ORIGINAL ARTICLE

IN VITRO INTERACTIONS OF CAPTOPRIL WITH H_2-RECEPTOR ANTAGONISTS

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ABSTRACT

Captopril is effective in the treatment of hypertension of all grades of severity. H_2-receptors antagonists block gastric acid secretion and some cardiovascular effects of histamine. In view of the fact that, simultaneous administration of both drugs may alter the antihypertensive effect of captopril, present paper deals with the *in vitro* availability studies of captopril in presence of commonly used H_2-receptor antagonists like cimetidine, ranitidine and famotidine. In order to simulate various pH levels in GI tract and to find out the kinetics and energetics of captopril-H_2 -receptor antagonist interactions, these studies were carried out in buffers of pH 4, 7.4 and 9 at 37ºC and at elevated temperatures. These studies clearly indicate that most of the H_2-receptor antagonists bind to captopril, forming charge-transfer complexes. As a result, the availability of captopril was affected by the concurrent administration of H_2- receptor antagonists. Accordingly coadministration of both the drugs should be avoided.

Keywords: ACE-inhibitors; captopril- H_2-receptor antagonists interactions; cimetidine; ranitidine; famotidine; drug interaction.

INTRODUCTION

Captopril is 1-[(2S)-3-mercapto-2-methyl-1-oxo-proptonyl]-L-proline (fig. 1) (Jaime and William, 1991), the first orally active and specific inhibitor of angiotensin-converting enzyme (ACE). It blocks the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin converting enzyme and inactivates bradykinin, a potent vasodilator. The hypotensive activity of captopril probably results both from inhibitory action on renin-angiotensin system and stimulating action on kallikerin-kinin system (Bertam 1998).

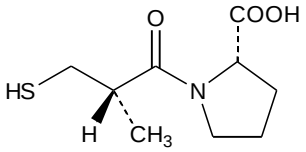

Fig. 1

A number of drug interactions of ACE inhibitors with other drugs are reported. Likewise drug interactions of captopril with azathioprine (Robert *et al.,* 1985), antacids (Swartz and Williams, 1982), quinidine (Augenstein *et al.,* 1988), probencid (Joseph *et al.,* 1995), digoxin (USP NF, 1995 and Alfanso, 1995,) allopurinol (Graham *et al.,* 1989), indomethacin (Ferguson *et al.,* 1977) and immunosuppressive agents (Colin, 1999) have been reported in the literature. H_2-receptors are found in the stomach, in rat uterus and in heart. Their stimulation causes gastric acid secretion, relaxation of the uterus and increased activity of heart (Taylor *et al.,* 1989). These antagonists compete with histamine for H_2-receptors and block gastric acid secretion and some cardiovascular effects of histamine (Prasun *et al.,* 1995) and provide incontrovertible evidence for the importance of endogenous histamine in the physiological control of gastric secretion and transform the treatment of peptic ulcer disease (Goodman and Gilman, 1996).

Currently available H_2-receptors antagonists are cimetidine, ranitidine, famotidine, nizatidine, roxatidine, ramioxitidine (Martindale, 1999) zaltidine and lafutidine (Laferla *et al.,* 1986; Farup, 1988), which are chemically histamine congeners that contain a bulky side chain in place of ethylamine moiety (Black, 1993). Out of these the effect of first three on the availability of captopril have been studied in this paper.

Cimetidine can affect a wide range of drugs particularly those, which have a narrow therapeutic index where the risk of toxicity may necessiate adjustment of dosage. Cimetidine binds to cytochrome P450 with subsequent inhibition of micosomal oxidative metabolism thus increase the bioavailability of drugs metabolized by these

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enzymes (Penston and Wormsley, 1986; Somogyi. and Mauirhead, 1987; Smith and Kendall, 1988; Shinn, 1992).

Few studies indicate that cimetidine does not alter the pharmacokinetis or pharmacological effects of captopril (Richer *et al.,* 1986) and other ACE-inhibitors such as enalepril, quinapril and fosinopril (Ischizaki *et al.,* 1988; Ferry *et al.,* 1988; Moore *et al*.,. 1988). One study reveals that concurrent use of cimetidine and pentopril reduces the renal clearance of pentopril by 11-14% and pentopril reduces cimetidine clearance by 21% (Kochak *et al.,* 1988) that means simultaneous administration of these drugs may affect their bioavailability, which may result in the loss of therapeutic effects of drug.

Coadministration of ranitidine or cimetidine with cisapride results in an increase in the rate of absorption and decrease in rate of bioavailability of ranitidine or cimetidine. Cimetidine has also been reported to enhance the bioavailability of oral cisapride (Kirch *et al.,* 1989; Rowbotham *et al.,* 1991). There have been occasional reports of theophylline toxicity after concomitant ranitidine therapy. (Fernandes and Melewics, 1984; Gardner and Sikorski 1985; Hegman and Gilbert., 1991). Few studies have suggested that ranitidine does not significantly inhibit theophylline metabolism, even at high doses (Kelly *et al.,* 1986).

Famotidine has also been reported to not alter theophylline disposition but one study found a significant decrease in the theophylline clearance in some patients with chronic obstructive pulmonary disease (Dal Negro *et al.,* 1993). One study showed that concurrent administration of famotidine with antacid resulted in a great reduction in the absorption of famotidine (Barzaghi *et al.,* 1989; Lin *et al.,* 1987). Inhibition of the renal tubular secretion of famotidine was observed after coadministration of famotidine and probenecid (Inotsume *et al.,* 1990).

From these studies, it is apparent that captopril may interact with H_2-receptor antagonists. Hence, in order to find out interactions of captopril with commonly used H_2-receptor antagonists, a study of the *in vitro* availability of captopril was carried out in presence of cimetidine, ranitidine and famotidine in simulated gastric and at blood pH at 37°C. The energetics of these interactions has also been determined.

MATERIALS AND METHODS

Material

Captopril was a gift from Bristol-Mayers Squibb Pharmaceuticals (Pvt.) Ltd. Cimetidine (cimetamat 200 mg), famotidine (flamulcer 20 mg), and ranitidine (zantac 150 mg) were of Indus Pharma (Pvt.) Ltd., Swiss Pharmaceuticals (Pvt.) Ltd. and Glaxosmithkline (Pakistan) Ltd., respectively and were purchased from the market. Reference standards of all these H_2-receptor antagonists were supplied by Lab-9 of Department of Chemistry, University of Karachi. All reagents used were of analytical grade from E. Merck (Germany).

Methods

Primary solutions of 1mMole concentration of captopril were prepared individually in simulated gastric juice in buffers of pH 4, 7.4 and 9. From these primary solutions stock solutions of 0.2mMole were prepared. Working standard solutions of concentration 0.05 to 0.14-mMole were prepared by diluting the appropriate amount of stock solution with the same buffer. Absorbance of all these solutions was measured at the absorbance maxima against blank. By scanning these solutions in the UV region, the maxima was found at 206 nm. Beer Lambert's law was obeyed at these concentrations and pH, where molar absorptivities were calculated for further calculations. Similarly, absorbance's of all the working standard solutions of H_2 -receptor antagonists were measured. The maxima of cimetidine was observed at 216 nm in simulated gastric juice and in all other buffers. For famotidine, it was at 265 nm in simulated gastric juice and in buffers of pH 4 and 7.4, while at 284 nm in buffer of pH 9. For ranitidine maxima was recorded at 225 nm in all buffers which obeyed Beer Lambert's law.

In vitro availability studies of captopril and H_2-receptor antagonists were carried out in simulated gastric, in buffers of pH 4, 7.4 and 9, using dissolution equipment, which was manufactured according to the B.P. 2002 Standards (British Pharmacopoeia, 2002). These studies were performed in absence and presence of H_2-receptor antagonists at 37ºC and at elevated temperatures in buffers of pH 4, 7.4 and 9 and in simulated gastric juice. In each of these sets of experiment, captopril 0.25 gm and H_2-receptor antagonists (cimetidine 200 mg, ranitidine 150 mg or famotidine 20 mg) was added to the dissolution medium at zero time. Aliquots of 5 ml were withdrawn at every 15 minutes time interval for 180 minutes and assayed for both the drugs. The volume of dissolution fluid was maintained by adding an equivalent amount of dissolution fluid withdrawn, which had previously been maintained at same temperature in the same bath. The samples were scanned in the range of 200-360 nm against reagent blank and captopril and the interacting drugs were quantitated using a simultaneous equation.

RESULTS AND DISCUSSION

The captopril molecule consists of a proline ring containing carboxylic, sulfhydryl and carbonyl group and propyl chain, which gives $\sigma - \sigma^*$, $\sigma - \pi^*$, n $-\sigma^*$, π to π^* and n to π^* transitions. The strong absorption of captopril is due to the presence of carboxylic and carbonyl groups. Carboxylic group shows the most intense n to π^*

Table 1: *In vitro* availability of captopril in absence and presence of H_2-receptor antagonists at pH 1.

Time	Captopril % availability	Captopril % availability in presence of		
		Cimetidine	Famotidine	Ranitidine
0	0.00	0.00	0.00	0.00
15	65.68	118.54	158.63	310.64
30	68.55	107.79	129.89	120.14
45	72.36	101.47	127.29	120.16
60	72.86	102.89	144.29	261.47
75	75.66	97.95	125.15	284.85
90	78.64	94.24	125.36	278.85
105	78.85	91.29	116.01	251.51
120	79.62	96.24	113.42	275.39
135	80.42	95.22	127.06	434.42
150	81.65	91.57	124.72	216.82
165	87.56	87.99	113.64	280.58
180	92.88	54.71	123.73	279.60

Table 2: *In vitro* availability of captopril in absence and presence of H_2-receptor antagonists at pH 4

Time	Captopril % availability	Captopril % availability in presence of		
		Cimetidine	Famotidine	Ranitidine
0	0	0.00	0.00	0.00
15	77.29	452.28	54.94	334.61
30	77.73	36.99	63.91	341.66
45	77.75	58.54	57.25	320.15
60	77.79	143.10	53.92	320.59
75	80.33	121.35	51.24	392.66
90	80.91	95.06	43.64	333.25
105	81.29	122.59	57.40	289.63
120	81.43	142.85	47.76	297.39
135	84.97	158.39	72.87	348.38
150	91.12	241.80	34.21	353.58
165	92.3	249.23	33.64	336.13
180	100.83	266.60	48.57	338.63

transition in the region of 205 nm, the carbonyl group shows π - π^* in 180-190 nm region and the sulfhydryl group shows n to σ^* transition at 210 nm region. Sulfhydryl group is readily ionizible due to which hypsochromic shift i.e. change in absorption maxima on dilution is shown. In 1mMolar solution it gives absorption at 212 nm region, which on dilution shifts to 206 nm.

i *Simultaneous determination of captopril and H_2-receptor antagonists*

During these interactions studies, the interacting drugs were estimated from the aliquots by measuring the absorbance of the solution at the λmax of both interacting drugs and with the help of following simultaneous equations.

Table 3: *In vitro* availability of captopril in absence and presence of H_2-receptor antagonists at pH 7.4

Time	Captopril % availability	Captopril % availability in presence of		
		Cimetidine	Famotidine	Ranitidine
0	0.00	0.00	0.00	0.00
15	105.48	50.76	125.57	91.71
30	102.94	71.94	88.29	79.73
45	107.00	24.42	91.78	77.54
60	100.60	32.97	132.19	77.12
75	108.34	11.94	97.41	80.58
90	104.73	13.90	102.45	73.63
105	102.33	38.67	83.70	78.68
120	101.47	11.71	86.82	81.06
135	101.91	11.37	75.29	75.21
150	101.69	10.47	126.19	90.86
165	104.74	14.03	89.45	78.08
180	98.80	8.63	98.71	72.20

Table 4: *In vitro* availability of captopril in absence and presence of H_2-receptor antagonists at pH 9

Time	Captopril % availability	Captopril % availability in presence of		
		Cimetidine	Famotidine	Ranitidine
0	0.00	0.00	0.00	0.00
15	93.48	322.45	349.26	189.17
30	95.19	342.50	383.92	185.99
45	95.41	542.86	368.77	196.63
60	97.56	552.06	365.44	189.20
75	100.28	850.77	327.78	187.97
90	100.39	845.63	387.60	176.83
105	101.88	624.74	358.83	163.55
120	102.92	641.51	360.14	179.00
135	103.62	604.56	340.65	155.81
150	102.28	918.76	356.52	164.82
165	100.44	827.00	357.98	161.83
180	100.45	923.27	374.79	148.66

$$Ca = \frac{Ay.b2 - Az.b1}{a1\ b2 - a2\ b1} \quad (1)$$

$$Cb = \frac{Ay.a2 - Az\ a1}{a2\ b1 - a1\ b2} \quad (2)$$

Where, Ca and Cb were concentrations captopril and H_2-receptor antagonists a1 and a2 were the absorptivities of captopril at y & z nm and b1 and b2 were absorptivities of H_2-receptor antagonists at y & z nm, Ay & Az were absorptions of the solution at λmax of captopril and H_2-receptor antagonists respectively.

ii *Captopril interactions with H_2-receptor antagonists*

The interaction studies of captopril with H_2-receptor antagonists were carried out in simulated gastric, in buffer of pH 4, 7.4 and 9 at 37, 48 and 60˚C. The *in vitro* availability of captopril alone followed first order dissolution rate constant (fig. 2), while the results of the effects of H_2-receptor antagonists on the *in vitro* availability of captopril in simulated gastric juice (table 1), in buffers of pH 4 (table 2), pH 7.4 (table 3), and pH 9

(table 4) show deviation from these profiles. The extent of drug interaction in each of these cases is evident in figs. 3-6.

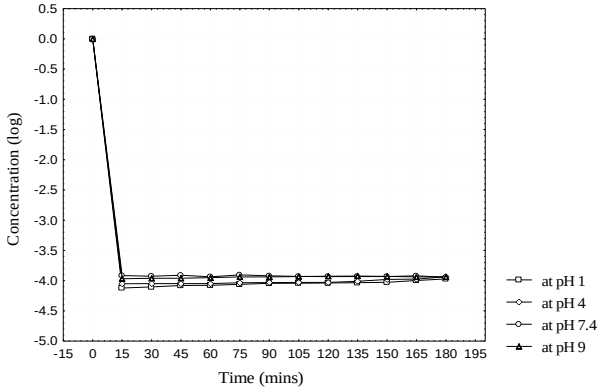

Fig. 2: Availability of captopril at 37°C.

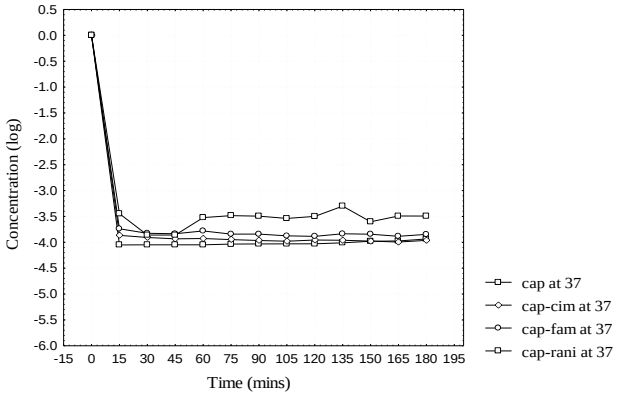

Fig. 3: Availability of captopril in presence of H_2-receptor antagonists in pH 1.

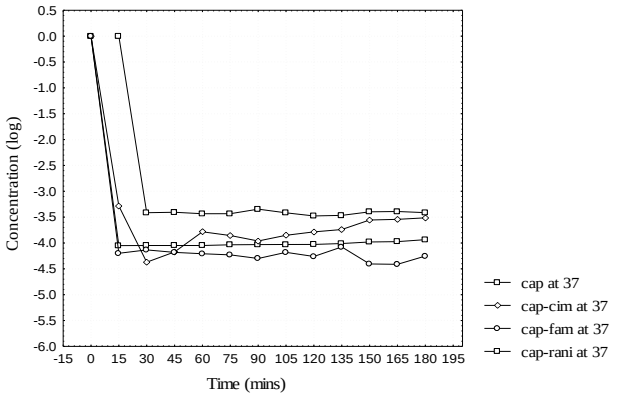

Fig. 4: Availability of captopril in presence of H_2-receptor antagonists in pH 4.

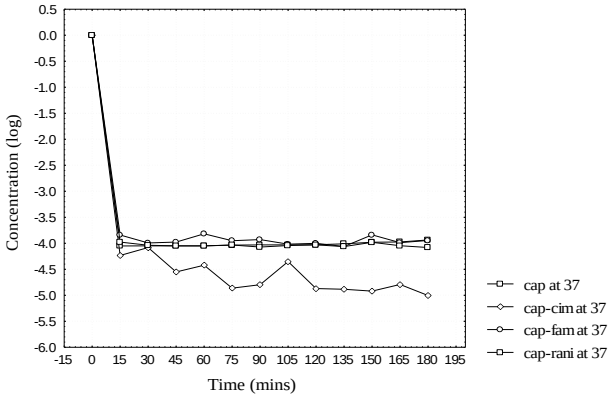

Fig. 5: Availability of captopril in presence of H_2-receptor antagonists in pH 7.4.

The availability of captopril in presence of cimetidine decreased in simulated gastric juice, at the start of experiment, 118.54 % of drug was available which decreased to 54 % till the end of the experiment. At 48 and 60 ˚C the interaction was more pronounced and only 14 and 58 % drug was available at the end of reaction respectively. Captopril formed a charge transfer complex with cimetidine in buffer of pH 4 which was evident from its vary high availability. In case of pH 4, initially 452 % drug was available while at the end only 266 % remained. The availability of captopril decreased significantly in buffer pH 7.4. In this pH, only 8.63% of captopril was available after 180 minutes. At accelerated temperature availability of captopril was also in the same pattern, whereas in pH 9 there was a significant rise in the availability i.e., 923, 897, and 950 % at 37, 48 and 60°C respectively, revealing formation of a charge transfer complex.

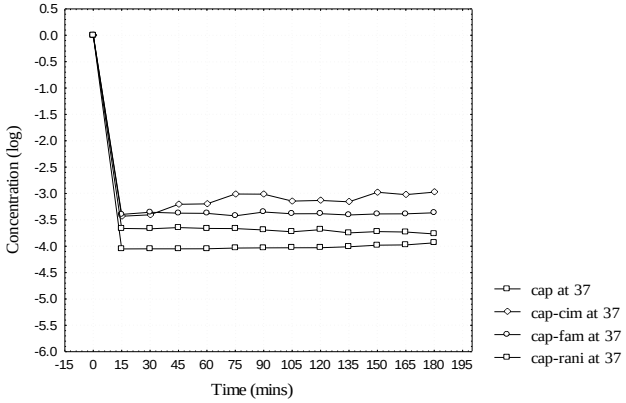

Fig. 6: Availability of captopril in presence of H_2-receptor antagonists in pH 9

The interaction of captopril with ranitidine in buffer of pH 7.4 also caused a reduction in the availability of captopril; initially 91% drug was available, which at the end

Table 5: Thermodynamic data of captopril on interaction with H_2-receptors antagonists.

H_2 receptor anta-gonists	T	Simulated gastric juice				pH 4			
		K	ΔG°	ΔH°	ΔS°	K	ΔG°	ΔH°	ΔS°
Cimetidine	37ºC	61.34216661	-2527.143027	3643.329892	19.90470968	1406.469761	-4449.954247	-10345.94544	-19.01951613
	48ºC	57.89925298	-2580.096223	3809.75923	19.90604361	10.24774959	-1479.297377	-7585.589085	-19.02271028
	60ºC	92.85999499	-2988.063016	3640.25974	19.90486486	475.2851711	-4063.399014	-10396.90643	-19.01957958
Famotidine	37ºC	1658.374793	-4550.318527	6591.770749	35.94216129	48489.31538	-6857.625367	11900.9548	60.50967742
	48ºC	4901.960784	-5401.730277	6137.752809	35.94853583	57423.41152	-6965.942182	12215.73034	59.75077882
	60ºC	3436.426117	-5369.274631	6600.532801	35.94534535	186385.9942	-8002.891689	11894.10589	59.74774775
Ranitidine	37ºC	219309.7882	-7549.938257	-94.46276893	24.04989677	8064.516129	-5718.103201	-12576.10515	-22.12293548
	48ºC	234860.8684	-7861.458766	-141.4459069	24.04847352	7246.376812	-5650.039256	-12955.37721	-22.88317757
	60ºC	216706.7935	-8102.198975	-93.57509158	24.04933934	1937.984496	-4991.178086	-12568.09857	-22.75405405

H_2 receptor anta-gonists	T	pH 7.4				pH 9			
		K	ΔG°	ΔH°	ΔS	K	ΔG°	ΔH°	ΔS°
Cimetidine	37ºC	72.88528803	-2632.936716	2527.572846	16.64667742	7247.847389	-5456.719643	40627.09237	148.6574194
	48ºC	116.9207745	-3028.333217	2318.426966	16.65647975	7975.753709	-5711.179707	42015.08828	148.6799688
	60ºC	96.28531264	-3011.86545	2452.230429	16.40858859	728825.7888	-8902.123713	40603.3966	148.6648649
Famotidine	37ºC	30581.03976	-6314.468114	7233.942963	43.70129032	40384.62315	-6510.955928	-10295.85245	-12.20919355
	48ºC	16474.46458	-6171.13096	7885.842697	43.78847352	378409.4693	-8163.282107	-12085.17175	-12.21775701
	60ºC	70422.53521	-7359.975717	7233.033633	43.78978979	12046.74136	-6196.622757	-10262.70396	-12.21051051
Ranitidine	37ºC	3906.25	-5076.170807	-6558.074534	-4.780096774	1865.671642	-4623.542043	9956.943583	47.02903226
	48ºC	1677.852349	-4719.100146	-6236.211878	-4.725545171	2659.574468	-5011.848294	10087.47994	47.03426791
	60ºC	1886.792453	-4972.956566	-6552.314352	-4.742042042	5747.126437	-5707.891215	9955.044955	47.03303303

decreased up to 72%. On the other hand at pH 1, 4 and 9 formation of a charge transfer complex was observed by the high percent availability values. These charge transfer complexes were quite stable at high temperatures. Similarly, earlier drug interaction studies of metformin and tetracyclines with H_2-receptor antagonists, similar type of charge transfer complexes were observed (Sultana *et al.*, 2006; Iftikhar *et al.*, 2005).

The interaction study of captopril with famotidine in buffer of pH 4 had a significant retardation effect on the availability of captopril and 48 % drug was available at the end of reaction. Similar pattern was observed at higher temperature. There was no interaction of captopril with famotidine at pH 7.4. In simulated gastric juice and in buffer of pH 9, captopril showed formation of charge transfer complex, which was evident from the high availability values of captopril.

The H_2-receptor antagonists interactions with captopril in all buffers at 206 nm showed that the availability of captopril increased more than 100% in presence of H_2-receptor antagonists except for cimetidine in pH 1 and 7.4 and famotidine in pH 4.

It is clearly indicated from these results that captopril has a tendency to bind with H_2-receptor antagonists that results in significant change in the availability of H_2-receptor antagonists which remained with in 100% except for cimetidine in pH 1, 4 and 7.4, famotidine in pH 7.4 and 9, and ranitidine in pH 9 where availability of these drugs increased more than 100 %. In conclusion, present studies reveal that captopril interacted with all H_2-receptor antagonists and availability of captopril increased due to complex formation with H_2-receptor antagonists.

Thermodynamic studies further supported the results of interaction studies. To calculate the stability constant of complex, we used Bensei-Hildebrand equation (Slifkin, 1971; Cerullo *et al.,* 2007; Reha 2002). Stability constant K and thermodynamic functions $\Delta G°$, $\Delta H°$ and $\Delta S°$ for captopril and H_2 -receptor antagonists complexation in buffer of pH 1, 4, 7.4 and are shown in table 5.

In these results the minus sign of standard Gibb's free energy showed that the reaction between the captopril and H_2-receptor antagonists was spontaneous.

Furthermore, in pH 1, 9 and 7.4 when captopril was interacted with cimetidine positive sign of thermodynamic functions $\Delta H°$ and $\Delta S°$ shows that charge transfer complex was formed due to hydrophobic interaction. In case of famotidine complex was formed due to hydrophobic interaction when interacted with captopril in pH 1, 4 and 7.4. When captopril interacted with ranitidine in pH 4 and 7.4, minus sign of enthalpy ($\Delta H°$) and entropy ($\Delta S°$) indicated that donor acceptor complex was formed due to chelation and hydrogen bonding. In the same way cimetidine in pH 4 and famotidine in pH 9 also formed complexes due to chelation and hydrogen bonding. When captopril interacted with ranitidine in buffer of pH 1 then resultant thermodynamic functions showed (negative sign of $\Delta H°$ and positive sign of $\Delta S°$) that chelation has taken place, which causes complex formation. Enthalpy studies of captopril were first studied by Ortiz-Salmeron (Ortiz-Salmeron *et al.,* 1998). Conclusively, the results of thermodynamic studies showed formation of charge transfer complexes. Hence it is obvious to recommend a gap in the administration of both types of drugs.

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