Interaction Studies of Cephradine with H_2-Receptor Antagonist

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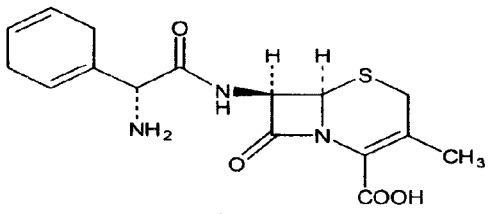
Summary: Cephradine, a first generation semisynthetic cephalosporin antibiotic, is widely used in clinics for its activity against both Gram-positive and Gram-negative bacteria. It is indicated for the treatment of urinary tract infections, skin and skin structure infections, respiratory tract infections, and otitis media. Interactions of cephradine with H_2-receptor antagonists (cimetidine, ranitidine and famotidine) were investigated by UV/visible spectrophotometer in simulated gastric juice (pH 1) and blood pH (pH 7.4) at body and elevated temperatures. The availability of cephradine at 37 °C in both media was increased to 102 and 105 % when interacted with cimetidine, while at elevated temperatures the availability of cephradine was increased only in simulated gastric juice. It was observed that at 37 °C cephradine availability increased in presence of ranitidine only in buffer of pH 7.4 whereas at 48 °C no remarkable change was observed. However, at 60 °C the availability of cephradine increased to 115 % in both media. In presence of famotidine, at 37 °C it was observed that % availability of cephradine increased only in simulated gastric juice. However, at higher temperature, results similar to cimetidine were observed. Hence forth, it was concluded on the basis of the above results that cephradine and H_2-receptor antagonists affect each other's availability and may decrease activity, *in vitro* as well as *in vivo*.

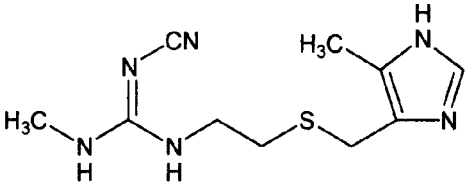
Introduction

Cephradine is a semisynthetic cephalosporin antibiotic, containing a cyclohexadienyl ring. It is orally administered and almost completely absorbed from the GI tract. Like cephalexin, cephradine is less active against most bacterial species including enterococci (e.g., *Enterococcus faecalis*), methicillin-resistant staphylococci, *Citrobacter* sp., *Enterobacter* sp., *Proteus* sp. other than *P. mirabilis*, *Providencia* sp., *Pseudomonas* sp., and *Serratia* sp. It inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall. Although cephradine has largely been superseded by second and third generation cephalosporins, it nevertheless remains an important antibiotic in the developing world [1].



Cephradine

H_2-receptor antagonists (H_2-A) are used to suppress excess acid secretions and to treat peptic ulcer conditions. Cimetidine, a H_2-receptor antagonist, contains imidazole ring, inhibits hepatic cytochrome P450 (CYP) 1A2, 2C9, 2D6, and 3A4 P450 isoforms [2]. Clinically relevant drug interactions include theophylline, aminophylline, metoprolol, nifedipine, propranolol and quinidine. However, it is safe with atenolol and nadolol [3].



Cimetidine

Ranitidine hydrochloride is *N*-{2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl}-*N'*-methyl-2-nitro-1,1-ethenediamine, a histamine H_2-receptor antagonist with a furan ring structure that increases its potency to inhibit gastric acid secretion induced by various stimuli, while lacking the anti-androgenic and hepatic microsomal enzyme inhibiting effects [4].

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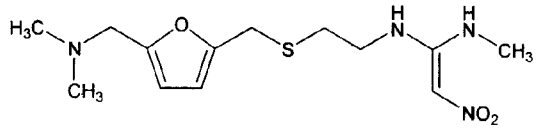
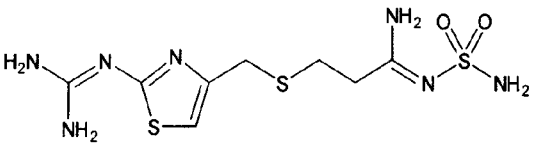


Ranitidine

Famotidine, 3-{[[2-[(aminoiminomethyl)-amino]4-thiazolyl]methyl]thio]- *N*-(aminosulfonyl) is highly selective histamine H_2-receptor antagonist, indicated for the treatment of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, Zollinger-Ellison syndrome [5], and in the treatment of Parkinson's diseases. It inhibits basal and nocturnal gastric secretion as well as secretion stimulated by food and pantagastrin [6].



Famotidine

Simultaneous use of antibiotics and acid suppressing drugs is common not only in treating infectious diseases in peptic ulcer patients, but also in patients having cephalosporin therapy and complaints of routine G.I. tract complications. Simultaneous drug therapy not only affects the antibiotic levels, but also doesn't improve GIT complications.

Cephalosporins are reported to cause drug-drug interactions with alcohols [7-14], aminoglycosides antibiotics [15], cholestyramine [16], frusemide [17, 18], probenecid [19, 20], anticoagulants [21] and theophyline [22, 23]. We previously reported drug interactions of cephradine with essential and trace elements [24, 25]. Like other cephalosporins and β-lactam antibiotics, cephradine may cause gastric irritations and H_2-receptor antagonist may be used to suppress excess acid secretions and to treat peptic ulcer conditions and as H_2-receptor antagonist alters the gastrointestinal pH. A number of drug interactions of H_2-receptor antagonist are also reported [3, 26-29]. Concurrent use of cephradine with H_2-receptor antagonist may result in mild to severe drug interactions. The question of whether or not these co-administrations result in drug-drug interaction is the basis of present study. For this purpose cephradine was interacted with three selected H_2-receptor antagonist by simulating body media and these studies were carried out on dissolution apparatus and assayed spectrophotometrically.

Results and Discussion

Various methods are reported in the literature for the assay of cephradine, including fluorometric [30-32], colorimetric [33], polarographic [34], HPLC [35-37], GC [38], spectrophotometric [39-43] and capillary electrophoresis [44]. UV spectroscopic method is used in these studies. Cephradine was interacted with commonly used H_2-receptor antagonists like cimetidine, ranitidine and famotidine in simulated gastric juice and blood pH at 37, 48 and 60 °C simulating body temperature and accelerated temperatures so as to study stability constant and thermodynamic functions of the interaction.

To measure the concentration of the two drugs, for instance cephradine and cimitidine present in the same solution, without separating them posed a problem because the two drugs interfere at each other's λ_{max} (255 and 216 nm respectively). To remove this interference simultaneous equation (equation 1 & 2) was developed by modifying Beer's law. The molar absorptivity values of both drugs were calculated at their own and at the λ_{max} of each other and the quantity of each drug was measured by simultaneous equations.

$$C_b = \frac{A_{255}.\, a_2 - A_{216}.\, a_1}{a_2\, b_1 - a_1\, b_2} \qquad (1)$$

Similarly,

$$C_a = \frac{A_{255}.\, b_2 - A_{216}.\, b_1}{a_1\, b_2 - a_2\, b_1} \qquad (2)$$

where C_a and C_b are concentrations of cephradine and cimitidine present in the same solution, a_1 and a_2 are molar absorptivity values of cephradine at 255 and 216 nm, and b_1 and b_2 are molar absorptivity values of cimitidine at 255 and 216 nm respectively. Results of interaction studies of cephradine in presence of H_2-receptor antagonist are shown in Tables 2-4 and are plotted in Figs. 1-6.

The % availability of cephradine (through dissolution) was found to be 99.8 % in simulated

Table-1: Availibility of cephradine and H_2-receptor antagonist in simulated gastric juice and buffer pH 7.4 at 37 °C.

S. No.	Time (mins)	< Cephradine > pH 1	pH 7.4	< Cimetidine > pH 1	pH 7.4	< Ranitidine > pH 1	pH 7.4	< Famotidine > pH 1	pH 7.4
1	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	15	57.9	49.9	96.9	97.5	89.9	96.6	86.4	82.7
3	30	99.1	95.7	97.5	97.7	93.0	96.6	87.2	86.5
4	45	99.2	97.8	97.6	97.7	93.4	97.3	88.9	87.8
5	60	99.3	99.1	98.0	97.8	94.1	97.3	90.5	90.9
6	75	99.3	99.2	98.1	97.9	94.5	97.3	92.2	91.5
7	90	99.4	99.4	98.4	98.4	95.3	98.2	96.3	91.5
8	105	99.4	99.6	98.8	98.6	95.3	98.2	96.3	92.8
9	120	99.5	99.8	99.1	98.7	95.7	98.5	98.0	94.7
10	135	99.5	99.8	99.3	98.2	96.1	99.0	98.8	94.7
11	150	99.5	99.9	100.0	98.2	98.9	99.0	99.7	97.9
12	165	99.7	99.9	100.0	99.6	99.0	100.0	100.0	99.8
13	180	99.8	99.9	100.0	99.9	100.0	100.0	100.0	99.8

Table-2: % Availability of cephradine in presence of cimitidine.

S. No.	Time (mins)	<– Simulated gastric juice –> at 37°C	at 48°C	at 60°C	<—— pH 7.4 ——> at 37°C	at 48°C	at 60°C
1	0	0	0	0	0	0	0
2	15	104.7	98.7	98.7	102.7	79.2	99.9
3	30	102.1	98.3	111.0	99.0	78.5	92.3
4	45	100.0	98.9	108.1	97.3	80.7	91.8
5	60	100.0	99.3	111.0	96.2	74.4	95.5
6	75	98.9	101.0	106.0	95.7	75.1	93.4
7	90	101.0	103.9	126.0	94.6	72.9	96.8
8	105	99.7	104.1	107.8	95.4	71.2	93.2
9	120	98.6	121.6	120.0	93.2	71.4	103.9
10	135	98.9	105.2	114.9	90.8	69.3	100.7
11	150	102.4	107.8	120.9	93.3	69.1	94.8
12	165	99.9	108.1	126.0	91.1	58.0	86.2
13	180	99.9	107.5	130.3	89.7	67.7	89.5

Table-3: % Availability of cephradine in presence of ranitidine.

S. No.	Time (mins)	<— Simulated gastric juice —> at 37°C	at 48°C	at 60°C	<—— pH 7.4 ——> at 37°C	at 48°C	at 60°C
1	0	0 0	0	0	0	0	
2	15	94.8	90.8	97.8	103.6	90.8	97.8
3	30	90.8	91.3	103.4	103.2	91.3	103.4
4	45	93.3	89.4	102.2	102.9	89.4	102.2
5	60	90.4	91.3	101.8	101.5	91.3	101.8
6	75	89.9	86.0	102.0	100.8	86.0	102.0
7	90	92.0	90.2	114.5	99.6	90.2	114.5
8	105	91.2	91.3	102.8	98.9	91.3	102.8
9	120	89.2	94.3	106.7	83.5	94.3	106.7
10	135	89.2	94.3	107.1	82.0	94.3	107.1
11	150	89.5	92.5	108.5	82.0	92.5	108.5
12	165	89.5	93.6	101.8	80.7	93.6	101.8
13	180	88.8	94.0	105.6	80.3	94.0	105.6

Table-4: % Availability of cephradine in presence of famotidine.

S. No	Time (mins)	<— Simulated gastric juice —> at 37°C	at 48°C	at 60°C	<—— pH 7.4 ——> at 37°C	at 48°C	at 60°C
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	15.0	105.6	99.4	107.4	51.8	82.1	71.8
3	30.0	118.0	96.8	107.1	99.6	72.1	93.3
4	45.0	106.7	98.3	105.2	98.2	77.4	93.7
5	60.0	108.8	102.0	107.7	95.7	75.3	85.3
6	75.0	106.1	101.7	109.5	95.5	72.3	87.2
7	90.0	103.9	100.7	111.3	94.6	70.9	87.7
8	105.0	106.1	101.7	104.5	84.9	67.9	91.6
9	120.0	100.1	102.1	113.3	94.6	68.4	89.2
10	135.0	99.0	98.9	112.6	93.0	62.4	91.8
11	150.0	99.6	102.8	108.5	91.9	60.5	96.1
12	165.0	101.4	102.9	105.0	90.8	58.8	80.3
13	180.0	101.1	100.7	106.3	90.9	57.0	74.2

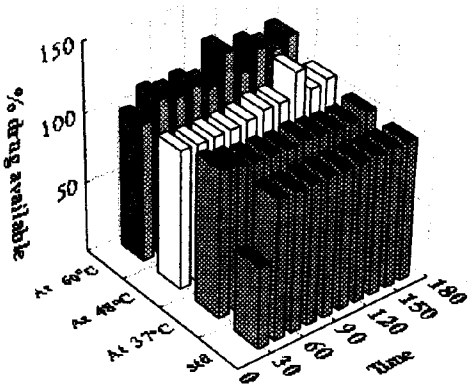


Fig. 1: % Availability of cephradine alone and in presence of cimetidine in simulated gastric juice.

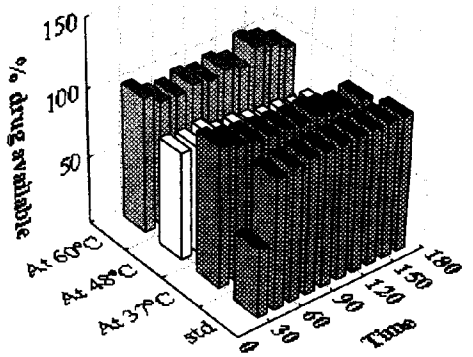


Fig. 2: % Availability of cephradine alone and in presence of cimetidine in buffer pH 7.4.

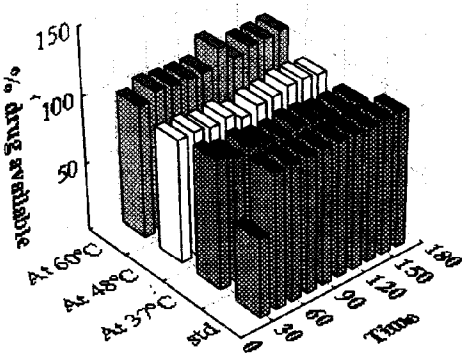


Fig. 3: % Availability of cephradine alone and in presence of ranitidine in simulated gastric juice.

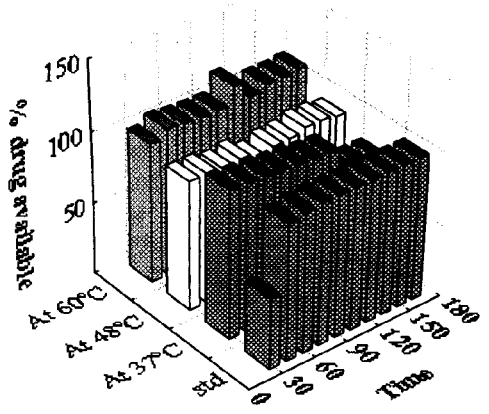


Fig. 4: % Availability of cephradine alone and in presence of ranitidine in simulated buffer pH 7.4.

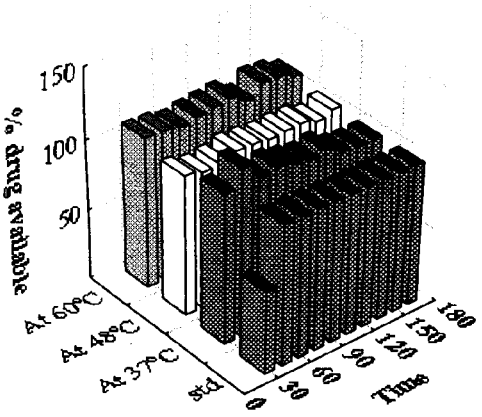


Fig. 5: % Availability of cephradine alone and in presence of famotidine in simulated gastric juice.

gastric juice and at pH 7.4 and that of cimetidine (through dissolution) was found to be 100 and 99.9 % in simulated gastric juice and in pH 7.4 respectively.

Interaction of cephradine with cimetidine at 37 °C showed that the availability of cephradine in simulated gastric juice and at pH 7.4 was increased to 105 and 102 % respectively and all the drug was available after 15 minutes showing that cimetidine has stimulated the release of cephradine while at 48 and 60 °C the availability of cephradine increased with increase in temperature in simulated gastric juice, but in buffer of pH 7.4 there was no change. This increase in availability of drugs reflects that the

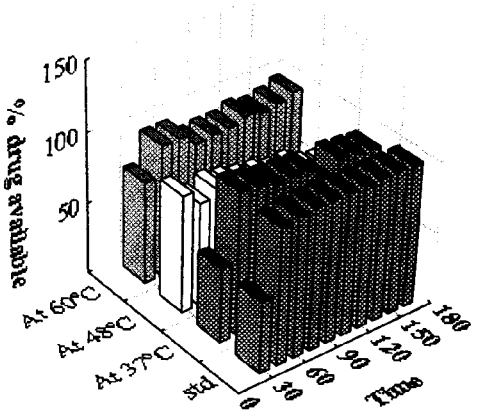


Fig. 6: % Availability of cephradine alone and in presence of famotidine in buffer pH 7.4.

drug has undergone some changes at its chromophoric group resulting in increased molar absorptivity value.

The availability of cephradine in presence of ranitidine at 37 °C increased only in buffer of pH 7.4 and not in simulated gastric juice. When the interaction was carried out at 48 °C, there was no change, but at 60 °C the availability of cephradine increased to 115 % in both mediums.

In presence of famotidine, at 37 °C the % availability of cephradine increased in simulated gastric juice and not in buffer of pH 7.4. At higher temperature, the availability of cephradine increased in simulated gastric juice but there was no effect of increase in temperature in buffer of pH 7.4.

The availability of cephradine after interactions with cimetidine, ranitidine and famotidine are more than 100 % which itself is an evidence of drug interaction with H_2-receptor antagonist. We can safely assume that these interactions have resulted in the formation of charge transfer complex. In case of hydrophobic or charge-transfer interactions, the species formed may have a very high molar absorptivity as compared to original species with no change in λ_{max}. These results also indicate that these interactions were pH dependent, comparatively more in acidic than alkaline pH and also temperature dependent to some extent that is the rate of complex formation increases with increase in temperature.

Experimental

Equipment and Materials

The dissolution equipment was manufactured to the B.P 2000 [45] standards, with slight modifications, details of which are described elsewhere [46]. A double beam UV/Visible spectrophotometer (Shimadzu 1601) coupled with a Pentium IV PC was used to quantify the drugs.

Cephradine reference standard was gift from Bristol Myers Squibb Laboratories Karachi, cimetidine, ranitidine and famotidine were gifts from SKB, GlaxoWelcome and Merck Sharp and Dhome Pakistan Ltd., respectively while Tagamet® tablets (400 mg), Zantac® tablets (150 mg) and Pepcidine® tablets (20 mg) were purchased from the market.

Reference Standards

Cephradine, cimetidine, ranitidine and famotidine obeyed Beer and Lamberts law at their respective λ_{max} in the concentration range of M x 10^{-4} to M x 10^{-5} in all mediums under study. Molar absorbtivities of all the drugs were calculated for their quantification from unknown solutions.

Availability Studies

In the first set of experiments, *in vitro* availability of cephradine and H_2-receptor antagonist were studied in individual dosage formulations in different dissolution mediums, each being 1000 ml of simulated gastric juice or buffer pH 7.4. Samples were withdrawn periodically with an interval of 15 minutes for 180 minutes. The volume of dissolution fluid was maintained by adding an amount equal to dissolution fluid withdrawn, which had been maintained at the same temperature in the same bath. The samples withdrawn were analyzed spectrophotometrically and measured at the λ_{max} of each drug and quantified with the help of Beer's equation.

Interaction Studies

The *in vitro* interaction of cephradine with H_2-receptor antagonist was carried out in simulated gastric juice and at pH 7.4 at 37 °C and at higher temperatures. In each set of experiments Velosef® tablet was added at zero time into the dissolution medium already maintained at specified temperature (37 °C) while H_2-receptor antagonist tablet was added after 15 minutes time interval. Aliquots were withdrawn and assayed as before, this time using simultaneous equation. Graphs were plotted for % availability of drug versus time in each set of experiment (Figs. 1-6).

Conclusions

Interactions of cephradine in presence of H_2-receptor antagonist *in vitro* revealed that the availability of cephradine increased which reflects the complexation of cephradine with almost all H_2-receptor antagonist, but to a lesser extent with ranitidine. The effect of various dissolution mediums with respect to pH on these drug-drug interactions and availability reveals that cephradine dissolves maximally and more quickly in simulated gastric juice followed by buffer of pH 7.4. The influence of temperature on the energetic of these reactions reveals that complexation increases in most of the cases. It can be fairly concluded that cephradine should not be co-administered with cimetidine and famotidine, ranitidine is safer only if taken with an interval of 90 minutes between the oral intake of two drugs.

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