ORIGINAL ARTICLE

INTERACTION STUDIES OF OMEPRAZOLE WITH MEFLOQUINE, PYRIMETHAMINE AND SULFADOXINE

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ABSTRACT

Mefloquine hydrochloride, pyrimethamine and sulfadoxine as readily tolerated antimalarial drugs that are highly active against both usual and multidrug resistant strains of *Plasmodium falciparum*. Omeprazole reduce gastric acid secretion, irreversibly by inhibition of H^+–K^+ ATPase of the apical membrane of the parietal cell. In order to study the drug interactions of the later with antimalarials, *in vitro* availability of omeprazole has been studied in presence of mefloquine hydrochloride, pyrimethamine and sulfadoxine. The availability of antimalarial drugs was found to be influenced considerably in presence of omeprazole. The effect of dissolution mediums, simulating various body environments with respect to pH and the influence of temperature on these interactions has been examined in order to elucidate the mechanism of these interactions.

Keywords: Mefloquine hydrochloride; pyrimethamine; sulfadoxine; omeprazole; drug interactions.

INTRODUCTION

Mefloquine is (R,S)-α-(2-piperidyl)-2,8-bis(trifluoromethyl) -4-quinilinemethanol, a 4-quinolinemethanol derivative (structure 1), usually available in the form of its hydrochloride (Physician's Desk References 2000). Mefloquine is usually administered orally as tablets that contain 250 mg of mefloquine, 25 mg of pyrimethamine and 500 mg of sulfadoxine. Both erythro and threo recemates of mefloquine) have been prepared by Yanko and Deebel (Florey 1985), using the method of Ohnmacht. Carbonation of 2, 8-bis (trifluoromethyl) quinolyl-4-lithium with ^{14}cabondioxide produced the 2, 8-bis (trifluoromethyl) cinchonic acid, which on reacting with pyridyl lithium and reducing the product gave mefloquine (Ohnmacht *et al*., 1971). Likewise, pyrimethamine, 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine (Structure 2) is synthesized by heating α-propionyl-p-chlorophenyl acetonitrile with aniline and treating the product with the calculated amount of sodium hydroxide in ethanol and cyclizing with guanidine (Florey 1992).

Sulfadoxine, N'-(5, 6-dimethoxy-4-pyrimidinyl) sulfanilamide (structure 3), a long acting sulfonamide is bacteriostatic antimicrobial that block the incorporation of p-aminobenzoic acid to form dihydropteroic acid (Van Miert 1994; Prescott and Baggott 1993; Appelgate 1983). Pyrimethamine-sulfadoxine is an antifolate combination of antimalarials used for non-severe malaria (Watkins 1995), which inhibits dihydrofolate residue (Ferone *et al*., 1969). Its major use is in prophylaxis, suppression and combined chemotherapy of chloroquine resistant strains of *F. malaria*. Sequential blockade of folate pathways by sulphone or sulphonamide plus pyrimethamine (structure 2) results in considerable potentiation in the treatment of malaria (Hurly 1959).

Omeprazole is 5-methoxy-2-(4-methoxy-3,5-dimethyl–2-pyridinylmethylsulfinyl) benzimidazole (structure 4), a proton pump inhibitor offers a mean to inhibit acid secretion to any desired level and is especially useful in hypergastrinemia, peptic ulcer and to faster the healing rates that have not been produced by H_2-receptor antagonists (Goodman and Gilman 1996). Omeprazole has been reported to inhibit the cytochrome P450 system and alter the mechanism of some drugs that are metabolized by these enzymes.

A number of drug interactions of mefloquine and other antimalarials have been reported in the literature. Administration of primaquine could increase blood concentrations of mefloquine and might increase the incidence of adverse effects due to mefloquine. Combination of mefloquine and tetracycline is equally effective and less toxic than quinine plus tetracycline for treatment of acute uncomplicated *F. malaria* in areas requiring combination therapy for drug resistance (Looareesuwan *et al*., 1994). It has also been reported that 2 mg lorazepam given with pyrimethamine for a week was associated with abnormalities of liver functions in 2 of 5 normal volunteers (Briggs & Briggs 1974). Similarly, omeprazole may prolong the elimination of diazepam (Walt *et al*., 1983; Anderson 1996), phenytoin, and warfarin. The increase in gastric pH due to omeprazole treatment alters the release rate of salicylates from enteric-coated formulations,

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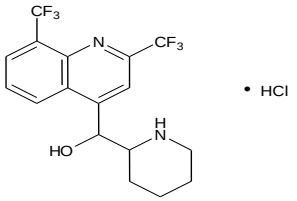
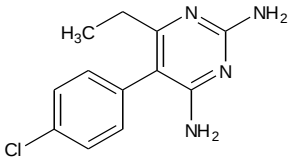
while it does not influence the bioavailability from uncoated tablets (Nefesoglu *et al*., 1998).

Most of these antimalarials have an inherent toxicity to disturb GI motility and when co-administered with omeprazole, is likely to cause severe drug interactions. Hence, it was considered worthwhile to study the interaction of omeprazole with mefloquine, pyrimethamine and sulfadoxine.



(Structure 1)



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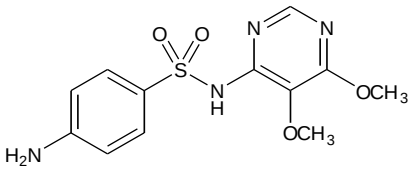
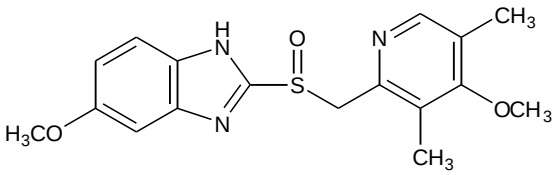


(Structure 3)



(Structure 4)

EXPERIMENTAL

Materials

Mefloquine hydrochloride, pyrimethamine and sulfadoxine reference standards were provided by Lab 9, department of chemistry, University of Karachi while omeprazole was a gift from Getz Pharma Pakistan Ltd. Fansimef™ and Omelcid™ tablets were purchased from the market. Fansimef contained mefloquine hydrochloride (250 mg), pyrimethamine (25 mg) and sulfadoxine (500 mg), while Omelcid contained omeprazole (20 mg).

Equipment

The dissolution equipment (Pharmacopoeia of the United State XX) was manufactured to the B.P. 2003 standards (British Pharmacopoeia 2003), with slight modifications as described earlier (Abid *et al*., 2005). A double beam UV/visible spectrophotometer (Shimadzu) model UV1601A coupled with a Pentium III PC was used for analysis of drug samples.

In vitro availability studies

The *in vitro* availability of mefloquine hydrochloride, pyrimethamine, sulfadoxine and omeprazole and their dosage formulations Fansimef and Omelcid were studied in simulated gastric juice (pH 1) and in buffer of pH 4, 7.4 and 9 on the dissolution apparatus maintained at 37°C over a period of three hours with intermittent sampling of fifteen minutes. The volume of dissolution fluid was maintained by adding an equivalent amount of dissolution fluid withdrawn, which had previously been maintained at the same temperature in the same bath. Each sample was analyzed for its drug contents at its absorption maxima on a UV/visible spectrophotometer.

Drug interaction studies

In vitro interaction studies of the antimalarials with omeprazole were carried out at 37, 48 and 60°C. In each sets of experiments a dosage form of antimalarial drug was added in the dissolution medium at zero time while omeprazole tablet (20 mg) was added after 15 minutes time interval so as to let the antimalarials dissolve first to a considerable extent. Aliquots were withdrawn and assayed for the drug content as before.

RESULTS AND DISCUSSION

There are a number of drug interactions of antimalarials with other drugs reported in the literature. Interaction of mefloquine with primaquine (McLeod 1990; Karbwang 1992), ampicillin (Karvwang 1991), tetracycline (Karvwang 1992) and metoclopramide (Na Bangchang 1991) are reported. Similarly, administration of pyrimethamine with other antagonists as co-trimoxazole, trimethoprim, methotrexate, or phenytion may exacerbate bone marrow depression and mild liver toxicity. Further, the antifolate properties of pyrimethamine may exacerbate those of other antifolates such as methotrexate (Ansdell *et al*., 1976) and toxoplasmosis (MacCabe and Remington 1983) in man. The substituted benzimidazoles omeprazole, lansoprazole, rabeprazole, and pantoprazole were found to have *in vitro* activity against three different isolates of *Plasmodium falciparum*: D6 (which is chloroquine and pyrimethamine sensitive), W2 (chloroquine and pyrimethamine resistant), and TM91C235 (multidrug resistant) (Michael 2002). Omeprazole reduces gastric acid secretion irreversibly by inhibition of parietal cell H^+–K^+ ATPase (the proton pump), which is unique to parietal cells. Multiple dose administration of omeprazole increased the C_{max}, AUC0-infinity and elimination of half life (t½e) of carbamazepine (Dixit *et al*., 2001). Furthermore, omeprazole increased the concentration of clarithromycin in gastric tissues and mucous and provided the mechanism of synergy between clarithromycin and omeprazole (Gustavson *et al*., 1995).

As omeprazole alters the gastrointestinal pH; concurrent use of these antimalarials with omeprazole may result in mild to

Table 1: Interaction of omeprazole with mefloquine, pyrimethamine and sulfadoxine in simulated gastric juice.

Time (min)	<——— at 37ºC———>				<——— at 48ºC———>				<——— at 60ºC———>			
	Ca	Cb	Cc	Cd	Ca	Cb	Cc	Cd	Ca	Cb	Cc	Cd
0	1	1	1	1	3	3	3	10	4	4	4	10
15	11	11	11	33	28	28	28	77	111	112	111	317
30	23	24	23	66	42	43	42	116	141	143	142	395
45	28	28	28	76	52	52	52	145	146	148	147	405
60	31	32	31	91	56	57	56	157	146	147	146	403
75	37	38	37	111	66	67	66	186	157	159	158	431
90	42	43	42	137	68	69	68	189	163	165	164	447
105	45	45	45	137	73	73	73	205	166	168	167	442
120	49	49	49	151	81	82	82	229	165	167	165	447
135	48	49	48	146	81	82	82	229	172	174	173	420
150	51	51	51	155	80	81	80	225	165	167	166	464
165	58	59	58	178	87	88	87	246	167	169	167	444
180	63	64	63	194	91	92	91	259	167	169	167	445

Ca = % availability of mefloquine; Cb= % availability of pyrimethamine;
Cc = % availability of sulfadoxine; Cd = % availability of omeprazole

Table 2: Interaction of omeprazole with mefloquine, pyrimethamine and sulfadoxine in buffer of pH 4.

Time (min)	<——— at 37ºC———>				<——— at 48ºC———>				<——— at 60ºC———>			
	Ca	Cb	Cc	Cd	Ca	Cb	Cc	Cd	Ca	Cb	Cc	Cd
0	2	2	2	15	1	1	1	1	13	13	13	68
15	64	65	64	270	89	90	89	424	88	89	88	353
30	70	71	71	288	97	99	98	410	106	107	106	402
45	72	73	72	277	100	101	100	525	109	111	110	588
60	79	80	79	321	101	103	101	511	110	111	110	494
75	79	80	79	331	103	104	103	453	114	115	114	588
90	79	80	79	338	103	104	103	453	117	119	117	494
105	80	81	80	332	104	105	104	487	119	121	120	534
120	81	82	81	338	106	107	106	501	114	115	114	534
135	81	82	82	341	105	106	105	492	123	125	123	547
150	82	83	83	338	108	109	108	506	125	127	125	577
165	83	84	83	348	108	109	108	519	119	121	120	566
180	84	85	85	351	106	107	106	510	124	126	124	566

Ca = % availability of mefloquine; Cb= % availability of pyrimethamine;
Cc = % availability of sulfadoxine; Cd = % availability of omeprazole

sever drug interactions. In order to study these interactions four different mediums were selected. These comprised of simulated gastric juice (pH 1), buffer of pH 4 (simulating full stomach), buffer of pH 7.4 simulating blood pH and buffer of pH 9 simulating intestine pH. These interactions were carried out at 37, 48 and 60°C simulating body temperature and accelerated temperatures so as to measure the energetics of the reaction like ΔE, ΔG ΔH etc.

In order to measure the quantities of interacting drugs, two different methods were adopted. In the first method, simultaneous equations were employed. Molar absorptivities of all antimalarial drugs as well as omeprazole were calculated at each drug's λ_{max} as well as interacting drug's λ_{max} and the quantities of each drug was measured by employing following equations, which were developed by modifying Beer's law, where,

$A = \varepsilon bc$ or $\varepsilon = A/bc$ (1)

When more than one component is present in a solution, which absorb at the same wavelength but to a different extent, then the equation (1) may be written as

Table 3: Interaction of omeprazole with mefloquine, pyrimethamine and sulfadoxine in buffer of pH 7.4.

Time (min)	<——— at 37ºC———>				<——— at 48ºC———>				<——— at 60ºC———>			
	Ca	Cb	Cc	Cd	Ca	Cb	Cc	Cd	Ca	Cb	Cc	Cd
0	26	27	26	0	2	2	2	2	9	9	9	9
15	145	145	141	120	91	92	89	102	159	160	156	152
30	196	196	191	188	163	164	159	154	240	241	235	236
45	198	199	194	192	170	171	166	170	251	252	245	254
60	207	208	202	200	164	165	160	166	268	269	261	277
75	165	165	161	211	182	183	178	189	300	301	293	301
90	228	229	223	223	178	179	174	179	313	315	306	320
105	230	231	224	226	185	186	181	190	317	318	309	331
120	227	228	222	222	200	201	196	206	307	309	300	317
135	237	238	232	228	202	203	197	207	307	309	300	311
150	235	236	230	229	202	203	197	209	308	309	301	314
165	236	237	231	241	219	220	214	227	338	339	330	352
180	313	315	306	275	211	212	207	220	324	325	316	332

Ca = % availability of mefloquine; Cb= % availability of pyrimethamine;
Cc = % availability of sulfadoxine; Cd = % availability of omeprazole

Table 4: Interaction of omeprazole with mefloquine, pyrimethamine and sulfadoxine in buffer of pH 9

Time (min)	<——— at 37ºC———>				<——— at 48ºC———>				<——— at 60ºC———>			
	Ca	Cb	Cc	Cd	Ca	Cb	Cc	Cd	Ca	Cb	Cc	Cd
0	49	49	49	855	23	23	23	290	53	53	53	502
15	49	49	49	855	34	34	35	358	64	63	64	1144
30	76	75	76	1094	34	34	35	358	81	81	82	1366
45	86	85	86	1194	42	42	42	390	87	86	87	1487
60	92	92	93	1230	50	50	51	434	92	91	92	1572
75	95	94	95	1242	48	47	48	523	92	91	92	1572
90	97	96	97	1258	49	49	49	552	93	93	94	1519
105	106	105	106	1333	49	49	49	552	94	93	94	1546
120	102	101	102	1300	53	53	53	563	98	97	98	1531
135	104	103	104	1307	51	50	51	567	97	97	98	1543
150	106	105	106	1281	54	53	54	612	102	101	102	1561
165	106	105	106	1330	54	53	54	582	104	103	104	1582
180	107	106	108	1360	54	53	54	582	104	103	104	1586

Ca = % availability of mefloquine; Cb= % availability of pyrimethamine;
Cc = % availability of sulfadoxine; Cd = % availability of omeprazole

$$A_{drug} = \varepsilon C_a + \varepsilon' C_b + \varepsilon'' C_c + \varepsilon''' C_d \quad (2)$$

Where, C_a, C_b, C_c and C_d are concentrations of four components present in the solution. In this interaction mefloquine, pyrimethamine, sulfadoxine and omeprazole formed four-component system each of which had an absorption maxima (in simulated gastric juice) at 222, 208, 264 and 284 nm respectively. Hence,

$$A_{222} = a_1C_a + b_1C_b + c_1C_c + d_1C_d \quad (3)$$
$$A_{208} = a_2C_a + b_2C_b + c_2C_c + d_2C_d \quad (4)$$
$$A_{264} = a_3C_a + b_3C_b + c_3C_c + d_3C_d \quad (5)$$
$$A_{284} = a_4C_a + b_4C_b + c_4C_c + d_4C_d \quad (6)$$

Where, $a_1 \ldots a_4$, $b_1 \ldots b_4$, $c_1 \ldots c_4$ and $d_1 \ldots d_4$ are the molar absorptivities of mefloquine, pyrimethamine, sulfadoxine and omeprazole respectively.

In the other method, a program was developed in Microsoft excel, which calculated the quantity of each component in solution at a particular time interval. This was done despite the fact that other available softwares like *Mathamatica* and *LINEQUSL* failed to give appropriate results even with reference.

Mefloquine, pyrimethamine and sulfadoxine gave characteristic λ_{max} i.e. in simulated gastric juice at 222, 208

Table 5: Gibb's free energy of antimalarial interactions with omeprazole

Temp (˚C)	<——— ΔG (calories) ———>			
	mefloquine	pyrimethamine	sulfadoxine	omeprazole
0.1N HCl				
37	567(341)	1772(1418)	14(-283)	1418(7939)
48	441	1541	-264	1249
60	15.	914	-670	914
pH 4				
37	14(283)	1106(1418)	-624(-283)	1275(16303)
48	412	1235	-293	768
60	183	1370	-457	702
pH 7.4				
37	-312(369)	822(2412)	-964(-170)	1136(567043)
48	-147	998	-763	1176
60	-457	944	-1127	1068
pH 9				
37	283(312)	-30(284)	-284(-283)	142(8506)
48	660	1908	88	471
60	32	1585	-351	-76

Values given in parenthesis are before interaction.

Table 6: Entropy and enthalpy of antimalarial interactions with omeprazole at different temperature

Drugs	37-48˚C <———>		48-60˚C <———>		37-60˚C <———>	
	ΔS	ΔH	ΔS	ΔH	ΔS	ΔH
0.1NHCl						
Mefloquine	12	4146	35	11809	24	8007
Pyrimethamine	21	8282	52	18340	37	13350
Sulfadoxine	25	7820	34	10624	30	9233
Omeprazole	15	6180	42	14730	22	8210
pH 4						
Mefloquine	19	6538	19	6538	-7.0	-2264
Pyrimethamine	-11	-2433	-11	-2433	-11	-2453
Sulfadoxine	14	4067	14	4067	-47	-1516
Omeprazole	46	15591	5.0	2506	5.0	8998
pH 7.4						
Mefloquine	-15	-4990	25	81456	6.0	1629
Pyrimethamine	-16	-4138	5	2442	-5	-822
Sulfadoxine	-18	-6599	30	8947	7.0	1234
Omeprazole	-4.0	9.0	9.0	4092	3.0	2066
pH 9						
Mefloquine	-34	10342	52	17459	11	3666
Pyrimethamine	-176	-54646	27	10548	-70	-21797
Sulfadoxine	34	10768	37	11831	3	619
Omeprazole	30	9130	46	15103	9	3080

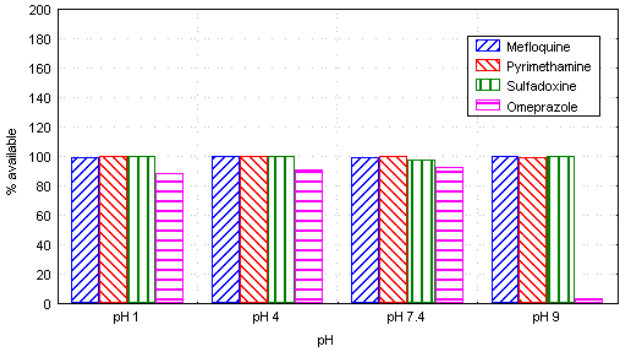
and 264 nm respectively. If we overlap the spectra of all three antimalarials on each other, they intersect at 222 nm, which was then selected as the λ_{max} for the three antimalarials. The interacting drug i.e. omeprazole was calculated at its respective maxima at 284 nm, the % availability of antimalarials and omeparzole in the same solution (in presence of each other) was calculated using equation 3-6.

***In vitro* availability**

The *in vitro* availability of mefloquine, pyrimethamine and sulfadoxine and their dosage formulation fansimef was

studied at 37°C in simulated gastric juice and in buffer of pH 4, 7.4 and 9. All these drugs were found to be in pharmacopoeial range (99-100 %). On the contrary, availability of omeprazole in all these mediums was found to be 88, 91, 92 and 3 % respectively, which showed that the later drug was not soluble in alkaline medium (figure 1).

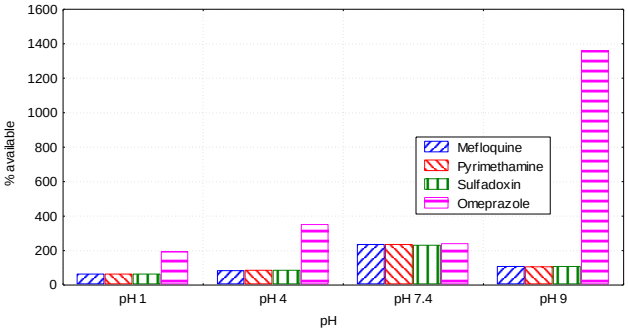
Figure 1
Availabilitynof antimalarials and omeprazole at 37 °C



Interactions studies

Interaction studies of antimalarials with omeprazole were carried out at three different temperatures i.e., at 37, 48 and 60°C. Availability of all the antimalarials (tables 1-4) decreased in simulated gastric juice and in buffer of pH 4 while it increased in pH 7.4 and 9 (figure 2). The data in the later case show that availability of these drugs reached more than 100%, which itself is an evidence of drug interaction with omeprazole. 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 indicate that these interactions were pH dependent, increasing from acidic to alkaline pH.

Figure 2
Availability of antimalarials & omeprazole in presence of each other
at 37°C



Likewise, to study the kinetics of the reaction, interaction studies under similar conditions were carried out at higher temperatures i.e. at 48 and 60˚C (figure 3 & 4). The availability of antimalarials at 48ºC decreased in simulated gastric juice and in pH 9 and increased in pH 4 and 7.4; at 60˚C the availability was found to increase in all mediums. Omeprazole availability increased at all temperatures and mediums (tables 1-4).

Figure 3
Availability of antimalarials and omeprazole in prasance of each other
at 48°C

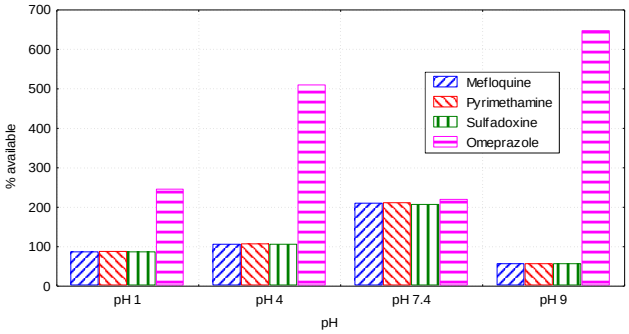
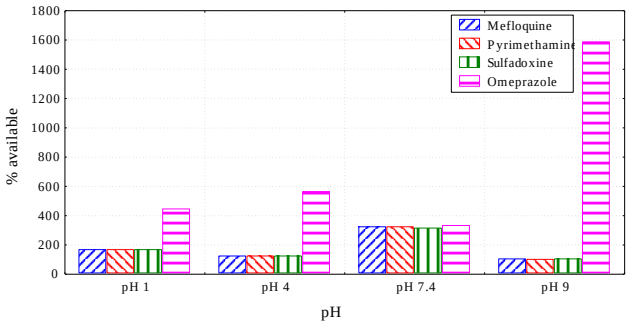


Figure 4
Availability of antimalarials in presance of omeprazole
at 60°C



Kinetic studies

To study the energetics of antimalarials in presence of omeprazole, Gibbs free energy (ΔG), entropy (ΔS) and enthalpy values (ΔH) were studied. When a reaction is irreversible or spontaneous, ΔG is negative and when system is reversible or non-spontaneous, ΔG is either positive or equal to zero. The free energy function (ΔG) can be measured by equation 7,

$$\Delta G = -Rt \ln Ka \qquad (7)$$

Using the calculated ΔG values, ΔS values can be found out by the equation;

$$\Delta G = \Delta H - T\Delta S \qquad (8)$$

At three different temperatures, the above equation can be written as,

$$\Delta G_{37^oC} = \Delta H - 310*\Delta S \qquad (9)$$
$$\Delta G_{48^oC} = \Delta H - 321*\Delta S \qquad (10)$$
$$\Delta G_{60^oC} = \Delta H - 333*\Delta S \qquad (11)$$

Subtracting Eq 10 from Eq 9, Eq 11 from Eq 10 and Eq 11 from Eq 9 we get these equations,

$$\Delta S = \Delta G_{37^oC} - \Delta G_{48^oC} / \Delta T \qquad (12)$$
$$\Delta S = \Delta G_{48^oC} - \Delta G_{60^oC} / \Delta T \qquad (13)$$
$$\Delta S = \Delta G_{37^oC} - \Delta G_{60^oC} / \Delta T \qquad (14)$$

Table 7: $T_{50\%}$ and $T_{90\%}$ (min) values of antimalarials after interaction with omeprazole

↓Temp	<——— $T_{50\%}$ ———>				<——— $T_{90\%}$ ———>			
Drugs →	Ca	Cb	Cc	Cd	Ca	Cb	Cc	Cd
0.1N HCl								
37°C	60(105)	60(105)	60(105)	60(120)	165(150)	165(150)	165(150)	165(150)
48°C	45	45	45	45	120	120	120	120
60°C	15	15	15	15	60	60	60	60
pH 4								
37°C	15(45)	15(45)	15(30)	15(30)	60(120)	60(120)	60(120)	60(180)
48°C	15	15	15	15	30	30	30	30
60°C	15	15	15	15	30	30	30	30
pH 7.4								
37°C	30(45)	30(45)	30(45)	30(45)	165(165)	165(165)	165(165)	165(165)
48°C	30	30	30	30	120	120	120	120
60°C	15	15	15	15	75	75	75	75
pH 9								
37°C	30(90)	30(90)	30(90)	30(45)	105(120)	105(120)	105(120)	75(150)
48°C	15	15	15	15	60	60	60	75
60°C	00	00	00	15	60	60	60	45

Values given in parenthesis are before interaction.
Ca = mefloquine; Cb = pyrimethamine; Cc = sulfadoxine; Cd = omeprazole

The above equations gave $\Delta S_{37\text{-}48^oC}$, $\Delta S_{48\text{-}60^oC}$ and $\Delta S_{37\text{-}60^oC}$ values. If heat was absorbed then ΔS was positive and there was increase in entropy, if heat was evolved then ΔS was negative and there was decreased in entropy. Substituting the respective ΔS values in Eq. 9, 10 and 11 we get $\Delta H_{37\text{-}48^oC}$, $\Delta H_{48\text{-}60^oC}$ and $\Delta H_{37\text{-}60^oC}$ values. The value of ΔH may be either zero, negative or positive. When ΔH was zero, the enthalpies of products and reactants were same; heat was neither evolved nor absorbed in the reaction. When ΔH was positive (endothermic reactions, the heat content of reactants is less than that of product and equivalent heat is absorbed by the system from the surroundings, such reactions are accompanied by absorption of heat. When ΔH is negative (exothermic reactions), the enthalpy of reactants is more than that of products and the difference in enthalpies is given out in the form of heat.

When ΔH was positive, the heat content of reactants was less than that of product and equivalent heat was absorbed by the system from the surroundings; such reactions were accompanied by absorption of heat. When ΔH was negative, the enthalpy of reactants was more than that of products and the difference in enthalpies was given out in the form of heat.

The ΔG, ΔS and ΔH values in all respective pH (1, 4, 7.4 and 9) at 37˚C, 48 and 60˚C for interaction studies of antimalarials with omeprazole (tables 5 and 6) showed that all drugs undergo non-spontaneous behavior except sulfadoxine which gives spontaneous behavior at 37˚C. Furthermore, in most cases reactions were endothermic.

$T_{50\%}$ and $T_{90\%}$ studies

$T_{50\%}$ and $T_{90\%}$ values of these antimalarials (table 7) in presence omeprazole in dosage forms in simulated gastric juice and buffer systems of pH 4, 7.4 and 9 were found to decrease after interaction than their actual values which indicated that the dissolution of antimalarials and omeprazole increased when coadministered with each other. These results may have implication of high serum half life *in vivo*.

CONCLUSION

The effect of various dissolution mediums with respect to pH on these drug-drug interactions and availability reveals that availability of antimalarials increased to smaller extent, which was reflected by the small increase in molar absorptivity of these drugs. Complex formation between antimalarials and omeprazole was observed mostly at pH 7.4. The influence of temperature on the energetics of these

reactions reveals that complex formation increased with the increase in temperature. The kinetic studies of antimalarials with omeprazole reveal that the reactions were in equilibrium and required higher energy to interact with each other. Hence it can be fairly concluded that antimalarial drugs can be administered concurrently with omeprazole.

REFERENCES

Abid I, Arayne MS and Sultana N (2005). *In vitro* release of tetracyclines in presence of H_2-receptor antagonists. *Pak. J. Pharm. Sci.*, **18**(2): 55-60

Anderson T (1996). Pharmakokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantaprazole, *Clin. Pharmacokinetics*, **31**: 9-28.

Ansdell VE, Wright SG and Hutchinson DBA (1976). Megaloblastic anaemia associated with combined pyrimethamine and cotrimoxazole adminstration. *Lancet*,**2**: 1257.

Appelgate J (1983). Clinical pharmacology of sulfonamides. *Mod. Vet. Pract.*, 667-9.

Briggs M and Briggs M (1974). Pyrimethamine toxicity, *British. Medical. Journal*, **1**: 40.

British Pharmacopoeia (2003). Her Majesty Stationery Office, 2, p. A 143.

Dixit RK, Chawala AB, Kumar N and Garg SK (2001). Effect of omeprazole on the pharmacokinetics of sustained-release carbamazepine in healthy male volunteers. *Method Find Exp. Clin. Pharmacol.*, **23**(1): 37-9.

Ferone R, Buhchall JJ and Hitching GS (1969). *Plasmodium berghei* dehydofolate reductase isolation; properties and inhibition by antifolates, molecular. *Pharmacology*, **5**: 49.

Florey K (1985). *Analytical profile of drug substances*, **14**: 171.

Florey K (1992). *Analytical profile of drug substances*, **12**: 174.

Goodman and Gilman's the pharmacological basis of therapeutics, McGraw-Hill Press, New York (1996), 9th edition, p.907.

Gustavson LE, Kaiser JF, Edmonds AL, Locke CS, DeBurtolo ML and Schneck DW (1995). Effect of omeprazole on clarithromycin in plasma and gastric tissue at steady state. *Antimicrob. Agent Chemother*., **39**(9): 2078-83.

Hurly MGD (1959). Potentiation of pyrimethamine by sulphadiazine in human malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **53**: 412-413.

Karbwang J (1991). Effect of ampicillin on mefloquiine pharmacokinetics in Thai males. *Eur. J. Clin. Pharmacol*., **40**: 631.

Karbwang (1992). Pharmacokinetics of mefloquine pharmacokinetics in Thai males. *Eur. J. Clin. Pharmacol.*, **42**(5): 59-60, 567-9.

Looareesuwan S, Vanijanonta S, Viravan C, Wilairatana P, Charoenlarp P, Lasserre R, Canfield C, Kyle DE and Webster HK (1994). Randomized trial of mefloquine-tetracycline and quinine-tetracycline for acute uncomplicated falciparum malaria. *Acta. Trop*., **57**(1): 47-53.

MacCabe RE and Remington JE (1983). The diagnosis and treatment of toxoplamosis. *European Journal of Clinical. Microbiology*, **2**: 95-10.

McLeod CM (1990). Interaction of primaquine with mefloquine in healthy males. *J. Clin. Pharmacol.*, **30**: 841.

Michael A Riel, Dennis E Kyle, Apurba K Bhattacharjee and Wilbur K Milhous (2002). *Antimicrobial Agents and Chemotherapy*, **46**(8): 2627-2632

Na Bangchang K (1991). The effect ofmetoclopramide on mefloquine pharmacokinetics. *Br. J. Clin. Pharmacol.*, **32**: 640-1.

Nefesoglu FZ, Ayanoglu-Dulger G, Ulusoy NB and Imeryuz N (1998). Interaction of omeprazole with enteric-coated salicylate tablets. *Int. J. Clin. Pharmacol.*, **36**(10): 549-53.

Ohnmacht CJ, Patel AR. and Lutz RE (1971). Antimalarials.7.Bis (trifluoromethyl)-(2-piperidyl)-4-quinolinemethanols, *J. Med. Chem.*, **14**: 926.

Pharmacopoeia of the United State XX (2002). Easten, Mack, Printing, p.289.

Physician's Desk References (2000). 54th Ed., p.2648.

Prescott JF and Baggott JD (1993). Antimicrobial therapy in veterinary medicine, 2nd ed. Ames, Iowa: Iowa State University Press, pp.19-26.

Van Miert AM (1994). The sulfonamide-diaminopyridine story. *J. Vet. Pharmacol. Ther*., **17**: 309-16.

Walt RP, Gomes M de FA, Wood EC, Logan LH and Pounder RE (1983). Effect of daily oral omeprazole on 24 hours intragastrine acidity. *British Medical Journal*, **287**: 12-14.

Watkins WM (Mars) (1995). Pharmacology and pharmacokinetics of new antimalarials. *Med. Trop.*, **55**(4): Suppl , 33-6.

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