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INVITRO INTERACTION STUDIES OF LEVOCETIRIZINE WITH CIMETIDINE

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ABSTRACT

H_2-receptor antagonist is useful in a number of peptic disorders due to their capability of inhibiting all phases of gastric acid section. Cimetidine is one of the early members of this group. Levocetirizine belongs to non-sedative third generation antihistamine, improved as compare to its enantiomers cetirizine. In order to evaluate drug- drug interaction studies of levocetirizine with cimetidine, levocetirizine (5mg tablet) and cimetidine (200mg tablet) were introduced in dissolution medium together at the zero time (start of experiment). Samples of 5 ml were taken after every 15 minutes, keeping the volume of dissolution medium maintained. Absorbance maxima for both the drugs were obtained and the absorbance for each concentration was measured to the corresponding wavelength of the drugs. Levocetirizine and cimetidine interfere at each other's wavelength; therefore, simultaneous equation is used to measure the percent availability of both the drugs in each other's presence. Percent availability was 3684.74, 3563.14,

4199.80 and 1127.96 for levocetirizine and 3.22, 1.91, 0.00 and 0.00 for cimetidine in simulated gastric pH, pH 4, pH7.4 and pH9 respectively. On the basis of these studies, drug interaction of levocetirizine is proved with cimetidine.

Keywords: Levocetirizine, cimetidine, drug interaction

INTRODUCTION

H_2-receptor antagonist such as cimetidien, famotidine and ranitidine are well known to exhibit anti-histamine property by preventing histamine release at receptor level on parietal cells of stomach. H_2-receptor antagonist such as cimetidien, famotidine and ranitidine are well known to exhibit anti-histamine property by preventing histamine release at receptor level on parietal cells of stomach. These drugs are useful in a number of peptic disorders due to their capability of inhibiting all phases of gastric acid section such as peptic and duodenal ulcer, stress ulcer, Zollinger-Ellison syndrome, reflux oesophagitis, short bowel syndrome and as pre-operative medicine to reduce the risk of aspiration of acidic contents (Francis; 2017, Eriksson et al.; 1995, Panula et al.; 2015)

Cimetidine shows high oral bioavailability of about 60-70% and plasma half life of about 2 hour which can be altered if the patient presents renal or hepatic impairement. Several studies have been conducted for the quantification of cimetidine in variety of pharmaceutical and biological samples. Although several H_2-receptor antagonists interactions studies have been conducted but it has been reported that interaction risk of cimetidine with alprazolam and triazolam occurred due to alteration of drug clearance from the body in the context of psychopharmacology. In addition to this, cimetidine is also recorded to reduce apparent oral clearance of lornoxicam and theophylline but no effect on valaciclovir absorption. This drug is found to change the pharmacokinetics of single- dose oral cyclosporine to the significant level reduce the metabolic clearance of warfarin (Humphries and Merritt; 1999).

Levocetirizine belongs to non-sedative third generation antihistamine, improved as compare to its enantiomers cetirizine in some aspects including pharmacokinetic and pharmacodynamic, therefore, producing better efficacy and safety profile (Wallace et al; 2008). One of the reasons to prefer this drug over citirizine is its longer duration of action and lower comparitive dose that is 2.5 mg rather than 5.0 mg of cetirizine in the management of chronic allergic conditions such as rhinitis and chronic idiopathic

urticaria (Grant et al;2002). In a double-blind, parallel-group, placebo-controlled, and randomized study, levocetirizine 5 mg/daily proved to decrease not only sign and symptoms of rhinorrhea and nasal obstructions but tends to improve IL-4 levels as well as eosinophil infiltration (Ciprandi et al; 2005). In addition to this, levocetirizine is a better option for clinicians where attention and tracking capabilities of patients are not preferred to compromise even after acute or subchronic administration of the same dose (5 mg), where another antihistamine influences the psychomotor performance such as diphenhydramine (50 mg) (Verster et al; 2003)..

Several methods for validation and determination of levocetirizine have been reported in pharmaceutical dosage form, in human plasma and other samples (Nilesh et al; 2016, Eeckhaut, and Michotte,; 2006). Levocetirizine may interact a drug which is P-glycoprotein inducer, inhibitor or substrate such as ketoconazole, cyclosporine, verapamil, rifampicin, erythromycin, azithromycin or itraconazole. Several mechanisms have been proposed to evaluate its reason such as formation of complex between drugs due to electron charge transfer (Thiessen et al.; 1990, Abdinee et al; 2005).

2. METHODOLOGY

Several in vito drug- drug interaction studies and methods to evaluate that have been reported using Spectrophotometer.

In the current study raw levocetirizine and cimetiine were used as reference standard, gifted from Hilton Pharma (Pvt.), Karachi and Smithkline Beecham (Pvt.) Ltd. Respectively. At the time of receiving both the drugs were critically examined for several pharmaceutical parameters especially expiry dates.

Preparation of buffers; Levocetirizine and cimetidine were analysed in the buffers of pH ranges from 1 to 9. Chloride buffers of pH 1-5 were prepared by mixing 0.1 M potassium chloride to 0.1 M hydrochloric acid to get required pH [reference]. Phosphate buffer of pH 6-8 were prepared by using disodium hydrogen orthophosphate dehydrate, potassium hydrogen orthophosphate, sodium hydroxide and sodium chloride chemicals. Buffer of pH 9 of ammonia was done in with 4.98 g of ammonium chloride in 1 liter water with the addition of 10% liquid ammonia to adjust pH.

***Primary, stock and working solution*;** levocetirizine (0.04254 g) and cemitidine (0.0252g) were accurately weighed using electrical balance and dissolved in buffer simulated to gastric acid of 1 liter to get primary solution of 1mMole. The same

procedure was followed to prepare 1mMole concentration solution in buffer of pH 1-9. Stock solution was obtained by diluting 25ml of primary solution in 250ml of the buffer to get 0.1 mMole concentration working standard solutions were prepared by diluting the stock solution from 0.01 to 0.1mMole in buffer of pH 1to 9 by taking 5, 10, 15, 20, 25, 30, 35, 40 and 45ml of stock solution solution with 50ml volumetric flask.

Calibration curve studies; for calibration curve studies of both the drug, first of all working standard solutions of each concentration were scanned in the region ranges from 200- 700 nm against reagent blank. Absorbance maxima for levocetirizine appeared at 231nm whereas 216nm for cimetidine. Straight lines for the values of absorbance against concentration reflected that Beer Lambert's law was followed with the help of these calibrated curves, epsilon was calculated.

In vitro availability studies; the in vitro availability of levocetirizine and cemitidine were conducted in simulated gastric juice, simulated intestinal juice and in buffers of pH 4 and 7.4 using B.P 2007 dissolution apparatus with an internal diameter of 100mm and capacity of 1 liter dissolution fluid in corporation with 100023 µf capacitor in speed control with $\pm$ 0.5% of required speed at 37°C$\pm$0.1°C [215]. 5mg of levocetirizine and 200mg of cimetidine were separately introduced in 1 liter dissolution medium. Aliquots of each drugs of 5 ml were withdraw intermittently at 15 minutes time intervals for 2 hours for analysis. Throughout the experiment, the volume of 1 liter was maintained by adding equivalent volume of dissolution fluid and the samples of both the drugs were individually scanned in the region of 200-700mm against blank using UV spectrophotometer.

Drug- drug interaction studies of levocetirizine and cimetidine; In order to evaluate drug- drug interaction studies of levocetirizine with cimetidine, levocetirizine (5mg tablet) and cimetidine (200mg tablet) were introduced in dissolution medium together at the zero time (start of experiment). Samples of 5 ml were taken after every 15 minutes, keeping the volume of dissolution medium maintained. Absorbance maxima for both the drugs were obtained and the absorbance for each concentration was measured to the corresponding wavelength of the drugs.

RESULT

Increases in absorption of both the drugs measured at correspondence wavelength with the increase in concentrations showing that

Beer Lambert's law is followed as shown in table 1 and 2.

Figure 1 and 2 are reflecting the same impression that increases in concentration will also cause increase in absorption of the drugs in all mentioned pH.

The lone availability of levocetorizin and cimetidine is almost 100% in mentioned four buffers except in buffer of pH 9 the case of cimetidine.

At the end of experiment, it was observed that highly altered percent availability of both the drugs refers to the drug- drug interactions between levocetirizine and cimetidine. Extremely low availability of cimetidine in buffer of pH simulated to gastric pH and pH 4 and even zero percent in buffer of pH 7.4 and 9, on the other hand, extremely high percentages of levocetirizine in all of the four buffers may be due to the formation of chelates after the transfer of electrons between the two molecules of drugs as shown in table 3 and presented in figure 3.

Table 1: UV absorbance of levocetirizine reference standard at various pH at 37°C at max (231nm)

S. NO.	Concentration ($M*10^{-5}$)	Simulated gastric pH	pH 4	pH 7.5	pH 9
1	0.01	0.2000	.2054	0.1782	0.6935
2	0.02	0.3650	.4005	0.3882	0.7976
3	0.03	0.5919	.5928	0.5980	0.9266
4	0.04	0.7848	.7859	0.8307	1.0333
5	0.05	0.9788	.9716	1.0310	1.1447
6	0.06	1.1735	1.1722	1.2615	1.2589
7	0.07	1.3707	1.3607	1.4535	1.3552
8	0.08	1.5671	1.5660	1.6790	1.4702
9	0.09	1.7548	1.7770	1.8981	1.5786
10	0.10	1.9225	1.9556	2.0964	1.6799

Table 2: UV absorbance of cimetidine reference standard at various pH at 37°C at max (231nm)

S. NO.	Concentration ($M*10^{-5}$)	Simulated gastric pH	pH 4	pH 7.5	pH 9
1	0.01	0.1675	0.1431	0.1278	0.1414
2	0.02	0.3270	0.2711	0.2500	0.2843
3	0.03	0.4965	0.4159	0.3739	0.4274
4	0.04	0.6499	0.5904	0.4697	0.5695
5	0.05	0.8054	0.7032	0.6152	0.7112
6	0.06	0.9690	0.8503	0.7390	0.8602
7	0.07	1.1246	0.9906	0.8638	0.9860
8	0.08	1.4390	1.1398	0.9844	1.1398
9	0.09	1.4498	1.2775	1.1123	1.2853
10	0.10	1.6012	1.4381	1.2350	1.4541

Table 3: % availability of levocetirizine and cimetidine in different buffers

Drugs	Simulated gastric pH	pH 4	pH 7.4	pH 9
levocetirizine	3684.74	3563.14	4199.80	1127.96
cimetidine	3.22	1.91	0.00	0.00

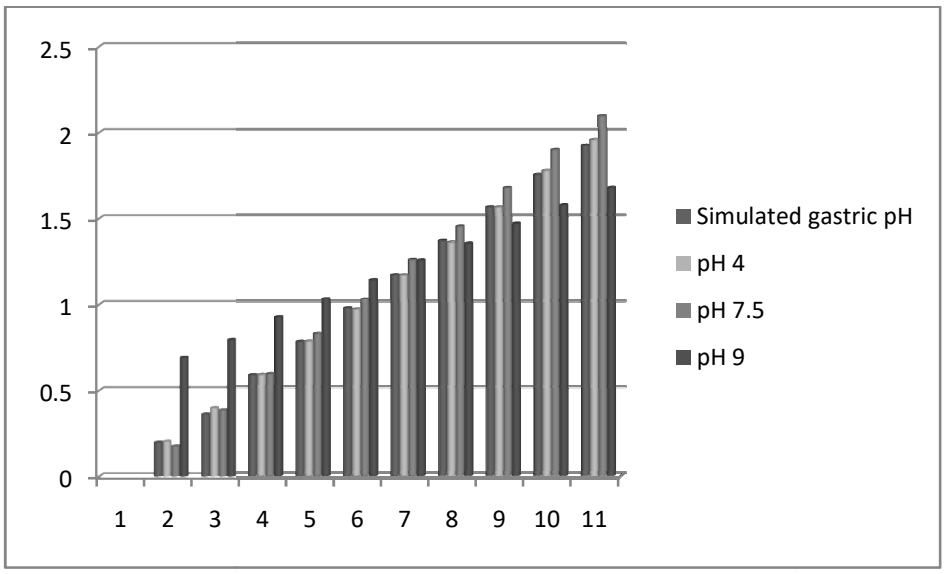

Figure 1: UV absorbance of levocetirizine reference standard at various pH at 37˚C at max (231nm)

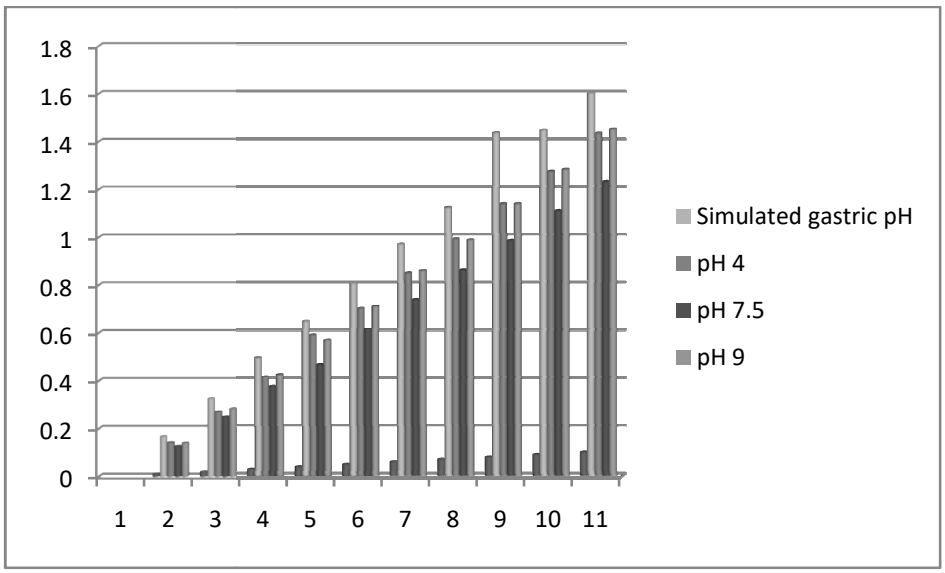

Figure 2: UV absorbance of levocetirizine reference standard at various pH at 37˚C at max (231nm)

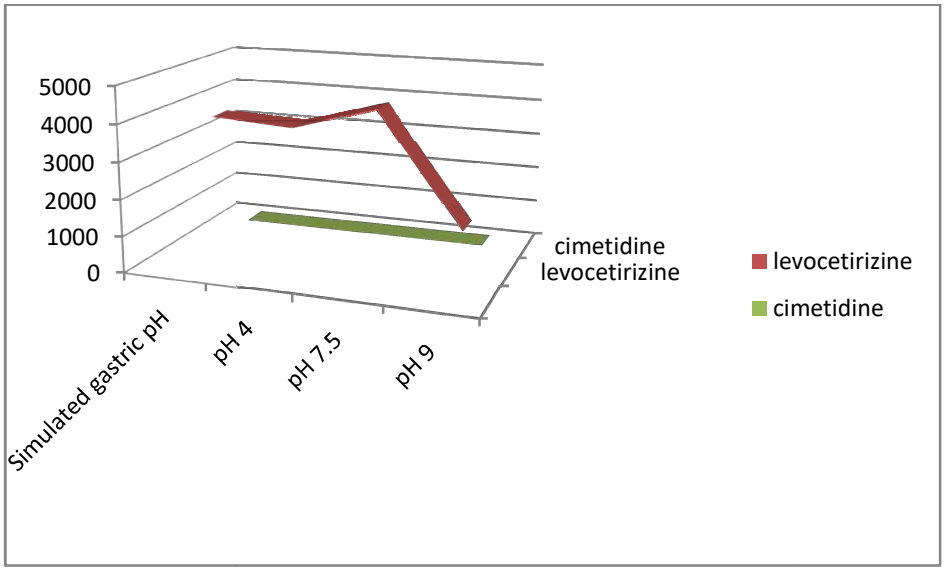

Figure 3: % availability of levocetirizine and cimetidine in different buffers

DISCUSSION

Cimetidine interferes with metabolism and elimination of other drugs through cytochrome p-450 (CYP) pathway via different enzymes such as CYP-1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. Therefore, it is capable to increase the serum concentration of other drugs even up to toxic concentrations. These drugs includes lidocaine, quinidine, metroniadazole, calcium channel blockers and phenytoin (Humphries and Merritt; 1999). In the same way, Levocetirizine also interact with P-glycoprotein inducer, inhibitor or substrate and effect the serum concentration of other drugs as cyclosporine, verapamil, erythromycin, azithromycin and itraconazole (Thiessen et al.; 1990). The drug-drug interaction in vitro are also reported which is due to the electron charge transfer forming complex which alter the percent availability of any or both of the interacting drugs (Abdinee et al; 2005).

In the present study, cimetidine and levocetirizine percent availability was evaluated by simultaneous equation because both the drugs were available in the same medium. Percent availability was 3684.74, 3563.14, 4199.80 and 1127.96 for levocetirizine and 3.22, 1.91, 0.00 and 0.00 for cimetidine in simulated gastric pH, pH 4, pH7.4 and pH9 respectively.

. Single tablet of both the drugs were used in the experiment, the marked altered level in the percent availability of the drugs which is upto zero percent in the case of cimetidine and in thousands in levocetirize at the end of the experiment indicates the interaction between both the drugs may be due to charge transfer, altering the absorbance of the drugs.

Levocetirizine interactions have also been observed with gliquidone (Arayne et al; 2010), atorvastatin, simvastatin and rosuvastatin (Arayne et al; 2014) losatin potassium (Khalid et al; 2017) and atenolol (Mehboob et al; 2017).

This may result in changes in vivo availability of the drugs which may affect the efficacy of any or both the drugs, therefore, further investigations should be done. Furthermore, it is recommended that both the drugs should not be taken at a time rather than time regime should be decided to avoid co-administration of these two medicines to manage the increase, decrease or lost of their therapeutic values.

CONCLUSIONS

On the basis of these studies, it is concluded that levocetirizine is a form of charge-complex with

Cimetidine, therefore, the co-administration of these drugs should be avoided.

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