Interaction Studies of Gliquidone with Citrus Fruit Juices by UV-Visible Spectrophotometry

Huma Naseem, Nighat Shafi, Farhan Ahmad Siddiqi, Najma Sultana and M. Saeed Arayne

Abstract— Gliquidone is a second generation anti-diabetic drug in the sulfonylureas class. It is an effective oral hypoglycemic agent for treating patients with non-insulin dependent diabetes (NIDDM or type II diabetes). Gliquidone due to the presence of lone pairs of electrons and bonding affinities cause pharmacokinetic interactions with drugs particularly those which are metabolized via cytochrome P450 (CYP) 3A4 isoenzyme. Grapefruit and its juice is a potent inhibitor of the intestinal cytochrome P450 enzyme CYP3A4, when coadministerd with a variety of drugs can increase the bioavailability of drugs and have an impact on the oxidative metabolism. Therefore, present research work comprises of the interaction studies of gliquidone with citrus fruit juices. As, many of fruit juices also contain this enzyme system, coadministration of gliquidone with fruit juices may also result in severe fruit juice drug interactions. The fruit juices used in these studies are grapefruit (*Citrus paradise*), lemon (*Citrus lemon*), pomegranate (*Punica granatum*), orange (*Citrus sinensis*) and sweet lime (*Citrus limetta*). These interaction studies were conducted in simulating body temperature at 37^{o}C and deliberated by means of UV spectrophotometric technique. First reference standard studies of gliquidone and ascorbic acid were carried out in methanol. Maxima of gliquidone were observed at 230 and 313 nm while ascorbic acid showed maxima at 250nm. Molar absorptivities of both gliquidone and ascorbic acid were then calculated and used for further calculations of the left over drug after interactions with fruit juices using Beer-Lambert's law. Interaction studies of gliquidone with citrus fruit juices it has been found that ascorbic acid in fruit juices caused a decline to gliquidone's availability that was more significant with respect to 230nm. This may be due to the formation of charge transfer complexes between gliquidone and ascorbic acid. Hence, it is suggested from the above findings and results that combined use of fruit juices with gliquidone is highly not recommended and should be avoided.

Key Words— Gliquidone, Interaction studies, UV-Vis, Spectrophotometry, Fruit Juice, Validation, Antidiabetic

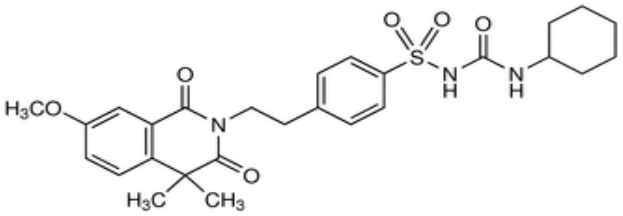
1 INTRODUCTION

Serious drug-drug interactions have been widely recognized. These interactions involved the induction or inhibition of metabolizing enzymes and efflux transporters, resulting adverse drug reactions or loss of efficacy. Drug-dietary supplement and drug-citrus fruit interactions could also cause adverse drug reactions or loss of efficacy **[1]**. Grapefruit juice can alter drug pharmacokinetics by different mechanisms. Grapefruit and its juice is a potent inhibitor of the intestinal cytochrome P450 enzyme CYP3A4, which can increase the bioavailability of drugs and have an impact on the oxidative metabolism of a variety of drugs, when administered orally [**2][3][4][5][6**]. Grapefruit juice may also inhibit intestinal P-glycoprotein-mediated efflux transport of cyclosporine to increase its oral bioavailability **[7]**. HMG-CoA reductase inhibitors atorvastatin, lovastatin or simvastatin after interacted with grapefruit juice may enhance the risk of rhabdomyolysis when dyslipidemia is treated and pravastatin, fluvastatin or rosuvastatin are potential alternative agents. Administration of grapefruit juice in angina pectoris could result in atrioventricular conduction disorders with verapamil or attenuated antiplatelet activity with clopidrogel. Grapefruit juice may also reduce the effect of losartan. From commercial grapefruit juice, irreversible inactivation of intestinal cytochrome P450 (CYP) 3A4 is produced which reduced presystemic metabolism and increased oral drug bioavailability **[5]**. The effects of grapefruit juice on two benzodiazepine hypnotics, triazolam (metabolized by CYP3A4) and quazepam (metabolized by CYP3A4 and CYP2C9) were also observed **[8]**. These interactions appear to be clinically significant for drugs with low oral bioavailability, which are substantially meabolized and inactivated in the intestinal tract by the cytochrome P450 3A4 enzyme in the intestinal wall **[9]**. So many other drugs have also been assessed for an interaction with grapefruit juice. Clinically relevant interactions seem likely for most dihydropyridines, terfenadine, saquinavir, midazolam and verapamil and may also occur with cisapride and astemizole. The importance of the interaction appears to be influenced by individual patient susceptibility, type and amount of grapefruit juice and administration-related factors [**10**]. Grapefruit juice is a well-known potent inhibitor of cytochrome P450 3A4 activity. Lemon juice significantly inhibits by 60+/-3% the CYP3A4-mediated oxidation [**11**]. Lemon and lime juices also effect the modulation of digoxin transport -across Caco 2 cell monolayers. Apical-to-basal (A-to-B) digoxin flux was increased by 50% lemon and lime juices [**12**]. Pomegranate juice can alter the pharmacokinetics of many drugs; it is a potent inhibitor of human CYP2C9 [**13**]. The components of pomegranate juice also inhibit the CYP3A-mediated drug metabolism and inhibit the human CYP3A-

mediated metabolism of carbamazepine. Furthermore, pomegranate juice also alters the carbamazepine pharmacokinetics in rats [**14**]. Orange juice can significantly change the pharmacokinetics of several drugs and has inhibitory effects on the pharmacokinetics of the beta-blocking. A concomitant administration with atenolol significantly decreased the AUC and means peak plasma concentration (Cmax) and thus inhibits the intestinal absorption of atenolol [**15**]. It also inhibits the intestinal absorption of celiprolol and contents in citrus juice are responsible for this action [**16**]. When taken together with pravastatin, orange juice significantly increases the bioavailability of pravastatin when administered orally. It increases oatp1 and oatp2 mRNA and protein in the intestine of rats, thus increases the pharmacokinetics of pravastatin [**17**]. It has been reported that 12 ounces of calcium-fortified **orange juice** significantly decreased the bioavailability of ciprofloxacin. Similarly when levofloxacin is co-administered with calcium-fortified **orange juice,** it was observed that orange juice decreased the values of levofloxacin C_{max} by 14 to 18% and thus inhibited the bioequivalence of a dose of levofloxacin **[18].** Concomitant administration of sweet lime juice with chloroquine significantly decreased the area under the plasma concentration-time curve (AUC) and mean peak plasma concentration (C (max) of chloroquine and thus inhibits its intestinal absorption [**19**]. It has been reported that sweet lime juice in concentration above 5% may enhance the transport of digoxin across cell membranes. As a result, the levels of digoxin may be affected in the blood, and may cause altered effects or potentially serious adverse reactions **[20]**.

Gliquidone is *N*-(cyclohexylcarbamoyl)-4-[2-(7-methoxy-4,4-dimethyl-1,3-dioxo-3,4-dihydroisoquinolin-2(1*H*)-yl) ethyl] benzenesulfonamide (Figure 1) a second generation sulfonyleurea is an anti-diabetic drug, an effective oral hypoglycemic agent for treating patients with non-insulin dependent diabetes (NIDDM or type 2 diabetes) **[21]**.

Fig1.Gliquidone



Present work will deal with the *in vitro* availability studies of gliquidone in presence of citrus fruit juices like grapefruit (*Citrus paradise*), lemon (*Citrus lemon*), pomegranate (*Punica granatum*), orange (*Citrus sinensis*) and sweet lime (*Citrus limetta*). These interaction studies will be carried out in simulating body temperature at 37°C and deliberated by means of UV spectrophotometric technique.

2 EXPERIMENTAL

2.1 Instrumentation

The main equipment used in the research work was UV visible spectrophotometer (Model 1601, Shimadzu, Japan) with 10-mm path length connected to a P-IV computer loaded with Shimadzu UVPC version 3.9 software. Furthermore, electrical balance, Shimadzu AUW220, 1 cm rectangular quartz cells, quick fit ground distillation assembly, distillation unit (GFL Type 2001/2) ,Ultrasonic LC 30H (Elma) and water bath were also used in these studies.

2.2 Material and Methods

Gliquidone was obtained from Brookes Lab I. For interaction studies citrus fruits used were grape fruit, orange, lemon, pomegranate and sweet lemon. They all were freshly purchased from the local markets and their juices were extracted. The only reagent used in this research work is methanol and the interaction studies were carried out in distilled methanol which was obtained by distillation of raw methanol.

2.3 Assay of Gliquidone

Various methods appeared in literature for the determination and quantitation of gliquidone employ techniques such as spectrophotometry **[22]**, atmospheric pressure chemical ionization liquid chromatographic-mass spectrometric (APCI-LC-MS) LC-MS and HPLC **[23][24]**. The method selected in our studies is simple, linear, precise and accurate. Gliquidone exhibit strong absorbance in the UV region of the spectrum at 230 and 313 nm in methanolic medium. Measurement of this absorbance has been employed for the assay of gliquidone which followed Beer Lambert's law in the concentration range of 12 ppm to 30 ppm.

2.4 Preparation of Gliquidone and Ascorbic acid Solutions

i Primary Solutions

In order to prepare the 100 ppm solution of gliquidone and ascorbic acid 10 mg of each drug were individually weighed and dissolved in few ml of distilled methanol, sonicated for 5-10 min to get the complete dissolution. Finally the volume of the solution was made up to the mark with methanol.

ii Working Standard Solutions

By using the primary solution working standard solutions of gliquidone and

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ascorbic acid were made ranging from 12-30 μgmL^{-1} and 4-22 μgmL^{-1} respectively. With the help of these solutions further studies were carried out.

2.5 Validation of Calibration Curves of Gliquidone and Ascorbic Acid

For the validation of calibration curve, working standard solutions of each concentration were drawn and scanned in the region of 200-360 nm against the reagent blank (Figure 2). The maxima were recorded at 230 nm and 313 nm. The same procedure was used for the validation of calibration curve of ascorbic acid. Similarly the maximum of ascorbic acid was observed at 250nm (Figure 3). A graph was plotted for absorbance against respective concentration in order to ensure the validity of Beer Lambert's law (Figure 4 and 5). From these observations the values of epsilon were calculated.

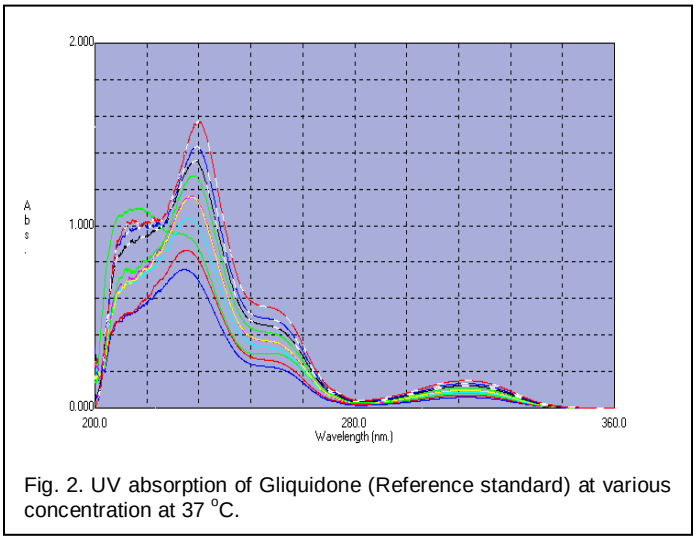

Fig. 2. UV absorption of Gliquidone (Reference standard) at various concentration at 37 °C.

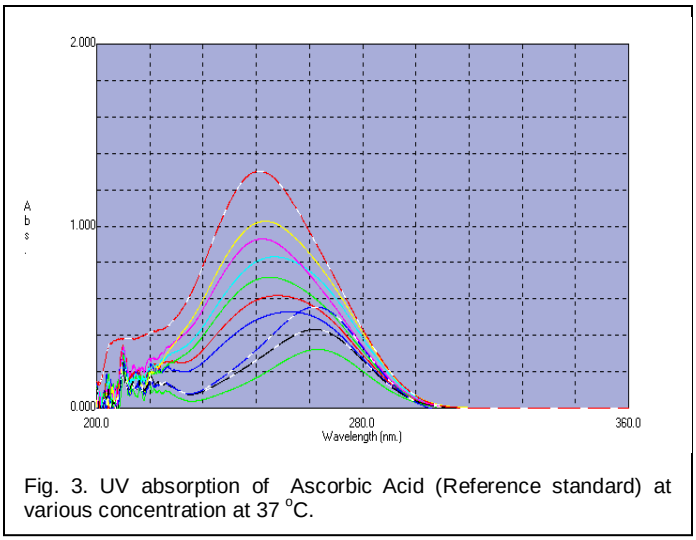

Fig. 3. UV absorption of Ascorbic Acid (Reference standard) at various concentration at 37 °C.

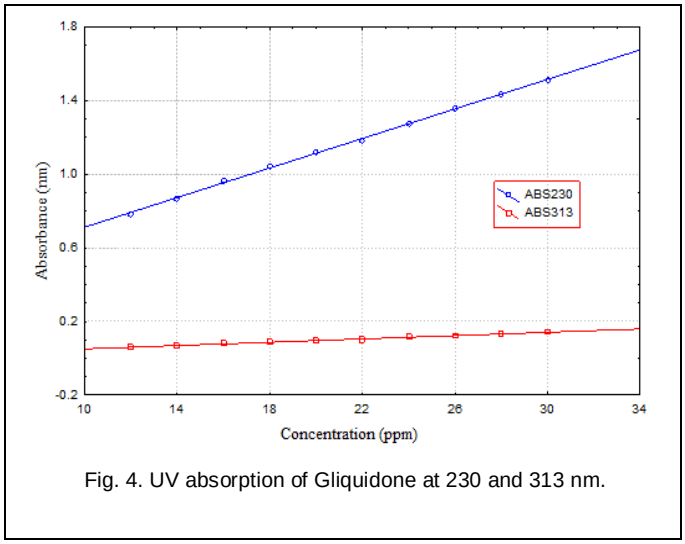

Fig. 4. UV absorption of Gliquidone at 230 and 313 nm.

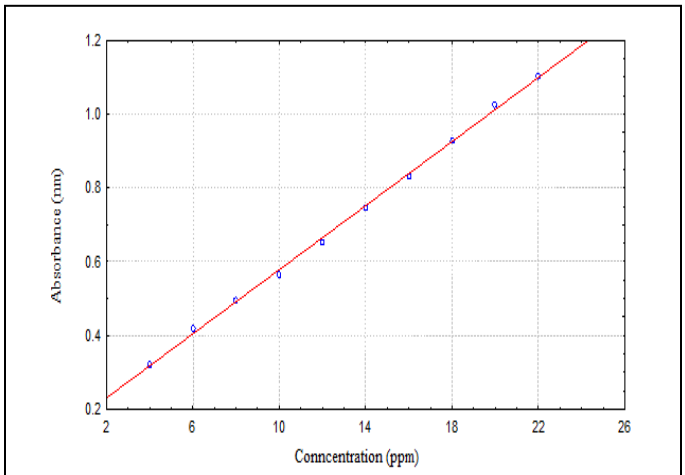

Fig. 5. UV absorption of Ascorbic Acid at 250 nm.

2.6 Preparation of Citrus Fruit Juices Solutions

i Extraction of Juices and Stock Solutions

For making stock solutions of citrus fruits juices such as grape fruit, orange, lemon, pomegranate and sweet lemon juices, first these juices were centrifuged at 60 rpm (rounds per minute) for 5-6 minutes to separate the pulp and other impurities present in the juices. In this way we got the clear solutions of these juices which were further purified by the process of simple filtration in the laboratory. Then 20 mL from each juice was pipetted out into 100 mL volumetric flasks separately to make the stock solutions of each juice. The volume of these solutions were made up to the mark with methanol and shaken well for proper mixing. The concentration of these stock solutions was 20%. From these 20% stock solutions we further made primary solutions.

ii Primary Solutions

For grape fruit and lemon juices, different dilutions ranging from 3-12% were prepared by diluting their stock solutions (20%) with methanol. Similarly for orange, pomegranate and sweet lemon juices, different dilutions ranging from 2-11% were prepared separately.

iii Working Standard Solutions

The final working standard solutions were made by pipetting the required milliliters from the required percent of primary solutions of juices into 50 mL volumetric flasks. Then 16ppm of the drug concentration was introduced in the same volumetric flasks. Finally the volume was made up to the mark with methanol. For instance if 3% working standard solution of grape fruit juice is required to prepare then 7.5 mL was pipetted out from 3% primary solution of grapefruit juice into a 50mL volumetric flask along with the addition of 16 ppm of drug (gliquidone) and then made up the volume to the mark with methanol. The same procedure had been adopted for the preparation of working standard solutions of different percentages of fruit juices by taking the constant value of drug (gliquidone) that is 16 ppm for each fruit juice.

3 RESULT AND DISCUSSION

Drug-food interactions can affect the total amount of drug absorbed (bioavailability), but most often they only slow absorption. For example, the hypoglycemic effect of glipizide may be delayed slightly if taken with a meal versus 30–60 minutes before a meal, although hemoglobin A1c (A1C) values are unaffected [**25] [26**]. Similarly grapefruit juice may cause pharmacokinetic interactions with glinides which are metabolized via cytochrome P450 (CYP) 3A4 isoenzyme [**27**]. It has already been established that, grape fruit juice is well known as potent inhibitors of cytochrome P450 3A4 activity. It increases bioavailability of many drugs known to be metabolized by CYP3A4. Owing to clinical relevance of grapefruit juice-drug interactions, an investigation of drug interactions of gliquidone was investigated invitro with citrus fruit juices at human body temperature.

3.1 Interaction Studies of Gliquidone with Fruit Juices

The interaction studies of gliquidone with different citrus fruit juices were carried out in methanol at 37°C using UV/visible spectrophotometer. We took five different citrus fruit juices: grapefruit, orange, pomegranate, lemon and sweet lime (mousambi). In these studies we added the standard concentration of gliquidone (16 ppm) in the solutions of each fruit juices having different percentages ranging from 2-11%. We kept the final interacting solutions on a water bath which was maintained at 37°C. Aliquots were withdrawn every 15 minutes till three hours and observed the absorbance of the left over drug (gliquidone) during three hours with the help of UV/visible spectrophotometer.

As each of these fruit juices interfered with the absorption maxima of the drug, an attempt was made to develop a method for simultaneous determination of gliquidone and ascorbic acid present in citrus fruit juices in presence of each other.

This procedure was designed to simultaneously measure the quantities of two components present in the same solution, without separating them. For this purpose molar absorptivities of gliquidone at λ_{max} of its own and λ_{max} of Ascorbic acid were calculated. Similarly the molar absorptivities of ascorbic acid were calculated at λ_{max} of gliquidone and λ_{max} of its own. These calculated values are given in table 1.

Table 1

Molar Absorptivities of gliquidone and ascorbic acid at 37°C

Analytes	Wavelength (nm)	($moles^{-1}Lcm^{-1}$)
Gliquidone	230	2600
	313	27700
	250	9600
Ascorbic acid	250	9300
	230	4500
	313	15

These molar absorptivities were used to calculate the concentration of both the drug and ascorbic acid. As the λ_{max} of both the drug and ascorbic acid was quite far apart, hence simultaneous equations (1 and 2) were developed to quantitate drug (gliquidone) from the solution, while countering the interference of the ascorbic acid.

$$C_a = \frac{A_{gliquidone} \cdot b_2 - A_{ascorbic\ acid} \cdot b_1}{a_1 b_2 - a2\, b_1} \quad (1)$$

$$C_b = \frac{A_{gliquidone} \cdot a_2 - A_{ascorbic\ acid} \cdot a_1}{a_2 b_1 - a_1 b_2} \quad (2)$$

Where C_a and C_b were concentrations of the two components present in the solution, A was absorbance, a_1 and a_2 were the absorptivities of gliquidone at λ_{max} of gliquidone and λ_{max} of ascorbic acid present in fruit juices, while b_1 and b_2 were the absorptivities of ascorbic acid at λ_{max} of gliqui-

done and λ_{max} of ascorbic acid, respectively. Equations (1) and (2) can be used to determine the quantity of gliquidone and ascorbic acid in fruit juices simultaneously, present in a solution. Results of these interaction studies of gliquidone with grapefruit, orange, pomegranate, lemon and sweet lemon juices are shown in tables (2-11).

These interactions of gliquidone with citrus fruit juices were studied at 230 and 313 nm. Absorption at 230nm is due to the O-N-O functionality of gliquidone. Sulfonamide group shows no absorbance above 300 nm but due to partial photolysis it gives absorbance at 313 nm in gliquidone. It is very much like wise other sulfa drugs which give absorbance at 332 nm [28]. Ascorbic acid also reacted at this sulfonamide group and formed a charge transfer complex but to a lesser extent. This is evident from the decrease in availability of gliquidone with respect to its absorption at 313nm as given in tables (2, 5, 7, 9 and 11).

In 3% grape fruit juice with respect to 230 nm, an opposite behavior between gliquidone and ascorbic acid was observed where as in 4% formation and decomposition of complexes were observed from time to time. In 5- 12% solutions of grape fruit juice, availability of ascorbic acid increased up to 1068, 649, 837, 1102, 136, 1380, 2139 and 408% respectively while of gliquidone remained significantly decreased at the end of experiment. With respect to 313 nm gliquidone and ascorbic acid suppressed the availabilities of each other in 3-9% grape fruit juice while in 10- 12% availabilities of both were slightly increased.

With 2- 11% lemon juice, the interaction studies showed a significant reduction in the availability of gliquidone at 230nm. In 2% an unstable complex was formed but at the end of experiment only 17% gliquidone was available. Where as the availability of ascorbic acid was found to be increased from 52- 1162%. With respect to 313 nm a retardation effect to gliquidone and ascorbic acid availability was observed i.e. from 65- 6% and 70 to -2% respectively.

In case of orange juice (2- 11%) gliquidone stimulated the release of ascorbic acid and their % availability exceeded from 1400%, while ascorbic acid suppressed the availability of gliquidone that was more significant at 230nm. At 313 nm a decrease in availabilities from 88- 5% of gliquidone was observed.

In the presence of sweet lime (mousambi) juice, when gliquidone was interacted with ascorbic acid, the interaction results showed that at 230 nm the availability of ascorbic acid was significantly increased at 37˚C, maximum availability was 2551%. In contrary it was also found that at the end of experiments gliquidone was not available in free form. Where as at 313 nm there was a decrease in the availability of gliquidone from 419-4%.

Similarly, through the interaction studies of gliquidone with pomegranate juice it was observed that ascorbic acid caused a decline to gliquidone's availability that was more significant with respect to 230nm. At the end of experiment, availability of gliquidone becomes -990, -1259, -631, -1858, -2187, -6552, -3077, -3948, -4203 and -6952% in 2- 11% pomegranate juice respectively. At 313 nm in 2- 5% pomegranate juice interactions showed a decrease in the availabilities of gliquidone and ascorbic acid. Where as in 6- 11%, % availability of gliquidone was found to be increased.

Table 2

Gliquidone sweet lime juice interaction at 37°C

Time (min)	% Availability																			
	2%		3%		4%		5%		6%		7%		8%		9%		10%		11%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	4.7	16.7	12.2	25.9	12.1	19.1	19.3	22.8	22.4	19.4	24.0	19.1	26.2	16.2	419.7	236.4	118.7	118.7	36.3	18.71
15	4.7	16.7	12.2	25.9	12.2	18.8	12.2	15.0	20.4	18.8	24.0	19.1	26.2	16.5	191.6	106.2	118.7	118.7	36.3	18.71
30	4.7	16.7	12.2	25.9	12.2	18.8	22.3	23.3	22.4	19.4	24.0	19.1	29.7	18.6	419.7	236.4	118.7	118.7	259.3	117.1
45	4.8	16.7	8.3	16.1	12.1	19.1	12.1	15.2	20.3	18.8	24.2	19.1	26.2	16.2	419.7	236.4	118.7	118.7	259.3	117.1
60	5.1	16.0	8.2	15.7	12.1	19.1	12.1	15.2	22.4	19.4	20.4	16.1	26.2	16.2	419.7	236.4	120.6	120.6	237.4	109.6
75	5.1	16.0	11.6	17.5	12.1	19.1	22.0	22.0	20.4	18.8	24.0	19.1	29.7	18.6	191.6	106.2	118.7	118.7	237.4	109.6
90	5.4	17.9	9.1	16.1	16.6	17.1	19.4	20.0	22.4	19.4	24.0	19.1	29.7	18.6	419.7	236.4	120.6	120.6	259.3	117.1
105	5.4	17.3	8.9	15.6	13.4	17.4	19.7	20.4	20.3	18.8	20.4	16.1	26.2	16.2	191.6	106.2	120.6	120.6	259.3	117.1
120	5.4	17.3	8.8	15.1	13.3	17.3	20.2	20.5	22.4	19.4	20.4	16.1	26.2	16.2	419.7	236.4	118.7	118.7	259.3	117.1
135	24.9	66.5	8.7	14.7	13.3	16.9	20.4	20.6	22.4	19.4	24.0	19.1	29.7	18.6	419.7	236.4	118.7	118.7	237.4	109.6
150	4.7	14.1	9.3	15.5	9.3	11.6	20.4	20.6	20.4	18.8	26.2	18.5	29.7	18.6	419.7	236.4	120.6	120.6	237.4	109.6
165	5.4	16.2	8.6	13.5	8.6	10.1	8.6	8.1	20.4	18.8	24.0	19.1	26.2	16.2	419.7	236.4	118.7	118.7	36.3	18.71
180	5.4	16.2	13.1	19.9	13.1	14.9	13.1	11.9	20.4	18.8	20.4	16.1	26.2	16.2	419.7	236.4	20.5	20.5	237.4	109.6

Ca: % Availability of Gliquidone at 313 nm.

Cb: % Availability of Ascorbic acid at 250 nm.

Table 3

Gliquidone sweet lime juice interaction at 37°C

Time (min)	% Availability																			
	2%		3%		4%		5%		6%		7%		8%		9%		10%		11%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	-454	229	-891	303	-901	230	-820	249	-1313	225	-228	323	-156	200	-221	2551	-131	135	-202	191
15	-454	229	-891	303	-891	227	-891	182	-1272	217	-228	323	-156	200	-113	2293	-131	135	-202	191
30	-454	229	-891	303	-891	227	-823	255	-1313	225	-228	323	-179	229	-221	2554	-131	135	-144	135
45	-454	229	-676	227	-901	230	-901	184	-1276	218	-228	323	-156	200	-221	2551	-131	135	-144	135
60	-459	230	-666	223	-901	230	-901	184	-1313	225	-127	186	-156	200	-221	2255	-138	142	-138	129
75	-459	230	-733	247	-901	230	-1219	251	-1272	217	-228	323	-179	229	-113	2129	-131	135	-138	129
90	-513	257	-689	231	-886	225	-1177	241	-1313	225	-228	323	-179	229	-221	2255	-138	142	-144	135
105	-524	261	-696	232	-900	228	-1208	247	-1276	218	-127	186	-156	200	-113	2129	-138	142	-144	135
120	-524	261	-685	228	-904	229	-1214	248	-1313	225	-127	186	-156	200	-221	2251	-131	135	-144	135
135	-128	670	-686	228	-892	226	-1236	252	-1313	225	-228	323	-179	229	-221	2255	-131	135	-138	129
150	-413	207	-708	236	-708	177	-1236	252	-1272	217	-156	228	-179	229	-221	2255	-138	142	-138	129
165	-446	225	-656	218	-656	163	-656	130	-1272	217	-228	323	-156	200	-221	2255	-131	135	-202	191
180	-446	225	-870	291	-870	218	-870	175	-1272	217	-127	186	-156	200	-221	2551	-202	211	-138	129

Ca: % Availability of Gliquidone at 230 nm.

Cb: % Availability of Ascorbic acid at 250 nm.

Table 4

Gliquidone grape fruit juice interaction at 37°C

Time (min)	% Availability																			
	3%		4%		5%		6%		7%		8%		9%		10%		11%		12%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	138	-19	216	-23.5	-487	1061	-142	266	-510	837	-46	674	-24	14	-11	1267	-18	1918	-41	408
15	138	-19	400	-72.6	-490	1068	-121	231	-390	641	-45	652	-36	34	-12	1370	-18	1919	-41	408
30	138.3	-19	-2034	598	-464	1011	-361	649	-418	686	-47	677	-12	49	-14	1361	-18	1869	-41	408
45	138	-19	-2034	598	-485	1055	-212	413	-434	712	-41	599	-92	52	-15	1334	-17	1827	-41	408
60	138	-19	-2784	778	-480	1041	-677	137	-413	676	-47	679	-83	87	-18	1284	-18	1850	-41	408
75	138	-19	560	-116	-445	967	-446	96.6	-434	714	-43	626	-17	98	-11	1311	-20	2139	-41	408
90	138	-19	120	27.3	-480	1043	-222	55.0	-388	637	-44	647	-67	106	-11	1289	-18	1862	-41	408
105	138	-19	120	27.3	-457	990	-222	55.0	-373	610	-42	616	-14	112	-12	1380	-18	1856	-41	408
120	138	-19	-3147	892.5	-486	1053	-101	196	-397	650	-44	642	-20	121	-11	1351	-18	1885	-41	408
135	-101	151	572	-119	-467	1011	-110	213	-398	652	-43	623	-29	129	-11	1332	-17	1829	-41	408
150	-101	151	-1751	556	-355	770	-340	76.9	-411	661	-76	1102	-41	130	-12	1360	-18	1900	-41	408
165	-101	151	-20	76.19	-480	1043	-721	145	-390	641	-45	645	-50	132	-12	1371	-17	1834	-33	372
180	-101	151	13	52.07	-469	1016	-910	178	-389	635	-43	623	-93	136	-12	1344	-12	1265	-29	340

Ca: % Availability of Gliquidone at 230 nm.

Cb: % Availability of Ascorbic acid at 250 nm

Table 5

Gliquidone grape fruit juice interaction at 37°C

Time (min)	% Availability																			
	3%		4%		5%		6%		7%		8%		9%		10%		11%		12%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	7	22	20	23.	89	11	22	36	10	12	95	10	21	9	104	75	34	65	35	59
15	7	22	25	16	89	11	20	34	80	28	93	10	16	14	110	90	42	76	47	67
30	7	22	61	18	81	10	43	67	90	10	97	10	24	13	117	100	50	89	65	77
45	7	22	61	28	85	11	39	69	91	10	87	21	15	6	124	118	65	94	77	82
60	7	22	60	10	83	10	17	27	87	10	96	10	15	6	133	127	75	101	86	87
75	7	22	25	11	78	10	16	22	91	10	91	19	19	8	144	134	88	110	87	98
90	7	22	62	41	86	10	14	17	79	56	92	10	22	11	149	140	92	129	97	101
105	7	22	62	41	82	10	14	17	76	41	89	23	13	4	149	145	98	132	100	109
120	7	22	96	11	87	10	20	32	80	56	73	27	33	15	149	156	102	137	102	115
135	36	10	27	10	83	10	21	33	84	47	52	17	34	8	150	160	117	142	109	126
150	36	10	10	11	67	79	16	20	83	48	16	17	31	21	150	165	128	157	115	137
165	36	10	31	49	88	10	19	28	80	58	22	25	34	24	151	166	137	168	120	142
180	36	10	46	44	82	10	20	30	77	43	19	33	37	33	159	165	140	174	135.	166

Ca: % Availability of Gliquidone at 313 nm.

Cb: % Availability of Ascorbic acid at 250 nm.

Table 6

Gliquidone Orange juice interaction at 37°C

Time (min)	% Availability																			
	2%		3%		4%		5%		6%		7%		8%		9%		10%		11%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	-17	1410	-42	232	-28	116	-86	282	-69	187	-24	504	-69	139	-20	401	-15	249	-42	617
15	-16	1340	-41	227	-29	119	-84	278	-58	156	-19	462	-70	143	-21	408	-15	249	-43	632
30	-16	1315	-39	216	-32	132	-93	305	-55	146	-19	463	-65	132	-28	470	-15	248	-42	629
45	-16	1331	-39	215	-28	114	-87	287	-54	145	-20	470	-76	155	-28	470	-16	251	-42	616
60	-17	1460	-38	208	-29	122	-87	285	-61	162	-18	440	-65	130	-20	386	-16	254	-55	815
75	-14	1209	-43	236	-29	118	-92	302	-66	180	-20	474	-65	130	-27	453	-16	259	-49	721
90	-15	1294	-40	222	-27	110	-90	295	-63	171	-20	470	-65	131	-28	466	-15	237	-42	617
105	-15	1302	-40	216	-26	109	-89	290	-68	182	-19	459	-67	135	-13	294	-16	257	-42	612
120	-16	1313	-40	220	-31	127	-92	300	-64	173	-19	454	-65	132	-19	384	-16	254	-42	612
135	-15	1270	-43	234	-31	129	-86	280	-53	142	-19	462	-55	109	-19	378	-18	274	-54	799
150	-16	1307	-45	247	-29	123	-94	307	-63	168	-20	475	-54	107	-28	463	-16	259	-47	687
165	-15	1233	-44	242	-31	129	-96	329	-61	162	-20	467	-66	132	-21	399	-16	260	-45	660
180	-16	1340	-49	263	-36	151	-101	329	-61	164	-20	480	-54	107	-23	442	-16	258	-46	697

Ca: % Availability of Gliquidone at 230 nm.

Cb: % Availability of Gliquidone at 250 nm.

Table 7

Gliquidone Orange juice interaction at 37°C

Time (min)	% Availability																			
	2%		3%		4%		5%		6%		7%		8%		9%		10%		11%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	31	132	8	21	5	10	16	27	9	15	34	22	9	11	52	54	11	16	65	48
15	29	125	8	21	5	11	19	26	7	12	34	44	10	12	53	53	11	16	66	49
30	28	122	8	20	6	12	17	28	6	10	34	43	9	10	52	44	11	16	69	51
45	29	127	8	19	5	10	16	26	6	10	33	43	11	14	52	44	11	16	66	48
60	33	145	8	18	5	11	16	25	8	12	33	43	8	10	52	53	11	16	78	73
75	26	107	9	20	5	11	17	27	9	16	34	43	8	10	53	67	12	17	74	55
90	28	118	8	19	5	9	18	26	8	14	33	43	9	10	54	23	9	15	64	45
105	28	119	8	18	5	9	16	25	9	15	32	43	9	11	60	64	12	16	63	44
120	28	120	8	19	5	12	17	26	8	14	33	42	9	10	53	54	11	16	63	44
135	26	111	8	20	6	12	16	24	6	10	33	43	7	7	52	51	11	16	88	70
150	28	118	8	20	5	12	17	27	8	13	34	44	6	7	53	17	12	16	66	53
165	26	106	8	20	6	12	17	28	7	12	33	42	8	10	50	49	12	16	71	52
180	29	121	8	21	7	16	17	28	8	12	34	44	6	7	55	54	11	16	49	71

Ca: % Availability of Gliquidone at 313 nm.

Cb: % Availability of Gliquidone at 250 nm.

Table 8

Gliquidone lemon juice interaction at 37°C

Time (min)	% Availability																			
	2%		3%		4%		5%		6%		7%		8%		9%		10%		11%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	20	5	-135	52	-549	139	-100	198	-736	112	-702	920	-901	1040	-385	400	-409	381	-531	455
15	81	-23	-175	65	-503	128	-101	201	-616	934	-702	920	-727	827	-364	377	-409	381	-519	443
30	37	-3	-195	72	-481	123	-101	201	-763	1162	-709	930	-727	827	-357	369	-409	381	-536	460
45	58	-13	-214	78	-516	131	-103	204	-763	1162	-720	943	-727	827	-727	753	-337	311	-672	569
60	-12	66	-195	72	-516	131	-986	194	-763	1162	-746	983	-727	827	-337	346	-471	444	-672	569
75	-35	16	-247	89	-482	123	-103	204	-616	934	-677	884	-727	827	-337	346	-337	311	-672	569
90	57	-23	683	104	-476	122	-103	202	-763	1162	-702	920	-901	1040	-727	753	-337	311	-727	616
105	28	-11	-219	80	-503	128	-103	202	-616	934	-720	943	-727	827	-337	346	-471	444	-672	569
120	52	-10	-219	80	-484	124	-101	200	-616	934	-707	927	-901	1040	-727	753	-337	311	-672	569
135	25	2.5	-223	80	-551	140	-104	206	-736	1121	-720	943	-901	1040	-727	753	-471	444	-672	569
150	35	-3	-202	74	-698	175	-106	210	-763	1162	-707	927	-727	827	-727	753	-471	444	-672	569
165	35	-3	-220	79	-548	139	-105	208	-763	1162	-616	802	-727	827	-727	753	-471	444	-672	569
180	17	5	-226	81	-517	131	-105	207	-616	934	-702	920	-727	827	-337	346	-298	361	-672	569

Ca: % Availability of Gliquidone at 230 nm.

Cb: % Availability of Ascorbic acid at 250 nm.

Table 9

Gliquidone lemon juice interaction at 37°C

Time (min)	% Availability																			
	2%		3%		4%		5%		6%		7%		8%		9%		10%		11%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	7.69	10.86	10.12	12.41	17.85	18.30	22.86	21.67	16.76	67.42	19.39	56.19	38.93	70.21	39.12	29.27	41.74	26.94	59.27	36.81
15	6.30	8.10	10.64	12.84	17.45	17.27	25.32	22.22	6.82	52.59	19.39	56.19	14.41	45.70	36.16	26.54	41.74	26.94	55.83	34.59
30	7.74	9.64	11.36	13.87	15.89	16.77	25.32	22.22	22.60	67.28	19.39	57.25	14.41	45.70	36.29	25.18	41.74	26.94	59.15	37.44
45	6.64	8.79	11.41	14.34	16.10	17.32	24.14	22.82	22.60	67.28	18.67	57.25	14.41	45.70	70.41	53.09	28.21	19.76	65.55	40.31
60	6.75	9.74	10.73	13.24	16.10	17.32	23.42	21.20	22.60	67.28	27.45	64.44	14.41	45.70	28.21	21.96	52.87	35.44	65.55	40.31
75	9.77	-2.71	11.63	15.31	16.07	16.15	23.25	23.19	6.82	52.59	12.38	52.33	14.41	45.70	28.21	21.96	28.21	19.76	65.55	40.31
90	7.16	4.48	6.66	88.83	15.95	16.87	23.49	21.68	22.60	67.28	19.39	56.19	38.93	70.21	70.41	53.09	28.21	19.76	70.41	43.44
105	6.63	9.46	11.09	14.39	16.15	17.23	23.49	21.68	6.82	52.59	18.67	57.25	14.41	45.70	28.21	21.96	52.87	35.44	65.55	40.31
120	6.76	8.89	11.09	14.39	17.02	16.79	23.49	22.30	6.82	52.59	17.00	57.58	38.93	70.21	70.41	53.09	28.21	19.76	65.55	40.31
135	7.01	10.35	10.95	13.78	17.66	18.81	24.67	23.49	16.76	67.42	18.67	57.25	38.93	70.21	70.41	53.09	52.87	35.44	65.55	40.31
150	6.81	9.17	10.58	13.47	25.63	20.28	24.28	23.58	22.60	67.28	17.00	57.58	14.41	45.70	70.41	53.09	52.87	35.44	65.55	40.31
165	6.81	9.17	10.90	13.62	18.28	17.56	24.14	22.74	22.60	67.28	6.82	45.17	14.41	45.70	70.41	53.09	52.87	35.44	65.55	40.31
180	7.14	10.02	11.41	14.01	17.26	17.36	24.17	22.90	6.82	52.59	19.39	56.19	14.41	45.70	28.21	21.96	41.99	10.9	65.55	40.31

Ca: % Availability of Gliquidone at 313 nm.

Cb: % Availability of Ascorbic acid at 250 nm.

Table 10

Gliquidone pomegranate juice interaction at 37°C

Time (min)	% Availability																			
	2%		3%		4%		5%		6%		7%		8%		9%		10%		11%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	-1018	38	-1341	34	-477	91	-1767	27	-2031	25	-7329	83	-3313	31	-3948	33	-4986	38	-6108	43
15	-940	35	-1242	31	-466	89	-1763	26	-2022	25	-6270	70	-3313	31	-3559	30	-4203	32	-6952	49
30	-967	36	-1227	31	-585	114	-1758	26	-2123	27	-6657	75	-3077	29	-3710	31	-4986	38	-6952	49
45	-2291	88	-1254	31	-643	125	-1802	27	-2110	27	-6957	78	-3077	29	-3710	31	-4986	38	-6952	49
60	-953	35	-1195	30	-500	96	-1760	26	-2105	26	-7466	85	-3077	29	-3710	31	-4986	38	-6952	49
75	-982	36	-1188	30	-510	98	-1810	27	-2091	26	-7166	81	-3077	29	-3710	31	-4986	38	-5912	42
90	-938	35	-1204	30	-505	97	-1753	26	-2141	27	-6940	78	-3313	31	-3948	33	-4294	33	-6952	49
105	-928	348	-1225	31	-593	114	-1845	28	-2141	27	-6703	75	-3077	29	-3710	31	-4986	38	-6108	43
120	-950	35	-1279	32	-531	103	-1833	28	-2171	27	-6478	72	-3077	29	-3559	30	-4986	38	-5912	42
135	-962	36	-1257	31	-496	95	-1795	27	-2107	26	-6151	68	-3313	31	-3948	33	-4203	32	-6952	49
150	-414	16	-1257	31	-642	12	-1850	28	-2156	27	-6365	71	-3077	29	-3559	30	-4986	38	-5912	42
165	-979	36	-1256	31	-580	11	-1857	28	-2169	27	-6547	73	-3077	29	-3948	33	-4986	38	-6952	49
180	-990	37	-1259	31	-631	12	-1858	28	-2187	28	-6552	73	-3077	29	-3948	33	-4203	32	-6952	49

Ca: % Availability of Gliquidone at 230 nm.

Cb: % Availability of Ascorbic acid at 250 nm.

Table 11

Gliquidone pomegranate juice interaction at 37°C

Time (min)	% Availability																			
	2%		3%		4%		5%		6%		7%		8%		9%		10%		11%	
	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb	Ca	Cb
0	10.12	26.91	15.49	26.44	7.11	7.90	22.38	22.38	26.6	21.66	133.31	91.97	42.69	26.63	53.36	30.73	68.66	34.50	94.38	45.16
15	8.76	23.88	13.34	23.34	6.98	7.73	22.24	22.18	26.8	22.13	108.06	73.15	42.69	26.63	46.96	26.07	56.92	28.60	122.87	53.99
30	9.51	25.75	13.71	23.31	9.33	11.12	22.08	22.04	29.0	23.34	118.97	80.64	37.59	23.47	48.38	27.12	68.66	34.50	122.87	53.99
45	33.51	79.40	14.32	24.27	10.22	12.19	22.95	22.79	27.9	23.20	124.79	83.63	37.59	23.47	48.38	27.12	68.66	34.50	122.87	53.99
60	9.13	24.29	12.85	23.78	7.39	8.39	22.25	21.96	27.9	23.23	146.36	100.51	37.59	23.47	48.38	27.12	68.66	34.50	122.87	53.99
75	9.64	25.67	12.81	22.14	7.78	8.72	22.94	22.50	27.4	22.33	130.59	89.28	37.59	23.47	48.38	27.12	68.66	34.50	93.68	43.43
90	9.19	24.78	13.24	22.73	7.66	8.70	22.26	22.25	31.3	24.27	124.78	84.69	42.69	26.63	53.36	30.73	59.53	29.49	122.87	53.99
105	8.55	23.56	13.49	22.98	8.60	10.32	23.56	23.34	28.8	23.39	122.30	81.26	37.59	23.47	48.38	27.12	68.66	34.50	94.38	45.16
120	9.66	25.09	14.30	25.23	8.35	9.98	23.22	23.31	29.2	23.90	114.71	75.52	37.59	23.47	46.96	26.07	68.66	34.50	93.68	43.43
135	9.09	24.74	13.98	24.21	7.55	8.50	22.78	22.67	28.1	22.83	109.03	70.16	42.69	26.63	53.36	30.73	56.92	28.60	122.87	53.99
150	6.92	16.03	13.75	24.11	9.58	11.64	24.71	23.63	29.0	23.57	112.11	73.15	37.59	23.47	46.96	26.07	68.66	34.50	93.68	43.43
165	9.18	24.92	13.69	23.95	8.20	9.88	24.19	23.62	64.8	19.72	116.72	78.00	37.59	23.47	53.36	30.73	68.66	34.50	122.87	53.99
180	9.53	26.48	13.94	24.06	9.32	11.49	23.61	23.57	29.6	24.03	114.59	75.97	37.59	23.47	53.36	30.73	56.92	28.60	122.87	53.99

Ca: % Availability of Gliquidone at 313 nm.

Cb: % Availability of Ascorbic acid at 250 nm

4 CONCLUSION

The significance of interaction of gliquidone with citrus fruit juices was evaluated in this study. Results of the present study indicated that all citrus fruit juices studied bind to gliquidone, and hence caused a decline to gliquidone's availability that was more significant with respect to 230nm. This may be due to the formation of charge transfer complexes between gliquidone and ascorbic acid present in the fruit juices. The results of these interactions also proved a drastic change in availability of ascorbic acid in presence of gliquidone. Hence, it is suggested from the above findings and results that combined use of fruit juices with gliquidone is highly not recommended and should be avoided.

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