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Research Article

Bioavailability and Antihyperglycemic Effect of Four Glibenclamide Tablets: A Comparative Study

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Abstract

This study compared the bioavailability and antihyperglycemic effect of 5 mg glibenclamide tablets available in Sudan. Nine healthy subjects were given a 5 mg dose of either micronized glibenclamide tablets (Euglucon®) or conventional non-micronized glibenclamide tablets (locally manufactured items). Blood samples were collected at 0, 1, 2, 3, 4, 5, 6, 7, and 8 hours and analyzed for glucose concentrations. The maximum mean serum concentration of the drug (C_{max}) and the mean time to maximum serum concentration (T_{max}) were calculated, and the area under the concentration versus time curve (AUC) and the drug clearance (Cl) were also recorded. The mean glucose concentration was also determined in different time intervals. The results show no significant difference in the mean T_{max} between the tested items. However, the mean C_{max} is significantly higher (p 0.001) when the non-micronized tablets are taken (456 ng/mL) rather than the micronized tablets (291 ng/mL). Similarly, the mean $AUC_{0\text{-}8h}$ is significantly higher (p 0.001) with the non-micronized tablets (1915 ng/mL.h) than with the micronized tablets (1163 ng/mL.h). After 8 hours, the subjects in the micronized group had a drug clearance of 0.0430 L/Kg.h, and a clearance of 0.0260 L/Kg.h was recorded in the unmicronized group. Both tablets lower the mean glucose concentrations of the nine volunteers after 8 hours, 99 mg/dL for micronized tablets and 98 mg/dL for non-micronized tablets. Overall, the non-micronized glibenclamide tablet used in this study similarly lowered the glucose concentrations in healthy volunteer subjects to that of imported micronized glibenclamide tablets.

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INTRODUCTION

The physical, chemical, and biological qualities of medicines and pharmaceuticals are significant aspects. This is because the drug's pharmacological action in treating the target disease would primarily affect the quality of medicines and pharmaceuticals[1-3]. In Sudan, like other Sub-Saharan African countries, regulating the medicines and pharmaceuticals and maintaining their quality standard is governed mainly by the Federal Department of Pharmacy. The role of this department is to ensure that all the medicines and pharmaceuticals (imported and local items) used by Sudanese patients fulfill specific standards of quality standards, safety, and efficiency. Besides, the Federal Department of Pharmacy is also responsible for making medicines and pharmaceuticals available at affordable prices for all patients. The Federal Department of Pharmacy uses vigorous systems of medicines and pharmaceutical registrations and pharmacy premises licensing to implement all these essential requirements[4].

In Sudan, the need for medicines and pharmaceuticals has primarily increased during the last two decades. This might be attributed to factors such as the fast growth of the country's population and improvement in the health supply systems[5]. However, the high need for the Sudanese people's medicines and pharmaceuticals has burdened the Federal Departments

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of Pharmacy regarding testing their qualities and effectiveness[5-7]. As a consequence, variables in the clinical effectiveness, decrease of user's confidence (pharmacists, physicians, and patients), and batch-to-batch inconsistencies for medicines and pharmaceuticals have been reported in recent years in the local pharmaceutical markets in Sudan. The Federal Departments of Pharmacy seek primary criteria to ensure the best quality of medicines and pharmaceuticals to users and to prevent sub-standard products that do not fall within international standards. Quality control parameters of medicines and pharmaceuticals such as tablets and capsules are valuable tools for maintaining consistency in batch-to-batch manufacturing. All quality control parameters are closely related to each other and affect drug pharmacokinetic profiles, bioavailability, and drug pharmacological actions[8,9].

Glibenclamide is a potent oral hypoglycemic agent belonging to the sulphonylurea group. It is a slightly acidic drug with high lipophilicity. It is frequently prescribed for the treatment of late-onset (non-insulin-dependent) diabetes mellitus (DM). However, commercialized glibenclamide products, such as Daonil® and Euglucon®, are slowly and incompletely absorbed by the human gastrointestinal tract (GIT). This would cause the drug to have poor bioavailability after oral administration. Many factors influence the bioavailability of glibenclamide, such as the presence of food in the GIT and the physical form of the drug product[10]. Commercially available glibenclamide is present as a tablet containing 5 mg of the drug. This study aims to ensure conformity of the quality of glibenclamide tablets available in the Sudanese pharmaceutical market by checking their anti-hyperglycemic effect in healthy volunteer subjects. To fulfill this objective, the 5 mg glibenclamide tablets from four different companies (imported and locally manufactured items) were studied for their efficiency in lowering the glucose concentrations in healthy volunteer subjects.

MATERIALS AND METHODS

Materials

Four brands of 5 mg glibenclamide tablets (one imported item Euglucon® and three local items X®, Y®, and Z®) were collected from the Sudanese Pharmaceutical Markets for the study. All tablets were adequately checked for the manufacturer's name, batch number, date of manufacturing, and expiration before starting the study. All chemicals and solvents used in this study were of the highest analytical grade commercially available.

Methods

Weight variation test

Twenty tablets from each brand's batch were randomly selected from the four 5 mg glibenclamide tablets brands and weighed individually. The mean tablet weight was computed, and the deviation of each tablet from the mean was calculated. The standard and percentage deviation were calculated and compared with the standard pharmacopeial specification from the calculated mean and deviation[11].

Hardness test

Twenty 5 mg glibenclamide tablets were selected in a random way from each batch of the five brands. The tablets were crushed individually by a hardness tester (Erweka, Germany), and the force needed for crushing the tablets was recorded. The obtained data were used to calculate the mean tablet hardness[12].

Disintegration rate test

Six 5 mg glibenclamide tablets from each batch of the four brands were randomly selected and placed in tubes of basket-rack assembly of disintegration tester (Erweka, Germany). The apparatus was filled with distilled water as a disintegration medium at 37°C and operated, and all tablets' disintegration time was measured[13].

Content uniformity test

One 5 mg glibenclamide tablet from each brand was powdered, warmed with 10 mL 0.1 N methanolic hydrochloric acid, and centrifuged. The extraction was repeated with three quantities of 10 mL, and sufficient 0.1 N methanol hydrochloric acid was added to produce 50 mL. The absorbance of the resulting solution was measured, and the content of the glibenclamide was calculated[14].

Dissolution test

Six 5 mg glibenclamide tablets were randomly selected from each batch of the four brands and individually placed in Erweka dissolution tester's (apparatus 1, 100 rpm) beaker containing 500 mL phosphate buffer (pH 7.5). Samples were taken at predetermined time intervals (15, 30, 45, and 60 minutes) and assayed using a spectrophotometric method at 300 nm[15].

Clinical study design

Nine healthy male subjects were selected for the study. Before entering the study, all volunteers underwent medical history checkup, physical examination, and biochemical testing (The research ethics approval No: OIU_Phar_Ecs23001). The subjects participating in the experiments were comparable in age, height, and weight. All subjects were forbidden from vigorous work for three days before the beginning of the study. On the study day, an indwelling catheter was inserted in the vein, and 10 mL of blood samples were taken from each subject. The drug, either the Y-brand or Euglucon®, was taken with 150 mL distilled water, followed by taking standard breakfast after 1.5 hours of drug intake.

Pharmacokinetic study

The plasma glibenclamide concentration was used to determine the following pharmacokinetic parameters: the maximum drug concentration in plasma (C_{max}); time to reach C_{max} (T_{max}); area under the concentration area (AUC) from time 0 to the last quantifiable concentration (AUC_{0-last}) and clearance (Cl).

Anti-hyperglycemic effect

Serum samples were taken from the subjects at 0, 1, 2, 3, 4, 5, 6, 7, and 8 hours. All samples were subjected to clot retraction and centrifuged at 3500 rpm for 15 minutes. Lastly, the serum samples were divided into two portions, one used immediately for glucose analysis by the hexokinase method and the other kept at -20ºC for glibenclamide analysis by a unique the high-performance liquid chromatography (HPLC) technique. The concentrations of glibenclamide for the two brands were determined using HPLC method[16].

Data analysis

The statistical significance of the weight and hardness of tablets of different brands was carried out with SPSS-Computer software (version 15.0). At a 95% confidence interval, a 2-tailed p-value less than or equal to 0.05 was considered significant.

RESULTS AND DISCUSSION

Table I shows the mean hardness of the four brands of 5 mg glibenclamide tablets. In this study, all four tablet brands showed an acceptable crushing strength ranging between 3 to 6 kg/cm^2. This range is considered acceptable, and within the specified limits of tablet hardness determined by British Pharmacopoeia[17]. During the manufacturing, packing, shipping, dispensing, and storage of a tablet, it should possess a minimum mechanical strength to sustain the potential loading encountered[18]. The inter-particulate bonding, such as Van der Waals and mechanical interlock bonding, are the major bonding forces responsible for the mechanical strength of tables. During tablet manufacturing, there is a correlation between the hardness and the properties of constituent components, such as tablet porosity, particle shape and size, effective contact, and surface area[19].

Table I shows the weight variation of the four brands of 5 mg glibenclamide tablets. According to the British Pharmacopoeia monograph requirements, the four brands of tablets used in the study passed the weight variation test[17]. There are no significant differences in the tablet weight between all brands. Factors such as good in-process control during manufacture and correct weighing and mixing during the granulation step of tablet manufacture result in obtaining tablets without or with low weight variations[11,20].

Table I shows the disintegration rate test results of the four brands of 5 mg glibenclamide tablets. According to the British Pharmacopoeia, the disintegration time of the four brands of tablets was satisfactory[17]. Before exerting its pharmacological action, the tablet must disintegrate into its aggregates and finer particles and dissolve. If the tablet disintegrates within a short period, then the drug will be released quickly for action. Factors such as the type and amount of the active pharmaceutical ingredient(s) and excipients used in tablet manufacturing and factors related to the manufacturing conditions, such as compression forces, affect the rate of tablet disintegration[21].

Table I shows the drug content of the four brands of 5 mg glibenclamide tablets. The percent of glibenclamide in the four brands were as follows: Euglucon® 100%, X-brand 98%, Y-brand 96%, and Z-brand 96%. From these results, all brands passed the recommendation of the British Pharmacopoeia monograph for the drug content in tablet[17], which allows 92.5-107.5 variation in tablets weighing less than 250 mg gross weight.

Table I. Weight variation, hardness, and disintegration time test results.

Brand code	Hardness (mean Kg/inch²)	Weight variation (% deviation)	Disintegration time (minutes)	% glibenclamide per tablet
Euglucon®	6.4	1.7	3.0	100
X-brand	8.3	1.8	1.2	98
Y-brand	7.7	1.4	1.5	96
Z-brand	3.6	1.5	3.5	96

Table II shows the dissolution of the four brands of 5 mg glibenclamide tablets. The amount of dissolved drug from X-brand was over ~90%, and for Euglucon® was over ~75%, whereas the other brands do not exceed 60% after 2 hours (**Figure 1**). A variation in the amount of drug absorption following oral administration for the generically equivalent drug products is frequently encountered[22]. Differences in the extent of *in vitro* drug dissolution might be considered one of the main factors responsible for such variation *in vivo*. In addition, these differences have been correlated with the rate and extent of drug absorption from the GIT and, finally, with the drug safety and efficacy[23]. Glibenclamide, a weak acid and poorly water-soluble drug, is better absorbed from acidic media. However, at these pH levels, the solubility of glibenclamide is minimal. Consequently, the presence of the drug in a rapidly dissolving formula is essential to ensure complete absorption from the acidic media of the upper gastrointestinal tract[24-26]. In this study, Euglucon® tablets (in micronized form) and X-brand tablets (not micronized form) were used for further studies.

Table II. Dissolution test results.

Brand code	Drug dissolved (mg)		
	0.25 hour	0.5 hour	2 hours
Euglucon®	2.2	2.8	3.5
X-brand	2.7	3.4	4.5
Y-brand	0.7	1.5	1.9
Z-brand	0.8	1.2	2.1

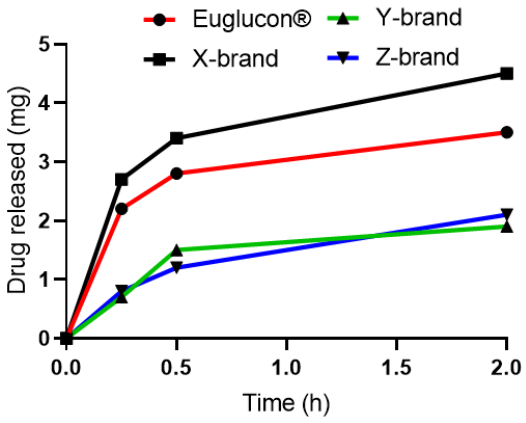

Figure 1. Amount of drug released versus time of all brands of glibenclamide tablets.

Table III shows the characteristics of subjects in the treatment groups and biochemical and hematologic screening results. All subjects were in a healthy state as the test results were confirmed. **Table IV** shows the pharmacokinetic parameters (C_{max} and T_{max}) of X-brand and Euglucon® tablets. The mean T_{max} was 3 minutes for both X-brand and Euglucon® tablets. The mean T_{max} when the micronized Euglucon® tablets were used was not significantly different from that of unmicronized Y-brand tablets. Unexpectedly, in this study, we found that the mean C_{max} when the micronized Euglucon® tablets were used significantly differed from that after using the unmicronized Y-brand tablets. The T_{max} for the micronized Euglucon® tablets is 290 ng/mL, and the unmicronized Y-brand tablets is 456 ng/mL.

Table III. The characteristic of subjects in the treatment groups.

Subject code	Sex	Age	Weight (Kg)	Height (cm)	Urine general
OM	Male	32	74	146	No infection
IA	Male	23	45	136	No infection
SE	Male	25	74	146	No infection
MA	Male	26	54	130	No infection
IM	Male	22	63	130	No infection
AB	Male	34	84	142	No infection
WE	Male	25	70	140	No infection
AM	Male	27	72	146	No infection
MS	Male	62	56	130	No infection

Table IV. Pharmacokinetic parameters (C_{max} and T_{max}) obtained from the nine volunteers.

Subject code	C_{max} (ng/mL)		T_{max} (hours)	
	Euglucon®	Y-brand	Euglucon®	Y-brand
OM	218	418	3.0	3.1
IA	280	518	3.0	3.0
SE	291	436	4.0	3.0
MA	269	425	4.0	3.0
IM	312	510	3.0	3.0
AB	274	470	4.0	2.5
WE	358	430	3.0	3.0
AM	287	365	3.0	3.0
MS	290	415	3.0	3.0
Mean	291	456	3.0	3.0

Table V shows the pharmacokinetic parameters (AUC and Cl) of X-brand and Euglucon® tablets. **Table V** shows that the mean AUC was significantly higher with the unmicronized Y-brand and the micronized Euglucon® tablets. Conversely, the Cl was 0.026 L/kg/h for the unmicronized Y-brand tablets and 0.043 L/kg/h for the micronized Euglucon® tablets. The *in vitro* dissolution studies have demonstrated that the extent of dissolution of the unmicronized Y-brand tablets was significantly higher than the micronized and Euglucon® tablets (**Table II**). The lower solubility of Euglucon® was responsible for the apparent incomplete absorption from the GIT in the *in vivo* situation compared to Y-brand tablets.

The present study showed a significant difference in the bioavailability of the micronized tablet (Euglucon®) compared to the unmicronized tablets (Y-brand). So, the micronized drug must be formulated in lower doses, as already seen in the literature. Micronized Y-brand tablets can be taken as an overdose, which may be associated with severe hazards such as hypoglycemia.

Table V. Pharmacokinetic parameters (AUC and Cl) obtained from the nine volunteers.

Subject code	AUC (ng/mL.h)		Cl (L/Kg.h)	
	Euglucon®	Y-brand	Euglucon®	Y-brand
OM	950	1065	0.0053	0.0047
IA	830	1870	0.0026	0.0027
SE	1025	1774	0.0049	0.0028
MA	822	1280	0.0061	0.0039
IM	1480	1630	0.0032	0.0031
AB	940	1530	0.0053	0.0043
WE	1209	1220	0.0041	0.0041
AM	925	1150	0.0050	0.0043
MS	860	1552	0.0057	0.0032
Mean	1163	1915	0.0430	0.0260

Table VI shows the mean glucose concentration obtained from the nine volunteers at different intervals. At baseline, the mean glucose concentration was 72 mg/dL for volunteers taking Euglucon® tablets and 62 mg/dL for Y-brand tablets after breakfast. **Table VI** shows that glucose concentration increased to 84 and 76 mg/dL for volunteers taking Euglucon® and Y-brand tablets, respectively. After 2 hours of taking the drug, the concentration was only 49.6 and 46 mg/dL for volunteers taking Euglucon® and Y-brand tablets, respectively. After 4 hours, glucose concentration for Y-brand tablets was 48 and 60 mg/mL for volunteers using Euglucon® tablets (**Figure 2**). In this study, we observed that in the elderly volunteers, the action of the Euglucon® tablets was more potent than that of the Y-brand tablets. The glucose concentration was decreased

dramatically for 62-year-old volunteers at 4 hours from drug intake, and the concentration of glucose was only 32 mg/dL, and glucose was given orally to overcome the hypoglycemia.

Table VI. The mean glucose concentration obtained from the nine volunteers in different time intervals.

Mean glucose concentration (mg/dL)	Fasting	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours	7 hours	8 hours
Euglucon®	72	84	49	50	60	103	92	77	99
Y-brand	62	76	46	51	48	74	75	64	98

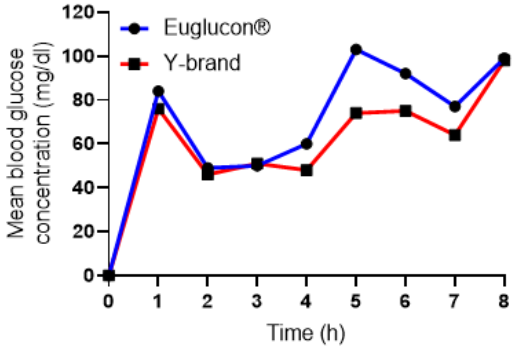

Figure 2. Mean blood glucose concentration in serum versus time of nine subjects taking Y-brand or Euglucon® tablets.

CONCLUSION

The present study showed no considerable difference in the hyperglycemic effect between the micronized Euglucon® and unmicronized Y-brand of 5 mg glibenclamide tablets available in the Sudanese pharmaceutical markets.

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AUTHORS' CONTRIBUTION

All authors have an equal contribution in carrying out this study.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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