofloxacin (Levo) + metal	Time (min)												
	0	15	30	45	60	75	90	105	120	135	150	165	180
Reference (drug)	0.0	72	84	90	96	98	98	98	99	99	99	100	100
Levo + magnesium	0.0	85	103	105	105	105	105	105	106	102	102	103	103
Levo + Calcium	0.0	49	79	92	101	108	109	101	107	107	108	103	103
Levo + Chromium	0.0	60	94	109	112	115	117	118	116	116	116	116	116
Levo + Manganese	0.0	61	85	85	95	102	98	96	102	101	100	102	99
Levo + ferrous	0.0	42	73	74	74	74	77	76	76	77	76	75	75
Levo +ferric	0.0	43	59	67	72	70	71	71	71	70	70	73	73
Levo +cobalt	0.0	58	89	101	104	103	103	103	106	105	106	95	101
Levo + nickel	0.0	54	90	101	104	105	104	104	109	106	108	96	106
Levo + copper	0.0	71	95	104	107	106	108	107	106	108	109	108	108
Levo +zinc	0.0	67	91	104	110	111	111	108	109	109	109	111	111
Levo + cadmium	0.0	72	84	90	96	98	98	98	99	99	99	100	100

Table-4
First-order dissolution rate constants of levofloxacin in presence of metals

Levofloxacin (Levo) + metal	Simulated gastric juice			Buffer of pH 7.4			Simulated intestinal juice		
	$T_{50\%}$	$T_{90\%}$	K_{2948nm}	$T_{50\%}$	$T_{90\%}$	K_{288nm}	$T_{50\%}$	$T_{90\%}$	K_{2881nm}
Reference (drug)	3.28	4.89	0.07	0.05	3.61	0.542	3.46	5.07	0.061
Levo + magnesium	0.09	3.14	5.02	0.09	3.07	0.911	0.13	2.74	4.35
Levo + Calcium	0.05	3.63	5.24	0.07	3.35	0.072	0.05	3.65	5.26
Levo + Chromium	0.08	3.25	4.86	0.10	3.01	0.098	0.08	3.23	4.83
Levo + manganese	0.02	4.44	6.04	0.04	3.97	0.046	0.04	3.78	5.39
Levo + ferrous	0.13	2.86	4.47	0.09	3.15	0.085	0.02	4.64	6.25
Levo + ferric	0.03	3.97	5.58	0.07	3.28	0.074	0.02	4.79	6.40
Levo + cobalt	0.11	3.19	4.80	0.1	3.01	0.098	0.05	3.83	5.44
Levo + nickel	0.08	3.15	4.76	0.06	3.49	0.061	0.05	3.81	5.42
Levo + copper	0.02	4.44	6.05	0.06	3.53	0.058	0.09	3.07	4.68
Levo + zinc	0.11	3.17	4.78	0.14	2.63	0.143	0.08	3.24	4.84
Levo + cadmium	0.05	3.77	5.37	0.07	3.32	0.075	0.05	3.70	5.50

CONCLUSION

The availability of oral levofloxacin can be affected by the concurrent ingestion of essential and trace elements in the form of food supplements or multivitamins containing multivalent cations. However, significant interactions have been reported with medications containing aluminum, magnesium, calcium and zinc. It is important to be aware of these interactions because they may so greatly affect levofloxacin bioavailability that it may compromise the patient's outcome. Finally, patients receiving oral levofloxacin should be counseled about how to take this medications and how to avoid metal-drug interactions.

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