In vitro Drug-Drug Interaction Studies of Gliclazide With Levofloxacin By Using HPLC: Guidelines for Co-prescription Drugs

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Abstract:

A simple, accurate reversed-phase high-performance liquid chromatography method was developed and validated for simultaneous determination of gliclazide (GLZ) and fluoroquinolone antibacterial levofloxacin (LVO). The method was developed by using a stainless steel analytical column , C18 (250,4.6 mm,5µm). The system was operated using a mobile phase consisting of methanol and phosphate buffer (pH 3.0) at a flow rate of 0.8mL min^{-1} with *ultraviolet* detection monitored at wavelength 228 nm. The above method was validated using *ICH* analytical method validation guidelines. Utilizing HPLC techniques, an assay was intended to determine in vitro effects of levofloxacin on sulphonyl urea an anti-diabetic gliclazide. Obtained results were further verified with UV spectrophotometric method. Availability of gliclazide was reduced in the presence of levofloxacin. This in vitro analyses confirms the co-administartion of gliclazide and levofloxacin and may serve the foundation for designing further in vivo studies.

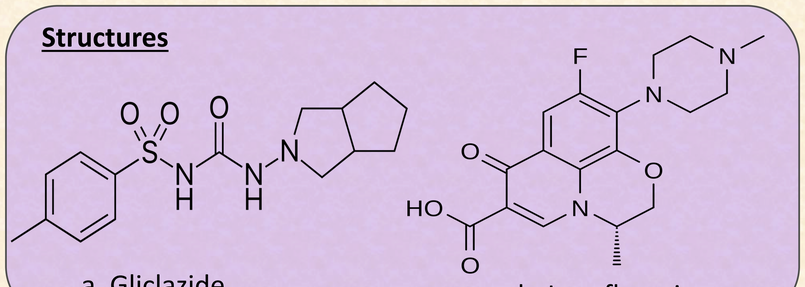
Introduction

Diabetes mellitus (DM), a major lifestyle disease is undoubtedly the most challenging public health problem of 21st century. Diabetes is a chronic metabolic disease that occurs when the human body is not able to produce enough of the hormone insulin.

Gliclazide (GLZ) is a well-known antidiabetic agent prescribed frequently for treatment of DM. GLZ known to act by its selective binding with sulfonylurea receptors (*SUR-1*) on the surface of the pancreatic beta-cells which in turn leads to exocytosis of insulin vesicles leading to insulin release.

Levofloxacin (LVO), is an fluoroquinolone class of antimicrobial agent use for the treatment of different infections. LVO is active against both Gram-positive and Gram-negative bacteria. It acts by inhibiting the two type enzymes, namely DNA gyrase and topoisomerase IV[1]

Structures



a. Gliclazide b. Levofloxacin

Earlier work: Literature

- Drug interaction occurs in between Levofloxacin and sulfonylurea class of anti-diabetic agents which leads to rare fatal side effects.
- Hence it is necessary to study absorption interactions occurring between these drugs.
- To the best of our knowledge, there is no analytical HPLC method reported for simultaneous estimation of these two *co-prescription* drugs.

Experimentals

In the present investigation, an attempt has been made to develop a sensitive, simple, accurate, rapid and reproducible reverse-phase HPLC method for simultaneous determination of LVO and GLZ, an representative sulphonylurea class of drug followed by its validation, in accordance with the *ICH* guidelines.

Optimized Chromatographic Conditions

Isocratic elution with mobile phase methanol: phosphate buffer pH 3.0 (70:30) (*v/v*) was carried out on phenomenex kinetex C18 column (250×4.6mm,5µm) at flow rate of 0.8mLmin^{-1} the wavelength was fixed at 228 nm.

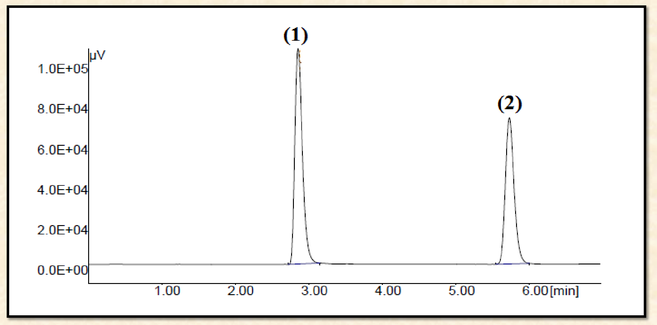


Fig: 3 Representative chromatogram of levofloxacin (1) and gliclazide (2)

Gliclazide					Levofloxacin				
Injection	Intraday		Interday		Intraday			Interday	
	Area	RSD (%)	Area	RSD (%)	Injection	Area	RSD (%)	Area	RSD (%)
1	75040		75964		1	357142.75		352537	
2	76511		76390.5		2	351285		358729	
3	76337	0.75	75626	0.40	3	355478	1.32	359271	1.34
4	76578.3		76321		4	362371		359271	
5	76329.8		76392		5	364444.5		358796	
6	76231		76193		6	359141		367542	

Table 2: Precision parameters of Drugs

Validation studies

Sample	Linear range (μgmL^{-1})	Correlation coefficient	LOD (μgmL^{-1})	LOQ (μgmL^{-1})
LVO	5-25	0.999	0.050407	0.319787
GLZ	1-5	0.999	0.10553	0.152748

Table1: Results obtained from linearity, LOD, and LOQ

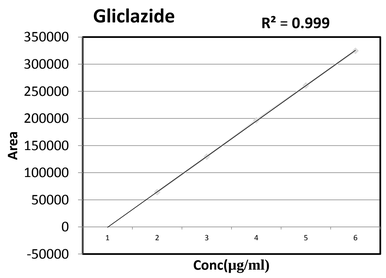


Fig. 1: Linearity Curve Of Levofloxacin

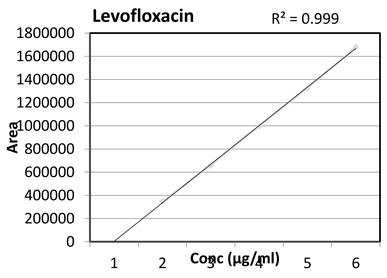


Fig.: 2 Linearity Of Gliclazide

Time (mins)	Gliclazide (μgmL^{-1})	Levofloxacin (μgmL^{-1})
0	-	-
15	4.75	0.48
30	13.47	3.49
45	15.84	10.63
60	25.33	23.64
75	31.6	43.10
90	36.77	54.23
105	45.47	66.14
120	51.50	83.49

Table 3: Percent availability of gliclazide after interaction with levofloxacin

Time (mins)	Gliclazide (μgmL^{-1})	Levofloxacin (μgmL^{-1})
0	-	-
15	8.49	0.51
30	12.42	3.09
45	19.86	11.48
60	26.47	25.11
75	34.44	42.50
90	45.63	54.67
105	52.55	65.97
120	62.94	83.55

Table 4: Percent availability of Gliclazide and Levofloxacin in individual dosage form

Results And Discussion

- Simple and reliable HPLC method for simultaneous estimation of drugs GLZ and LVO in the active have been developed for ***co-prescription*** drugs.
- It has been observed that absorption gliclazide was decreased significantly that is 0.28 percent when taken along with levofloxacine.
- The outcome of the developed HPLC method demonstrates that simultaneous determination of gliclazide and levofloxacin is very useful for pharmaceutical manufacturers, physicians and clinicians.

Conclusion

From the present study it is concluded that developed method was used to understand interaction of gliclazide on fluoroquinolone antibacterial levofloxacin with significant precision and robustness.

Key References

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3. Peleg AY, Weerarathna T, McCarthy JS, Davis TM. Common infections in diabetes: Pathogenesis, management and relationship to glycaemic control. Diabetes Metab Res Rev. 2007;23:3–13.)