Pakistan Journal of Pharmaceutical Sciences
Vol. 16, No.1, January 2003, pp.35-49

IN VITRO AVAILABILITY OF GLICLAZIDE IN PRESENCE OF ANTACIDS

M. SAEED ARAYNE, NAJMA SULTANA* AND M. KAMRAN ZAMAN
Department of Chemistry, University of Karachi
**Department of Pharmaceutical Chemistry, Faculty of Pharmacy*
University of Karachi

ABSTRACT

Gliclazide is the most commonly used sulfonylurea derivative for NIDDM therapy. Due to its prolonged therapy, there is always a likelihood of its use with other drugs. On the other hand antacids are commonly prescribed to encounter gastric acidity etc. Present paper deals with the *in vitro* availability studies of gliclazide in presence of antacids. These studies were carried out in simulated gastric juice and in buffer of pH 7.4 at body and accelerated temperature. The antacids used in these studies were aluminum hydroxide, aluminum trisilicate, magnesium oxide, magnesium trisilicate, sodium bicarbonate, calcium carbonate, magaldrate and simethicone (2,4-dimethoxypoly-siloxane). It has been found that in case of magnesium oxide, magnesium trisilicate and sodium bicarbonate, availability of gliclazide was enhanced while in rest of the antacids retarded the availability of gliclazide.

INTRODUCTION

Gliclazide is N-[[(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)amino]-carbonyl]-4-methyl benzene sulfonamide, or 1- (hexahydrocyclopenta[c] pyrrol-2-(1H)-yl)-3-(p-tolylsulfonyl) urea or N-(4-methylbenzene sulfonyl) -N'-(3-azabicyclo [3.3.0] oct-3-yl) urea or 1-(3-azabicyclo[3.3.0] oct-3-yl) -3-p-tolylsulfonyl urea $C_{15}H_{21}N_3O_3S$, molecular weight 323.4 is a white or almost white crystalline powder, odorless, tasteless, m.p., 165-170^{o}C (Fig. 1) (British Pharmacopoeia 1998, Martindale, 1999 and Parvez M. *et al.,* 1999). It is practically insoluble in water, sparingly soluble in acetone, slightly soluble in ethanol (96%) and freely soluble in dichloromethane. It is synthesized by the addition to the sulfonylurea grouping of a N-containing heterocyclic ring with an endocyclic bond, it is stable under normal conditions. It is marketed by various trade names such as Diamicron, Glimicron, Nordialex, etc.

Fig. 1: Gliclazide

It is readily absorbed in gastrointestinal tract and transported through bound plasma proteins. It treats diabetes mellitus by reducing the platelet adhesiveness and aggregation by antagonizing the abnormal fibrin deposition on the vessel wall and by reducing the excessive response of the diabetic microvessel to adrenative.

Gliclazide should not be used in insulin-dependent diabetes mellitus and used in patients with severe impairment of thyroid function (Colin D., 1999). Side effects of gliclazide treatment are similar to those of other sulfonylureas (Paice *et al.,* 1985). Gliclazide used in a standard dose is less likely than glyburide to cause hypoglycemia (Jennings *et al.,* 1989).

There are number of reported drug interactions of gliclazide (Uusitupa *et al.*, 1980; Koda Kimble, 1992; Mills and Horn, 1985; Chin *et al.,* 1984; Abramson and Arky, 1968 and Mackintosh, 1967). Gliclazide in presence of aspirin, clofibrate, sulfonamides and cimetidine (Archambeaud *et al.,* 1987 and MacWalter, 1985) may increase the hypoglycemic effect while on the other hand barbiturates, phenytoin, thiazide, diuretics, diazomide, glucocarticords, estrogens or sympathomimetic drugs and alcohol oppose the hypoglycemic action of sulfonylureas (Colin, 1999 and Paice *et al.,* 1985). However, there are less frequent evidences of drug interactions of cardio selective (β-1 selective) β-blockers (atenolol, metoprolol, betaxolol) drugs with gliclazide (O'Byrne & Feely, 1990 and Shorr *et al.,* 1997). Some studies have reported a potential interaction between fluconazole and gliclazide, resulting in enhanced hypoglycemic effects (Holmes *et al.,* 1984 and Anon, 1992). In clinical studies, the concurrent use of monoamine oxidase (MAO) inhibitors and insulin or oral hypoglycemic drugs have been reported to improve glucose tolerance (Cooper and Ashcroft, 1967, Cooper and Ashcroft, 1966, Bressler *et al.,* 1965 and Wickstrom & Pettersson, 1964). NSAIDs have not produced hypoglycemic effects (Shah *et al.,* 1984 and Whiting *et al.,* 1981 and Mork & Robertson, 1983) reported that the hypoglycemic effects of aspirin and ibuprofen, were minimal or negligible. There have been conflicting reports about the effects of calcium channel blockers on NIDDM drugs (Giugliano *et al.,* 1980, Heyman, 1989 and Fu Z.Z., 1992). There is no definite evidence of a reduction or improvement in glucose tolerance due to calcium channel blocker administration. Troglitazone added to glibenclamide or gliclazide therapy in patients with poorly controlled NIDDM significantly improved fasting plasma glucose (FPG) and glycosylated hemoglobin (Iwamoto, 1996).

Antacids are drugs used to neutralize the hydrochloric acid secreted by gastric parietal cells. Antacids are compared quantitatively in terms of their acid neutralizing capacity and are widely used for many disorders. The potential of antacids to interact with other concomitantly ingested drugs is well recognized. These interactions usually result in reduced or delayed absorption of the affected drugs (Albert and Rees, 1956; Waisbren *et al.,* 1950; Greenblatt *et al.,* 1976; Grasela *et al.,* 1989; Lebsack, 1988; Kunka, 1988; Campbell, 1992; Nix *et al.,* 1990; Noyes & Polk, 1988 and Flor, 1990) while in some cases antacids increase the bioavailability of some drugs (Miller, 1990 and Arayne & Sultana, 1993). These are not as efficacious as the H_2-receptor antagonists and proton pump inhibitors (Rang & Dale 1993). Present paper deals with the *in vitro* availability studies of gliclazide in presence of antacids like aluminum hydroxide, aluminum trisilicate, magnesium oxide, magnesium trisilicate, sodium bicarbonate, calcium carbonate, magaldrate and simethicone (2,4-dimethoxypolysiloxane). Most of these antacids contain di- and trivalent metal cations which have more affinity towards electron-rich binding sites. These studies were carried out in simulated gastric juice and in buffer of pH 7.4 simulating blood pH at body and accelerated temperatures.

MATERIALS AND METHODS

Gliclazide standard was obtained from M/s. Ali Gohar Pharmaceuticals (Pvt.) Ltd. It had expiry date not earlier than 365 days, at the time of these studies.

In vitro availability studies of gliclazide were carried out in absence and presence of these antacids at 37°C and 48°C by using standard dissolution apparatus. In these sets of experiments gliclazide 25 mg was added to the dissolution medium at zero time while after 15 minutes before collecting the sample, 2 gm of each antacid was added to the dissolution medium separately in each individual set of experiment. Aliquots were withdrawn every 15 minutes till three hours and assayed for the gliclazide content. Although there are number of methods reported for the

quantitation of gliclazide in blood, plasma, various laboratory and analytical samples, which include titrimetric British Pharmacopoeia 1998, spectrophotometric (El Kousy, 1991; El Kousy & Ashoor, 1990 and Hussein *et al.,* 1989), TLC (Frank *et al.,* 1986), high performance liquid chromatography [Yuqin *et al.,* 1995; Huichen *et al.,* 1995; Noguchi *et al*., 1992; Bogusz & Moutain, 1991; Bustamante *et al.,* 1990; Shenfield *et al.,* 1990; Igaki *et al.,* 1989; Tamoto *et al*., 1988; Poirier *et al.,* 1987; Sidhu *et al.,* 1987; Igaki, 1986; Charles & Ravenscroft, 1984; Kimura *et al.,* 1980; Kimura *et al.,* 1980 and Waahlin-Boll & Melander, 1979), gas chromatography (Maeda *et al.,* 1981), RIA methods (Suzuki *et al.,* 1981 and Heptner *et al.,* 1984) and coulometric method (Nikolic *et al.,* 1992). The method selected for our studies is simple, accurate and quick. Gliclazide exhibits strong absorption in the ultraviolet region of the spectrum at 225 nm, measurement of which have been employed for the assay of gliclazide, which followed Beer's Lambert law in the concentration range studied.

Validation of Calibration Curve of Gliclazide

For the validation of calibration curve, 5 ml working standard solutions of each concentration ranging from 5, l0, l5 ... 50 µg/ml were drawn and the absorbance was measured in the same range against reagent blank. A graph was plotted for absorbance against respective concentration in order to ensure the validity of Beer Lambert's law. The molar absorptivity of gliclazide obtained in simulated gastric juice (15,121 ± 0.003 □ $Mole^{-1}cm^{-1}$), was used for further calculations of the left over drug after interactions with antacids using Beer-Lambert law. Graphs between drug concentration versus time were plotted which showed drug status during and at the end of the experiments.

RESULTS AND DISCUSSION

The results of the effect of antacids on the *in vitro* availability of gliclazide at different time intervals, in simulated gastric juice at 37° and 48^0C are given in Tables 1 and 2 respectively. Similarly, the *in vitro* availability of gliclazide in buffer of pH 7.4 at 37° & 48°C are mentioned in Tables 3 and 4 respectively. Graphs were plotted (Fig. 1-4) for the first order dissolution rate constant of drug concentration versus time in each set of experiment in presence or absence of antacids. The dissolution time T_{50} and T_{90} of gliclazide in presence of various antacids is given in Table 5.

Table 1 contains results of gliclazide-antacid interactions in simulated gastric juice at 37^0C. As can be seen from these profiles and Fig. 1, the dissolution rate of gliclazide decreased in presence of all the antacids studied except magnesium oxide, magnesium trisilicate and sodium bicarbonate, where it increased significantly.

Magnesium oxide and magnesium trisilicate exhibited a significant effect on the rate of dissolution of gliclazide. After an interval of 30 minutes 44 and 45% of the drug were present in the solution and after 120 minutes the entire drug was available. The T_{50} and T_{90} values of gliclazide in presence of both magnesium oxide and magnesium trisilicate were found to be 45, 91 and 44, 88 minutes respectively.

In case of sodium bicarbonate same effect on the rate of dissolution of gliclazide was shown. After an interval of 15 minutes 40% of the drug was present in the solution and after 135 minutes the entire drug was available. The T_{50} and T_{90} values of gliclazide in presence of sodium bicarbonate were found to be 44 and 90 minutes respectively.

Aluminum hydroxide and aluminum trisilicate exhibited a significant retardation effect on the dissolution of gliclazide. After an interval of 30 minutes only 32 and 27% and after 60 minutes 38

and 32% of the drug was dissolved so that T_{50} and T_{90} values for gliclazide in presence of aluminum hydroxide and aluminum trisilicate were 121, 269 minutes and 132, 262 respectively.

In case of calcium carbonate similar trend was observed, dissolution and availability of gliclazide slowed down; only 34% in first 15 minutes and at the end of the experiment 62% of the drug was available. T_{50} and T_{90} values were 104 and 260 minutes respectively.

There was a delay in the availability of gliclazide with magaldrate; only 11% of drug was available after 15 minutes. This may crop up due to large molecule, which was not completely soluble in the medium. T_{50} and T_{90} values were 329 and 593 minutes respectively.

Simeco™ tablet, a combination of aluminum hydroxide, magnesium carbonate, magnesium hydroxide and dimethylpolysiloxane had the greatest retardation effect on the dissolution behavior of gliclazide. Only 12% of the drug was dissolved after 15 minutes, so that T_{50} and T_{90} for gliclazide in presence of Simeco™ tablets were 228 and 411 minutes.

Temperature as well as medium effects are shown in the tables 1-4 and in Figs. 1-4. There was a slight increase in the values, which may be either due to increase in temperature or effect of dissolution medium.

Although it had previously been suggested that antacids decrease the dissolution of other antibiotics by raising the pH of the medium (Sultana *et al.,* 1983 and Sultana *et al.,* 1984) and the dissolution rate is markedly reduced at high pH values [Barr *et al.,* 1972], while there was no significant increase in pH by the addition of these antacids in the dissolution medium. On the contrary, we used two dissolution mediums, simulating stomach and blood pH. In both of these mediums the T_{50} and T_{90} values were increased which showed delay in availability of drug. Chelate formation may be involved as has been observed in case of tetracyclines or in case of dicoumarol (Neuvonen and Kivisto, 1994), where magnesium hydroxide increased the absorption of later drug.

In our studies, the dissolution of gliclazide increased in case of magnesium oxide, magnesium trisilicate and sodium bicarbonate as well as retarded by small amounts of antacids as aluminum hydroxide, aluminum trisilicate, calcium carbonate, magaldrate and simethicone, these containing polyvalent cations. Furthermore, there was a linear behavior of these drugs with respect to temperature and dissolution medium.

Eliot and Armstrong concluded that all capsular medications were functionally inactive when given under conditions in which the contents of the stomach were neutral or alkaline. They proposed an inhibitory effect of increased pH on the dissolution of capsule itself. According to Juhl and Blaug pH is probably not a major factor for the dissolution of capsule medications. They found that at body temperature, varying pH did not affect the average release time of the capsule, however at room temperature pH did affect the release times.

In conclusion, simultaneous administration of antacids with gliclazide may increase (as in case of magnesium oxide, magnesium trisilicate and sodium bicarbonate) or decrease the rate and extent of absorption of these sulphonylureas.

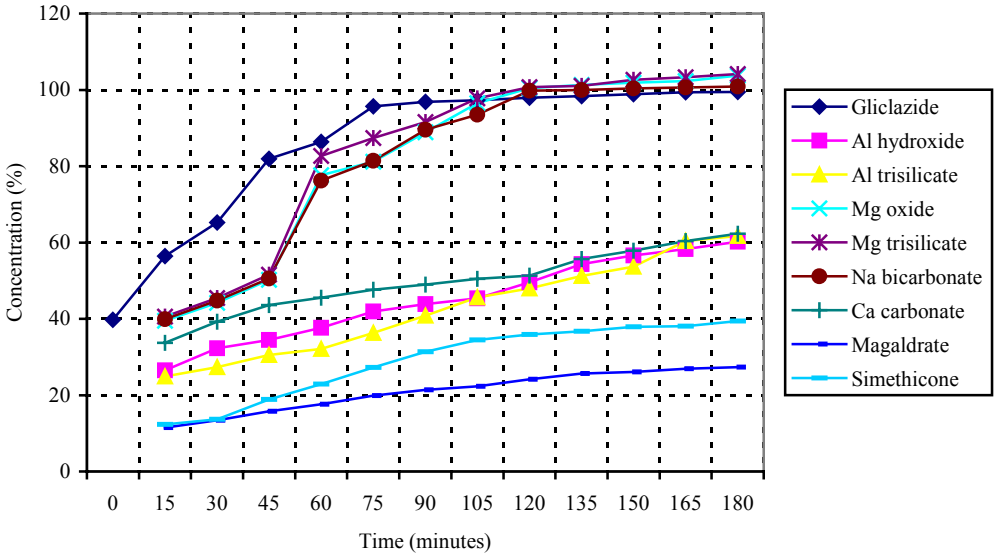

Fig. 1: Concentration of gliclazide (%) in presence of antacids at different time intervals in simulated gastric juice at 37 ^{0}C.

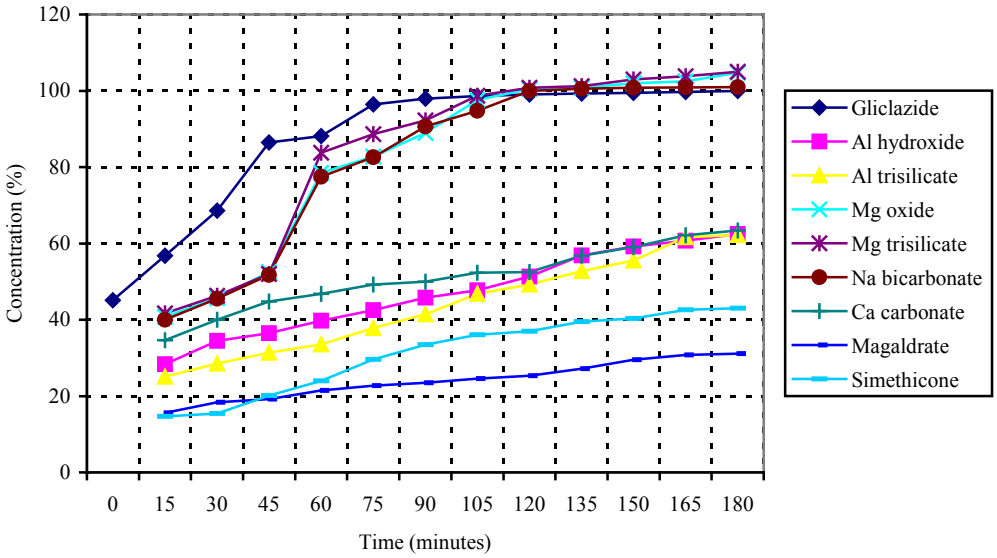

Fig. 2: Concentration of gliclazide (%) in presence of antacids at different time intervals in simulated gastric juice at 48 ^{0}C.

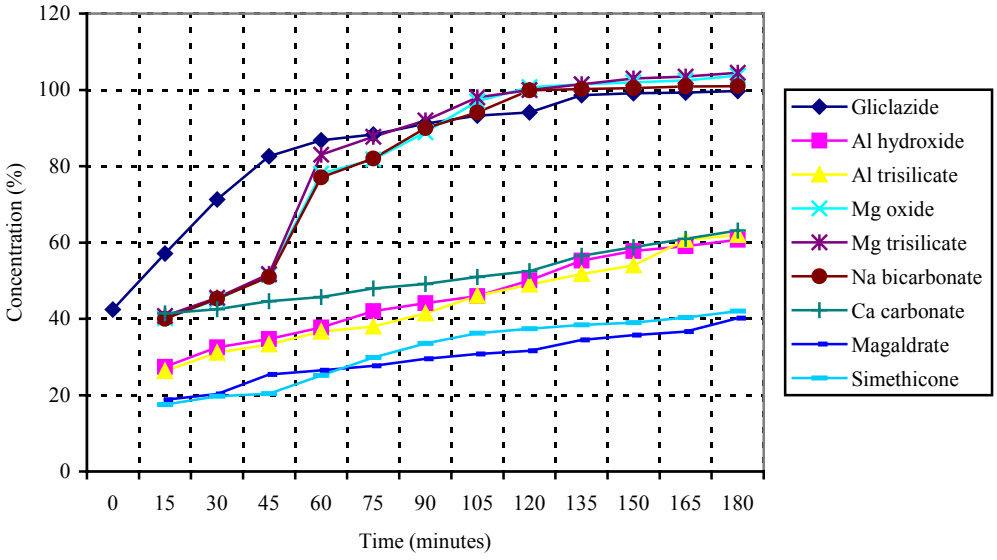

Fig. 3: Concentration of gliclazide (%) in presence of antacids at different time intervals in buffer of pH 7.4 at 37 ^{0}C.

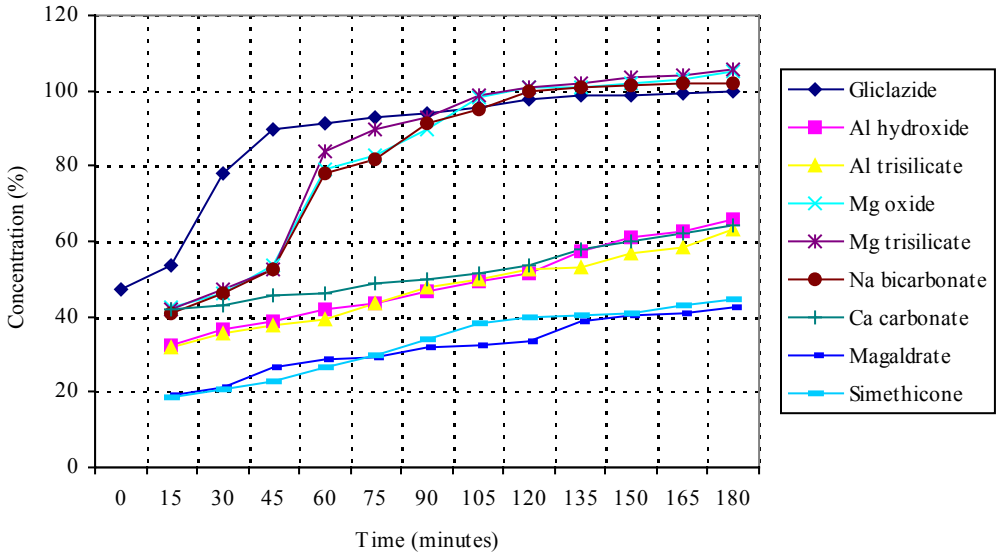

Fig. 4: Concentration of gliclazide (%) in presence of antacids at different time intervals in buffer of pH 7.4 at 48 ^{0}C

Table 1
Concentration of gliclazide (%) in presence of antacids at different time intervals in simulated gastric juice at 37 ^{0}C

Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
Gliclazide	39.74	56.43	65.22	81.91	86.35	95.65	96.87	97.30	97.91	98.35	98.87	99.39	99.48
Gliclazide + aluminum hydroxide	-	26.50	32.32	34.47	37.64	41.97	43.82	45.33	49.60	54.37	56.63	58.32	60.20
Gliclazide + aluminum trisilicate	-	24.88	27.36	30.50	32.14	36.34	40.87	45.66	48.00	51.22	53.65	60.34	61.72
Gliclazide + magnesium oxide	-	39.50	44.18	50.20	77.64	81.20	88.87	96.51	100.46	101.32	101.86	102.31	103.77
Gliclazide + magnesium trisilicate	-	40.60	45.44	51.60	82.66	87.37	91.59	97.76	100.70	101.07	102.68	103.34	104.11
Gliclazide + sodium bicarbonate	-	39.88	44.76	50.54	76.21	81.44	89.53	93.50	99.80	100.00	100.40	100.67	100.87
Gliclazide + calcium carbonate	-	33.73	39.21	43.64	45.50	47.60	48.97	50.47	51.32	55.70	57.84	60.40	62.31
Gliclazide + magaldrate	-	11.50	13.41	15.77	17.61	19.84	21.40	22.33	24.18	25.62	26.04	26.88	27.34
Gliclazide + simethicone	-	12.35	13.64	18.87	22.92	27.24	31.40	34.50	35.87	36.74	37.93	38.11	39.45

Table 2
Concentration of gliclazide (%) in presence of antacids at different time intervals in simulated gastric juice at 48 ^{0}C

Sample	**0**	**15**	**30**	**45**	**60**	**75**	**90**	**105**	**120**	**135**	**150**	**165**	**180**
Gliclazide	45.13	56.78	68.61	86.43	88.17	96.43	97.91	98.61	99.04	99.30	99.48	99.74	100.00
Gliclazide + aluminum hydroxide	-	28.32	34.45	36.50	39.75	42.50	45.75	47.68	51.30	56.89	59.22	60.71	62.50
Gliclazide + aluminum trisilicate	-	25.10	28.50	31.33	33.52	37.78	41.40	46.80	49.20	52.75	55.50	61.65	62.26
Gliclazide + magnesium oxide	-	40.75	45.63	52.47	78.50	82.80	89.00	97.60	100.50	100.80	101.97	102.50	104.77
Gliclazide + magnesium trisilicate	-	41.70	46.30	52.00	83.75	88.67	92.21	98.69	100.80	101.20	103.00	103.78	105.00
Gliclazide + sodium bicarbonate	-	40.00	45.50	51.74	77.50	82.64	90.65	94.75	99.97	100.54	100.76	100.89	101.00
Gliclazide + calcium carbonate	-	34.67	40.00	44.75	46.80	49.20	50.00	52.31	52.50	56.75	59.00	62.11	63.40
Gliclazide + Magaldrate	-	15.60	18.33	19.22	21.50	22.75	23.50	24.61	25.33	27.14	29.50	30.75	31.09
Gliclazide + Simethicone	-	14.70	15.42	20.10	24.00	29.60	33.50	36.10	37.00	39.50	40.37	42.63	43.00

Table 3
Concentration of gliclazide (%) in presence of antacids at different time intervals in buffer of pH 7.4 at 37 ^{0}C

Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
Gliclazide	42.40	57.10	71.30	82.61	86.81	88.31	91.12	93.21	94.11	98.61	99.11	99.31	99.71
Gliclazide + aluminum hydroxide	-	27.45	32.50	34.75	37.75	42.00	44.10	45.95	50.10	55.25	57.75	59.00	60.70
Gliclazide + aluminum trisilicate	-	26.30	31.10	33.32	36.61	38.00	41.41	46.00	49.00	51.75	54.00	60.75	62.00
Gliclazide + magnesium oxide	-	40.15	45.00	51.50	78.04	81.75	88.90	97.00	100.75	101.50	102.00	102.50	103.75
Gliclazide + magnesium trisilicate	-	40.75	45.50	51.75	83.00	87.75	92.00	98.00	100.00	101.50	103.00	103.50	104.50
Gliclazide + sodium bicarbonate	-	40.00	45.25	51.00	77.10	82.00	90.00	94.10	99.90	100.25	100.50	100.88	101.00
Gliclazide + calcium carbonate	-	41.40	42.50	44.65	45.74	48.00	49.10	51.00	52.50	56.50	58.75	61.00	63.15
Gliclazide + magaldrate	-	18.75	20.32	25.45	26.50	27.65	29.50	30.79	31.63	34.50	35.75	36.67	40.14
Gliclazide + simethicone	-	17.50	19.70	20.35	25.16	29.83	33.56	36.19	37.40	38.40	39.00	40.36	42.00

Table 4
Concentration of gliclazide (%) in presence of antacids at different time intervals in buffer of pH 7.4 at 48 ^{0}C

Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
Gliclazide	47.40	53.60	77.81	89.61	91.11	92.71	94.11	95.31	97.71	98.71	98.91	99.51	99.91
Gliclazide + aluminum hydroxide	-	32.50	36.74	38.66	41.75	43.50	46.89	49.40	51.63	57.50	61.25	62.50	66.00
Gliclazide + aluminum trisilicate	-	31.80	35.75	37.50	39.43	43.50	47.87	50.15	52.33	53.10	56.90	58.17	63.40
Gliclazide + magnesium oxide	-	42.35	46.00	53.50	79.10	83.00	89.50	98.00	100.75	101.00	102.00	103.00	105.00
Gliclazide + magnesium trisilicate	-	42.00	47.10	52.35	84.00	89.50	93.00	99.00	101.00	102.00	103.75	104.00	105.75
Gliclazide + sodium bicarbonate	-	41.00	46.00	52.50	78.00	82.00	91.10	95.00	100.00	100.75	101.50	101.75	102.00
Gliclazide + calcium carbonate	-	42.00	43.00	45.75	46.00	49.10	50.00	51.25	53.50	57.75	60.00	62.25	64.00
Gliclazide + magaldrate	-	19.00	21.50	26.30	28.50	29.00	31.75	32.50	33.50	38.65	40.25	41.00	42.25
Gliclazide + simethicone	-	18.75	20.64	23.00	26.75	30.00	34.10	38.00	39.75	40.50	41.00	43.10	44.50

Table 5
Dissolution of gliclazide ($T_{50\%}$ and $T_{90\%}$) in presence of antacids

Antacids	In simulated gastric juice				In buffer of pH 7.4			
	37°C		48°C		37°C		48°C	
	T_{50}	T_{90}	T_{50}	T_{90}	T_{50}	T_{90}	T_{50}	T_{90}
Reference standard	13.29	62.54	13.21	61.24	13.13	88.89	13.99	45.19
Aluminium hydroxide	120.96	269.10	116.95	259.20	119.76	266.89	106.27	245.45
Aluminium trisilicate	131.78	262.47	121.95	260.20	130.43	261.29	104.68	255.52
Magnesium oxide	44.82	91.14	42.88	91.01	43.69	91.11	42.05	90.50
Magnesium trisilicate	43.60	88.44	43.27	87.48	43.48	88.04	42.98	75.42
Sodium bicarbonate	44.52	90.47	43.49	89.35	44.12	90.00	42.86	88.91
Calcium carbonate	104.02	260.00	90.00	255.52	102.91	256.53	90.00	253.12
Magaldrate	329.19	592.54	289.48	521.07	224.21	403.59	213.02	383.43
Simethicone	228.14	410.65	209.30	376.74	214.29	385.71	202.25	364.04

REFERENCES

Abramson, E.A. and Arky, R.A. (1968). Role of beta-adrenergic receptors in counter regulation to insulin-induced hypoglycemia, *Diabetes.* **17**: 141-146.

Albert, A. and Rees, C.W. (1956). Avidity of the tetracyclines for the cations of metals. *Nature*. **177**: 433-434.

Agarwal, S.P. and Nwaiwu, J. (1986). Detection of diurectic and oral hypoglycemic drugs on thin-layer plates using pi-acceptors as spray reagent. *J. Chromatogr.* **351**(2): 383-387.

Anon (1992). Safety of fluconazole in women taking oral hypoglycaemic agents. *Lancet.* **339**: 255-256.

Arayne, M.S. and Sultana, N. (1993). Erythromycin antacid interaction. *Die Pharmazie*. **48**(H8): 599-602.

Archambeaud-Mouveroux, F., Nouaille, Y., Nadalon, S., Treves R. and Merle, L. (1987). Interaction between gliclazide and cimetidine. *European Journal of Clinical Pharmacology*. **31**: 631.

Bogusz, M. and Moutian, Wu. (1991). Standardized HPLC/DAD system, based on retention indexes and spectral library, applicable for systematic toxicological screening. *J. Anal. Toxicol*. **15**(4): 188-197.

Bustamante, R.C., Ospina, de N.L.S. and Ponce, de L.L.F. (1990). High Performance Liquid Chromatography determination of Gliclazide in human plasma. *Rev Colomb*. **18**: 17-21.

Bressler, R., Marler, E. and Styron, C.W. (1965). Oral agents in cases of diabetes mellitus previously controlled by low doses of insulin. *N.C. Med. J*. **26**: 6-8.

British Pharmacopoeia (1998). The Stationery Office, United Kingdom, pp.637-638.

Campbell, N.R.C. (1992). Norfloxacin interaction with antacids and minerals. *Br. J. Clin. Pharmacol*. **33**: 115.

Colin, D. (1999). Therapeutic Drugs. 2nd Edition, United Kingdom, Churchill Livingstone G53-G56 & G64-G69.

Charles, B.G. and Ravenscroft, P.J. (1984). Measurement of gliclazide in plasma by radial compression, reversed phase liquid chromatography. *Clinical Chemistry*. **30**: 1789-1791.

Chin, B., Fenderson, R.W. and Samuel, P., Kostis, J.B. and De Felice, E.A. (1984). Beta-blockers in the treatment of cardiovascular disease. New York, Raven Press, pp.211-228.

Cooper, A.J. and Ashcroft, G. (1967). Modification of insulin and sulfonylurea hypoglycemia by monoamine-oxidase inhibitor drugs. *Diabetes.* **16**: 272-274.

Cooper, A.J. and Ashcroft, G. (1966). Potentiation of insulin hypoglycaemia by M.A.O.I. antidepressant drugs. *Lancet*. **1**: 407-409.

El Kousy, N. (1991). Colorimetric determination of the antidiabetic drug Gliclazide. *J. Drug Res*. **20**(1-2): 157-162.

El Kousy, N. and Ashoor, F. (1990). Colorimetric determination of two antidiabetic drugs using cobalt chloride. *J. Drug Res.* **19**(1-2): 35-43.

Flor, D. (1990). Effects of magnesium-aluminum hydroxide and calcium carbonate antacids on bioavailability of ofloxacin. *Antimicrob Agents Chemother*. **34**: 2436.

Frank, H., Heinisch, G. and Neumayer, E. (1986). Identity control of formulated drugs by Thin-layer chromatography Part 1: some selected tablets. *Sci. Pharm*. **54**(4): 305-311.

Fu, Z.Z., Chen, Y.T., Chen, Y.J. and Sang, J.Q. (1992). Thromboxane / prostacycline balance in type II diabetes: gliclazide effects. *Metabolism.* **41**(5, Suppl. 1): 33-35.

Gaolin, L., Shen, G., Shixiang, W., Weirong, T., Yujun, Z., Sulan, M. and Xuebin, T. (1994). HPLC determination of Gliclazide in human plasma. *Yaowu Fenxi Zazhi*. **14**(1): 13-16.

Giugliano, D., Torella, R. and Cacciapuoti, F. (1980). Impairment of insulin secretion in man by nifedipine. *Eur. J. Clin. Pharmacol.* **18**: 395-398.

Grasela, T.H., Schentag, J.J., Sedman, A.J., Wilton, J.H., Thomas, D.J., Schultz, R.W., Lebsack, M.E. and Kinkel, A.W. (1989). Inhibition of enoxacin absorption by antacids or ranitidine. *Antimicrob Agents Chemother.* **33**(5): 615-617.

Greenblatt, D.J., Shader, R.I., Harmatz, J.S., Franke, K. and Koch, W.J. (1976). Influence of magnesium and aluminum hydroxide mixture on chlordiazepoxide absorption. *Clin. Pharmacol. Ther*. **19**(2): 234-239.

Heptner, W., Badian, M., Baudner, S., Hellstern, C.I.R., Rupp, W., Weimer, K. and Wissmann, H. (1984). A radioimmunassay for determination of Glibenclamide and other sulfonylureas. *Pharm. Res*. **5**: 215-220.

Heyman, S.N., Heyman, A. and Halperin, I. (1989). Diabetogenic effect of nifedipine. *D.I.C.P.* **23**: 236-237.

Holmes, B., Heel, R.C. and Brogden, R.N. (1984). Gliclazide. *Drugs.* **27**: 301-327.

Huichen, L., Yuqin, H., Xinfang, L., Guangwen, Z. and Yanqin, X. (1995). Bioavailability of domestic Gliclazide tablets. *Zhongguo Yiyao Gongye Zazhi.* **26**(2): 63-65.

Hussein, S.A., Mohamed, A.M.I., Abdel, A. and Abdel, A.M. (1989). Utility of certain pi-acceptors and tolazide. *Analyst* (London). **114**(9): 1129-1131.

Igaki, A., Kobayashi, K., Kimura, M., Sakoguchi, T.H.M., Matsuoka, A. and Rinsho Byori (1986). *High Performance Liquid Chromatographic determination.* **34**(2): 201-205.

Igaki, A., Kobayashi, K., Kimura, M., Sakoguchi, T. and Matsuoka, A. (1989). Determination of serum sulfonylureas by High Performance Liquid Chromatography with flourimetric detection. *J. Chromatogr*. **493**(1): 222-229.

Iwamoto, Y., Kosaka, K. and Kuzuya, T. (1996). Effect of combination therapy of troglitazone and sulphonylureas in patients with type 2 diabetes who were poorly controlled by sulphonylurea therapy alone. *Diabet. Med.* **13**: 365-370.

Jennings, A.M., Wilson, R.M. and Ward, J.D. (1989). Symptomatic hypoglycaemia in NIDDM patients treated with oral hypoglycaemic agents. *Diabetes Care.* **12**: 203-208.

Kimura, M., Kobayashi, K., Hata, M., Takashima, S., Takahiro, I., Matsuoka, A., Kitamura, H. and Kimura, Y. (1980). Determination of Gliclazide in human plasma by High Performance Liquid Chromatography and Gas Chromatography. *Hyogo Ike Daigakun igakkai Zashi.* **5**(1): 49-55.

Kimura, M., Kobayashi, K., Hata, M., Matsuoka, A., Masako, Kaneko, S., Kitamura, H. and Kimura, Y. (1980). Reversed-phase High Performance Liquid Chromatographic determination of Gliclazide in human plasma. *Chem Pharm*. **28**(1): 344-346.

Koda Kimble, M.A. (1992). Diabetes mellitus. *In*: Koda-Kimble, M.A. and Young, L.Y. (eds). Applied Therapeutics - The Clinical Use of Drugs, 5th ed. Applied Therapeutics, Vancouver, WA, p.23-87.

Kunka, R.L. (1988). Effect of antacid on the pharmacokinetics of lomefloxacin. *Pharm. Res*. **10**(Suppl): S165.

Lebsack, M. (1988). Impact of gastric pH on ranitidine enoxacin drug-drug interaction. *J. Clin. Pharmacol*. **28**: 939.

MacKintosh, T.F. (1967). Propranolol and hypoglycaemia. *Lancet.* **1**: 104-105.

MacWalter, R.S. (1985). Potentiation by ranitidine of the hypoglycaemic response to glipizide in diabetic patients. *Br. J. Clin. Pharmacol*. **19**: 121P-122P.

Maeda, T., Yamaguchi, T. and Hashimoto, M. (1981). Gas Chromatographic determination of the hypoglycemic agent Gliclazide in plasma. *J. Chromatogr*. **223**(2): 357-363.

Martindale The Complete Drug Reference (1999). Pharmaceutical Press, London 32nd ed., p.320.

Miller, L.C. (1990). Effect of concurrent sucralfate administration on the absorption of erythromycin, *J. Clin. Pharmacol*. **30**: 39.

Mills, G.A. and Horn, J.R. (1985). Beta-blockers and glucose control. *Drug Intell. Clin. Pharm*. **19:** 246-251.

Mork, N.L. and Robertson, R.P. (1983). Effects of nonsteroidal anti-inflammatory drugs in conventional dosage on glucose homeostasis in patients with diabetes. *West J. Med*. **139**: 46-49.

Neuvonen, P.J. and Kivisto, K.T. (1994). Enhancement of drug absorption by antacids. An unrecognized drug interaction. *Clin. Pharmacokinet.* **27**(2): 120-128.

Nikolic, K., Pavlov, S. and Bogavac, M. (1992). Aresenijevic and Lucija, Coulometric determination of some oral antidiabetics. *Arh. Farm*. **42**(2-3): 53-56.

Nix, D.E., Wilton, J.H., Ronald, B., Distlerath, L., Williams, V.C. and Norman, A. (1990). Inhibition of norfloxacin absorption by antacids. *Antimicrob Agents Chemother*. **34**(3): 432-435.

Noguchi, H., Tomita, N., Naruto, S. and Nakano, S. (1992). Determination of Gliclazide in serum by High Performance Liquid Chromatography used solid-phase extraction. *J. Chromatogr., Biomed.Appl*. **583**(2): 266 -269.

Noyes, M. and Polk, R.E. (1988). Norfloxacin and absorption of magnesium aluminum. *Intern. Med.* **109**(2): 168-169.

O'Byrne, S. and Feely, J. (1990). Effects of drugs on glucose tolerance in non-insulin-dependent diabetes (Part I). *Drugs*. **40**: 6-18.

Parvez, M., Arayne, M.S., Zaman, M.K. and Sultana, N. (1999). Acta Crystallographica-Section C- Crystal Structure Communication. **55** (pt 1): 74-75.

Paice, B.J., Paterson, K.R. and Lawson, D.H. (1985). Undesired effects of the sulphonylurea drugs. *Adverse Drug Reactions and Acute Poisoning Reviews.* **1**: 23-36.

Poirier, J.M, Perez, M. and Cheymol, G. (1987). High Performance Liquid Chromatographic determination of Gliclazide in human plasma. *J. Chromatogar*. **421**(1): 223-226.

Rang, H.P. and Dale, M.M. (1993). Pharmacology. 2nd ed., Churchill Livingstone, ELBS, p.451.

Shah, S.J., Bhadnardar, S.D. and Satoskar, R.S. (1984). Drug interaction between chlorpropamide and nonsteroidal anti-inflammatory drugs, ibuprofen and phenylbutazone. *Int. J. Clin. Pharmacol. Ther. Toxicol*. **22**: 470-472.

Shenfield, G.M., Boutagy, J.S. and Webb, C. (1990). A screening test for detecting sulfonylureas in plasma, *Three Drug Monit.* **12**(4): 393-397.

Shorr, R.I., Ray, W.A. and Daugherty, J.R. (1997). Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA*. **278**: 40-43.

Sidhu, A.S., Kennedy, J.M. and Deeble, S. (1987). General method for the analysis of pharmaceutical dosage form by High Performance Liquid Chromatography. *J. Chromatogr*. **391**(1): 233-242.

Sultana, N., Ghazali, F. A. and Arayne, M.S. (1983). Effect of Antacids on the Dissolution Behaviour of Tetracycline and Oxytetracycline. *J. Pharm. Univ. Kar.* **1**: 139-146.

Sultana, N., Arayne, M.S. and Ghazali, F.A. (1984). Effect of antacids on the dissolution behavior of methacycline and doxycycline. *J.P.M.A*. **34**(3): 59-63.

Suzuki, H., Miki, M., Sekine, Y., Kagemoto, A., Negoro, T., Maeda, T. and Hashimoto, M. (1981). Determination of new hypoglycaemic drug Gliclazide in human serum by radio immunoassay. *J. Pharmacobio-Dyn*. **4**(3): 217-225.

Tamoto, S., Ogawa, K. and Matsui, N. (1988). Gliclazide determination by High Performance Liquid Chromatography. *Kankyo Igaku Kenkyusho Nenpo*. **39**: 221-222.

Uusitupa, M., Aro, A. and Pietikainen, M. (1980). Severe hypoglycemia caused by physical strain and pindolol therapy; A case study. *Ann. Clin. Res.* **12**(1): 25-27.

Waahlin-Boll, E. and Melander, A. (1979). High Performance Liquid Chromatographic determination of Gliclazide and some other sulfonylurea drugs in serum. *J. Chromatogr*. **164**(4): 541-546.

Waisbren, B.A., Huckel, J.S. (1950). Reduced absorption of aureomycin caused by aluminum hydroxide gel. *Proceedings of Society for Experimental Biology and Medicine.* **73**: 73-74.

Wickstrom, L. and Pettersson, K. (1964). Treatment of diabetics with monoamine oxidase inhibitors. *Lancet.* **2:** 995.

Whiting, B., Williams, R.L. and Lorenzi, M. (1981). Effect of naproxen on glucose metabolism and tolbutamide kinetics and dynamics in maturity onset diabetes. *Br. J. Clin. Pharmacol*. **11**: 295-302.

Yuqin, H., Huichene, L., Xinfang, L. and Guangwen, Z. (1995). Analysis of Gliclazide in human serum by HPLC. *Sepu*. **13**(3): 227-228.