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Research Article

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H_2 -receptor antagonist interactions with Ceftiofur sodium

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ABSTRACT

Ceftiofur sodium is a third generation cephalosporin which is active against number of gram positive and gram negative bacteria. It has bactericidal properties, acting by inhibition of the bacteria cell wall synthesis. Cephalosporins are reported to cause the gastrointestinal complications for which the simultaneous use of the acid suppressing drugs like H_2-receptor antagonists are prescribed. It is quite possible that co-administration of one drug may affect the performance of the other drug and vice versa. The aim of the present work is to investigate the effect of the co-administration of ceftiofur sodium and cimetidine which is well established H_2-receptor antagonist. The studies have been carried out by pH simulation as full gut at normal and elevated temperature.

Key words: H_2-receptor antagonists, cephalosporins, bioavailability, cimetidine, absorbance

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INTRODUCTION

Cephalosporium acremonium, the first fungal source of cephalosporins, was isolated in 1948, by Brotzu [1] from the sea near a sewer outlet off the sardinian coast. Crude filtrates from the cultures of this fungus were found to inhibit the *in vitro* growth of *S. aureus* and were used to cure staphylococcal infections and typhoid fever in man. This fungus was later found to produce at least six antibiotic substances five of which were steroidal, namely cephalosporins P1-P5 [2-4] and sixth major component was named as cephalosporin N, which was only one hundredth as active against gram positive organisms as penicillin G, but was 2-6 times active against gram negative organisms [1, 5, 6]. The culture fluids of *cephalosporium acremonium* were found to contain three distinct antibiotics, namely cephalosporin P, N and C [7-8]. Cephalosporin C was assigned structure as (**1, Fig-1**) it contained a D-α-amino acid moiety, showed an infrared absorption band at 5.62μ indicative of *β*-lactam ring and yielded one mole of carbon dioxide on hydrolysis with warm acid.

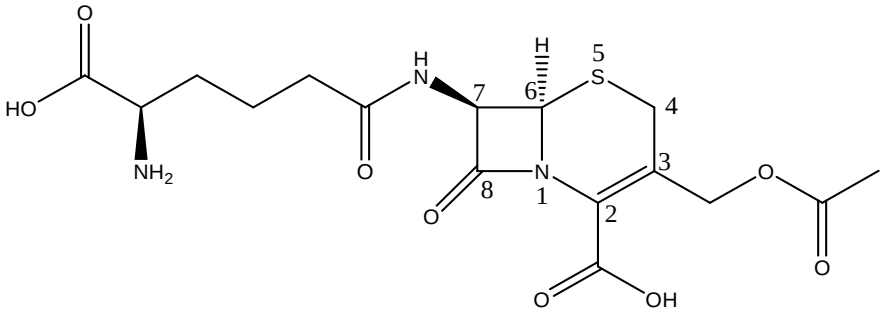

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Fig-1: Cephalosporin C

With the isolation of the active nucleus of cephalosporin C (i.e. 7-aminocephalosporanic acid) and the addition of side chains, it became possible to produce semi synthetic cephalosporin C derivatives having much greater antibacterial activities as compared to the parent substance. The continuing interest in this area led to the discovery of more β-lactam ring containing structures such as cephamycins, nocardicins, clavulanic acid and thienamycin. These compounds become very important in pharmaceutical industry as they are active against gram negative as well as gram positive strains of bacteria

Simultaneous use of the cephalosporins and acid suppressing drugs like H_2-receptor antagonists (H2RAs) is very common in treatment of peptic ulcer. Cephalosporins are reported to cause the gastrointestinal complications for which the simultaneous use of the acid suppressing drugs are prescribed [9]. H_2-Receptor antagonists (H2RAs) are the class of drugs which suppress the meal stimulated as well as normal secretion of acid by parietal cells. Famotodine, ranitidine and cimetidine are the examples of marketedH_2-Receptor antagonists. The interaction of histamine released by enterochromaffin like (ECL) cells with H_2-receptors on parietal cells trigger the gastric acid secretion. H2RAs bind to H_2-receptor on the parietal cells of stomach and thus suppress the excess acid secretion [10]. H2RAs drugs are thus mostly prescribed for the prevention of peptic ulcer disease [11], gastroesophageal reflux disease [12], dyspepsia and stress induced ulcers in critically ill patients [13]. These are also used as preanaesthetic medication in emergency operations to reduce the danger of aspiration of acidic gastric contents [14]. Either of the antacids or H_2-receptor antagonists may be given to those suffering from infrequent heartburn. The H_2-receptor antagonists offer several advantages over antacids, including longer duration of action (6–10 hours versus 1–2 hours for antacids), greater efficacy and ability to be used prophylactically before meals to reduce the chance of heartburn. Proton pump inhibitors, however, are the preferred treatment for erosive esophagitis since they have been shown to promote healing better than H_2-receptor antagonists.

There is a possibility that the co-administration of these two drugs may affect the bioavailability of each other by mutual interaction.A number of reports are available on the investigation of interactions of cephalosporins with alcohols [15-18], aminoglycosidic antibiotics [19], cholestyramines [20], probenecids [21-22], anticoagulants [23] and theophylines [24]. However, the literature survey revealed only limited reports regarding the study of interaction of cephalosporins with H_2-receptor antagonists. The bioavailability of the first generation cephalosporins like cephradine was reported to increase in the presence of different H_2-receptor antagonists like cimetidine and ranitidine [25].However, *In vivo* interaction studies of cephalexin which is another member of first generation of cephalosporins, with ranitidine and aluminum magnesium hydroxide antacid has been reported in literature by Deppermann *et al* [26].However, *In vivo* interaction studies of second generation Cefuroxime sodium with ranitidine and aluminum magnesium hydroxide antacid showed the decrease in the bioavailability of Cefuroxime sodium due to its chelation with Mg(II) and Al(III) ions [27]. Bioavailability of third generation cephalosporins like Cefixime [28] and Cefpodoxime Proxetil [29] has also been observed to influence in the presence of different antacids. The aim of the present work is to study the interaction between ceftiofur sodium and cimetidine which is a H_2-receptor antagonist at pH = 7.4 which corresponds to full gut at normal and at elevated temperature to investigate the possible drug-drug interactions.

EXPERIMENTAL SECTION

All the chemicals used were of analytical grade and purchased from Merck. Reference standard tablet formulations of ceftiofur sodium (250mg, Naxcel, Pfizer, Inc.), cimetidine (300mg, Tagamet, Glaxo SmithKline) were purchased from local pharmacy. Reference standard active pharmaceutical ingredients of the two drugs were obtained as gratis from Mcleods pharmaceutical, Mumbai. Double distilled water was used for the preparation of all the solutions. UV spectrophotometer (Shimadzu UV-1800 ENG 240Vl) was used for measuring the absorbance of the samples.

Preparation of pH 7.4 phosphate buffer

17.90 g of disodium hydrogen phosphate ($Na_2HPO_4.12H_2O$) was dissolved in double distilled water in 500 ml volumetric flask and volume made up to the mark. 6.80 g of potassium dihydrogen phosphate (KH_2PO_4) was dissolved separately in double distilled water in 100 ml volumetric flask and the volume made up to the mark.Forone litre of pH 7.4 buffer, 5.7 ml of potassium dihydrogen phosphate solutionand 31.4 ml of disodium hydrogen phosphate solution were taken in one litrevolumetric flask and the volume was madeup to the markusing double distilled water. The pH of the solution was measured and if found less than 7.4, it was achieved by the addition of a few drops of disodium hydrogen phosphate solution.

Preparation of solutions of H_2-receptor antagonists and ceftiofur sodium

Stock Solutions

The reference standards of cimetidine (0.025g, 0.1mmol) and ceftiofur sodium (0.055g, 0.1mmol) individually were weighed accurately and introduced in the 100 ml volumetric flasks with the help of the funnel. The volume was made up to the mark with the help of phosphate buffer solution. The concentration of the solution so obtained was 1 mmol/L which has been referred as 1mmol for discussion.

Working standard solutions

Different dilutions ranging from 0.01 mmole to 0.2 mmole were made by diluting stock solution of 1 mmol concentration. For this purpose 1 to 20 ml of primary stock solution was pipetted out in each of 100 ml volumetric flask and the volume was made up to the mark with the buffer solution.

Calculation of λ_{max} for ceftiofur sodium and cimetidine

The λ_{max} of each reference standard of cimetidine and ceftiofur sodium was calculated at concentration of 0.001 mmol. For this purpose, 1ml of stock solution was pipetted out individually in 100 ml volumetric flask and the volume was made up to the mark with the help of phosphate buffer.

Calibration curve for ceftiofur sodium and cimetidine

Prior to the bioavailability and drug interaction studies, the concentration range of Beer-Lambert law validation was determined. For this purpose working standards of cimetidine and ceftiofur sodium were prepared in concentrations ranging from 0.01 mmol to 0.2 mmol in 7.4 phosphate buffer solution. The absorption maxima for each of these solutions were scanned in the UV region against the blank. The ceftiofur sodium samples were scanned in the region of its absorption maxima and at the maxima of cimetidine against reagent blank. In the same way, H_2-receptor antagonist samples were scanned at its own absorption maxima and at the absorption maxima of the ceftiofur sodium. The graphs were plotted for absorption maxima against concentration. The straight lines were observed in each case which confirmed linearity of Beer-Lambert law. ε values were calculated from these values by using these values using eq 1.

$$\varepsilon = A/(b.C) \qquad \text{……(eq 1)}$$

Where, A = absorbance at a certain wave length
ε = molar absorptivity
b = path length of cell
C = concentration of the solution

Bioavailability investigation studies of ceftiofur sodium and cimetidine

General procedure

The *in vitro* availability of cimetidine and ceftiofur sodium tablet formulation was studied at pH 7.4 at 37^{o}C and 60^{o}C. The known amount of tablet formulations of cimetidine (300 mg) and ceftiofur sodium (250 mg in 5 ml of double distilled water) was poured in 1 litre of dissolution medium (buffer pH 7) maintained at specified temperature at the beginning of the experiment. Aliquots were withdrawn periodically at fifteen minutes of time intervals for 240 minutes and assayed for the drug content. The volume of the dissolution medium was maintained by adding equivalent amount of the dissolution media withdrawn as aliquots, which had previously been maintained at the same temperature in the same bath. The ceftiofur sodium samples and cimetidine samples were scanned in the region of their absorption maxima against reagent blank and were assayed by using eq 2.

$$\%\text{age of drug dissolved} = (C/x).100 \qquad \text{……(eq 2)}$$

Where x= amountof drug formulation dissolved initially
C= concentration obtained from eq 1

Interaction of ceftiofur sodium with H_2-receptor antagonists

In vitro interaction studies of ceftiofur sodium with cimetidine were carried out in the same manner as mentioned above. In each set of experiments, ceftiofur sodium (250mg in 5 ml of double distilled water) was added to 1 litre of dissolution medium (buffer pH = 7) at zero time and known quantity of cimetidinetablet formulation (300 mg) was added after 15 minutes in separate experiment. Aliquots were withdrawn after every 15 minutes upto 3 hours and

assayed for the concentration of the both the drugs according to eq 3 and eq 4 given in section 4.3.5. The ceftiofur sodium samples were scanned in the region of its absorption maxima and at the maxima of cimetidine against reagent blank. In the same way, cimetidine samples were scanned at its own absorption maxima and at the absorption maxima of the ceftiofur sodium in order to calculate the interactions of each drug. The interaction of ceftiofur sodium with cimetidine was studied in buffer of pH 7.4 at 37°C and 60°C. Ceftiofur sodium was assayed in the presence of cimetidine.

$$C_b = \varepsilon_{a'}.A_{293} - \varepsilon_a .A_{232}/ \varepsilon_{a'}.\varepsilon_{b'} - \varepsilon_a .\varepsilon_{b'} \quad \text{……(eq 3)}$$

and

$$C_a = \varepsilon_{b'}.A_{293} - \varepsilon_b .A_{232}/ \varepsilon_a .\varepsilon_{b'} - \varepsilon_{a'}.\varepsilon_b \quad \text{……(eq 4)}$$

Where
C_a be the concentration of ceftiofur sodium
C_b the concentration of cimetidine

RESULTS

λ_{max} of ceftiofur sodium and cimetidine

For the comparison of absorbance for each drug at different concentration, firstly the λ_{max} was selected for each ceftiofur sodium and cimetidine. For this purpose the solution of ceftiofur sodium and cimetidine of concentration 0.001mmol was scanned in the region of 150-400 nm to calculate the λ_{max} of the respective antagonist and cephalosporin separately. It was observed that cimetidine exhibits strong absorption maxima in the ultraviolet region of the spectrum cimetidine at 209 nm and 219 nm and ceftiofur sodium at 293 nm. Wavelength chosen for cimetidine was 219 and was used for further studies.

Linearity of Beer-Lambert law

In order to investigate the drug interaction studies, the first requirement is to establish the linearity of the Beer-Lambert law for each drug. For this, the working standard solution of cimetidine and ceftiofur sodium was prepared and then subjected to spectrophotometric analysis. The data obtained from these studies are presented in Table-1 for ceftiofur sodium and Table-2 for cimetidine.

Table-1: UV absorption of ceftiofur sodium

S. No.	Stock (ml)	Buffer (ml)	Conc. (mmol)	Absorbance at λ_{max}	
				293nm	219nm
1	1	99	0.01	0.230	0.191
2	2	98	0.02	0.481	0.453
3	3	97	0.03	0.803	0.667
4	4	96	0.04	1.012	0.832
5	5	95	0.05	1.441	1.060
6	6	94	0.06	1.460	1.106
7	7	93	0.07	1.660	1.200
8	8	92	0.08	1.844	1.350
9	9	91	0.09	1.681	1.350
10	10	90	0.10	1.955	1.534
11	11	89	0.11	2.391	1.890
12	12	88	0.12	2.631	2.050
13	13	87	0.13	2.840	2.133
14	14	86	0.14	3.267	2.460
15	15	85	0.15	3.462	2.354
16	16	84	0.16	3.701	3.033
17	17	83	0.17	3.622	3.150
18	18	82	0.18	3.819	3.041
19	19	81	0.19	4.051	3.120
20	20	80	0.20	4.150	2.980

Table 2 UV absorption of cimetidine

S.No.	Stock (ml)	Buffer (ml)	Conc. (mmol)	Absorbance at λ_{max}	
				293nm	219nm
1	1	99	0.01	0.0020	0.225
2	2	98	0.02	0.0042	0.443
3	3	97	0.03	0.0064	0.665
4	4	96	0.04	0.0083	0.799
5	5	95	0.05	0.0115	1.015
6	6	94	0.06	0.0106	1.150
7	7	93	0.07	0.0145	1.375
8	8	92	0.08	0.0178	1.780
9	9	91	0.09	0.0182	1.992
10	10	90	0.1	0.0212	2.205
11	11	89	0.11	0.0221	2.255
12	12	88	0.12	0.0262	2.600
13	13	87	0.13	0.0263	2.935
14	14	86	0.14	0.0284	3.250
15	15	85	0.15	0.0311	3.275
16	16	84	0.16	0.0346	3.540
17	17	83	0.17	0.0357	3.875
18	18	82	0.18	0.0382	3.995
19	19	81	0.19	0.0394	4.265
20	20	80	0.20	0.0428	4.430

Calculation of molar absorptivity (ε) values forceftiofur sodium and cimetidine

The ε values of ceftiofur sodium and cimetidine thus obtained are given in Table-3 and Table-4, respectively and have been further used in the bioavailability studies of these drugs at pH 7.4 individually and in the presence of the interacting drug.

Table-3 ε value of ceftiofur sodium

S.NO.	Conc. (M)	Absorbance at λ_{max}		ε	
		293nm	219nm	219nm	293nm
1	0.00001	0.230	0.191	19100	23000
2	0.00002	0.481	0.453	22650	24050
3	0.00003	0.803	0.667	22233	26766
4	0.00004	1.012	0.832	20800	25300
5	0.00005	1.441	1.060	21200	28820
6	0.00006	1.460	1.106	18433	24333
7	0.00007	1.660	1.200	17142	23714
8	0.00008	1.844	1.350	16875	23050
9	0.00009	1.681	1.350	15000	18677
10	0.00010	1.955	1.534	15340	19550
11	0.00011	2.391	1.890	17181	21736
12	0.00012	2.631	2.050	17083	21925
13	0.00013	2.840	2.133	16407	21846
14	0.00014	3.267	2.460	17571	23335
15	0.00015	3.462	2.354	15693	23080
16	0.00016	3.701	3.033	18956	23131
17	0.00017	3.622	3.150	18529	21305
18	0.00018	3.819	3.041	16894	21216
19	0.00019	4.051	3.120	16421	21321
20	0.00020	4.150	2.980	14900	20750
			Summation	358413	456910
			Mean	17920	22845

Table 4 ε value of cimetidine

S.No.	Conc. (M)	Absorbance at λ_{max}		ε	
		293nm	219nm	ε_{293}	ε_{219}
1	0.00001	0.0020	0.225	201.00	22500.00
2	0.00002	0.0042	0.443	208.00	22150.00
3	0.00003	0.0064	0.665	213.33	22166.00
4	0.00004	0.0083	0.799	208.00	19975.00
5	0.00005	0.0115	1.015	230.00	20300.00
6	0.00006	0.0106	1.150	176.66	19166.00
7	0.00007	0.0145	1.375	207.14	19642.00
8	0.00008	0.0178	1.780	222.50	22250.00
9	0.00009	0.0182	1.992	202.22	22133.00
10	0.00010	0.0212	2.205	212.00	22050.00
11	0.00011	0.0221	2.255	200.90	20500.00
12	0.00012	0.0262	2.600	218.33	21666.00
13	0.00013	0.0263	2.935	202.30	22576.00
14	0.00014	0.0284	3.250	202.85	23214.00
15	0.00015	0.0311	3.275	207.33	21833.00
16	0.00016	0.0346	3.540	216.25	22125.00
17	0.00017	0.0357	3.875	210.00	22794.00
18	0.00018	0.0382	3.995	212.22	22194.00
19	0.00019	0.0394	4.265	207.36	22447.00
20	0.00020	0.0428	4.430	214.00	22150.00
			Summation	4172.44	433836.00
			Mean	208.62	21691.00

Bioavailability studies

The bioavailability data obtained are summarized in Tables-5 for ceftiofur sodium andTable-6 for cimetidine.

Table-5 Bioavailability of ceftiofur sodium at λ_{293}

S.No.	Time(min.)	Absorbance	Conc. (M)	log[conc]	% of drug dissolved
At 37 °C					
1	15	0.9511	$4.1632x10^{-5}$	-4.3806	90.90
2	30	0.9671	$4.2333x10^{-5}$	-4.3733	92.43
3	45	0.9678	$4.2365x10^{-5}$	-4.3730	92.5
4	60	0.9649	$4.2237x10^{-5}$	-4.3743	92.22
5	75	0.9590	$4.1980x10^{-5}$	-4.3770	91.66
6	90	0.9540	$4.1760x10^{-5}$	-4.3792	91.18
7	105	0.9380	$4.1060x10^{-5}$	-4.3866	89.65
8	120	0.9321	$4.0803x10^{-5}$	-4.3893	89.09
9	135	0.9053	$3.9626x10^{-5}$	-4.4020	86.52
10	150	0.9038	$3.9562x10^{-5}$	-4.4027	86.38
11	165	0.8966	$3.9246x10^{-5}$	-4.4062	85.69
12	180	0.8813	$3.8577x10^{-5}$	-4.4137	84.23
13	195	0.8763	$3.8358x10^{-5}$	-4.4161	83.75
14	210	0.8668	$3.7941x10^{-5}$	-4.4209	82.84
15	225	0.8588	$3.7593x10^{-5}$	-4.4249	82.08
16	240	0.8551	$3.7432x10^{-5}$	-4.4268	81.73
At 60 °C					
1	15	0.9880	$4.3249x10^{-5}$	-4.3640	94.43
2	30	0.9837	$4.3061x10^{-5}$	-4.3659	94.02
3	45	0.9707	$4.2489x10^{-5}$	-4.3717	92.77
4	60	0.9511	$4.1632x10^{-5}$	-4.3806	90.90
5	75	0.9104	$3.9851x10^{-5}$	-4.3996	87.01
6	90	0.8690	$3.8037x10^{-5}$	-4.4198	83.05
7	105	0.8675	$3.7973x10^{-5}$	-4.4205	82.91
8	120	0.8617	$3.7721x10^{-5}$	-4.4234	82.36
9	135	0.8603	$3.7657x10^{-5}$	-4.4242	82.22
10	150	0.8595	$3.7625x10^{-5}$	-4.4245	82.15
11	165	0.8588	$3.7593x10^{-5}$	-4.4249	82.08
12	180	0.8581	$3.7561x10^{-5}$	-4.4253	82.01
13	195	0.8443	$3.6956x10^{-5}$	-4.4323	80.69
14	210	0.8348	$3.6544x10^{-5}$	-4.4372	79.79
15	225	0.8304	$3.6351x10^{-5}$	-4.4395	79.37
16	240	0.8283	$3.6255x\ 10^{-5}$	-4.4406	79.16

Table-6 Bioavailability of cimetidine at λ219nm

S.No.	Time(min.)	Absorbance	Conc.(M)	Log[conc]	% of drug dissolved
At 37°C					
1	15	2.0652	$9.5212x10^{-5}$	-4.0213	80.01
2	30	2.1995	$1.0140x10^{-4}$	-3.9940	85.21
3	45	2.3319	$1.0750x10^{-4}$	-3.9686	90.34
4	60	2.4408	$1.1253x10^{-4}$	-3.9487	94.56
5	75	2.5206	$1.1620x10^{-4}$	-3.9348	97.65
6	90	2.5322	$1.1674x10^{-4}$	-3.9328	98.10
7	105	2.5407	$1.1713x10^{-4}$	-3.9313	98.43
8	120	2.5492	$1.1752x10^{-4}$	-3.9299	98.76
9	135	2.5552	$1.1780x10^{-4}$	-3.9289	98.99
10	150	2.5621	$1.1812x10^{-4}$	-3.9277	99.26
11	165	2.5634	$1.1818x10^{-4}$	-3.9275	99.31
12	180	2.5632	$1.1817x10^{-4}$	-3.9275	99.30
13	195	2.5756	$1.1874x10^{-4}$	-3.9254	99.78
14	210	2.5781	$1.1886x10^{-4}$	-3.9250	99.88
15	225	2.5797	$1.1893x10^{-4}$	-3.9247	99.94
16	240	2.5815	$1.1901x10^{-4}$	-3.9244	100.01
At 60°C					
1	15	2.1620	$9.9674x10^{-5}$	-4.0014	83.76
2	30	2.3301	$1.0742x10^{-4}$	-3.9689	90.27
3	45	2.4264	$1.1186x10^{-4}$	-3.9513	94.00
4	60	2.4398	$1.1248x10^{-4}$	-3.9489	94.52
5	75	2.5386	$1.1704x10^{-4}$	-3.9317	98.35
6	90	2.5412	$1.1716x10^{-4}$	-3.9312	98.45
7	105	2.5699	$1.1848x10^{-4}$	-3.9264	99.56
8	120	2.5701	$1.1849x10^{-4}$	-3.9263	99.57
9	135	2.5727	$1.1861x10^{-4}$	-3.9259	99.67
10	150	2.5756	$1.1874x10^{-4}$	-3.9254	99.78
11	165	2.5722	$1.1858x10^{-4}$	-3.9260	99.65
12	180	2.5841	$1.1913x10^{-4}$	-3.9240	100.11
13	195	2.5815	$1.1901x10^{-4}$	-3.9244	100.01
14	210	2.5848	$1.1917x10^{-4}$	-3.9238	100.14
15	225	2.5872	$1.1927x10^{-4}$	-3.9235	100.23
16	240	2.5872	$1.1927x10^{-4}$	-3.9235	100.23

Interaction studies of ceftiofur sodium and H_2-receptor antagonists

The results for the interaction studies are summarized in Table-7 and Table-8 for ceftiofur sodium-cimetidine interactions at 37 °C and 60 °C.

Table-7 Ceftiofur sodium-cimetidine interactions at 37 °C

S.No.	Time (min)	A_{293}	A_{219}	C_a	log[C_a]	C_b	log[C_b]	%age of ceftiofur sodium	%age of cimetidine
1	0	1.3320	2.4832	$5.7699x10^{-5}$	-4.2388	$6.6813x10^{-5}$	-4.1751	125.87	56.24
2	15	1.4175	2.8482	$6.1316x10^{-5}$	-4.2124	$8.0653x10^{-5}$	-4.0934	133.76	67.89
3	30	1.4343	3.1312	$6.1934x10^{-5}$	-4.2081	$9.3187x10^{-5}$	-4.0306	135.11	78.44
4	45	1.3263	3.2498	$5.7121x10^{-5}$	-4.2432	$1.0263x10^{-4}$	-3.9887	124.61	86.39
5	60	1.2861	3.4866	$5.5251x10^{-5}$	-4.2577	$1.1509x10^{-4}$	-3.9389	120.53	96.88
6	75	1.2367	3.5044	$5.3064x10^{-5}$	-4.2752	$1.1772x10^{-4}$	-3.9292	115.76	99.09
7	90	1.2380	3.5169	$5.3115x10^{-5}$	-4.2748	$1.1825x10^{-4}$	-3.9272	115.87	99.54
8	105	1.2186	3.4876	$5.2271x10^{-5}$	-4.2817	$1.1760x10^{-4}$	-3.9296	114.03	98.99
9	120	1.1294	3.4856	$4.8338x10^{-5}$	-4.3157	$1.2076x10^{-4}$	-3.9181	105.45	101.65
10	135	1.1163	3.4582	$4.7770x10^{-5}$	-4.3208	$1.1996x10^{-4}$	-3.9209	104.21	100.98
11	150	1.1130	3.5216	$4.7600x10^{-5}$	-4.3224	$1.2303x10^{-4}$	-3.9100	103.84	103.56
12	165	1.0870	3.6826	$4.6385x10^{-5}$	-4.3336	$1.3145x10^{-4}$	-3.8812	101.19	110.65
13	180	1.0966	3.7274	$4.6789x10^{-5}$	-4.3299	$1.3319x10^{-4}$	-3.8755	102.07	112.11
14	195	1.0901	3.8185	$4.6463x10^{-5}$	-4.3329	$1.3765x10^{-4}$	-3.8612	101.36	115.87
15	210	1.0836	4.0627	$4.6074x10^{-5}$	-4.3365	$1.4924x10^{-4}$	-3.8261	100.51	125.62
16	225	1.0865	4.1213	$4.6179x10^{-5}$	-4.3356	$1.5185x10^{-4}$	-3.8186	100.74	127.82
17	240	1.0616	4.1570	$4.5065x10^{-5}$	-4.3462	$1.5442x10^{-4}$	-3.8113	98.31	129.98

C_a = conc. of ceftiofur sodium; C_b = conc. of cimetidine

Table-8 Ceftiofur sodium-cimetidine interactions at 60 °C

S.No.	Time (min)	A_{293}	A_{219}	C_a	log[C_a]	C_b	log[C_b]	%age of ceftiofur sodium	%age of cimetidine
1	0	1.0700	3.1955	0.00004584	-4.3388	0.0001095	-3.9608	100	92.13
2	15	1.0686	3.1566	0.00004579	-4.3392	0.0001077	-3.9678	99.9	90.65
3	30	1.0684	3.1713	0.00004578	-4.3393	0.0001084	-3.9650	99.87	91.23
4	45	1.0358	3.2649	0.00004430	-4.3536	0.0001139	-3.9434	96.65	95.89
5	60	1.0253	3.5062	0.00004374	-4.3592	0.0001255	-3.9013	95.41	105.65
6	75	1.0232	3.6353	0.00004359	-4.3606	0.0001316	-3.8808	95.09	110.76
7	90	1.0100	3.7048	0.00004298	-4.3667	0.0001353	-3.8687	93.76	113.88
8	105	0.9638	3.8074	0.00004090	-4.3883	0.0001417	-3.8485	89.22	119.31
9	120	0.9488	3.9424	0.00004018	-4.3960	0.0001486	-3.8281	87.65	125.05
10	135	0.9627	4.0418	0.00004075	-4.3899	0.0001527	-3.8162	88.9	128.51
11	150	0.9645	4.2289	0.00004075	-4.3899	0.0001613	-3.7924	88.9	135.77
12	165	0.9367	4.0813	0.00003959	-4.4024	0.0001554	-3.8084	86.36	130.85
13	180	0.8795	4.1594	0.00003703	-4.4315	0.0001612	-3.7927	80.78	135.66
14	195	0.8350	4.2357	0.00003504	-4.4555	0.0001663	-3.7790	76.43	140.01
15	210	0.7792	4.1820	0.00003260	-4.4868	0.0001659	-3.7802	71.11	139.62
16	225	0.7689	4.2120	0.00003213	-4.4931	0.0001676	-3.7756	70.09	141.11
17	240	0.7528	4.2222	0.00003142	-4.5028	0.0001687	-3.7729	68.54	142

C_a = conc. of ceftiofur sodium; C_b = conc. of cimetidine

DISCUSSION

Linearity of Beer-Lambert Law

The graphical presentation of Beer-Lambert law for the drugs under investigation at various λ_{max} values have been given in Figs 1-5. It may be observed that the reference standards of ceftiofur sodium and cimetidine obey Beer-Lambert law in the concentration range 0.01-0.2 mmol**.**

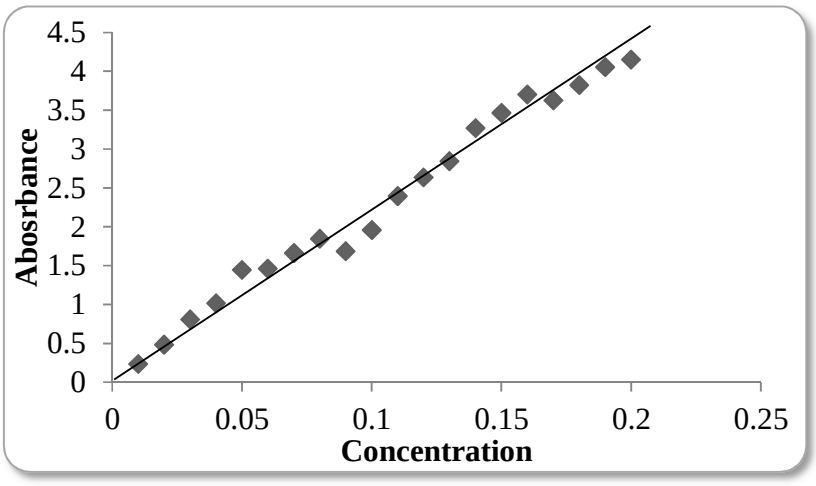


Fig-1: Linearity of Beer-Lambert law for ceftiofur sodium at 293 nm

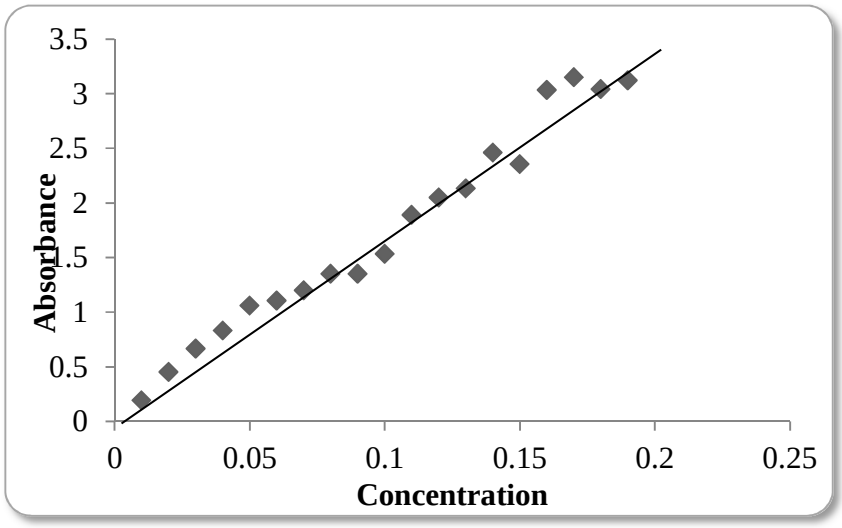


Fig-2: Linearity of Beer-Lambert law for ceftiofur sodium at 219 nm

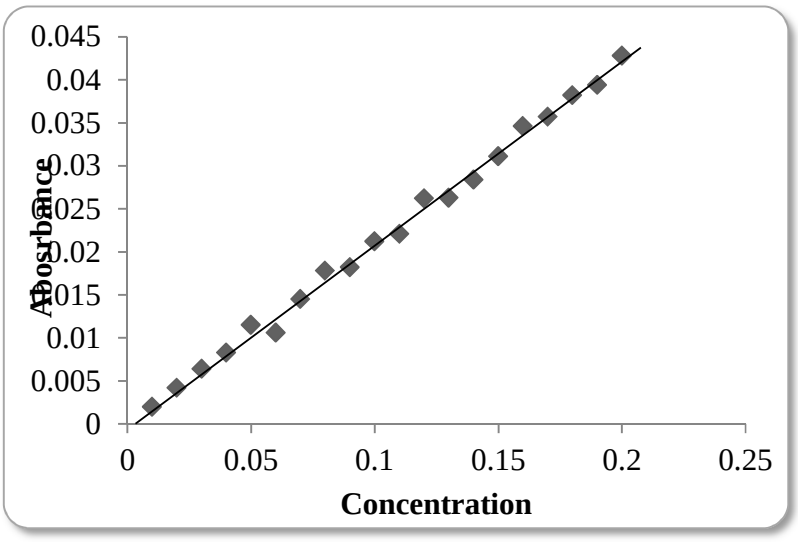


Fig-3: Linearity of Beer-Lambert law for cimetidine 293 nm

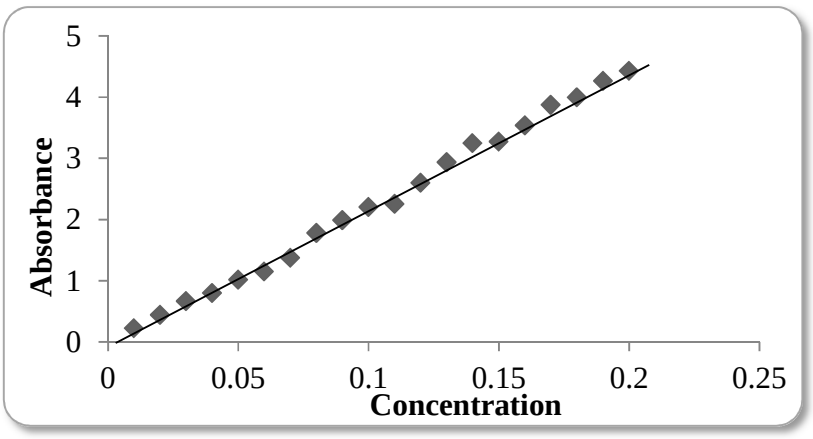


Fig-4: Linearity of Beer-Lambert law for cimetidine sodium at 293 nm

Bioavailability of ceftiofur sodium

The bioavailability of ceftiofur sodium at 293nm at normal (37°C) and elevated temperature (60°C) is represented graphically in Fig-5. It is clear that at 37°C, the drug shows 91% of the availability after 15 minutes of dissolution, which reaches to a maximum value of 93% after 45 minutes, thereafter the availablity of the drug starts decreasing steadily with time, reaching to a minimum value of 82% after 240 minutes. This decrease may be attributed to the degradation of ceftiofur sodium at blood pH = 7.4, as reported in the case of cefixime [28]. In contrast, the bioavailability of cephradine has been reported to increase with time [25].

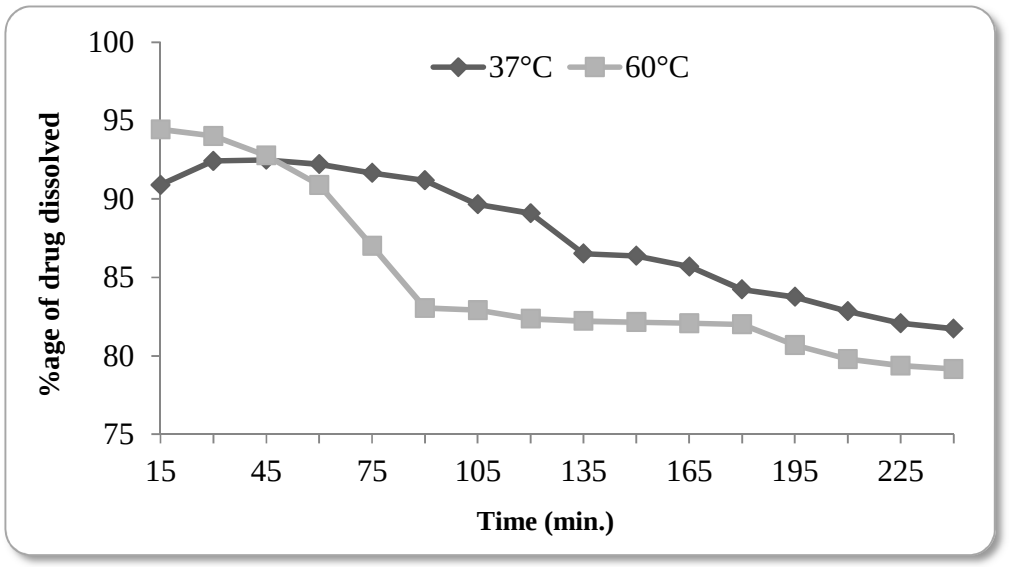


Fig-5: Bioavailability of ceftiofur sodium

At elevated temperature i.e., 60°C, the availability of ceftiofur sodium is 94% after 15 minutes and starts decreasing thereafter with time reaching to a minimum value of 79% after 240 minutes. The comparison of the bioavailability of ceftiofur at both the temperatures reveals that the drug is more available after 15 minutes of dissolution at 60°C (94%) than at 37°C (90%). Around 45 minutes, the availability at both the temperatures becomes almost same i.e., about 92.5%. At higher time intervals, the degradation of the drug is more at 60^0C than at 37°C as evident from the percentage of drug available at 240 minutes in both the cases (79.1% and 81.7%, respectively). The results found are in contrast to the results reported in case of cefixime, where increase in temperature has no effect on the availability of antibiotic [28].

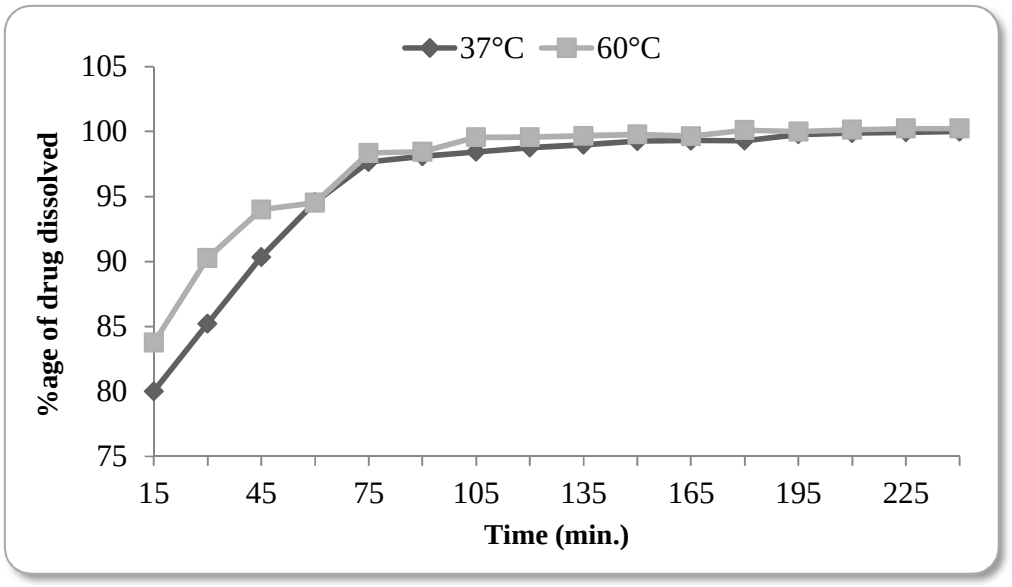


Fig-6: Bioavailability of cimetidine

Bioavailability of cimetidine

The bioavailability of cimetidine is investigated at 219nm absorption maxima at both the temperatures under study. The results are represented as graph in Fig-6 which shows that the temperature has no effect on its bioavailability

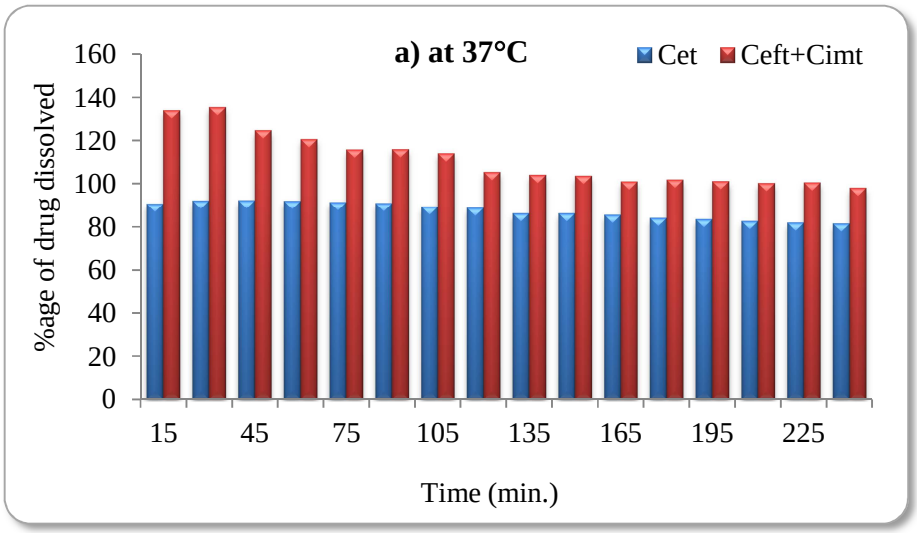
after initial 45minutes. 80-84% of the drug is available after 15 minutes which increases steadily with time up to 105 minutes. The comparison of the availability data at both the temperatures show that high temperature assists quick release of the drug till 45 minutes after which same availability of the drug is observed at both the temperatures.

Ceftiofur sodium - cimetidine interactions

The comparison of bioavailability of ceftiofur sodium in the presence and absence of cimetidine at 37°C and 60°C is represented in Fig-7. At 37 ^{o}C, the presence of cimetidine increases the availability of ceftiofur sodium drastically. The availability reaches to more than 100% immediately after 15 mins of the beginning of experiment. The comparative graph (Fig-7a) shows that the bioavailability of ceftiofur alone reduces to the extent of 82% after 240mins in contrast to its 98% availability in the mixture.

Fig-7b represents the bioavailability of ceftiofur sodium alone and in the presence of cimetidine at 60°C. As is clear from the graph, availability of the drug is almost 100% within 15 minutes, which then decreases with time. Till 165 minutes, the availability of the drug is more in the presence of cimetidine as compared to that in the absence of cimetidine. Post 165 minutes, availability of the drug is less in presence of cimetidine reaching to a minimum value of 68% as compared to 79% availability of the drug alone.

The comparison of bioavailability of ceftiofur sodium in the presence of cimetidine at 37°C and 60°C is represented in Fig-7c. It is well understood from the comparison that presence of cimetidine greatly influences the availability of ceftiofur sodium at both temperatures, decreasing its availability with time at both the temperatures. The drug shows more than 100% bioavailability at 37°C, which may be due to interactions between ceftiofur sodium and cimetidine due to the formation of a week complex probably absorbing at the wavelengths chosen for with high absorptivity. Similar observations have been reported in literature for cefixime-cimetidine interactions at pH = 1 [28]. The drug shows almost 100% bioavailability after 15 minutes which decreases sharply after that as compared to its availability at 37°C. This may be due to the degradation of ceftiofur sodium at higher temperature.



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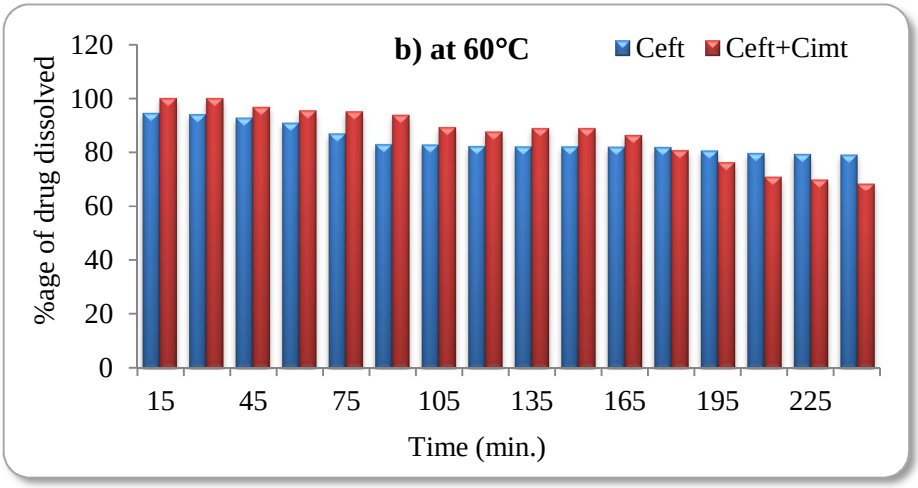

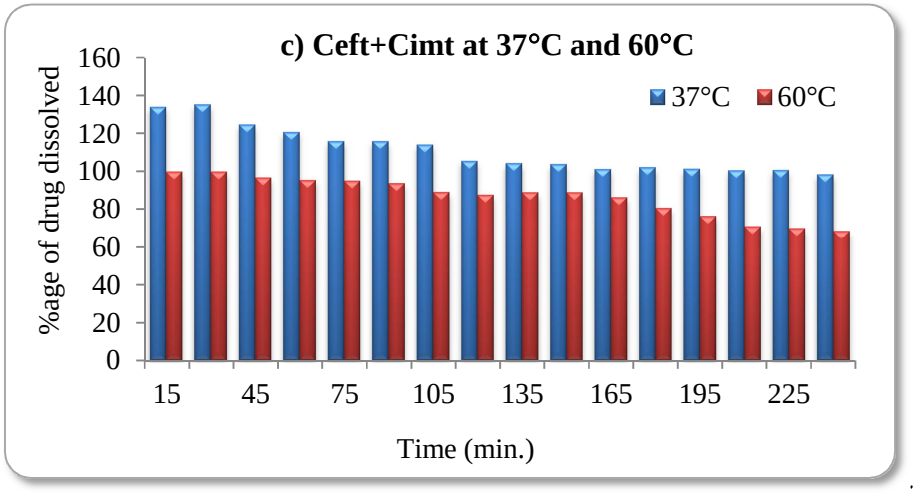

Fig-7: Ceftiofur sodium-cimetidine interactions

CONCLUSION

As discussed earlier, cephalosporins are reported to cause the gastrointestinal complications for which the simultaneous use of acid suppressing drugs is prescribed. In view of the literature survey indicating the possible interactions between different cephalosporins and H_2-receptor antagonist, ceftiofur sodium has been investigated for its interaction with H_2-receptor antagonist cimetidine using spectrophotometry. The results show that cimetidine interact with ceftiofur sodium as an increase in the bioavailability of ceftiofur sodium on simultaneous co-administration is observed. More than 100% availability is observed indicating the possibility of strong complexation between the two drugs which can give rise to a formation of a new intermediate having higher absorbance value than ceftiofur sodium.

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REFERENCES

[1] G Brotzu; E.P. Abraham. *Pharmacol. Rev.***1962**, (14), 473-500.

[2] H. Crawford; N.G. Heatley; P.F. Boyd; C.W. Haley; B.K. Kelley, G.A. Smith; M. Smith. *J. Gen. Microbiol.***1952**, (6), 47-59.
[3] H.S. Burton; E.P. Abraham. *Biochem. J.***1951**, (50), 168-174.
[4] H.S. Burton; E.P. Abraham; H.M.E Cardwell. *Biochem. J.* **1956**, (62), 171-176.
[5] E.P. Abraham; G.G.F. Newton;K. Crawford; H.S. Burton;C.W. Haley. *Nature***1953**, (171), 343.
[6] E.P. Abraham; G.G.F. Newton; C.W. Hale. *Biochem. J.***1954**, (58), 94-102.
[7] G.G.F. Newton; E.P. Abraham. *Nature***1955**, (175), 548.
[8] G.G.F. Newton; E.P. Abraham. *Biochem. J.***1956**, (62), 651-658.
[9] T.S. Foster; C.L. Raehi; H.D. Wilson. *Am. J. Hosp. Pharm.***1980**, (37), 858-859.
[10] J.Q. Huang. *Best. Pract. Res.* **2001**, (15), 355-370.
[11] A.S. Taha; N. Hudson; C.J. Hawkey. *N. Engl. J. Med*. **1996**, (334), 143-149.
[12] I.T. Beck;M.C. Champion;S. Lemire. *Can. J. Gastroenterol.* **1997**, (11), 583-587.
[13] D. Cook; G. Guyatt; J. Marshall. *N. Engl. J. Med.***1998**, (338), 791-797.
[14] R.N Brodgen; A.A. Carmine; R.C. Heel; T.M. Speight; G.S. Avery. *Drugs***1982**, (24), 267-303.
[15] S. Drummer; W.E. Hauser; J.S. Remington. *N. Eng. J. Med.* **1980**, (303),1417-1418.
[16] RM. Elenbas;J.L. Ryan; W.A. Robinson; M.J. Singsank;M.J. Harvey; C.D. Klaasen. *Clin. Pharmacol. Ther.* **1982**, (32), 347-355.
[17] K.R. Brown; B.J. Guglielmo; V.G. Pones; R.A. Jacobs. *Ann. Int. Med.***1982**, (97), 621-622.
[18] J.M. Wellwood; P.M. Simpson; J.R. Tighe; E.E. Thompson. *Brit. Med. J.* **1975**, (3), 278-281.
[19] E.L. Marino; M.T. Vicente; G. Dominguez. *Int. J. Pharmaceut.***1983**, (16), 23-30.
[20] P.G. Welling; S. Dean; A. Selen; M.J. Kandall; R. Wise. *Braz. J. Clin. Pharmacol.***1979**, (8), 491-495.
[21] D.S. Reeves; D.W. Bullaock; M.J. Bywater; H.A. Holt; L.O White; D.P. Thornhill. *Braz. J. Clin. Pharmacol.* **1981**, (11), 506-508.
[22] L.M. Babiak; M.J. Rybak. *Drug. Intell. Clin. Pharm.* **1986**, (20), 833-836.
[23] V.P. Gotz; G.G. Ryerson. *Drug. Intell. Clin. Pharm.***1986**, (20), 694-697.
[24] K. Bachmann; J. Schwartz; R.B. Forney; L. Jauregui. *Ther. Drug. Monit.* **1986**, (8), 151-154.
[25] M.S. Arayne; N. Sultana; M. Afzal; A.Z. Mirza. *J. Chem. Soc. Pak.* **2008**, (30), 734-739.
[26] K.M.Deppermann; H. Lode; G. Hoffken; G. Tschink; C. Kalz; P. Koeppe. *Antimicrob. Agent. Chemotherap.* **1989**, (33), 1901-1907.
[27] N. Sultana; T. Mubeen; M.S. Arayne M.S; R. Ifzal. *Pak. J. Pharmaceutic. Sci.* **2001**, (14), 1-8.
[28] M.S. Arayne; N. Sultana; S.S. Bahadur. *J. Chem. Soc. Pak.***2008**, (30), 726-733.
[29] Y.M. Utsui, Inoue; S. Mitsuhashi. *Antimicrob. Agent. Chemotherap*. **1987**, (31), 1085-1092.