

Drug interaction studies of gliquidone with fexofenadine, cetirizine, and levocetirizine

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Abstract Controlling blood sugar levels is crucial for diabetic patients and is managed through administration of drugs such as gliquidone. Coadministration of antidiabetic drugs with H₁-receptor antagonists is common but is also a source of concern due to potential coadministered drug interaction, especially in patients prone to allergic disorders. In this work, we describe in vitro drug interactions of gliquidone with commonly coadministered H₁-receptor antagonists (fexofenadine hydrochloride, cetirizine dihydrochloride, and levocetirizine dihydrochloride). These studies were performed at 37°C in different pH environments simulating human body compartments using UV spectrophotometry and high performance liquid chromatography (HPLC). It was observed that the percentage availability values of gliquidone and H₁-receptor antagonists were not affected in the presence of each other. No significant difference between gliquidone and H₁-receptor antagonists and no remarkable changes in availability values were observed when these interactions were studied using UV-visible and HPLC techniques. This study thus supports the safe coadministration of gliquidone and H₁-receptor blockers as an effective diabetic health management regimen.

Keywords Gliquidone · Fexofenadine · Cetirizine · Levocetirizine · Drug interaction · Spectrophotometry · HPLC

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Introduction

Drug interaction is defined as an interaction between one or more coadministered medications that results in an alteration of the efficacy or toxicity of any of the coadministered medications. It can result from interaction between prescription and over-the-counter medications, herbal products or vitamins, foods, and diseases (Curtis, 2006). Drug interaction may also result from formation of insoluble complexes or chelation with coadministered medications, which may significantly reduce their absorption (Sorenson, 2002).

H₁-receptor antagonists, commonly known as antihistamines, are stable amines. They exhibit their effect through binding to and inhibition of H₁ receptors and their mediated responses and are used to treat allergies (Chen *et al.*, 2003). Histamine H₁-receptor antagonists can easily penetrate the blood-brain barrier and cause potent sedation in diabetics (Stauber *et al.*, 1981). In vitro drug interactions of cetirizine (Ihsan *et al.*, 2005a, b; Sultana *et al.*, 2009) have also been reported in the literature.

Gliquidone, a sulfonylurea derivative, is known to improve glycemic control. It causes marked and dose-dependent stimulation of acid production in gastric glands and potentiates the stimulatory effect of both histamine and carbachol. It also increases the rate of pepsinogen release in gastric glands (Del *et al.*, 1998). Potential interferences may occur between glucose-lowering agents and other drugs. Some antihypertensive agent, especially ACE inhibitors, when coprescribed with sulfonylurea, may favor hypoglycemic episodes, which seem to result from a pharmacodynamic drug–drug interaction (Scheen, 2005). Association with hydroxypropyl-β-cyclodextrin contributes to improved safety and efficacy of gliquidone (Miro *et al.*, 2004). Formation of metal complexes of gliquidone has also been reported in the literature (Arayne *et al.*, 2009a). Since gliquidone and H₁-receptor antagonists are also commonly coadministered, it is important to study their interactions.

To study drug interactions, preliminary tests were carried out under both *in vivo* (*in living organism*) and *in vitro* (*in an artificial environment*) conditions, which also provided other information concerning the drug's pharmacokinetic properties. The most common conditions for *in vitro* studies were the use of simulated intestinal and gastric fluids and the use of a device for agitating the solution at a fixed speed (Remington, 2005). Several *in vitro* drug–drug interactions have also been reported in the literature (Arayne *et al.*, 2007, 2008a, b, 2009b; Sultana *et al.*, 2007a, b). In this paper, we report *in vitro* interactions of gliquidone with H₁-receptor antagonists, in simulated human body environments which were analyzed using UV spectrophotometry and HPLC.

The main objective of this study was to evaluate the *in vitro* effect of H₁-receptor antagonists (fexofenadine hydrochloride, cetirizine dihydrochloride, and levocetirizine dihydrochloride) in patients receiving antidiabetic therapy utilizing UV spectrophotometric and HPLC techniques.

Experimental

Materials

Gliquidone reference standard was a kind gift from Pharmatec Private Ltd. (Karachi, Pakistan). The H₁-receptor antagonists fexofenadine hydrochloride, cetirizine dihydrochloride, and levocetirizine dihydrochloride were obtained from various pharmaceutical companies of pharmaceutical purity. Glurenor (30-mg), Fexet (30-mg), Zyrtec (10-mg), and Xyzal (45-mg) tablets were purchased from a local pharmacy. Methanol used was of HPLC grade (99%). All reagents used were of analytical grade. Deionized water was freshly prepared in the laboratory.

Instrumentation

The dissolution equipment was manufactured to the British Pharmacopoeia (1998) specifications with slight modification (Arayne *et al.*, 2006a). A UV-visible 1601 Shimadzu double-beam spectrophotometer with 1-cm rectangular quartz cells was used. A Shimadzu HPLC system equipped with an LC-10 AT VP pump and an SPD-10A VP UV-visible detector utilizing a Purospher STAR RP-18 end-capped (5-μm, 25 × 0.46-cm) column was used. The integrated chromatographic data were recorded using a CBM-102 Shimadzu, and Shimadzu Class-GC 10 software (version 2) was used for data acquisition and mathematical calculations.

UV-visible spectrophotometry

Preparation of standard solutions

Primary solutions of a 1 mM concentration of gliquidone and H₁-receptor antagonists (fexofenadine hydrochloride, cetirizine dihydrochloride, and levocetirizine dihydrochloride) were prepared individually in buffers of pH 9. Stock solutions of 0.1 mM were then prepared from them. Working standard solutions of 0.01 to 0.1 mM concentrations were prepared by diluting the appropriate amount of stock solution in the same buffer.

Availability studies

In the first set of experiments, the in vitro availability of gliquidone and H₁-receptor antagonists was studied in individual dosage forms in 500 ml of simulated intestinal juice, which also served as the organic solvent. This buffer medium was selected on the basis of availability of gliquidone (British Pharmacopoeia, 1998). Aliquots were withdrawn periodically from 0 to 120 min, at 15-min intervals. The volume of dissolution fluid was maintained by adding an equal amount of previously withdrawn dissolution medium, which had been maintained at the same temperature in the same bath. Samples withdrawn were measured at the λ_{max} of each drug and quantified with the help of Beer's equation (Table 1).

Table 1 Percentage availability of gliquidone, fexofenadine, cetirizine, and levocetirizine in individual dosage forms

Sample no.	Time (min)	Gliquidone (%)	Fexofenadine (%)	Cetirizine (%)	Levocetirizine (%)
1	0	21	9	0	1.19
2	15	11	13	33.95	105.51
3	30	18	13	76.75	103.56
4	45	21	13	94.32	105.07
5	60	42	14	95.36	103.55
6	75	48	13	97.16	106.72
7	90	58	13	97.87	101.47
8	105	85	13	98.45	104.45
9	120	100	12	98.58	105.19

Table 2 Percentage availability of gliquidone, fexofenadine, cetirizine, and levocetirizine after interaction (UV)

Time (min)	Gliquidone (%)	Fexofenadine (%)	Gliquidone (%)	Cetirizine (%)	Gliquidone (%)	Levocetirizine (%)
0	0	0	0	0	0	1.19
15	10.32	5.24	9.33	20.23	2.33	100.21
30	12.02	8.57	10.23	26.35	8.23	99.32
45	20.36	10.25	26.12	30.25	16.02	100.45
60	25.32	13.25	27.65	90.53	29.87	101.30
75	40.25	14.25	45.21	92.32	48.00	102.83
90	55.32	15.24	50.23	95.19	52.56	104.55
105	66.32	14.28	69.12	98.78	77.12	110.23
120	95.32	14.25	99.32	98.32	98.78	110.23

Interaction studies

In vitro interactions of gliquidone and H₁-receptor antagonists were carried out at pH 9. In each set of experiments, tablets of gliquidone and H₁-receptor antagonists were added at 0 min into dissolution medium already maintained at 37°C. Aliquots were withdrawn periodically from 0 to 120 min, at 15-min intervals and assayed, and calculations were performed (Table 2).

HPLC technique

Interaction studies

The developed and validated HPLC method which is the feature of an upcoming publication was used to monitor the interactions. Briefly, this method comprises a

Table 3 Availability of gliquidone, fexofenadine, cetirizine, and levocetirizine after interaction (HPLC)

Time (min)	Percentage recovery					
	Gliquidone	Fexofenadine	Gliquidone	Cetirizine	Gliquidone	Levocetirizine
0	100	100	100	100	100	100
30	100.23	100.86	103.25	99.23	100.01	100.58
60	101.25	101.32	102.52	99.58	100.21	103.15
90	98.34	100.25	100.25	99.98	100.25	102.04
120	96.73	100.84	99.23	99.78	100.25	106.02

mobile phase containing methanol:water (80:20, v/v) with a flow rate of 1 ml min⁻¹, and effluent was monitored at 230 nm with a UV detector. The pH was adjusted to 3.5 using phosphoric acid. Retention times were 2.71, 3.16, and 11.05 min for fexofenadine hydrochloride, cetirizine or levocetirizine dihydrochloride, and gliquidone, respectively. The proposed method is suitable for simultaneous analysis of active ingredients in tablet dosage forms and human serum and also beneficial for studies of drug interaction. Interaction studies were performed by preparing 200 µg ml⁻¹ stock solutions of each drug at intestinal pH (pH 9). An equal volume of gliquidone was mixed with either fexofenadine hydrochloride, cetirizine dihydrochloride, or levocetirizine dihydrochloride to produce final concentrations of 100 µg ml⁻¹ in reaction flasks. These flasks were kept in a water bath at a constant temperature (37°C) with constant stirring. Two milliliters was drawn from the reaction flask at 0 min and periodically after 30 min for 2 h. Aliquots withdrawn were mixed with up to 10 ml of methanol, filtered through a Millipore filter (0.45 µm), and chromatographed (Table 3).

Result and discussion

In vitro availability of gliquidone, fexofenadine hydrochloride, cetirizine dihydrochloride, and levocetirizine dihydrochloride was determined in simulated intestinal juice in individual dosage forms (Table 1). Absorption maxima of gliquidone, fexofenadine, cetirizine, and levocetirizine were observed at 225 nm (Arayne *et al.*, 2006b), 218 nm, 220 nm, and 220 nm, respectively (Fig. 1). The λ_{max} of all the drugs was observed to be very close to the λ_{max} of gliquidone, which made it tough to derive concentration measurements through simple simultaneous equations. The derivative spectrophotometric technique has great utility for extracting both qualitative and quantitative information from spectra of unresolved bands. It tends to emphasize delicate spectral features by representing them in a new way, allowing the resolution of multicomponent systems and minimizing the effect of spectral background interferences in pharmaceutical applications (Ojeda *et al.*, 1995; Rojas *et al.*, 1988). It has led to significant developments in the analysis of drugs in the presence of their degradation products or in multicomponent mixtures (Pappano *et al.*, 1997).

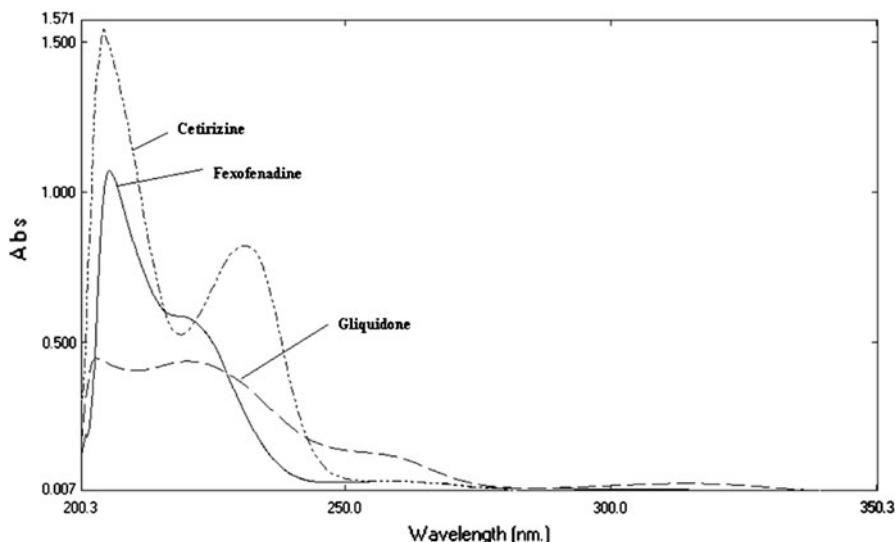


Fig. 1 UV spectra of gliquidone, fexofenadine, and cetirizine

Table 4 First-order regression parameters of gliquidone and H₁-receptor antagonists at various wavelengths

Drug	Slope	Intercept	Correlation coefficient
Gliquidone	0.005	0.0050	0.9999
Fexofenadine	0.005	0.0002	0.9999
Gliquidone	0.873	0.0231	0.9974
Cetirizine	0.051	0.0002	0.9958
Levocetirizine	0.049	0.0001	0.9960

For linearity studies, different concentrations of each drug were scanned and epsilon values were calculated (Table 4). Calibration curves of these drugs were constructed by plotting first derivative values versus concentration. The first derivative maxima used were 260 nm for gliquidone and 210 nm for fexofenadine, 230 nm for gliquidone and 210 nm for cetirizine and levocetirizine interaction (Figs. 2, 3, 4). Regression curves were calculated by the least-squares method. The linear calibration regression function for the determination of analyte at a selected wavelength is given by $y = mx + c$, where y is the absorbance, m is the slope of the linear regression, x is the concentration of analyte (mM), and c is the intercept value, which reflects the difference between the ideal and the real system (Table 4).

For further verification the same study was performed using HPLC. The validated and developed method was successfully employed for quantitation of gliquidone and H₁ antagonists. The drugs were analyzed by measuring the area under the curve and percentage recoveries; results obtained were in accordance with the spectrophotometric data (Table 2 and Figs. 5, 6, 7). Availability values of gliquidone in the

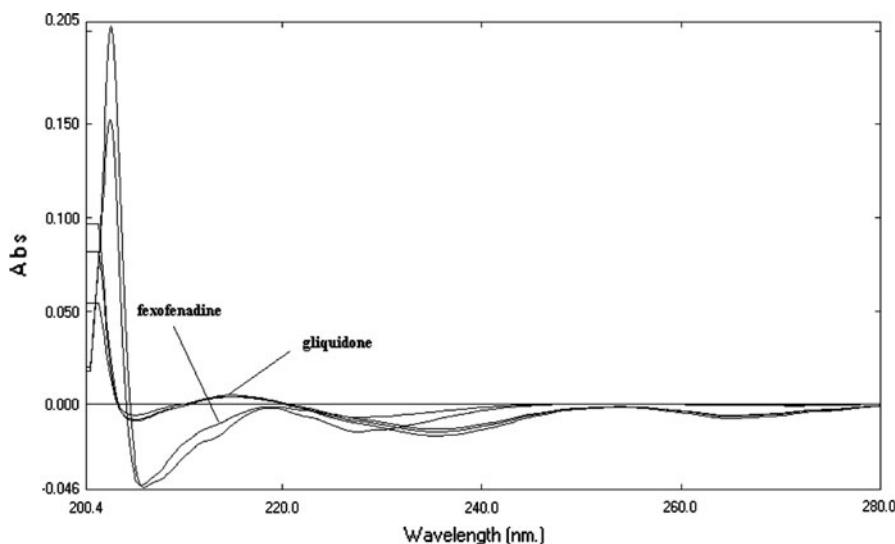


Fig. 2 First-order spectra of gliquidone and fexofenadine

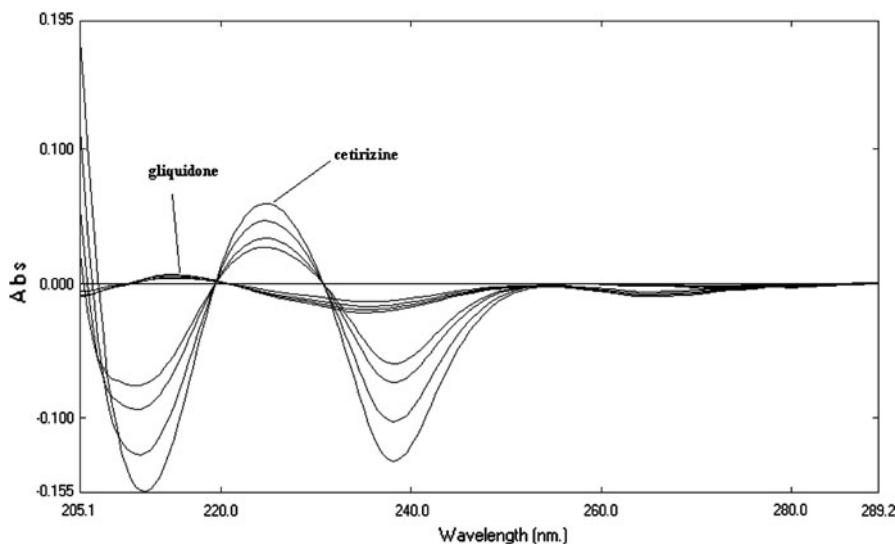


Fig. 3 First-order spectra of gliquidone and cetirizine

presence of fexofenadine, cetirizine, and levocetirizine were found to be 100%, showing no changes in availability values in the absence or presence of each other.

Results were compared with HPLC and it was evident that no interactions occurred and no change in percentage availability values was observed.

From the current study, it is also suggested that the synergistic effects produced by the combination of these drugs should be studied at the-receptor or enzyme level.

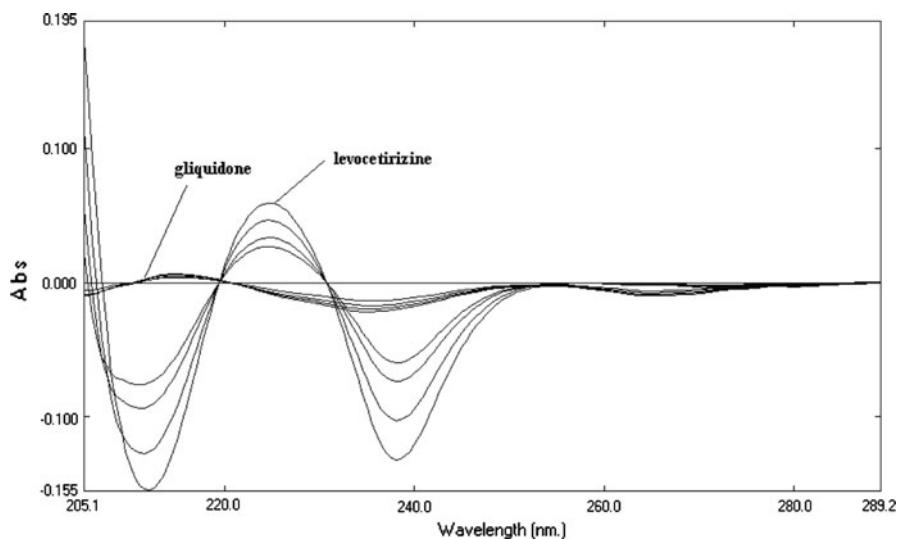


Fig. 4 First-order spectra of gliquidone and levocetirizine

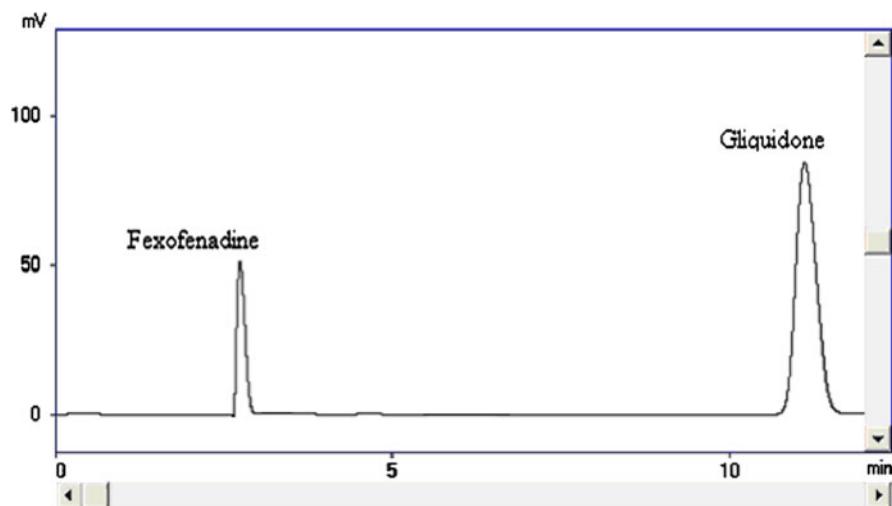


Fig. 5 Representative chromatogram of gliquidone and fexofenadine after interaction

Conclusion

We have developed simple methods to study interactions between commonly coadministered drugs: gliquidone and H₁-receptor blockers. These methods are based on application of a derivative UV-visible spectrophotometric technique followed by HPLC and reveals no significant interaction between gliquidone and H₁ blockers. No remarkable changes in availability values were observed. This *in vitro*

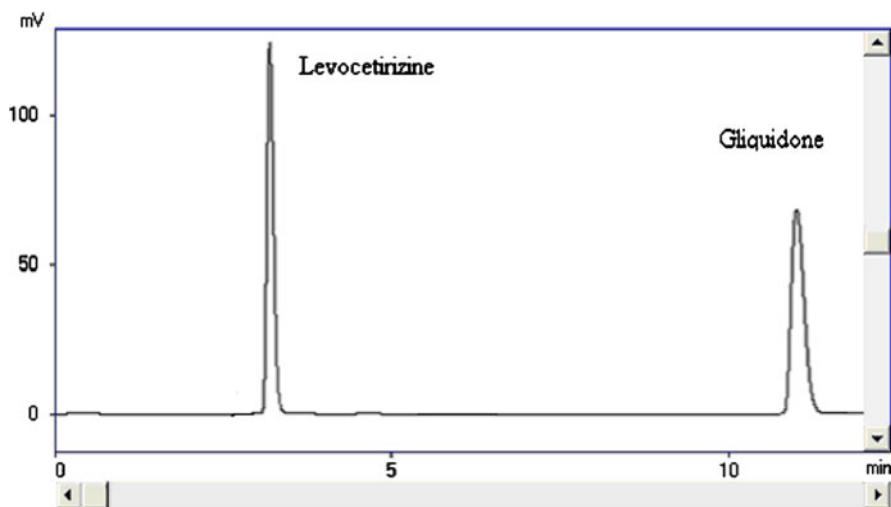


Fig. 6 Representative chromatogram of gliquidone and levocetirizine after interaction

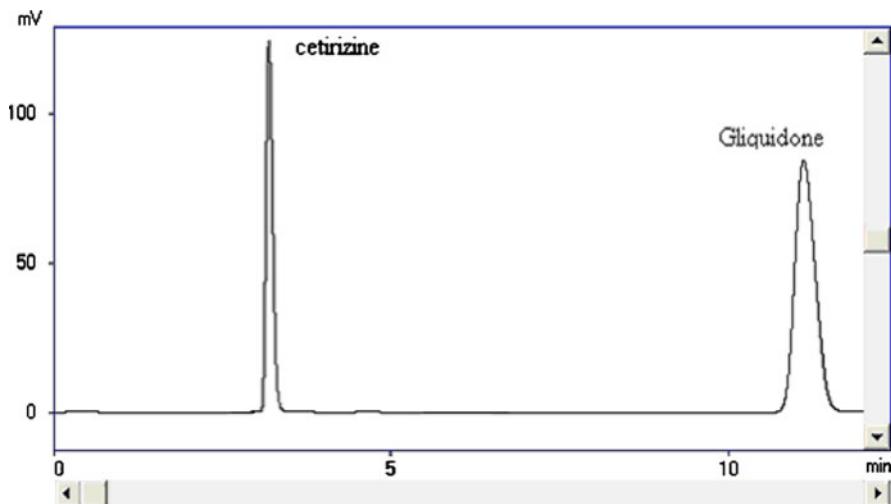


Fig. 7 Representative chromatogram of gliquidone and cetirizine after interaction

analysis lends support to the safe coadministration of gliquidone and H₁-receptor antagonists and is expected to serve as the foundation for in vivo studies. In future we intend to use the same methods to study in vivo interaction of these drugs in murine models, which will truly reveal the safety of their coadministration.

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