doi.org/10.36721/PJPS.2021.34.4.SUP.1639-1644.1

Spectroscopic interactions of non-insulin-dependent diabetes mellitus with levocetirizine

Shafaque Mehboob[1]*, Moona Mehboob[2], Mehjabeen[3], SM Tariq Rafi[4], Tariq Khan[5], Humaira Anser[6], Shaheen Perveen[7], Noor Jahan[8], Asma Wazir[9] and Farah Owais[10]

[1]Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University, Karachi, Pakistan
[2]Department of Pharmaceutical Chemistry, School of Pharmacy, Dow University of Health Science, Karachi, Pakistan
[3,5,10]Department of Pharmacology, Faculty of Pharmaceutical Sciences, Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan
[4]Department of ENT, Jinnah Sindh Medical University, Karachi, Pakistan
[6]Department of Pharmacology, Institute of Pharmaceutical sciences, Jinnah Sindh Medical University, Karachi, Pakistan
[7]Department of Pharmaceutics, Institute of Pharmaceutical sciences, Jinnah Sindh Medical University, Karachi, Pakistan
[8]Department of Pharmacology, School of Pharmacy, Dow University of Health Science, Karachi, Pakistan
[9]Department of Pharmacognocy, Faculty of Pharmaceutical sciences, Jinnah University for Women, Karachi, Pakistan

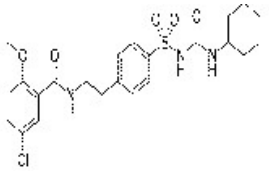
Abstract: Non insulin dependent diabetes mellitus (NIDDM) drugs such as glibenclamide and metformin is employed to heterogeneous disorder characterized by alteration in production of glucose due to impairment of both insulin secretion and insulin action. These patients might suffer with allergic rhinitis and in this case, there is a possibility to maintain patient on levocetirizine, an anti-allergic drug commonly used in rhinitis. The object of the present study is to detect possible interaction between glibenclamide or metformin with levocetirizine Current study was performed using UV spectroscopic technique sing simultaneous equation in pH simulated to gastric juice (pH 1), pH 4, pH 7.4 and in pH 9. All drugs followed Beer Lambert's Law. Results showed that glibenclamide and metformin can increase or decrease availability of levocetirizine and in the same way levocetirizine can alter availabilities of glibenclamide and metformin in different pH. Hence, drug interaction between glibenclamide or metformin with levocetirizne occurred. This may be due to his may be due to the charge transfer or binding capabilities of these drugs which resulted in significantly changed availability of NIDDIM as well as levocetirizine. Therefore, co-administration of these drugs should be avoided and furtherinvestigations at clinical and pre-clinical levels should be done.

Keywords: Non-insulin-dependent diabetes mellitus, glibenclamide, levocetirizine, drug interaction.

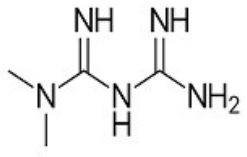
INTRODUCTION

Non insulin dependent diabetes mellitus (NIDDM) is a heterogeneous disorder characterized by overproduction and underproduction of glucose due to impairment of both insulin secretion and insulin action (Teichert *et al.,* 2005). Different treatment protocol is available for NIDDM including oral administration of sulonylureas, biguanide, alpha glucosidase inhibitor and subcutaneous administration of insulin (Tan and Nelson, 1996). One member of sulonylureas is glibenclamide in which nitrogen heterocyclic ring is present (Jing *et al.,* 2007). Glibenclamide can be determined by high performance liquid chromatography (HPLC) and UV spectroscopic method (Gianotto *et al.,* 2007, Sharpiro *et al.,* 1986). Metformin is another commonly employed drug for the treatment of NIDDIM, belongs to biguanide class. It was also reported to be determined by spectroscopic technique using multivariate (Arayne *et al.,* 2009).

Both drugs have potential to be subjected for drug interactions with other drugs. Glibenclamide was reported by Speders (1993) to have potential for drug interaction with mofebutazone (Speders *et al.,* 1993). Azole antifungal was reported to decrease catabolism of glibenclamide (Masaki *et al.,* 2003). warfarin also interacts with glibenclamide (Self *et al.,* 1989). Increased hypoglycemic effects was reported when it was co-administered with verapamil (Avery, 1973), chloramphenicol succinate, ,cefaloridine (Zuccara *et al.,*1983) and antacid (Islam *et al.,*1989). Glibenclamide forms complexes with magnesium, chromium, cobalt, nickel and cadmium salts and also with antacid (Arayne *et al.,* 2004). Diabetes mellitus usually involves combined therapy of more than one drug in order to obtain optimum blood glucose levels or to manage co-morbidities along with it. Additive glucose lowering effects were observed when metformin co-administered with sulphonylureas and thiazolidinediones (Arayne *et al.,* 2006). metformin interactions with metal (Arayne *et al.,* 2013) and H2 receptor antagonists (Sultana *et al.,* 2006) .



Glibenclamide



Metformin

*Corresponding author: e-mail: shafaque.mehboob@hotmail.com.

Patient of diabetes mellitus might suffer with allergic rhinitis (Chen *et al.,* 2019) and in this case,there is a possibility to maintain patient on levocetirizine, an anti-allergic drug commonly used in rhinitis. This drug is also reported to interact with other drugs (Mehboob *et al.,* 2017; Mehboob *et al.,* 2019).

The object of the present study is to detect possible interaction between glibenclamide or metformin with levocetirizine by UV spectroscopic technique using simultaneous equation. In this way, current study may be helpful for health care takers to avoid co-administration of glibenclamide or metformin with levocetirizine if observed interacted with each other.

MATERIALS AND METHODS

Drug interaction between glibenclamide or metformin with levocetirizine, UV spectrophotometric technique using simultaneous equation was employed (Mehboob *et al.,* 2019). All the reagents were of analytical grade. Reference standards of glibenclamide, metformin and levocetirizine were gifted from different pharmaceutical companies with proper label.

Solutions

Primary solutions of glibenclamide, metformin and levocetirizine were prepared by taking 0.0494, 0.01291 and 0.04254 gm of respective drugs in buffers ranges from pH 1~9 of 1 mmol concentration. This solution was used to prepare stock solution of 0.1 mmol. Working solutions from 0.01 to 0.1 mmol was prepared with this stock solution to study calibration curve.

Calibration Curve Studies

Working solutions of glibenclamide, metformin and levocetirizine were scanned (200~700 nm) and absorbance maxima for each drug was observed. Calibration curve was plotted and Beer Lambert's Law was followed.

Availability Studies

The availability of metformin (500gm) and levocetirizine (5mg) were studied in pH simulated to gastric juice (pH 1), pH 4, pH 7.4 and in pH 9 but glibenclamide in pH 1and 7.4. Temperature of fluid (1 liter) in dissolution apparatus B.P (2007) was maintained at 37 °C. Aliquots (5 ml) were withdrawn and maintained by the same liquid at every 15 minutes time interval and subjected for scanning (200~700 nm) to calculate the lone availabilities of each drug.

Interaction studies of glibenclamide (or metformin) with levocetirizine was performed by introducing both the drugs at the same time apparatus and same procedure was followed to calculate absorbance maxima as adopted for lone availabilities. Simultaneous equation was used to calculate availabilities of each drug after interaction.

STATISTICAL ANALYSIS

Simultaneous equation was used to calculate availabilities of each drug.

RESULTS

Drug interaction was assayed under different environmental conditions in four mediums; one containing 0.1 N hydrochloric acid (simulated to gastric juice, pH of empty stomach), buffer of pH 4 (simulated to gastric juice, pH of filled stomach), buffer of pH 7.4 (simulated to blood pH) and buffer of pH 9 (simulated to intestinal pH) but or glibenclamide only pH 1 and 7.4 was selected due to solubility factor.

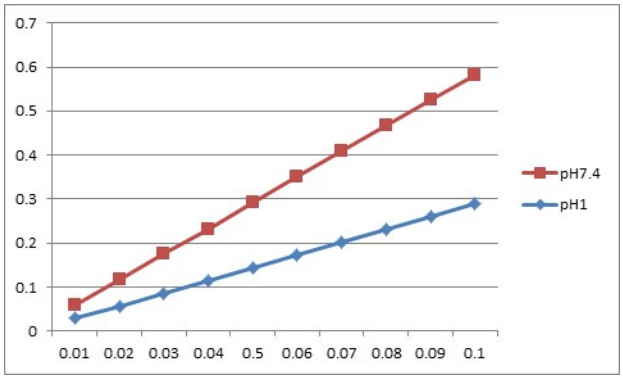


Fig. 1: Glibenclamide reference standard followed Beer Lambert's Law at different concentrations (0.01 to 0.1 mmole)

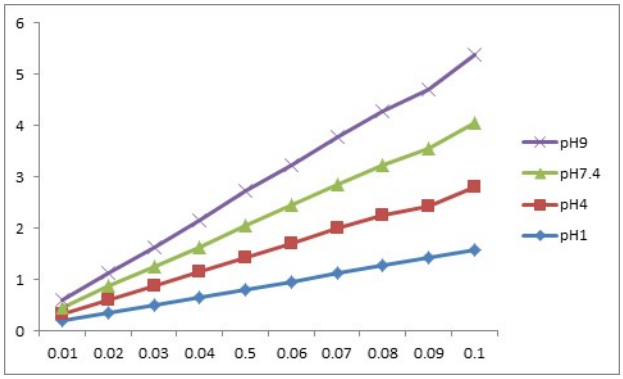


Fig. 2: Metformin reference standard followed Beer Lambert's Law at different concentrations (0.01 to 0.1 mmole).

As mentioned in our previous study, UV method was also adopted to calculate *in vitro* availability of levocetirizine in pH 1, 4, 7.4 and 9 which were 106.25%, 108.36%, 128.14% and 115.46%, respectively.

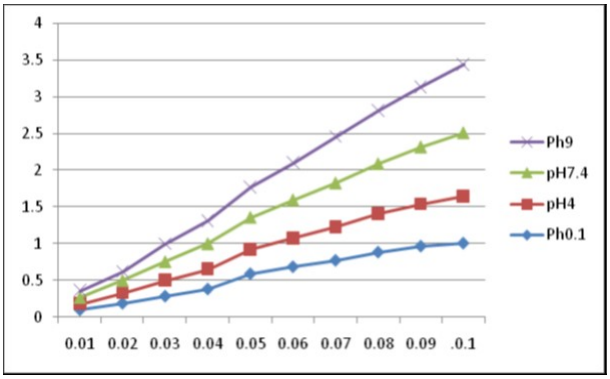


Fig. 3: Levocetirizine reference standard followed Beer Lambert's Law at different concentrations (0.01 to 0.1 mmole)

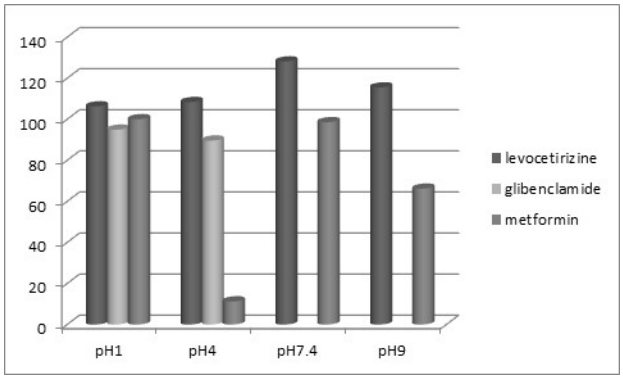


Fig. 4: Lone availabilities of glibenclamide ,metformin and levocetirizine in different pH.

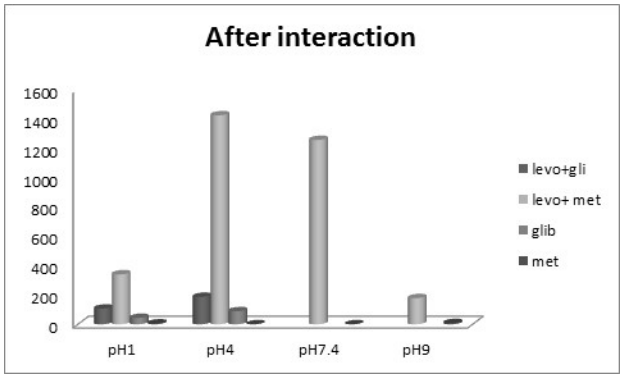


Fig. 5: Availabilities of glibenclamide,, metformin and levocetirizine in different pH after interaction.

First of all, reference standard of glibenclamide and metformin was scanned. fig-1 and 2 showed that Beer Lambert's Law followed by glibenclamide and metformin

Lone availabilities (fig. 4) of levocetirizine was also calculated which not less than 90% and more than 115% in all concerned buffers for 120 minutes as shown in figure 4. Glibenclamide showed 94.9% and 89.6% available in pH 1 and 7.4, respectively. Lone availability of metformin in pH 1,4,7.4 and 9 was 100%,11.23%, 98.54 %and 66.15%,respectively which showed negligible availability in pH 4.

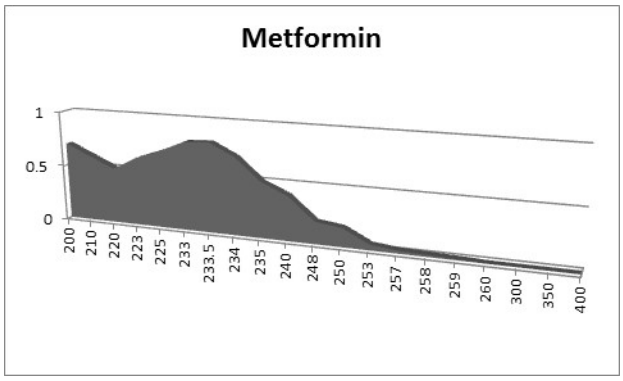


Fig. 6: UV spectrum of metformin before interaction in pH simulated blood.

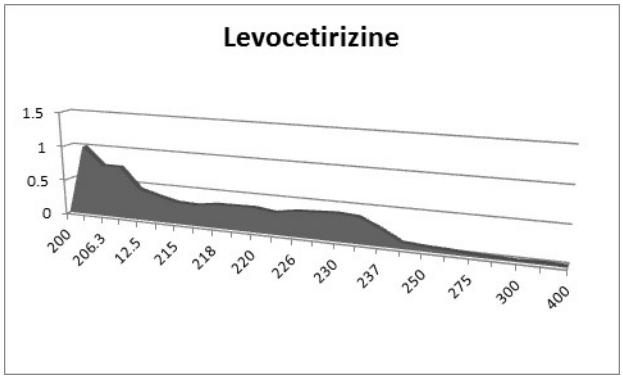


Fig. 7: UV spectrum of levocetirizine before interaction in pH simulated blood.

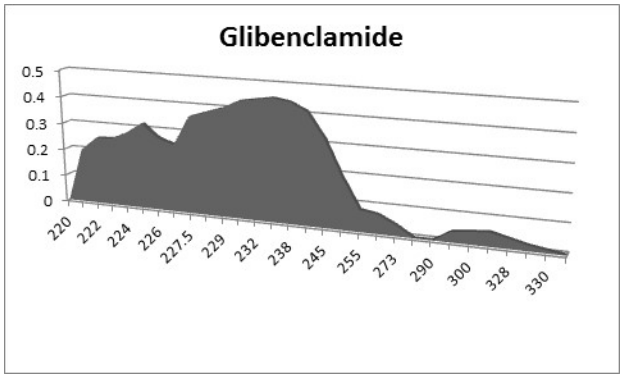


Fig. 8: UV spectrum of glibenclamide before interaction in pH simulated blood.

However, interacting study (availability of levocetirizine with glibenclamide or availability of levocetirizine with metformin) showed altered availabilities in most of the pH. At pH 1when levocetirizine was allowed to interact with glibenclamide, 43.542% of glibenclamide and 106.43% of levocetirizine was available at the end of the experiment (at 120 minute). At pH 7.4, 88.79% of glibenclamide and 186.62% of levocetirizine was available (fig. 5).

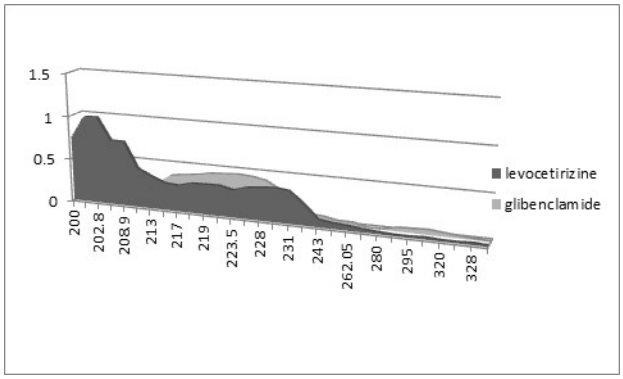


Fig. 9: UV spectrum of glibenclamide and levocetirizine in pH simulated blood after interaction.

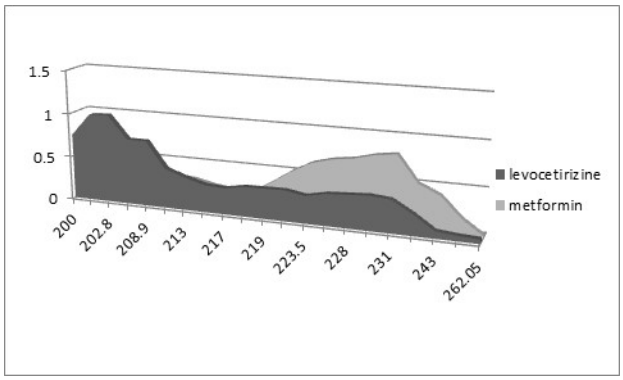


Fig. 10: UV spectrum of metformin and levocetirizine in pH simulated blood after interaction.

On the other hand, availability of levocetirizine in the presence of metformin was 339.45%, 1423%, 1255.54% and 178.21% was available in pH 1, 4, 7.4 and 9 but metformin availability was 5.36%, 0%, 0% and 8.5% in pH 1, 4, 7.4 and 9 at the end of the experiment (fig 5).

DISCUSSION

Patients with allergic rhinitis may also suffer diabetes mellitus and reported literature showed bidirectional association of diabetes mellitus and allergic condition (Lee *et al.,* 2021). Therefore, there is a possibility that patients maintained on glibenclamide or metformin or on both may also treated with levocetirizine if showed symptoms of allergic rhinitis. Therefore, we conducted interaction study of commonly used NIDDIM drugs (glibenclamide and metformin) with anti-allergic drug levocetirizine.

Non-insulin dependent diabetes mellitus is heterogeneous disorders, characterized by overproduction and underutilization of glucose due to imparement of both insulin secretion and action (Teichert *et al.,* 2005). Sulfonylurea comprises the largest oral hypoglycemic agent which are structurally similar but different at para-substitution of benzene ring R1 and group at terminal urea nitrogen of R2 (Weatherall *et al.,* 1996). Glibenclamide have been reported for drug interactions with azole, antifungals, warfarin, rifampicin, chloramphenicol succinate, cefloridine, antacid and cyclosporine (199-206). Metformin interacts with aluminium, lead, bismuth, arsenic and mercury (214). Levocetirizine can also interact with different drugs because it's a PgP substrate. It is reported to interact with ketoconazole, cyclosporine, verapamil, rifampicin, erythromycin, azithromycin and itraconazole (Molimard *et al.,* 2004, Hair and Scott 2006). *In vitro* studies showed that it can alter percent availability of atenolol, losartan potassium, kinetics of fexofenadine and cimetidine (Mehboob *et al.,* 2017; Aftab *et al*., 2017; Devillier *et al.,* 2008; Mehboob *et al.,* 2019).

Figures 6-8 showed spectrum of three selected drugs (lone drug) but figure 7 and 8 showed that both selected NIDDIM drugs (glibenclamide and metformin) and levocetirizine interfere at different wavelength with levocetirizine. That's why simultaneous equation was employed to calculate percent availabilities of NIDDIM drugs (glibenclamide and metformin) and levocetirizine after interaction as these drugs interfere at each other wavelength.

Levocetirizine and glibenclamide absorb maximum at 231nm and 288nm, respectively. Therefore, if Ca is the concentration of levocetirizine and Cb is the concentration of glibenclamide then simultaneous equation can be written as following;

$$Ca = \frac{A_{231}.b_2 - A_{288}.b1}{a_1b_2 - a_2b_1} \quad \text{and}$$

$$Cb = \frac{A_{231}.b_2 - A_{288}.b1}{a_2b_1 - a_1b_2}$$

In the same way, percent availabilityies of levocetirizine and metformin were determined using simultaneous equation.

In pH 1, negligible decreased availability of levocetirizine was observed but only 43.54% of glibenclamide was available. In pH 7.4, high availability of levocetirizine upto 186.62% was observed but glibenclamide was 88.79% was available.

The interaction study of levocetirizine with metformin resulted in significantly high percent availabity of levocetirizine in all pH as 339.45%, 1423.29%, 1255.54%% and 178.62% but very low availability of metformin as 5.36%and 8.5% in pH 1 and 9and 0% in pH 4 and 7.4.

These results showed that glibenclamide and metformin can increase or decrease availability of levocetirizine and in the same way levocetirizine can alter availabilities of glibenclamide and metformin in different pH. Hence,

drug interaction between glibenclamide or metformin with levocetirizne occurred. This may be due to his may be due to the charge transfer or binding capabilities of these drugs which resulted in significantly changed availability of NIDDIM as well as of levocetirizine (Mehboob *et al.,* 2017). Reported literature suggested that co-administration of two interacting drugs should be avoided (Kaleem *et al.,* 2018).

CONCLUSION

Glibenclamide and metformin changed availabilities of levocetirizine and in the same way levocetirizine also altered availabilities of glibenclamide and metformin in different pH. Hence, drug interaction between glibenclamide or metformin with levocetirizne occurred. This may be due to his may be due to the charge transfer or binding capabilities of these drugs which resulted in significantly changed availability of NIDDIM as well as levocetirizine. Therefore, co-administration of these drugs should be avoided and further investigations at pre-clinical and clinical level should be done as these interactions may result in increased, decreased or even lost of therapeutic efficacy of the drug.

REFERENCES

Aftab K, Mehboob S, Khan AM, Sultana N and Arayne S (2017). Drug-drug interaction studies of levocetirizine with losartan potassium. *J. Pharmacol. Clin.*, **2**(4): 1-5

Arayne MS, Sultana N and Rana MKZ (2004). *In vitro* availability of glibenclamide in the presence of antacids. *Pak. J. Pharm. Sci.,* **17**(2): 41-46.

Arayne MS, Sultana N and Zuberi MH (2009). Spectroscopic quantification of metformin in bulk drug and pharmaceutical formulations using multivariate technique. *Ind. J. Pharm. Sciences.,* **19**(2): 114-118.

Arayne MS, Sultana N, Hashim MZ and Haroon U (2010). *In vitro* Studies of Interaction between Metformin and NSAIDs (Non steroidal anti-inflammatory drugs) using spectrophotometry and RP-high performance liquid chromatography. *J. Chil. Chem. Soc.* **55**(2): 206-11.

Arayne MS, Sultana N, Kamran Z and Afghan F (2006). Synthesis and characterization of glibenclamide complex with magnecium, chromium, cobalt, nickel, zinc and cadmium salt. *Pak. J. Pharm. Sci.,* **19**(2): 114-118.

Arayne MS, Sultana N, Zuberi MH and Haroon U (2010). Invitro studies of interaction between metformin and NSAIDs using spectrophotometry and RP-HPLC. *J. Chil. Chem. Soc.,* **55**(2): 206-211.

Arayne MS, Sultana N, Zuberi MH, Siddiqui FA and Haroon U (2013). Simultaneous determination of metformin, captopril, lisinopril and enalapril by RP-HPLC: its applications in dosage formulations and in human serum. *Med. Chem. Res.,* **22**(12): 5717-5722.

Arayne MS, Sultana N, Zuberi MV and Siddiqui FA (2009). Spectrophotometric quantitation of metformin in bulk drug and pharmaceutical formulations using multivariate technique. *Indian J. Pharm. Sci.*, **71**(3): 33-335.

Avery GS (1973). Checklist to potential clinically important interactions, *Drugs*, **5**: 187-190.

British Pharmacopoea (2010). Her Majesty's Stationary Office. **2**: 257-248.

Chen HH, Li SY, Chen W and Kao CH (2019). Association between dipeptidyl peptidase-4 inhibitors and allergic rhinitis in Asian patients with diabetes. *Int. J. Environ. Res. Public Health,* **16**(8): 1323.

Devillier P Roche N and Faisy C (2008). Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine. *Clin. Pharmacokinet.,* **47**(4): 217-230.

Dhanya NB, Rai, R and Srinivas CR (2008). Histamine 2 blocker potentiates the effects of histamine 1 blocker in suppressing histamine-induced wheal. *Indian J. Dermatol. Ve,* **74**(5): 475.

Elisabeth ASD, Renata PA, Maurilio JL, Alexandre CS and Marlrnr MF (2007). Dissolution test for glibenclamide tablets, Quim. *Nova,* **30**(5): 1218-1221.

Hair PI and Scott LJ (2006). Levocetirizine. *Drugs*, **66**(7): 973-996.

Humphries TJ (1987). A notable lack of drug interactions. *Scand. J. Gastroenterol*., **22**(134): 55-60.

Islam SI, Masuda QN and Bolagi OO (1996). Possible interaction between cyclosporine and glibenclamide in post transplant diabetic patient. *Ther Drug Monit.,* **18**: 624-626.

Jing Y, Ya Qin S, Zhuo-Rong L and Shao-Hong J (2007). Development of RP-HPLC method for screening potentially counterfeit anti-diabetic drugs. *J. Chromatogr. B.* **835**(1-2): 254-259.

Jorissen M, Bertrand B, Stiels B and Vandenbulcke K (2006). Levocetirizine as treatment for symptoms of seasonal allergic rhinitis. *B-ent*, **2**(2): 55-62.

Kaleem Z, Khan JA, Mushtaq Z, Altaf S and Javed I (2018). Assessment of potential interaction between simvastatin and clarithromycin in healthy adult male subjects. *Pak. J. Pharm. Sci.*, **31**(3): 801-806.

Kubitza D, Becka M, Zuehlsdorf M and Mueck W (2006). Effect of food, an antacid, and the H2 antagonist ranitidine on the absorption of BAY 59-7939 (rivaroxaban), an oral, direct factor Xa inhibitor, in healthy subjects. *J. Clin. Pharmacol*., **46**(5): 549-558.

Lee TK, Jeon YJ and Jung SJ (2021). Bi-directional association between allergic rhinitis and diabetes mellitus from the national representative data of South Korea. *Scientific Reports*, **11**(1): 1-9.

Malasaki N, Yoichiro H, Yutaka M, Tadashi T and Makoto U (2003).A case of sustained release hypoglycemia induced by taking glibenclamide and warfare. *Japanese J. Stroke,* **25**(3): 334-337.

Mehboob S, Mughal, MA, Aftab K, Khan MM, Sultana N and Arayne S (2017). Drug-drug interaction studies of levocetirizine with atenolol. *J. Pharm. Pharmacol*. **5**: 18-124.

Mehboob S, Parween S, Saleem D, Perveen S and Tabussum S (2019) *In vitro* interaction studies of levocetirizine with cimetidine. *IJBPAS*, **8**(3): 518-527.

Molimard M, Diquet B and Benedetti MS (2004). Comparison of pharmacokinetics and metabolism of desloratadine, fexofenadine, levocetirizine and mizolastine in humans. *Fund Clin. Pharmacol.,* **18**(4): 399-411.

Olen O, Neuman A, Koopmann B, Ludvigsson JF, Ballardini N, Westman M, Melen E, Kull I, Simren M and Bergstrom A (2014). Allergy-related diseases and recurrent abdominal pain during childhood-a birth cohort study. *Aliment Pharm Ther*, **40**(11-12): 1349-1358.

Pletz MW, Preechachatchaval V, Bulitta J, Allewelt M, Burkhardt O and Lode H (2003). ABT-773: pharmacokinetics and interactions with ranitidine and sucralfate. *Antimicrob. Agents Chemother.*, **47**(3): 1129-1131.

Riley TN and Deruiter J (2002) Histamine and antihistamine agents. Wilson and Gisvold's Text Book of Organic Medicinal and Pharmaceutical Chemistry, **11**: 719-721.

SelfT H Tsiue SJ and Fowler JW (1989). Interaction between rifampin and glyburide. *Chest*, **96** (6): 1443-1444.

Shapiro ET, Cauter EV, Tillil H, Given BD, Hirsch L, Beebe C, Rubenstein AH and Polonsky KS (1989). Glyburide enhances the responsiveness of the β-cell to glucose but does not correct the abnormal patterns of insulin secretion in noninsulin-dependent diabetes mellitus. *J. Clin. Endocrinol. Metab*., **69**(3): 571-576.

Speders S (1993). Mofebutazone-evaluation of possible interaction with glibenclamide. *Fortschritte der Medizin*, **111**(22-23): 366-368.

Strolin Benedetti M, Whomsley R, Mathy FX, Jacques P., Espie P and Canning M (2008). Stereoselective renal tubular secretion of levocetirizine and dextrocetirizine, the two enantiomers of the H1-antihistamine cetirizine. *Fund. Clin. Pharmacol.,* **22**(1): 19-23.

Tan GH and Nelson RL (1996). Pharmacological treatment options for non-insulin dependent diabetes mellitus. *Mayo Clin. Proc*., **71**: 763-768.

Teichert J, Tuemmers T, Achenbach H, Preiss C, Hermann R, Ruus P and Preiss R (2005). Pharmacokinetics of alpha-lipoic acid in subjects with severe kidney damage and end-stage renal disease. *J. Clin. Pharmacol.,* **45**(3): 313-28.

Tripathi CB, Bhatt JD, Panchakshari UD, Hemavathi KG and Gulati OD (2002). Interaction between H2 receptor blocker and neuromuscular blockers *in vitro*. *Indian J. Pharmacol.*, **34**: 189-193.

Zhu S, Gao J, Shi Z, QLi G, Chen Z and Yao M, (2015). Inhibitory effect of Aristolochia fruit on Cytochrome P450 isozymes *in vitro* and *in vivo*. *Pak. J. Pharm. Sci,* **28**(3): 939-944.

Zuccaro P, Pacifici R, Pichini S, Vico V, Federzoni G, Pini LA and Sternieri E (1989). Influence of antacid on bioavailability of glibenclamide. *Drug Exp. Clin Res*., **15**(4): 165-169.