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Comparison of pharmacokinetics and pharmacodynamics of a conventional and a new rapidly dissolving glibenclamide preparation

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Summary

Glibenclamide is an oral hypoglycemic agent used in the treatment of non-insulin dependent diabetes. It is a weak acid and is poorly soluble in water. In this investigation, the pharmacokinetics and pharmacodynamics of a new rapidly dissolving formula (Oramide) containing only 3.5 mg of the drug was compared with a conventional 5 mg preparation (Daonil). The rate and extent of in vitro dissolution of Oramide was significantly higher than Daonil. Despite the higher amount of the drug in Daonil both preparations exhibited similar plasma glibenclamide concentration-time profiles. Furthermore, the release of insulin and the reduction of plasma glucose levels were not statistically different in both experimental groups. The faster dissolution rate of Oramide formulation has, therefore, rendered it bioequivalent to Daonil which contains a higher amount of active ingredient.

Introduction

Glibenclamide is an oral hypoglycemic agent of the sulphonylurea group and is frequently prescribed for the treatment of late-onset (non-insulin dependent) diabetes mellitus (O'Sullivan and Cashman, 1970). Despite its extremely poor solubility in water, it is absorbed fairly rapidly from the gastrointestinal tract (Martindale, The Extra Pharmacopoeia, 1982). Glibenclamide is primarily metabolized in the liver by hydroxylation at positions 3 and 4 of the cyclohexyl moiety. The metabolites are subsequently excreted in urine and feces (Rupp et al., 1972; Birk et al., 1978). Its acts by stimulating the release of insulin from the β-cells in the pancreas which in turn is responsible for the reduction of glucose levels in the blood (Schmidt et al., 1969).

Although it is extensively bound to plasma proteins, glibenclamide is less susceptible to displacement from protein binding by acidic drugs than other hypoglycemic agents (Brown and Crooks, 1976). The plasma concentrations were reported to reach a maximum level in 4 h after a dose of 5 mg in normal subjects, with no accumulation occurring even after repeated doses (Bhatia et al., 1970). The biological half-life was estimated

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to be 5–7 hours. Although no accumulation of the drug was observed in the extracellular fluid, it tends to accumulate in deep body compartments which could explain the hypoglycemic episodes occurring two days after the drug withdrawal (Balant et al., 1977).

Many factors are known to influence the bioavailability of glibenclamide; these include the presence of food (Balant et al., 1977; Muller et al., 1983) and its physical form (Borchert et al., 1976). The conventional amount of the drug per tablet is 5 mg; however, a recent pharmaceutical advancement, utilizing the enhancement of its dissolution rate (Ganley et al., 1984) has led to the development of a new formulation, claimed to be bioequivalent to the old preparation, but containing less of the active ingredient.

The purpose of the present investigation was to compare the in-vitro release properties, bioavailability, and the pharmacodynamic response (insulin and glucose levels in plasma) of the new 3.5 mg glibenclamide tablet formulation (Oramide, Al-Hikma Pharmaceuticals) with a conventional 5 mg glibenclamide preparation (Daonil, Hoechst).

Materials and Methods

After obtaining the approval of the Institutional Review Board, a group of 6 non-smoking healthy male volunteers signed the informed-consent forms to participate in the study. The volunteers had no abnormalities found on routine laboratory testing or by history or physical examination. The study was carried out completely under medical supervision at the University Hospital. Data on test subjects are shown in Table 1.

TABLE 1

Data on test subjects

Subject	Sex	Age (years)	Weight (kg)	Height (cm)
A.K.A.	Male	20	61	180
K.H.S.	Male	22	68	174
M.A.N.	Male	20	65	171
M.M.H.	Male	19	63	164
A.H.F.	Male	20	70	167
Y.M.K.	Male	21	66	175
Mean ± S.E.M.		20.3 ± 0.4	65.5 ± 1.2	171.8 ± 2.2

All subjects abstained from drinking alcohol and from drug intake two weeks prior to and throughout the study period.

A single dose of either Oramide (Al-Hikma, B.N. 130/VI 85) or Daonil (Hoechst, B.N. 349 D 449) was allocated in a randomized sequence and on a cross-over basis. A one-week wash-out period was allowed between experiments.

Oramide contained 3.5 mg of glibenclamide in a specially formulated tablet prepared in cooperation with Klinge Pharma (Munich 80, F.R.G.) and contained a mixture of a hydrophilic polymer (polyethylene glycol) and an alkalinizing agent (tromethamine).

The volunteers reported to the clinical pharmacology unit in a fasting state at 07.30 h. A standard breakfast and a 150 ml cup of tea containing 3 lumps of sugar were given to each volunteer. After 15 min the assigned glibenclamide tablet was administered orally with 150 ml water. The volunteers received a standard morning snack an hour and a half after the drug administration, and 5 h later they received a standard lunch.

Blood samples were collected prior to drug ingestion and after 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 10 h. Samples were centrifuged at 6000 rpm and stored at $-20\,^{\circ}C$ for subsequent analysis.

In-vitro dissolution studies:

The USP dissolution apparatus II at 100 rpm was used. The dissolution of both glibenclamide preparations was carried out at $37 \pm 1\,^{\circ}C$ in 500 ml phosphate buffer (pH 7.5). 1-ml aliquots were removed at specific time intervals and analyzed by HPLC, using a reverse-phase ODS column (15 × 0.46 cm) and a mixture of ammonium sulphate (0.023 M) and acetonitrile (55 : 45) as mobile phase.

HPLC determination of glibenclamide in plasma:

To 1 ml of plasma, 100 µl of a solution (0.5 µg/ml) of internal standard, *N*-(4-⟨2-(5-chloro-2-methoxybenzamide)-ethyl⟩-benzensulfonyl)*N'*-cyclopentylurea, and 2 ml of 0.1 M phosphate buffer (pH 4.0) were added and the mixture was extracted with 5 ml of dichloromethane. The

organic layer was evaporated to dryness, and the residue was reconstituted in the mobile phase (ammonium sulfate and acetonitrile) (58 : 42). The resulting solution was analyzed by an HPLC procedure (Othman et al., 1986).

Determination of plasma insulin levels:

The insulin levels were determined using the Coat-A-Count solid phase ^{125}I-radioimmunoassay for the in vitro quantitative measurements of insulin in serum (Diagnostic Products Corp., CA, U.S.A.).

Determination of glucose in plasma

Glucose was measured in plasma using the Beckman Astra System for the determination of glucose.

Statistical analysis:

Results were analyzed by a two-way analysis of variance with $P < 0.05$ being taken as the minimal level of significance.

Results

In-vitro dissolution:

Dissolution data were plotted as amount of glibenclamide (mg) dissolved against time in min (Fig. 1). More than 70% of Oramide dissolved in the first 10 min, and 90% dissolved in the first half hour. Complete dissolution was observed in less than 45 min. In contrast, the rate of dissolution of Daonil was significantly lower than Oramide throughout the dissolution test. The data presented in Fig. 1 clearly show that after 60 and 90 min, the dissolution of glibenclamide in Daonil was less than 50% and 60%, respectively. Furthermore, the dissolution of the active ingredient was not complete even after dissolving at 200 rpm for a further 20 min.

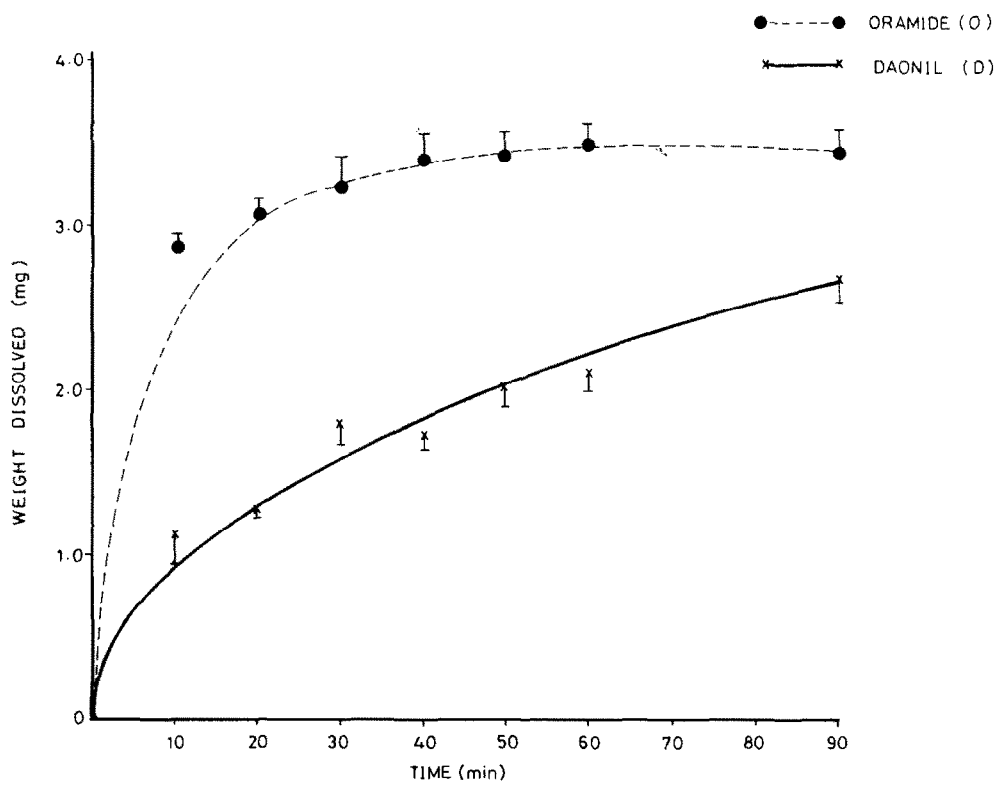

Fig. 1. In vitro dissolution of Oramide and Daonil. Values are mean ±S.E.M.

TABLE 2

Pharmacokinetic parameters of Oramide (Ora) and Daonil (Dao)

Subject	K_a		K_{el}		$t_{1/2}$ (h)		C_{max} (ng/ml)		t_{max} (h)		AUC (0–10) (ng/ml·h)		AUC (0–∞) (ng/ml·h)	
	ORA	DAO	ORA	DAO	ORA	DAO	ORA	DAO	ORA	DAO	ORA	DAO	ORA	DAO
A.K.A.	0.20	0.19	0.19	0.18	3.65	3.85	153	111	6.0	8.0	837	614	1216	1014
K.H.S.	0.33	0.30	0.30	0.29	2.31	2.39	106	118	3.0	6.0	538	795	675	923
M.A.N.	0.16	0.23	0.15	0.25	4.62	2.77	93	155	6.0	1.6	574	692	947	820
M.M.H.	0.78	0.19	0.21	0.19	3.30	3.65	118	74	2.0	6.0	731	458	874	589
A.H.F.	0.21	0.38	0.21	0.36	3.30	1.75	123	105	6.0	2.0	721	498	897	612
Y.M.K.	0.28	0.30	0.27	0.29	2.57	2.39	62	174	6.0	6.0	423	874	490	998
Mean ± S.E.M.	0.33 ± 0.09	0.26 ± 0.03	0.22 ± 0.02	0.26 ± 0.03	3.29 ± 0.33	2.81 ± 0.33	109 ± 13	123 ± 15	4.8 ± 0.8	4.9 ± 1.1	637 ± 62	665 ± 67	850 ± 101	826 ± 77

Pharmacokinetics

The pharmacokinetic parameters calculated from plasma concentrations after single oral doses of either Oramide or Daonil are summarized in Table 2. The mean plasma concentration–time profiles for both preparations are depicted in Fig. 2. All results are reported as mean ± S.E.M.

After the administration of either Oramide or Daonil C_{max} and t_{max} were similar in both groups; these were (mean ± S.E.M.) 109 ± 13 ng/ml and 123 ± 15 ng/ml at 4.5 ± 0.8 and 4.9 ± 1.1 h, respectively. Calculated AUCs (0-∞) and elimination half-lives ($t_{1/2}$) were comparable in the two experimental groups (AUC: 850 ± 101 ng/ml · h and 826 ± 77 ng/ml · h; $t_{1/2}$ 3.3 ± 0.3 h and 2.8 ± 0.3 h, respectively).

Insulin

No statistical difference was observed between plasma insulin levels after either Oramide or Daonil administration (Fig. 3). Mean fasting plasma insulin levels in both groups were (mean ± S.E.M.): 9.0 ± 1.0 U/ml. Thirty min after breakfast and prior to the administration of both drugs, these levels reached 104 ± 13 U/ml and 93 ± 8 U/ml, respectively. After the administration of Oramide, mean insulin concentrations peaked at 107 ± 17 U/ml, and 10 h later the insulin levels (37 ± 14 U/ml) were still several times higher than the fasting level. The corresponding mean insulin concentrations after the administration of Daonil were 138 ± 28 U/ml and 46 ± 12 U/ml.

Glucose

Mean fasting glucose concentrations were (mean ± S.E.M.): 103 ± 3 and 109 ± 4 mg/dl in Oramide and Daonil experiments, respectively. The corresponding mean levels half an hour after breakfast were 118 ± 6 mg/dl and 121 ± 8 mg/dl (Fig. 4). One hour after administration of both drugs, glucose levels fell to 97 ± 5 and 92 ± 9 mg/dl, respectively, and remained at around the same levels for the second hour. Another drop in glucose levels was observed in the third hour (67 ± 6 mg/dl and 66 ± 3 mg/dl). The data presented in Fig. 4 show identical glucose response curves for both Oramide and Daonil preparations.

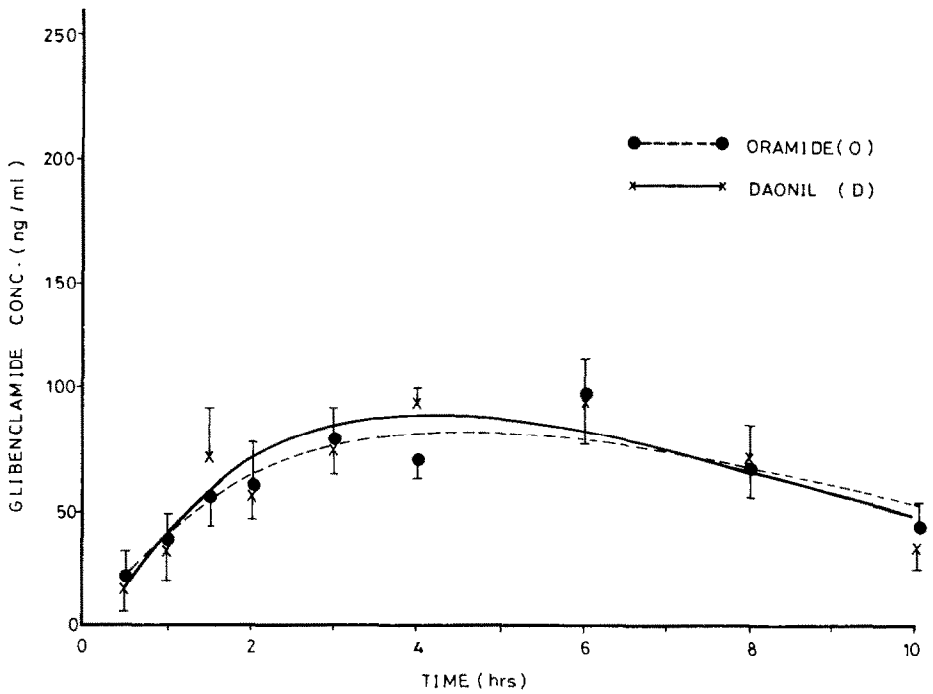

Fig. 2. Plasma glibenclamide concentration–time profile after administration of Oramide and Daonil. Values are mean ± S.E.M.

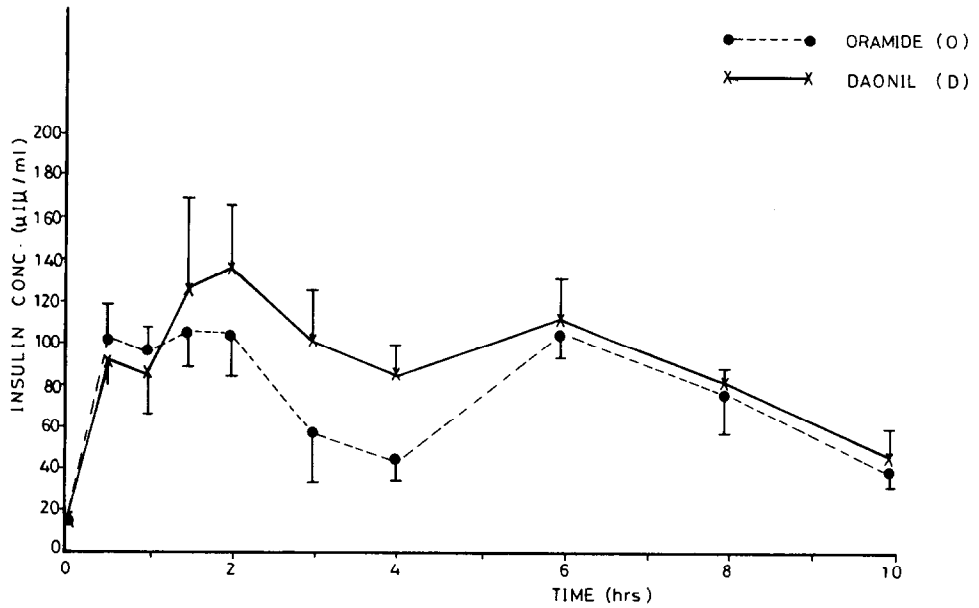

Fig. 3. Plasma insulin levels following administration of Oramide and Daonil. Values are mean ± S.E.M.

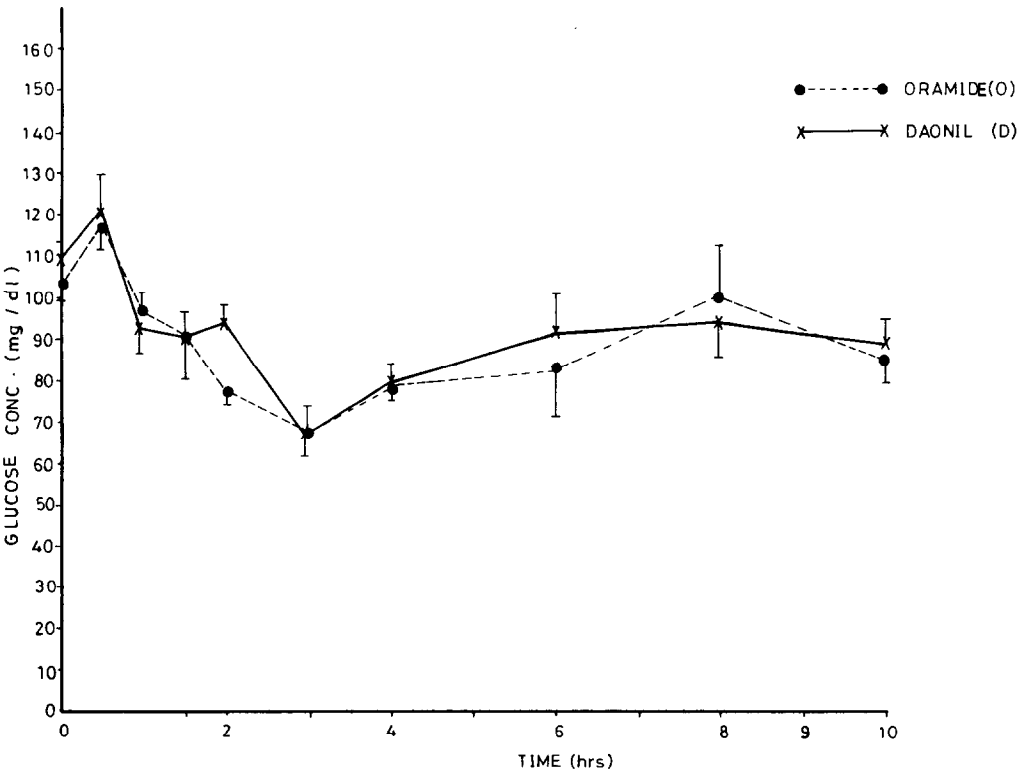

Fig. 4. Plasma glucose levels following administration of Oramide and Daonil. Values are mean ± S.E.M.

Discussion

Marked variations in the extent of absorption of many drugs following administration of generic equivalents are frequently observed. Differences in the extent and rate of in vitro dissolution of poorly water-soluble drugs may be considered one of the main factors responsible for such variations in vivo (Samyn, 1970). Also these differences have been correlated with the rate and extent of drug absorption from the gastrointestinal tract (Levi et al., 1966).

Glibenclamide, being a weak acid and a poorly water-soluble drug, is better absorbed from acidic media. However, at these pH levels the solubility of glibenclamide is minimal. It is available worldwide as a 5-mg tablet (Daonil). Since 1982, tablets containing 3.5 mg of glibenclamide and bioequivalent to the 5-mg tablet went on the market in the F.R.G. However, the 5-mg tablet still continued to be marketed elsewhere. The object of this report was to investigate the relative bioavailability of a new 3.5 mg tablet vs. Daonil (5-mg tablet).

It is well known from the literature that the dissolution rate can be increased by several processes, such as micronization which leads to an increase in the surface area of poorly water-soluble drugs (Higuchi, 1967), the incorporation of alkalinizing buffers which in turns raise the microenvironmental pH in the stomach (Javaid and Cadwallader, 1972), the addition of surface-active agents (Finholt and Solvang, 1968), the use of metastable polymorphic forms of the drug (Aguiar et al., 1967) or the dispersion of the drug in a water-soluble carrier (Chiou and Riegelman, 1969).

The dissolution rate of glibenclamide in the 3.5-mg tablet formulation (Oramide) was increased utilizing two main concepts: firstly, the addition of tromethamine, an alkalinizer, and secondly, incorporating glibenclamide in PEG, a water-soluble carrier. Such concepts are apparently absent in the Daonil 5-mg tablet formulation.

In vitro dissolution studies have demonstrated that the rate and extent of dissolution of the Oramide tablet containing only 3.5 mg glibenclamide was significantly higher than the Daonil 5-mg tablet. The lower degree of solubility of Daonil was responsible for the apparent incomplete absorption from the gastrointestinal tract in the in-vitro situation compared with 3.5 mg Oramide tablet. The AUCs were identical for both preparations in spite of the 30% less active ingredient present in the Oramide tablet. Furthermore, the incomplete absorption of glibenclamide from the Daonil 5 mg has been reported. In a recent report (Chalk et al., 1986), it was shown that the bioavailability of glibenclamide from the Daonil 5 mg tablet relative to oral solution, as assessed in terms of AUC ratio was as follows: oral solution : 1.0, and Daonil 5-mg tablet : 0.69 ± 0.21.

Pharmacokinetic analysis of the data obtained in this investigation has clearly demonstrated the close similarity in the bioavailability of both preparations. Also the release of insulin and the reduction of plasma glucose levels were identical after the administration of either glibenclamide preparations. While insulin levels started to rise immediately after breakfast as a result of food intake, and reached a maximum 1–2 h after taking glibenclamide, blood glucose levels fell to below 100 mg/dl in the first hour and were followed by a second drop in the third hour to around 65 mg/dl. These changes in insulin and glucose levels correspond to a gradual rise in glibenclamide concentrations in plasma which started as a broad peak after 2 h and reached maximum levels between 4 and 5 h after drug administration. Furthermore, glibenclamide could be detected in plasma even 10 h after administration of either Oramide or Daonil. The levels of the drug were similar in both groups and appeared to be present in appreciable concentrations. There was no drastic drop in the insulin levels, and 10 h later these levels were still several times higher than the fasting level.

When comparing the pharmacokinetic data obtained from either preparation used in our investigation with previously reported parameters, appreciable discrepancies were noted. Although Bhatia et al. (1970) estimated the biological half-life of glibenclamide at 5–7 h, our study yielded values primarily in the range of 2–4 h. The rapid elimination of glibenclamide observed here

is probably, in part, a function of its fast metabolism, since ethnic differences have been implicated in metabolic and pharmacokinetic changes in the process of drug action (Raghuram et al., 1984; Lennard et al., 1984). Regarding t_{max} values, Muller et al. (1983) reported values not exceeding 2 h following the administration of either a solution or a solid preparation of glibenclamide after food. Moreover, only female volunteers participated in their study. In our investigation, however, these values were invariably greater than 2 h and averaged around 4–5 hours. This is in agreement with Bhatia et al. (1970) who reported peak plasma concentrations appearing in 4 h. It is important to mention that the peak concentrations reached in this study were of comparable levels to those documented by other workers (Muller et al., 1983).

In conclusion, the data presented in this investigation indicate that the bioavailability of Oramide (3.5 mg) and Daonil (5 mg) were similar. The faster dissolution rate of Oramide formulation has, therefore, rendered it bioequivalent to Daonil which contains a higher amount of the drug. Furthermore, factors which may retard or enhance the absorption of Daonil may consequently result in various problems regarding variability in plasma levels due to the apparently incomplete absorption of this preparation.

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