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IN VITRO AVAILABILITY OF GLIBENCLAMIDE IN PRESENCE OF ANTACIDS

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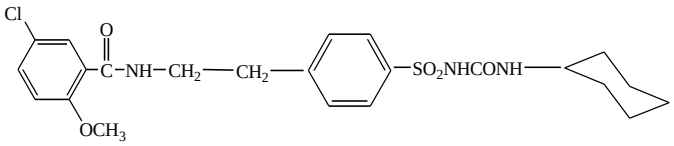
ABSTRACT

The *in vitro* availability studies of glibenclamide in presence of commonly used antacids are present in this paper. Glibenclamide is used for the treatment of Non-Insulin dependent diabetes mellitus. It is a sulfonylurea derivative. Antacids are prescribed to encounter gastric acidity etc. These studies were carried out in simulated gastric juice and in buffer of pH 7.4 at 37 and 48°C. Aluminum hydroxide, aluminum trisilicate, magnesium oxide, magnesium trisilicate, sodium bicarbonate, calcium carbonate, magaldrate and simethicone (2,4-dimethoxypolysiloxane) antacids were used in these studies. It has been observed that in case of magnesium oxide, magnesium trisilicate and sodium bicarbonate, availability of glibenclamide was enhanced while in rest of the antacids retarded the availability of glibenclamide.

INTRODUCTION

Glibenclamide is 1-[4-[2-(chloro-2-methoxybenzamido)ethyl]-benzenesulphonyl]-3-cyclo-hexylurea, 5-chloro-N-[2-[4[[[(cyclohexyl(amino)carbonyl]- amino]sulphonyl]-phenyl]ethyl]-2-methoxy benzamide or 1-[[p-[-2-(5-chloro-o-anisami do)ethyl]phenyl]-sulphonyl-3-cyclo-hexylurea, a sulphonyl urea derivative (structure 1) is a second generation oral hypoglycemic agent which is more potent than those of first group (Grodsky *et al.*, 1977) and is used to assist in the control of mild to moderately severe type II. diabetes mellitus (adult, maturity-onset) that does not require insulin, but that can be adequately controlled by diet alone. It is drug of choice for initiating treatment in noninsulin-dependent diabetes when diet and weight control fails. It stimulates the secretion and enhances the utilization of insulin by appropriate tissues (Drell and Notkins, 1987).



Structure 1: Glibenclamide

Treatment with glibenclamide is usually started with a single daily dose of 2.5 mg or 5 mg in the morning but in the elderly or those with significant renal impairment, the initial dose should be 2.5 mg or even 1.25 mg daily. It should not be used in insulin-dependent diabetes mellitus and in patients with severe impairment of thyroid function (Colin, 1999). It is relatively contraindicated in the presence of severe renal insufficiency due to the risk of profound and prolonged hypoglycemia (Jackson and Bressler, 1981, Alberti *et al.*, 1992 and Asmal and Marble, 1984). It is also not recommended in patients with a creatinine clearance less than 50 milliliters/minute because as much as 50% of a dose may be eliminated unchanged in the urine.

A number of drug interactions on glibenclamide have been reported many of which are potentially hazardous (Seltzer, 1979)**.** Glibenclamide binds to plasma proteins by non-ionic forces because of its large non-polar chemical group (Brown and Crooks, 1976), consequently, bound glibenclamide is less susceptible to displacement by other drugs. Glibenclamide when given with captopril and enalapril enhance the hypoglycemic effect (Rett *et al.,* 1988 and Arauz-Pacheco *et al.,* 1990), rifampicin reduces the glibenclamide serum level and hypoglycemic activity (Self *et al.,* 1989 and Self and Morris, 1980), verapamil resulted in higher level of glibenclamide (Semple, *et al.,* 1986, Ahmad, 1995, Whitecroft *et al.,* 1990 and Andersson and Rojdmark, 1981). During interaction between antibiotics, erythromycin (Avery, 1973), chloramphenicol succinate, cefaloridine with glibenclamide, these drugs increased the hypoglycemic effects, it is also found to influence metabolism of xenobiotics (Stroev and Belkina, 1989). Bioavailability of glibenclamide is influenced by antacids, Neuvonen and Kivisto (1991) reported that glibenclamide and antacids (alumiuium hydroxide, magnesium hydroxide and sodium bicarbonate) co-administration resulted in increased hypoglycemia. Similarly, simultaneously administered magnesium hydroxide and sodium bicarbonate with glibenclamide increased the rate and extent of absorption of glibenclamide (Neuvonen and Kivisto, 1991 and Kivisto and Neuvonen, 1991). Likewise, serum glibenclamide levels were determined by radioimmunoassay method by Zuccaro *et al.* (1989), however, no clinically remarkable effect was observed in the subjects. The hypoglycemic activity of glibenclamide was remained same when given with cimetidine (Shah *et al.,* 1984 and Shah *et al.,* 1985), while in another study plasma glucose concentrations were higher when glibenclamide was administered with cimetidine or ranitidine (Kubacka *et al.,* 1987). Simultaneously administered magnesium hydroxide or sodium bicarbonate can increase the rate and extent of absorption of non-micronized glibenclamide and glipizide. To clarify the mechanism of this interaction they have studied effect of pH on the dissolution of two different formulations of glibenclamide (micronized and non-micronized) and one formulation of glipizide. They concluded that the elevated pH of the gastric contents was the most likely explanation for the interactions previously demonstrated between antacids and sulphonylureas after their concomitant ingestion (Lehto *et al.,* 1996).

In view of the reported interactions of glibenclamide with some antacids, an opportunity prevailed to observe the behavior of glibenclamide with these antacids, which were not *in vitro* studied previously.

Antacids are drugs taken by mouth and work by neutralizing excess stomach acid. Antacids differ in how quickly they work and how long they provide relief. Those that dissolve rapidly in the stomach bring the fastest relief and others slowly and can take up to 30 minutes to begin working. The longer an antacid stays in the stomach, the longer it works. Antacids 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, 1990; Noyes and Polk, 1988 and Flor, 1990) while in some cases antacids increase the bioavailability of some drugs (Miller, 1990 and Arayne and Sultana, 1993). These are not as efficacious as the H_2-receptor antagonists and proton pump inhibitors (Rang and Dale, 1993).

MATERIALS AND METHODS

Materials

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

Methods

In vitro availability studies of glibenclamide were carried out in absence and presence of these antacids at 37°C and 48°C in simulated gastric juice and in blood pH by using standard dissolution apparatus. The dissolution equipment was manufactured to the British Pharmacopoeia (1998) standard, which included the dissolution motor and variable speed controller with a stainless steel basket assembly. The top of the basket was modified and replaced by a conical head in order to eliminate air entrapment during dissolution, which is not inconsistent with the present apparatus description. In these sets of experiments 5 mg of glibenclamide that was first dissolved in 50 ml methanol and than it was poured in 950ml of 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. 5 ml aliquots were withdrawn periodically at fifteen minutes time intervals for 180 minutes and assayed for the glibenclamide content. The volume of dissolution fluid was maintained by adding an equivalent amount of dissolution fluid withdrawn, which had previously been maintained at the same temperature in the same bath. There are several methods reported for the analysis of glibenclamide; Polarographic (Silvestri, 1972); Titrimetric (British Pharmacopoeia, 1998); Colorimetric (El-Kousy and Ashoor, 1990); Coulometric (Nikolic, 1992); Fluorimetric (Rau *et al.*, 1993, Girgis *et al.*, 1982 and Becker, 1977); NMR (Al-Badr and Abdullah, 1983); TLC (Lillsunde and Korte, 1991, Thelemann, 1973, Agarwal *et al.*, 1973, Surborg and Roder, 1973 and Romano *et al.*, 1994); HPTLC (Zaman *et al.*, 1994); HPLC (Valdes and Gonzalez, 1996, Sener *et al.*, 1995, Al-Khamis *et al.*, 1994, Bogusz *et al.*, 1994, Jankowski *et al.*, 1993, Beaulieu *et al.*, 1993, Drummer *et al.*, 1993, Rydberg *et al.*, 1991, Gupta, 1989, Abdel-Hamid *et al.*, 1989, Adams *et al.*, 1989, Starkey *et al.*, 1989, Othman *et al.*, 1988, Shifu and Xiaodong, 1987, Emilsson *et al.*, 1986, Das *et al.*, 1986, Nieder *et al.*, 1986, Gerlai *et al.*, 1986, Pearson *et al.*, 1985, Zecca *et al.*, 1985, Zhiri, *et al.*, 1985, Poetter and Huehn, 1983, Rogers *et al.*, 1982, Uihlein and Sistovaris, 1982, Daldrup *et al.*, 1982, Adams, *et al.*, 1982, Besenfelder, 1981, Adams and Krueger, 1979 and Wahlin-Boll and Melander, 1979); GLC (Castoldi and Tofanetti, 1979 and Beyer, 1972); Spectrophotometric (Zorya *et al.*, 1989 and Muzhanoyskii *et al.*, 1988) and RIA methods (Glogner *et al.*, 1977, Kawashima *et al.*, 1979, Kawashima and Kuzuya, 1979, Deelers *et al.*, 1982, Royer *et al.*, 1976, Glogner *et al.*, 1973 and Lindner and Reinauer, 1980). To increase the sensitivity of the assay method, UV method was selected for the analysis of glibenclamide. The UV method is simple and accurate glibenclamide exhibits strong absorption at 299 nm respectively (British Pharmacopoeia 1998). The reported absorption of glibenclamide at 299 nm was once used only as to endure the homogeneity of the drug in formulations. These studies have been extended by the use of sensitive instrument (having variable slit width 2.0-0.1) for the assay of the drug under various experimental conditions. Graphs between drug concentration versus time were plotted which showed drug status during and at the end of the experiments.

Validation of Calibration Curve of Glibenclamide

Absorbance of 50 µg of glibenclamide solution was measured in the range of 200-350 nm, which showed a maxima at 299 nm. For the validation of calibration curve, 5 ml working standard solution 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 concentration. The straight line was obtained which obeyed Beer Lambert's law. The molar absorptivity of glibenclamide obtained in simulated gastric juice ($2{,}811 \pm 0.004$ ε $Mole^{-1}cm^{-1}$) and in buffer of pH 7.4 ($2{,}866 \pm 0.003$ ε $Mole^{-1}cm^{-1}$) were used for further calculations of the left over drug after interactions with antacids using Beer Lambert's 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 glibenclamide at different time intervals, in simulated gastric juice and in buffer of pH 7.4 at 37 and 48ºC (At both of these temperatures i.e., 37ºC simulating body temperature and 48ºC simulating accelerated temperature studies difference in the extent of drug interaction was observed) are mentioned in Tables 1-4. Graphs were plotted (Figs. 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 glibenclamide in presence of various antacids is given in Table-5.

The results of glibenclamide-antacids interaction studies in simulated gastric juice at 37ºC are given in Tables-1 and 5 and shown in Fig. 1.

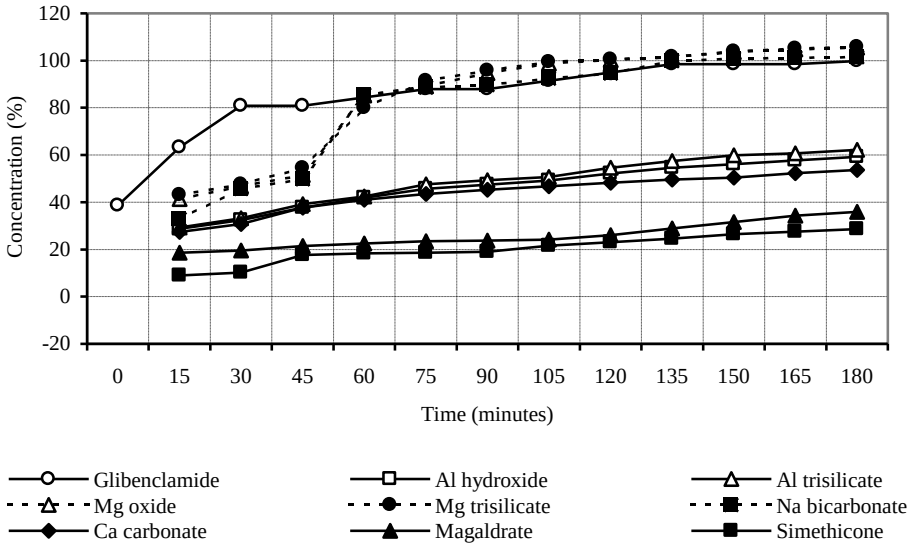


Fig. 1: Concentration of glibenclamide (%) in presence of antacids at different time intervals in simulated gastric juice at 37ºC.

Magnesium oxide and magnesium trisilicate revealed a significant effect on the rate of dissolution of glibenclamide. After an interval of 30 minutes 47-48% of the drug was present in the solution and after 120 minutes the entire drug was available. The T_{50} and T_{90} values of glibenclamide in presence of both magnesium oxide and magnesium trisilicate were found to be 44, 76 and 41, 74 minutes respectively.

The T_{50} and T_{90} values of glibenclamide in presence of sodium bicarbonate were found to be 45 and 90 minutes respectively. Sodium bicarbonate also showed same results on the rate of dissolution of glibenclamide. After an interval of 15 minutes 33% of the drug was present in the solution and after 150 minutes the entire drug was available.

Aluminum hydroxide and aluminum trisilicate also showed a significant retardation effect on the dissolution of glibenclamide. After an interval of 15 minutes only 29% and after 60 minutes 42% of the drug was dissolved so that T_{50} and T_{90} values for glibenclamide in presence of

aluminum hydroxide and aluminum trisilicate were 107, 274 minutes and 103, 261 minutes respectively.

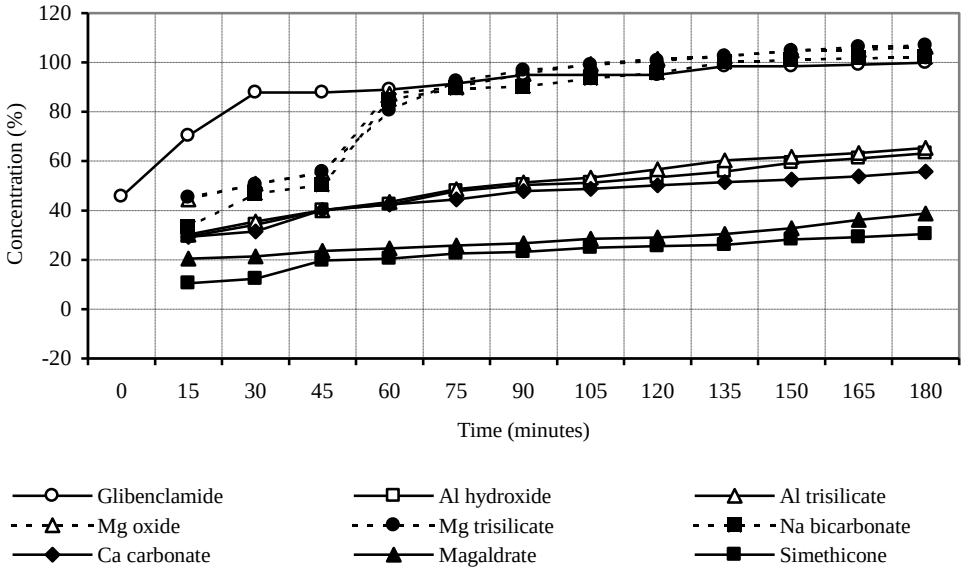


Fig. 2: Concentration of glibenclamide (%) in presence of antacids at different time intervals in simulated gastric juice at 48ºC.

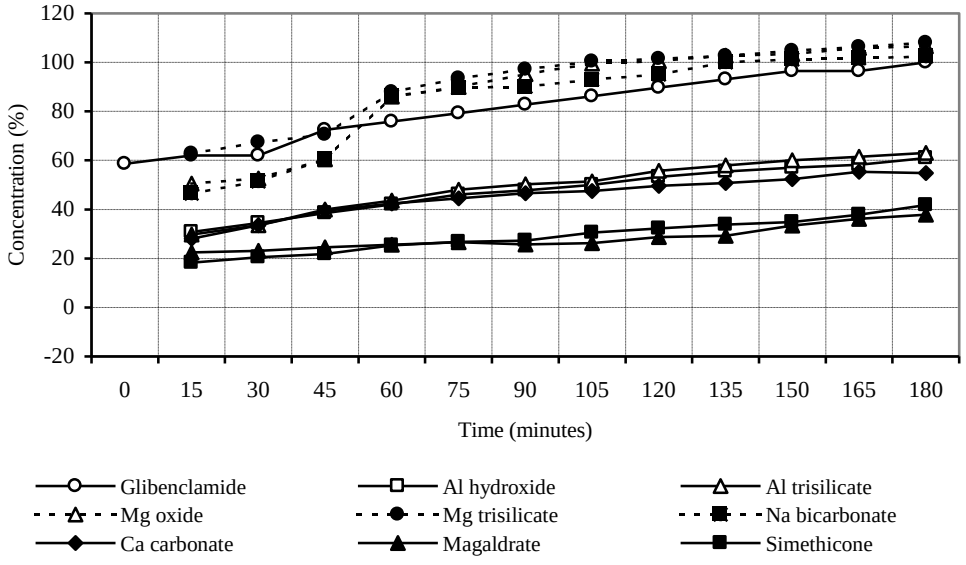


Fig. 3: Concentration of glibenclamide (%) in presence of antacids at different time intervals in buffer of pH 7.4 at 37ºC.

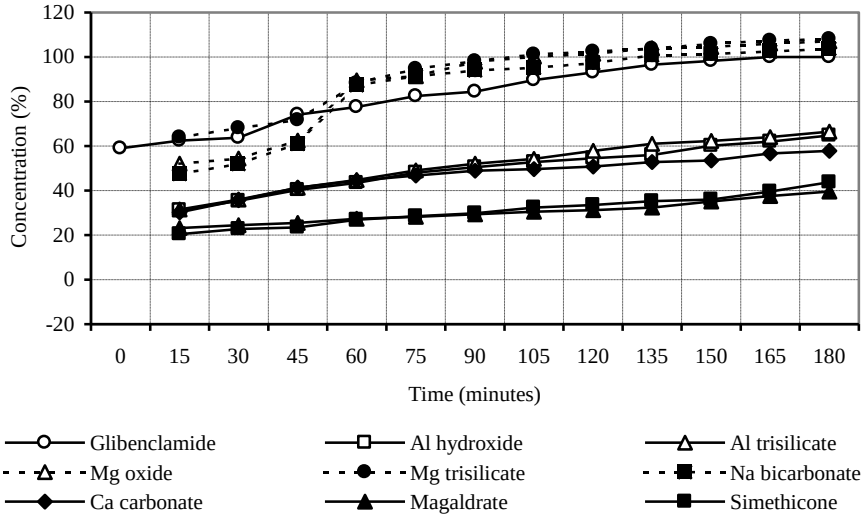


Fig. 4: Concentration of glibenclamide (%) in presence of antacids at different time intervals in buffer of pH 7.4 at 48°C.

In case of calcium carbonate a similar trend was observed. Availability of glibenclamide only 31% in first 30 minutes and at the end of the experiment was 54%. T_{50} and T_{90} values were 148 and 302 minutes.

There was a delay in the availability of glibenclamide in presence of magaldrate. Only 19% drug was available after 15 minutes, and T_{50} & T_{90} values were 251 and 452 minutes.

Simeco™ tablets also showed greatest retardation effect on the dissolution behavior of glibenclamide. Only 9% of the drug was dissolved after 15 minutes, so that T_{50} and T_{90} for glibenclamide in presence of Simeco™ tablets was 314 and 565 minutes.

Temperature as well as medium effects are shown in the Tables 2-5 and in Fig. 2-4. There was a slight increase in the values, which may be either due to increase in temperature or effect of dissolution medium.

Sultana, *et al.* (1984) had previously been suggested that antacids decrease the dissolution of other antibiotics by raising the pH of the medium, and the dissolution rate is markedly reduced at high pH values, 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.

Table-1

Concentration of glibenclamide (%) in presence of antacids at different time intervals in simulated gastric juice at 37°C

Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
Glibenclamide	38.67	63.27	80.85	80.85	84.37	87.88	87.88	91.40	94.91	98.43	98.43	98.43	99.83
Glibenclamide + aluminum hydroxide	-	28.73	32.41	37.68	41.87	45.62	47.44	49.15	52.10	54.65	56.12	57.74	59.14
Glibenclamide + aluminum trisilicate	-	29.31	33.22	39.14	42.36	47.52	49.36	50.74	54.63	57.41	59.87	60.67	62.17
Glibenclamide + magnesium oxide	-	41.30	46.73	51.44	85.21	89.14	94.65	98.77	100.21	101.41	103.67	104.70	105.55
Glibenclamide + magnesium trisilicate	-	43.10	47.62	54.47	79.87	91.44	95.71	99.46	100.50	101.52	103.93	105.07	105.72
Glibenclamide + sodium bicarbonate	-	32.76	45.64	49.68	85.46	88.53	89.62	92.33	94.48	99.76	100.84	101.17	101.43
Glibenclamide + calcium carbonate	-	27.34	30.83	37.64	41.12	43.56	45.23	46.74	48.30	49.62	50.47	52.36	53.64
Glibenclamide + magaldrate	-	18.60	19.54	21.44	22.5	23.50	23.80	24.16	26.00	28.92	31.52	34.24	35.87
Glibenclamide + simethicone	-	9.00	10.25	17.60	18.25	18.65	19.04	21.60	23.10	24.56	26.50	27.50	28.66

Table-2

Concentration of glibenclamide (%) in presence of antacids at different time intervals in simulated gastric juice at 48°C

Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
Glibenclamide	45.70	70.31	87.88	87.88	88.94	91.40	94.91	94.91	94.91	98.43	98.43	99.13	99.94
Glibenclamide + aluminum hydroxide	-	29.43	34.22	40.10	42.35	47.85	50.36	51.25	53.46	55.72	59.23	61.14	63.22
Glibenclamide + aluminum trisilicate	-	30.23	35.50	40.13	43.46	48.65	51.32	53.32	56.67	60.30	61.75	63.25	65.32
Glibenclamide + magnesium oxide	-	44.53	50.78	55.30	87.35	90.05	95.32	99.41	101.50	102.50	104.82	105.08	106.37
Glibenclamide + magnesium trisilicate	-	45.25	50.50	55.65	80.50	92.35	96.75	99.02	100.70	102.45	104.66	106.19	106.88
Glibenclamide + sodium bicarbonate	-	33.14	46.77	50.32	84.89	89.50	90.20	93.55	95.75	99.97	101.00	101.75	102.00
Glibenclamide + calcium carbonate	-	29.25	31.50	40.25	42.35	44.50	47.85	48.79	50.20	51.43	52.50	53.87	55.75
Glibenclamide + magaldrate	-	20.50	21.33	23.54	24.65	25.75	26.75	28.50	29.10	30.50	32.75	36.12	38.75
Glibenclamide + simethicone	-	10.50	12.35	19.75	20.45	22.50	23.15	24.87	25.50	26.09	28.25	29.13	30.50

Table-3

Concentration of glibenclamide (%) in presence of antacids at different time intervals in buffer of pH 7.4 at 37°C

Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
Glibenclamide	58.61	62.06	62.06	72.40	75.85	79.30	82.75	86.20	89.64	93.09	96.54	96.54	99.99
Glibenclamide + aluminum hydroxide	-	30.74	34.42	38.50	42.00	46.10	47.75	50.00	53.25	55.50	57.00	58.22	61.00
Glibenclamide + aluminum trisilicate	-	29.70	33.50	40.00	43.65	48.00	50.22	51.50	55.75	58.00	60.00	61.50	63.00
Glibenclamide + magnesium oxide	-	50.50	52.65	60.50	86.00	90.00	95.25	99.50	100.50	102.80	103.38	105.94	106.50
Glibenclamide + magnesium trisilicate	-	62.77	67.34	70.50	87.93	93.50	97.10	100.35	101.40	102.65	104.78	106.25	107.96
Glibenclamide + sodium bicarbonate	-	46.50	51.40	60.50	86.00	89.75	90.10	93.00	95.00	100.00	101.20	101.75	102.35
Glibenclamide + calcium carbonate	-	28.10	33.50	39.40	42.37	44.45	46.64	47.51	49.67	50.80	52.30	55.41	54.78
Glibenclamide + magaldrate	-	22.50	23.10	24.50	25.60	26.65	25.75	26.22	28.74	29.30	33.45	36.20	37.88
Glibenclamide + simethicone	-	18.30	20.50	21.75	25.31	26.74	27.25	30.50	32.26	33.78	34.79	37.86	41.78

Table-4

Concentration of glibenclamide (%) in presence of antacids at different time intervals in buffer of pH 7.4 at 48°C

Sample	0	15	30	45	60	75	90	105	120	135	150	165	180
Glibenclamide	58.96	62.41	63.78	74.13	77.58	82.40	84.47	89.64	93.09	96.54	98.26	99.99	99.99
Glibenclamide + aluminum hydroxide	-	31.21	35.33	40.25	43.50	48.00	50.50	52.75	54.50	56.00	60.15	62.00	64.75
Glibenclamide + aluminum trisilicate	-	31.50	36.00	41.25	44.75	49.00	52.10	54.20	57.80	61.00	62.25	64.00	66.50
Glibenclamide + magnesium oxide	-	52.15	54.33	62.45	89.50	91.40	97.80	100.14	101.40	103.90	104.40	106.00	107.00
Glibenclamide + magnesium trisilicate	-	63.85	68.10	71.65	88.25	94.65	98.20	101.10	102.50	103.78	105.85	107.34	108.00
Glibenclamide + sodium bicarbonate	-	47.45	52.00	61.00	87.34	91.40	94.00	95.10	97.25	100.75	101.25	102.50	103.75
Glibenclamide + calcium carbonate	-	30.20	35.65	41.23	44.50	46.70	48.90	49.70	50.78	52.75	53.50	56.74	57.82
Glibenclamide + magaldrate	-	23.15	24.50	25.40	27.35	28.15	29.40	30.50	31.25	32.40	35.12	37.50	39.50
Glibenclamide + simethicone	-	20.50	22.74	23.40	26.89	28.50	29.78	32.41	33.50	35.19	36.00	39.50	43.70

Table-5
Dissolution of glibenclamide ($T_{50\%}$ 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	11.85	92.17	10.67	60.71	0.00	120.48	0.00	105.42
Aluminum hydroxide	106.81	273.93	89.36	256.25	105.00	265.57	89.11	250.19
Aluminum trisilicate	103.47	260.58	87.68	248.00	89.60	257.14	86.37	243.61
Magnesium oxide	43.74	75.72	29.54	74.96	14.85	75.00	14.38	60.33
Magnesium trisilicate	41.31	73.82	29.70	73.09	11.95	72.19	11.75	61.19
Sodium bicarbonate	45.29	90.38	44.71	89.80	29.18	89.90	28.85	73.85
Calcium carbonate	148.60	302.01	119.52	290.58	132.87	295.73	118.16	280.18
Magaldrate	250.91	451.63	232.26	418.06	237.59	427.67	227.85	410.13
Simethicone	314.03	565.25	295.08	531.15	215.41	387.74	205.95	370.71

In our studies, the dissolution of glibenclamide 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 glibenclamide may increase (as in case of magnesium oxide, magnesium trisilicate and sodium bicarbonate) or decrease the rate and extent of absorption of these sulphonylureas.

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