

INTERACTION STUDY OF MOXIFLOXACIN AND LOMEFLOXACIN WITH CO-ADMINISTERED DRUGS

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ABSTRACT

Moxifloxacin and lomefloxacin are fluoroquinolone antibiotics used in treating urinary and respiratory tract infections. Fluoroquinolones are known to have interactions with drugs that are active in gastro intestinal tract. Being moxifloxacin and lomefloxacin fluoroquinolones the interaction study of was carried out with sucralfate, gelusil, erythromycin and multi minerals. The interaction was studied at neutral, acidic and basic conditions both at room temperature and 37°C. The effect of dissolution medium simulating various body environments with response to pH has been examined in order to elucidate the interactions. The response of moxifloxacin and lomefloxacin after interaction with co-administered drugs at different conditions and temperature were noted using a Shimadzu HPLC system with PDA detector. It was seen that interaction of these fluoroquinolones was more at 37°C than at room temperature. Moxifloxacin and Lomefloxacin reacts faster with sucralfate and gelusil in acidic media whereas with erythromycin in basic media and multi-minerals in neutral media. The study ensures the interaction of fluoroquinolones with selected class of drugs. In order to achieve the effective therapeutic effect appropriate time intervals between administrations of drugs is essential.

Keywords: Moxifloxacin, lomefloxacin, co-administered drug, interaction, HPLC.

INTRODUCTION

Moxifloxacin is a fourth generation fluoroquinolone and chemically known as 1-cyclopropyl-6-fluoro-1, 4 dihydro- 8- methoxy -7 [(4as,7as)-octa hydro -6H-pyrido [3,4-b]pyridine 6-yl] 4-oxo- 3 quinoline carboxylic acid. It is drug of choice for the treatment of respiratory infections including acute sinusitis, acute exacerbations of chronic bronchitis and community acquired pneumonia as well as skin and skin infections. Moxifloxacin is a DNA gyrase inhibitor, also inhibits topoisomerase IV. DNA gyrase (topoisomerase II) is an essential bacterial enzyme that maintains the super helical structure of DNA. DNA gyrase is required for DNA replication and transcription, DNA repair, recombination and transposition.

Lomefloxacin is a second generation fluoroquinolone antibiotic and chemically it is 1-Ethyl-6, 8-difluoro-1, 4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline-carboxylic acid. Drug of choice for acute exacerbations of chronic bronchitis due to susceptible gram negative organism and urinary tract infections. Lomefloxacin inhibits DNA gyrase in susceptible organisms thereby inhibits relaxation of super coiled DNA and promotes breakage of DNA strands.

Few procedures were reported for moxifloxacin estimation from human serum, urine and tablets (Hemanth Kumar AK and Geetha R 2009, Ulu ST 2007

and Sanjay KM *et.al.*, 2007). Bioequivalence study and estimation of lomefloxacin was from plasma and tablets were reported using HPLC (Sohan *et.al.*, 2006, Greci Tozo CG *et.al.*, 2006, Suhagia *et.al.*, 2006 and Shailesh AS *et.al.*, 2002). However there are no reports on their interaction studies with co-administered drugs. Fluoroquinolones are known to have many interactions with the agents that are active in the gastro intestinal system. Hence it is essential to study the interaction of moxifloxacin and lomefloxacin with co-administered drugs using a HPLC method developed for this purpose.

MATERIALS AND METHODS

Materials

Moxifloxacin and Lomefloxacin are provided by Dr. Reddy's Laboratory, Hyderabad, India. Tablets of erythromycin, gelusil, sucralfate and multi minerals were procured from local market. All chemicals and reagents were of HPLC grade and supplied by Merck Limited, India.

Equipment

The dissolution equipment (Pharmacopoeia of United States XX) was manufactured by Elecro Labs, India (Model TDT08L). A Shimadzu HPLC class LC 10AT system with PDA detector was used for analysis of drug samples.

In vitro availability studies

The *in vitro* availability of moxifloxacin and

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Table 1: Percentage reduction of Moxifloxacin with Erythromycin

Time	Room temperature			37°C		
	Neutral	Acidic	Basic	Neutral	Acidic	Basic
0	0	0	0	0	0	0
1	0.36	3.62	5.97	20.22	23.64	26.32
2	8.52	4.63	7.32	24.08	34.76	39.32
3	14.91	5.52	11.21	2.47	31.28	41.33
4	11.58	11.64	11.64	35.85	34.72	42.12

Table 2: Percentage reduction of Lomefloxacin with Erythromycin

Time	Room temperature			37°C		
	Neutral	Acidic	Basic	Neutral	Acidic	Basic
0	0	0	0	0	0	0
1	0.36	3.62	5.97	20.22	23.64	26.32
2	8.52	4.63	7.32	24.08	34.76	39.32
3	14.91	5.52	11.21	2.47	31.28	41.33
4	11.58	11.64	11.64	35.85	34.72	42.12

Table 3: Percentage reduction of Moxifloxacin with Gelusil

Time	37°C		Room temperature	
	Neutral	Acidic	Neutral	Acidic
0	0	0	0	0
1	2.36	9.26	1.47	2.10
2	5.67	17.56	1.68	7.24
3	9.24	19.81	2.69	9.04
4	11.35	20.35	5.04	10.58

Table 4: Percentage reduction of Lomefloxacin with Gelusil

Time	37°C		Room temperature	
	Neutral	Acidic	Neutral	Acidic
0	0	0	0	0
1	5.47	4.69	5.35	6.58
2	8.24	17.11	7.86	11.95
3	13.13	19.38	10.57	13.01
4	20.48	25.92	15.5	23.67

lomefloxacin with co-administered dosage forms of erythromycin, gelusil, sucralfate and multi minerals was studied in simulated gastric juice (pH 1), and in buffer pH 4, 7.4 and 9 on dissolution apparatus maintained at 37°C over a period of 4 hours with intermittent sampling of fifteen minutes. The volume of dissolution fluid was maintained by adding an equivalent amount of fluid withdrawn, which had previously been maintained at the same temperature in the same bath. Each sample was HPLC system attached to a PDA detector.

Drug Interaction studies

In vitro interaction studies of the co-administered drugs with moxifloxacin and lomefloxacin were conducted at room temperature and 37°C. In each sets of experiments a dosage form of moxifloxacin and lomefloxacin were added separately in the dissolution

media while co-administered drugs were added after fifteen minutes interval so as to allow the antibiotic dosages dissolve to a considerable extent. Aliquots were withdrawn and assayed for drug content as above.

RESULTS

Development of HPLC method for moxifloxacin and lomefloxacin

Fluoroquinolones undergo interaction with antacids, metal containing formulations etc. So far no reports for the interaction study of moxifloxacin and lomefloxacin. Hence to study the interaction of moxifloxacin and lomefloxacin with co-administered drugs a RP-HPLC method was developed and adapted.

A RP-HPLC method developed for the estimation of Moxifloxacin and Lomefloxacin, the chromatographic

parameters optimized were selection of wavelength for detection, effect of ionic strength of mobile phase, effect of ratio of mobile phase and effect of flow rate. The mobile phase system of potassium di hydrogen phosphate: acetonitrile was selected and the wavelength selected was 295nm for moxifloxacin and 287nm for lomefloxacin. Various ionic strengths of potassium dihydrogen phosphate were tried and 0.1%v/v was selected as the ionic strength. The ratio of 50:50%v/v was selected because of no tailing and the peak shape was comparatively good. A flow rate of 0.8ml was selected since in 1ml and 0.7ml the flow rate resulted in sharp and broad peaks, respectively. The chromatogram of moxifloxacin and lomefloxacin after injected to HPLC is shown in figs. 1-2.

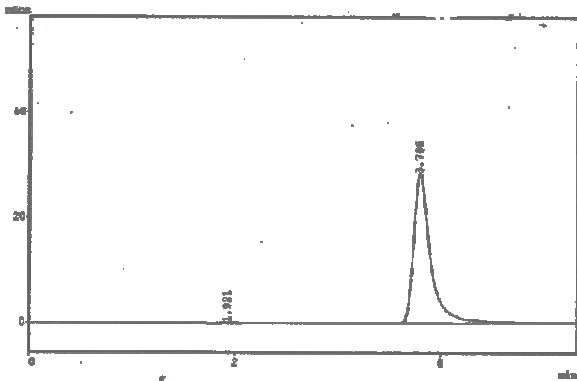


Fig. 1: Chromatogram of Moxifloxacin obtained from HPLC.

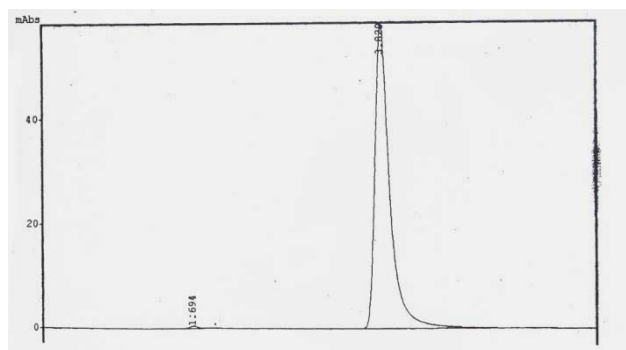


Fig. 2: Chromatogram of Lomefloxacin obtained from HPLC.

Different concentrations of moxifloxacin and lomefloxacin in mobile phase were prepared and the chromatograms of standard solutions of these drugs were recorded. Calibration graphs were plotted using concentration versus peak area of the standard solutions. Linearity was found to be in the range of 10-50 μgml^{-1} for moxifloxacin and 15-35 μgml^{-1} for lomefloxacin. The correlation co-efficient was found to be 0.9941 for moxifloxacin and 0.9952 for lomefloxacin. The retention time was found to be 3.7min for moxifloxacin and 3.01min for lomefloxacin.

The Limit of Detection was 1ng ml^{-1} and Limit of Quantification was found to be 10ng ml^{-1} . The intraday and inter day precision has shown low %RSD (<1.02) values which indicate a good precision of the method. Recovery studies were performed by standard addition method. To study robustness the conditions were slightly changed and the method was found to be robust. System suitability studies were performed which included column efficiency, resolution and tailing factor. The validation and system suitability parameters were calculated to confirm the suitability of the method.

The drugs which were selected for interaction the study are sucralfate, gelusil, erythromycin and multi-minerals. The interaction was studied at neutral, acidic and basic conditions in both room temperature and 37°C . The response of Moxifloxacin and Lomefloxacin after interaction with co-administered drugs at different conditions and temperature were noted using HPLC. The percentage reduction of moxifloxacin and lomefloxacin after interaction with sucralfate at room temperature and 37°C is shown in figs. 3-6. Interaction of drugs with erythromycin in three media after a period 4 hours is shown in tables 1 and 2. The percentage reduction of drugs after interaction with gelusil and multi minerals is shown in tables 3-6. A 10 % reduction of the amount found in less than 4 hours in many cases is shown in table 7.

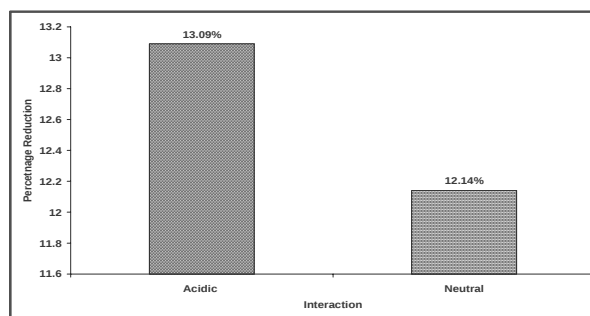


Fig. 3: Percentage reduction of Moxifloxacin with sucralfate at room temperature.

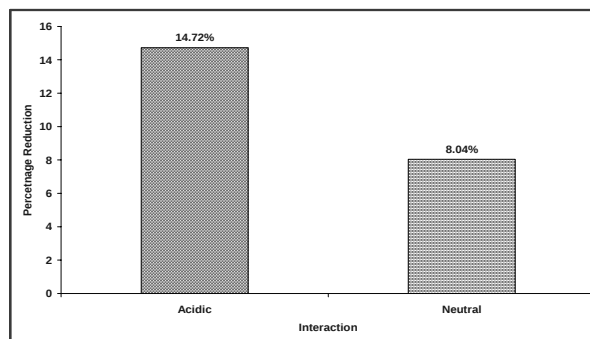


Fig. 4: Percentage reduction of Moxifloxacin with sucralfate at 37°C .

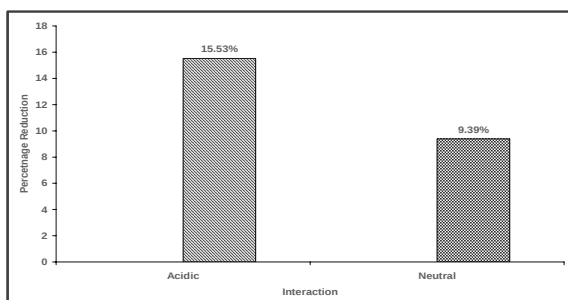


Fig. 5: Percentage reduction of Lomefloxacin with sucralfate at room temperature.

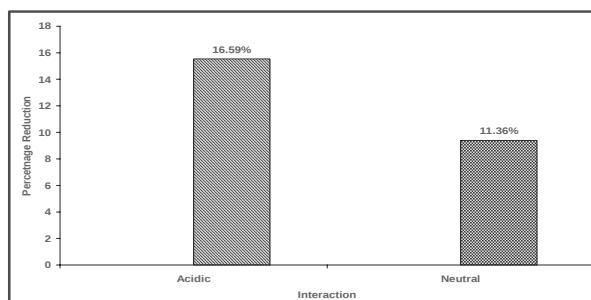


Fig. 6: Percentage reduction of Lomefloxacin with sucralfate at 37°C.

Table 5: Percentage reduction of Moxifloxacin with Multiminerals

Time	37°C		Room temperature	
	Neutral	Acidic	Neutral	Acidic
0	0	0	0	0
1	11.45	8.25	2.53	4.79
2	14.90	11.68	8.29	7.55
3	20.42	13.57	12.53	11.49
4	20.52	21.25	18.65	19.48

Table 6: Percentage reduction of Lomefloxacin with Multiminerals

Time	37°C		Room temperature	
	Neutral	Acidic	Neutral	Acidic
0	0	0	0	0
1	6.35	3.58	9.26	5.16
2	13.26	6.94	12.30	8.75
3	14.41	10.57	18.14	9.73
4	17.33	11.23	24.86	9.98

Table 7: The time (in hours) of 10% reduction of fluoroquinolones after interaction at 37°C

	Medium	Sucralfate	Erythromycin	Gelusil	Multi minerals
Moxifloxacin	Acid	3	3	2	3
	Base	4	<1	4	3
	Neutral	4	1	4	<2
Lomefloxacin	Acid	<1	2	2	4
	Base	3	<3	3	4
	Neutral	2	3	3	3

DISCUSSION

From the study it was seen that interaction of these fluoroquinolones was more at 37°C than at room temperature with these four drugs. The rate of interaction of Moxifloxacin and Lomefloxacin with co-administered drugs as follows: 1) Acidic > Neutral (in case of Sucralfate), 2) Basic > Neutral > Acidic (in case of Erythromycin), 3) Acidic > Neutral (in case of Gelusil) and 4) Neutral > Acidic (in case of Multiminerals).

It was observed that Moxifloxacin and Lomefloxacin reacts faster with sucralfate and gelusil in acidic media whereas with erythromycin in basic media and multiminerals in neutral media.

From the interaction study it can be concluded that, the order of interaction of drugs selected for the study with moxifloxacin is, Erythromycin > Sucralfate > Multiminerals > Gelusil. The interaction of Lomefloxacin is in the order of sucralfate > Erythromycin > Gelusil > Multiminerals. Moxifloxacin shown highest interaction with erythromycin at 37°C while lomefloxacin with sucralfate at 37°C.

CONCLUSION

In general all the fluoroquinolones interacts with wide classes of drugs but their interactions differ from one another. The formation of insoluble chelates with metal ions reduces the antibacterial activity of fluoroquinolones. The stability of the chelate formed seems to be an important factor in determining the degree of interaction. So it is of clinical importance as the serum levels of antibiotic as result of interaction may fall below minimal inhibitory concentrations so that treatment failures will occur. Hence, studying the interaction of each fluoroquinolones with an appropriate analytical tool would be essential for improving the clinical and therapeutic efficacy of them.

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