ORIGINAL ARTICLE

FOSINOPRIL H_2-RECEPTOR ANTAGONISTS INTERACTION STUDIES BY DERIVATIVE SPECTROSCOPY

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ABSTRACT

Fosinopril sodium, a phosphinic acid derivative is an angiotensin converting enzyme (ACE) inhibitor, which had been employed for the treatment of hypertension and congestive heart failure; long tem use of ACE inhibitor often result in stress ulcers due to which H_2 receptor antagonists are also concurrently prescribed. The later compete with histamine for H_2 receptors and block gastric acid secretion and some cardiovascular effects of histamine. Our studies are focused on the *in vitro* availability of fosinopril in presence of commonly used H_2 receptor antagonists. Derivative spectroscopy has been employed for the quantitation of fosinopril and H_2 receptor antagonists followed by linear regression analysis. These studies were carried out in buffers of pH 7.4 and 9 at 37, 48 and 60ºC. Stability constant and thermodynamic function had also been calculated in order to evaluate the reaction mechanism. Commonly prescribed H_2 receptor antagonists like cimetidine, ranitidine and famotidine were used in these studies. Present study clearly indicated that most of the H_2 receptor antagonists studied decreased the availability of fosinopril which conclude that availability of fosinopril can be affected by the concurrent administration of H_2 receptor antagonists.

Keywords: Fosinopril; H_2 receptor antagonists; derivative spectroscopy, interaction studies.

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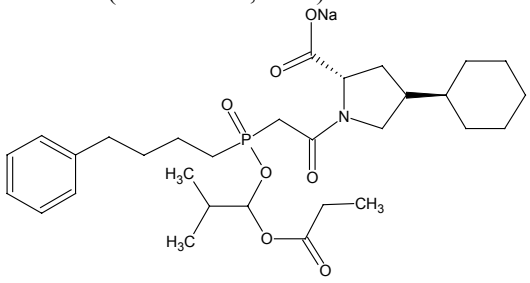
INTRODUCTION

Fosinopril sodium chemically designated as trans L-proline, 4-cyclohexyl-1-[2-methyl-1-(1-oxopropoxy) propoxy](4-phenylbutyl) phosphinyl] acetyl] sodium salt, is an ester prodrug which is hydrolyzed to pharmacologically active fosinoprilat, a specific competitive inhibitor of ACE (Kostis *et al*., 1995 and Gehr *et al*., 1993). It inhibits the active sites of a zinc glycoprotein, the angiotensin converting enzyme (ACE) blocking the conversion of angiotensin I to angiotensin II, whose levels are elevated in patients with hypertension. It is also used in the treatment of congestive heart failure and diabetic nephropathy. H_2-receptor antagonists inhibit gastric acid secretion elicited by histamine and other H_2-agonists in a dose-dependent, competitive manner; the degree of inhibition parallels the concentration of the drug in plasma over a wide range. Their clinical efficacy is largely due the inhibition of basal (fasting) and nocturnal acid secretion (Prasun *et al*., 1995).



Fosinopril sodium

Fosinopril has been studied and determined by several procedures such as high-performance liquid chromatography (HPLC) (Jemal and Mulvana, 2000) capillary zone electrophoresis (Lozano *et al*., 1995), NMR and mass spectroscopy (Thakur *et al*., 1993 and Lewen *et al*., 1995) and by ultraviolet spectroscopy in biological materials and tablets (Erk, 2002; Paraskevas and Themelis, 2003; Saglik *et al*., 2000).

Many drugs have the ability to interfere with each other when given concurrently. Antacids co-administered with quinolones formed complexes thus reducing their availability (Hoftkewn *et al*., 1988 and Nix *et al*., 1990). Similarly, H_2 receptor antagonists interfere with the absorption of many drugs when given concurrently; it decrease the dissolution rate of ketoconazole and thus alter its bioavailability (Leon, 1997) and also interferes with the absorption of anti-diabetics like metformin and glibenclamide (Lee *et al*., 1987 and Girardin *et al*., 1992).

In view of the potential interactions, which may ultimately be hazardous due to long term therapy of fosinopril as well as H_2-receptor antagonists, the present study is focused on the *in vitro* drug interactions of fosinopril with H_2-receptor antagonists, like cimetidine, ranitidine and famotidine, in buffers of pH 7.4 and 9 at 37°C and at elevated temperatures 48 and 60°C.

Fosinopril has no absorption maxima and the apparent spectrum appears in the cutoff region of the ultraviolet spectrum. Similarly, H_2 receptor antagonist possess characteristic functional groups that also absorb in the similar region. The two spectrums overlap in such a manner that the distinction between two peaks can not be done by direct spectroscopic measurements. In present work, we report the use of classical derivative spectroscopy for separating the spectral overlapping of fosinopril sodium and H_2 receptor antagonist. For a single-peak spectrum, the first derivative is a plot of the gradient $dA/d\lambda$ of the absorption envelope versus wavelength. Derivative spectra can be produced by processing the spectrophotometer output. The use of derivative spectra can increase the detection sensitivity of minor spectra features and reduce the error caused by overlapping of the analyte spectral band by interfering bands of other species in the sample Ojeda *et al*., 1995 and Hargis and Howell, 1988).

The determined individual gradient values, $dA/d\lambda$, are plotted against the wavelength values λ, to give the 1st order derivative plot, which in turn be subjected to a similar slope determining treatment to yield values of $d^2A/d\lambda^2$ which when plotted against the wavelength values gives a 2nd order derivative plot. An iteration of this process results in increasingly higher order, n, derivative plots, i.e. plots of $d^nA/d\lambda^n$ versus λ (Miller *et al*., 1982).

EXPERIMENTAL

Reagents and chemicals

Fosinopril sodium was a gift from Bristol Meyer Squibb. The antagonists used in the studies were cimetidine, ranitidine and famotidine of Smith Kline Beecham (Pvt.) Ltd., Bosch Pharmaceuticals (Pvt.) Ltd. and Remedica Ltd respectively.

Standard stock solutions of each drug were prepared in buffers of pH 7.4 and 9 and suitably diluted to different concentrations. Linearity was observed in the concentration range for 5-58.6 µg /ml for fosinopril, 2-25.2 µg/ml for cimetidine, 10.1-44 µg/ml for famotidine and 3-35 µg/ml for ranitidine.

Working calibration curves were plotted and evaluated by classical least square method. Linear regression equations were obtained and utilized for direct estimation for fosinopril and H_2 receptor antagonist in binary system, statistical analysis for the calibration graphs for fosinopril and H_2 receptor antagonist by derivative spectroscopy as given in table 1.

Apparatus

A Shimadzu 1601 double-beam spectrophotometer, equipped with a PC loaded with spectrophotometer software UVPC Ver. 3.91 was used. Suitable settings were: slit-width, 2.0 nm; scan speed, fast; wavelength interval, 0.5 nm employed by using a pair of 1cm matched quartz cell. Mettler Toledo mp 220 was used for pH measurements. The dissolution equipment (USP, 1997) was manufactured to the B.P. (2002) standards.

The *in vitro* interactions of fosinopril with H_2-receptor antagonists were carried out in buffer of pH 7.4 and 9. In these sets of experiments fosinopril 0.01 gm was added to the dissolution medium at zero time, while H_2-receptor antagonists (cimetidine 0.2 gm, famotidine 0.04 gm and ranitidine 0.15 gm) were added after 15 minutes time interval, separately in each set of experiment. Aliquots of 0.5 ml were withdrawn at every 15 minutes time interval for 180 minutes and assayed. A graph was plotted for the drug concentration versus time in each set of experiment and drug % available was calculated. Reference drug reading was also obtained under same experimental conditions. Data for the reference drugs were also obtained under same experimental conditions. The above experiments were repeated at temperatures 48 and 60ºC.

First and second derivative spectra for fosinopril cimetidine interaction

First derivative spectra for fosinopril with cimetidine had been recorded between 200-360 nm with Δλ of 5nm in the range of 5-58 µg/ml in the buffer of pH 7.4 (phosphate) and 9 (ammonia). First derivative spectra reveal that zero crossing amplitude occurs at 219nm for fosinopril while 230 nm for cimetidine in pH 7.4 (fig. 1 dashed lines represent the spectra for fosinopril).

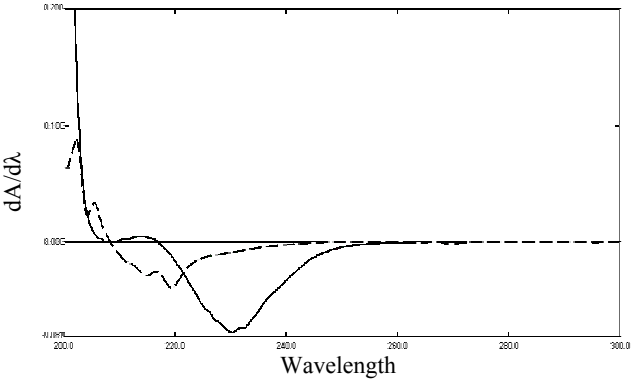


Fig. 1: First derivative fosinopril cimetidine reference standard in buffer pH 7.4.

In buffer of pH 9, first derivative plots were not able to resolve the spectrum so second derivative spectra were used to distinguish wavelength for both drugs. Fosinopril was resolved at 222 nm and cimetidine at 234 nm (dotted lines shows the spectrum of fosinopril).

Second derivative fosinopril famotidine interaction

The interacting spectra of fosinopril and famotidine were characterized by second derivative spectroscopy. The zero crossing wavelengths for fosinopril on famotidine wavelength was 222 nm in buffer of pH 7.4 and 9 while that for famotidine was 235 nm in both buffers (light color shows famotidine spectra). Similarly, second derivative plot was used to differentiate the interfering spectra of fosinopril and ranitidine. Zero crossing wavelengths for fosinopril was observed at 222 nm while that of ranitidine was observed at 250 nm in both buffers of pH 7.4 and 9 as shown in figs. 6 and 7.

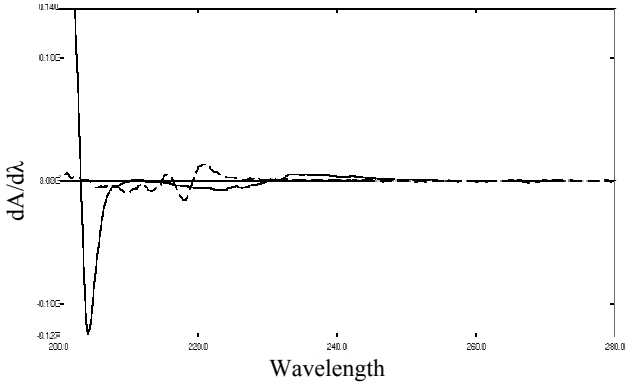


Fig. 2: Second derivative fosinopril cimetidine reference standard in buffer pH 9.

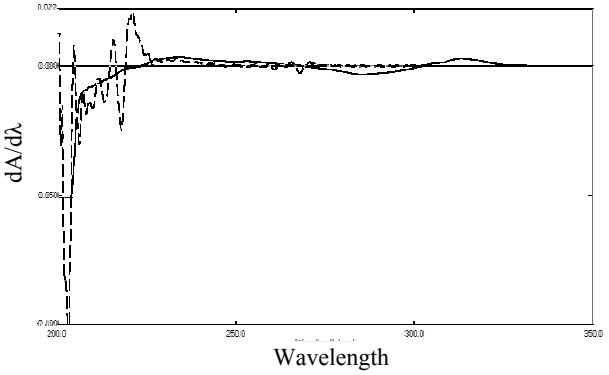


Fig. 3: Second derivative fosinopril famotidine reference standard in buffer pH 7.4.

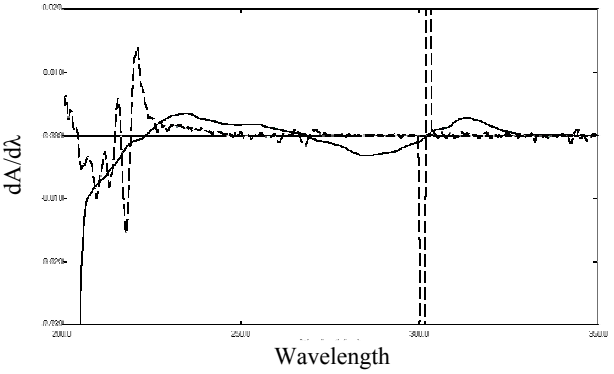


Fig. 4: Second derivative fosinopril famotidine reference standard in buffer pH 9.

Determination of the stability constant for fosinopril H_2 receptor complexation

In order to calculate the stability constant for fosinopril cimetidine donor acceptor complex Bensei-Hildebrand equation was used, here H_2 act as acceptor while fosinopril act as donor

$$A_0 /A = 1/\varepsilon+1/K\varepsilon. 1 /D_0 \quad (1)$$

Where, A_0 was initial concentration of acceptor, D_0 was concentration of donor, A was absorbance of the acceptor, ε was Molar absorptivity of the charge transfer complex at its particular wave length and K was stability constant given in liter/mole. A plot of A_0 /A versus 1 /D_0 gave the intercept of 1/ε while the slope of 1/Kε gave the stability constant.

Applying this equation the stability constant K for the fosinopril -H_2 receptor antagonist complexation was calculated which was further used to study the thermodynamic parameters ΔG, ΔH and ΔS.

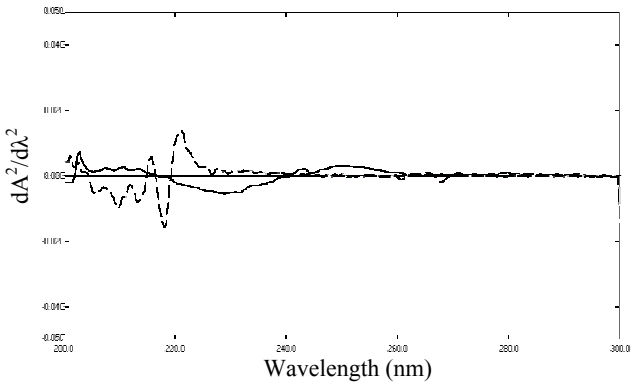


Fig. 5: Second derivative fosinopril ranitidine reference standard in buffer pH 7.4

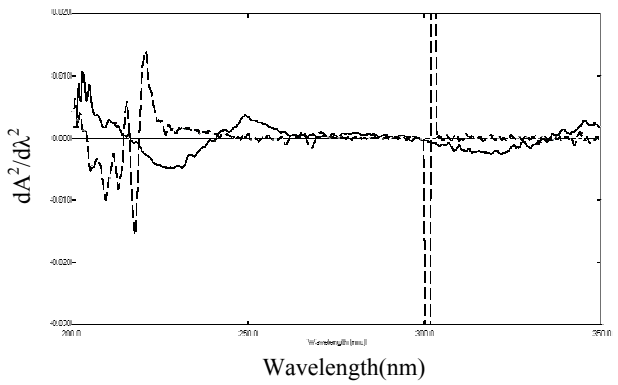


Fig. 6: Second derivative fosinopril ranitidine reference standard in buffer pH 9.

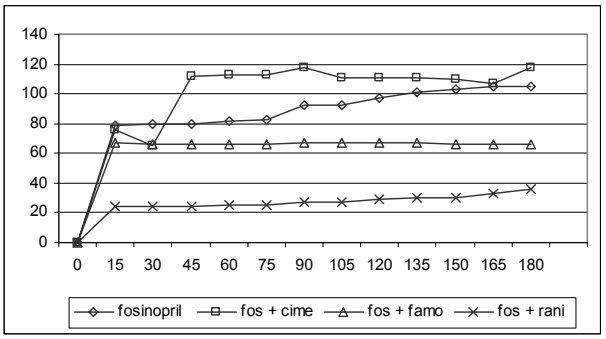


Fig. 7: Availability of fosinopril alone and in presence of H_2.

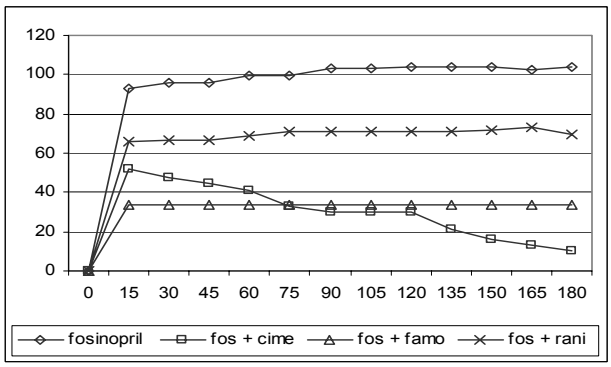


Fig. 8: Availability of fosinopril alone and in presence of H_2 receptor antagonist in buffer of pH 9.

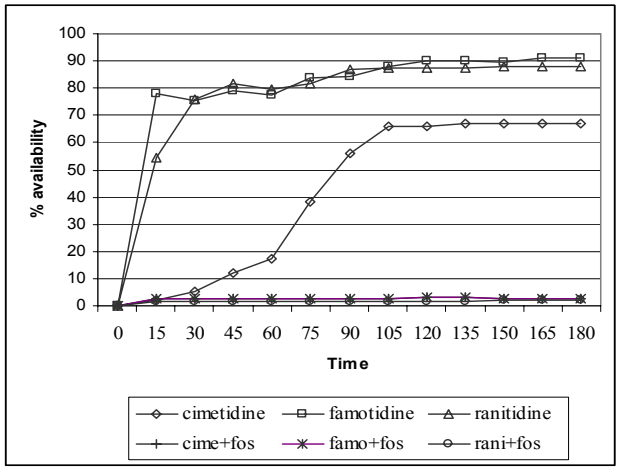


Fig. 9: Availability of H_2 receptor antagonist alone and in presence of fosinopril in buffer of pH 7.4.

RESULTS AND DISCUSSION

UV-Visible derivative spectrophotometry is an analytical tool for enhanced resolution of overlapping peaks for the separation of superposed spectra; particularly useful in multicomponent analysis. The derivatization of spectra

can lead to more accurate determination of the wavelengths of broad maxima and of peaks, which appear only as shoulders, as well as the isolation of small peaks from interfering large background absorption.

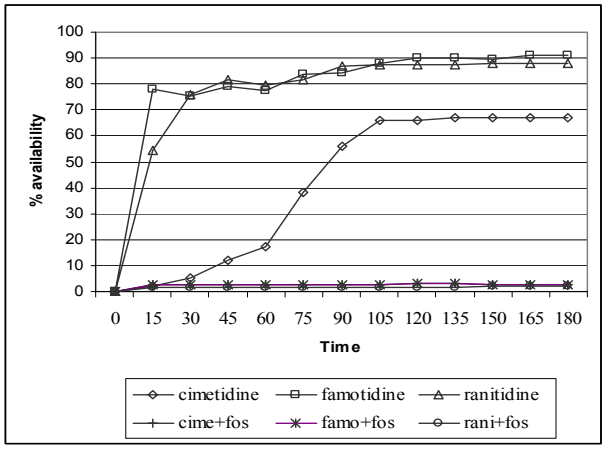


Fig. 10: Availability of H_2 receptor antagonist alone and in presence of fosinopril in buffer of pH 9.

The purpose of *in vitro* dissolution study is to provide a fast and inexpensive method that correlates with the performance of a dosage form in human subjects. Dissolution is rate limiting and rate controlling step in bioabsorption for drugs (Martin, 1999), because it is the slowest of the different stage involved in the release of drug from its dosage form and its entry into the systemic circulation.

The interaction studies of fosinopril with cimetidine showed spontaneous reaction between them. After 15 minutes the availability of fosinopril was increased too much higher extent i.e., 125% and till the end of experiment 117% of the drug was available while in buffer of pH 9, 53% of the drug was available which was decreased to 10%.

The interaction studies of fosinopril with famotidine also showed spontaneous reaction between them. After 15 min the availability of fosinopril was found to be 68% in buffer of pH 7.4 while in buffer of pH 9, 33% of fosinopril was available, which till the end of the experiment was increased to 38% of the drug in the dissolution medium.

Table 1: Regression parametersfor the calibration curve of fosinopril and H_2 receptor antagonist.

	pH	Deri-vative	R	R^2	STD error	Mean	Square	Slope	Interce pt	S_s	S_I
Fosinopril	7.4	1st	(219)	0.999	0.986	0.0007	0.0002	0.1666	0.0006	0.007	0.0005
	-	2nd	(222)	0.962	.926	0.0008	6.1x10-5	0.0904	0.0005	0.008	0.0005
Cimetidine	-	1st	(230)	0.999	0.999	0 .0009	0 .0065	-1.252	-0.0006	0. 014	0.0007
Famotidine	-	2nd	(235)	0.990	0.980	0 .0001	1x10-5	.0354	0.0004	0.002	0.0001
Ranitidine	-	2nd	(249)	0.990	0.981	0.0001	1.3x10-5	0.047	0.0001	0.002	0.0001
Fosinopril	9	2nd	(222)	0.966	0.920	.00161	0.000256	0.1076	5.7x10-4	0.0177	0.0011
Cimetidine	-	2nd	(234)	0.975	0.902	.00042	1.1x10-4	0.0625	0.0154	0.0062	0.0002
Famotidine	-	2nd	(235)	0.963	0.928	.00031	4.7x10-4	0.0427	.00043	0.0141	0.0011
Ranitidine	-	2nd	(249)	0.988	0.977	.00021	11x10-4	0.0533	.00045	0.0142	0.0008

R = correlation coefficient, R^2= coefficient of determination, S_s = Std error of slope, S_I = std error of intercept.

Table 2: Fosinopril and H_2 -receptor antagonist interaction at elevated temperature in buffer of pH 7.4.

	Temp °C↓	% availability											
	Time (min)→	15	30	45	60	75	90	105	120	135	150	165	180
Fosinopril C	48	24.2	75.9	63.6	64.2	69.5	62.4	79.5	77.7	84.2	67.7	59.4	99
	60	24.2	106	110.5	106.8	126.8	136.9	117.4	116.8	97.9	119.2	128.6	131.4
Cimetidine	48	93.6	92.7	91.3	90.6	89.6	89.1	88.3	81.3	39.3	11.9	11.8	11.1
	60	33.3	41.8	45.9	47.9	72	69.8	68.4	65.1	64.7	63	73.9	73.9
Fosinopril F	48	67.4	66.8	66.8	66.8	66.8	66.3	65.8	65.8	66.8	65.8	65.8	65.2
	60	65.8	68.4	67.4	67.9	66.3	66.8	67.4	68.9	66.8	67.4	65.8	67.4
Famotidine	48	2.5	2.5	2.4	2.4	2.4	2.5	2.5	2.5	2.4	2.4	2.4	2.4
	60	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Fosinopril R	48	29.4	29.9	23.1	23.6	23.6	23.6	23.6	23.6	23.6	23.6	24.6	24.6
	60	29.4	22.5	23.1	23.6	23.6	23.6	23.6	23.6	23.6	24.6	24.6	25.7
Ranitidine	48	0.2	0.40	0.70	0.80	0.80	0.80	0.90	0.90	0.90	0.90	1.00	1.00
	60	0.3	0.90	1.00	1.00	1.00	1.00	1.00	1.10	1.10	1.10	1.10	1.20

Here C, F and R represent the availability of fosinopril in presence of cimetidine, famotidine and ranitidine respectively, while alone drug represent the relative % availability of H_2 receptor antagonist in presence of fosinopril.

Table 3: Fosinopril and H_2 -receptor antagonist interaction at elevated temperature in buffer of pH 9.

	Temp°C↓	% availability											
	Time (min)→	15	30	45	60	75	90	105	120	135	150	165	180
Fosinopril[C]	48	30.9	30.9	45.5	42.9	42.9	37.9	37.9	36.6	47.4	50.6	54.4	10.5
	60	15.6	20.1	36.6	40.4	40.4	43.6	43.6	48.0	53.1	54.4	86.2	10.5
Cimetidine	48	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.0	1.3
	60	1.3	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.5
Fosinopril[F]	48	24.6	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7
	60	24.6	24.6	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7	24.7
Famotidine	48	3.9	3.9	3.9	3.9	3.8	3.7	3.6	3.6	3.6	3.6	4.0	3.8
	60	4.1	4.1	4.1	4.1	4.1	4.1	4.2	3.6	3.6	3.6	3.6	3.6
Fosinopril[R]	48	56.9	63.8	65.3	72.1	73.7	74.4	77.5	77.5	77.5	78.2	79.0	80.5
	60	63.8	63.8	65.3	65.3	72.1	73.7	74.4	77.5	77.5	77.5	78.2	79.0
Ranitidine	48	1.6	1.8	1.8	1.9	2.0	2.0	2.0	2.0	2.0	2.0	2.1	2.1
	60	1.4	1.5	1.5	1.6	1.6	1.6	1.7	1.7	1.7	1.7	1.7	1.7

Here C, F and R represent the availability of fosinopril in presence of cimetidine, famotidine and ranitidine respectively, while alone drug represent the relative % availability of H_2 receptor antagonist in presence of fosinopril.

Table 4: Thermodynamic stability parameters for fosinopril-H_2 receptor antagonist interaction

T	K	Δ G	Δ H	Δ S	K	Δ G	Δ H	Δ S
	◄——— pH 7.4 ———►				◄——— pH 9 ———►			
310	1.83E+03	4.61	120.71	55.8	4.83E+03	5.09	5.80	35.1
321	7.54E+03	-6.10	11.83	55.8	1.19E+03	-4.49	6.24	32.4
333	5.87E+03	-5.87	12.72	55.8	8.16E+03	-5.92	5.37	35.1
310	4.70E+04	6.61	24.43	57.5	1.30E+05	7.24	2.84	14.1
321	8.60E+04	7.23	24.92	55.1	4.80E+04	8.03	2.21	18.4
333	7.00E+05	8.59	24.43	47.5	1.70E+04	7.72	2.85	13.7
310	3.70E+04	-5.30	24.38	97.1	2.10E+04	-7.53	-11.31	60.7
321	4.50E+04	-6.73	24.01	95.1	3.33E+03	-5.12	-9.08	40.1
333	8.80E+04	-7.50	24.45	95.1	6.70E+04	-7.29	-11.39	56.1

K= stability constant fo*r* fosinopril-H_2 receptor antagonist interaction in moles/lit, T = temperature in °K and Δ G, Δ H = Gibbs free energy and standards enthalpy respectively in kcal/mole, while, Δ S =standard entropy in cal/(deg mole)

On interaction with ranitidine, 24% of the drug was available which increased to 35% till the end of the experiment, while in buffer of pH 9, 78% of the drug available was decreased to 69% till the end of the experiment.

During these studies the quantity of H_2 receptor antagonist was also found to be much reduced than calculated alone. Results of these interaction studies at accelerated temperatures are given in tables 2 and 3.

In order to study the interaction type, stability constant K and thermodynamic functions $\Delta G^{o,}$ ΔH^o and ΔS^o for fosinopril and H_2 receptor antagonist complexation in buffer of pH 7.4 and 9 at 37, 48 and 60°C were calculated by Bensei- Hildebrand equation as given in table 4.

The minus sign on the standard Gibb's free energy shows that the spontaneous reaction occurred when fosinopril was simultaneously given with H_2 receptor antagonist. Positive entropy and enthalpy values indicate that hydrophobic interaction occurred when fosinopril was concurrently given with cimetidine, famotidine and ranitidine in buffer of pH 7.4. In pH 9 the same relationship occurred with cimetidine and famotidine but with ranitidine the reaction is some what donor acceptor type.

Few studies indicate that cimetidine did not affect the pharmacokinetics or pharmacological effects of different ACE inhibitors like captopril (Richer *et al*., 1986), enalapril (Ferry *et al*., 1998) and quianapril (Shizaki *et al*., 1988). It did not interfere with the pharmacokinetics of fosinopril when given along, in healthy subjects (Moore *et al*., 1988). One study reveal that co-administration of cimetidine with pentopril (another ACE inhibitor) reduced its renal clearance by 11-14% (Kochak *et al*., 1998). *In vitro* interaction study of fosinopril with cimetidine, famotidine and ranitidine by dissolution divulge the fact that co administration of either drugs

reduces the availability of each other thus altering the systemic absorption and therapeutic effect off each other.

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