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Comparative Evaluation of the Quality Control Parameters and Hypoglycemic Drug Effect of Some Brands of Glibenclamide Tablet

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Authors' contributions

This work was carried out in collaboration between the authors. Author SOA designed and wrote up the work. Author JAN performed the statistical analysis and author AJU supervised the laboratory protocols. All the authors read and approved the final manuscript.

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ABSTRACT

Drug release profile and bioavailability indices have been well correlated with the quality of drug products. A comparative evaluation of the quality control parameters and hypoglycaemic drug performance check of some brands of glibenclamide tablets was studied. The physicochemical parameters of the brands were evaluated through uniformity of weight, friability and hardness tests along with disintegration and dissolution profile in phosphate buffer (pH 8). The hypoglycaemic drug performance of the brands was evaluated by twice daily oral dosing of 5mg glibenclamide tablet under controlled evening meal and fasting blood sugar (FBS) determinations. The statistical inferences about the groups' mean fasting blood sugar (MFBS) were compared with a postulated/expected population MFBS of 5.0 mmol/L and the hypothesis that there was no difference in the population from which the MFBS was obtained for each group treatment, was tested. The brands complied with the USP specifications for tablet hardness, weight uniformity, and friability and disintegration tests. There was no significant difference in the chemical content among

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the brands at CI=95%. The assay gave a chemical content between 92.4% and 102.5%w/w for the drug brands. The dissolution profiles in phosphate buffer revealed satisfactory C_{45} and T_{70} of ≥ 70% and ≤ 45 min respectively. The MFBS for each brand laid beyond 2xSE of the postulated population MFBS. The investigated brands were of comparable quality standards and can be regarded as pharmaceutical and therapeutic equivalent. The hypoglycaemic drug effect of the drug products at the twice a day dosing could not achieve the postulated MFBS level. The method can be applied as a performance check for different brands of oral hypoglycaemic dugs emanating from the possible differences in the quality/production factors.

Keywords: Diabetes; glibenclamide; hypoglycaemic effect; performance check; fasting blood sugar.

1. INTRODUCTION

Glibenclamide is an oral hypoglycemic agent of the sulphonyl urea group indicated for non-insulin dependent diabetes mellitus (NIDDM) [1]. The uses of drugs based on their generic names encourage free choice of drug among the available brands. Competitive pricing should therefore be matched with comparative drug performance and clinical efficacy. For effective cost reduction to enable affordability, manufacturers may choose active ingredients and recipients that lead to fair manufacturing cost which translates to the market cost [2]. The polymorphic form of drugs employed in the production of glibenclamide may characterize their bioavailability profile [3]. Two forms of glibenclamide are available commercially, namely, the glassy form or amorphous and the crystalline [4].

In synthetic chemistry, glibenclamide that exists in the crystalline form is convertible to the glassy form by quench–cooling of the melt and cryogenic milling [4,5]. The solid state properties of the amorphous samples, X–ray powder diffraction (XRD), Infra-red spectroscopy (FTIR), ultra-performance liquid chromatography (UPLC) and broad-band dielectric spectroscopy (BDS) have been exploited to distinguish the two forms based on their physiochemical profiles [4-6].

In quality control studies, it has been revealed that some drugs pass the quality control tests but show biological inequivalency [7]. This has been found to be due largely to the issues of polymorphism and choice of the crystalline form of drug used as the raw material. Since different lattice energies (and entropies) associated with different polymorphs give differences in physical properties such as solubility and dissolution rates, the variations may have impact on the absorption of drug from the dosage form [8-10]. The most critical issue related to drug substance polymorphism is equilibrium solubility which is the concentration of drug dissolved when there is equilibrium between the solid drug substance and solution. Drug dissolution testing is therefore appropriate for drug product evaluation [11].

This study was aimed at evaluating the quality control parameters of the six brands of glibenclamide sold in the market and to assess some biopharmaceutical indices of the drug products.

2. EXPERIMENTAL

2.1 Materials and Chemicals

HPLC system (Schimadzu LC26A pump, SPD26A UV detector and column C18x5µm) China, Doublee-Gee glucometer (Doublee-Gee, China); acetonitrile (HPLC grade), monobasic potassium phosphate, sodium hydroxide and hydrochloric acid, acetonitrile, monobasic ammonium phosphate and methanol were all analytical grade and obtained from Merck (Germany). Drug samples GL1, GL2, GL3, GL4, GL5 and GL6 were glibenclamide 5mg tablets procured from registered pharmaceutical outfits in Nigeria (Table 1). Glibenclamide powder was supplied as a gift sample from Sprem Chemicals and research centre, China and employed as reference powder.

2.2 Methods

2.2.1 Buffer preparation

Monobasic potassium phosphate buffer of pH 8.0 was prepared according to established protocols [12].

2.2.2 Standard solution

An accurately weighed amount of pure glibenclamide powder equivalent to 50mg was dissolved in 0.2M sodium hydroxide in a 50ml volumetric flask to give a concentration of

1mg/ml. Solutions of glibenclamide of 0.5–20µg/ml were prepared from the stock solution by diluting accurate volumes of the stock solution in phosphate buffer (pH, 8.0). A calibration curve was prepared using the dilutions.

2.2.3 Calibration graph

Linear calibration graphs for the determination of glibenclamide (0.5 – 20µg/ml) was plotted and the linear–regression analysis expressed in Fig. 1.

2.2.4 Linearity

The calibration curve was analyzed for linearity using the least square regression method with triplicate determinations for each concentration.

2.2.5 Sample preparation

An accurately weighed amount of tablet powder of the six samples equivalent to 12.5mg were individually transferred to a 50ml volumetric flask and 20ml of acetonitrile was added and sonicated for 5min. A 5.0ml aliquot of the resulting solution was mixed with the mobile phase to produce a final volume of 1L.

2.2.6 Drug quality control parameters

2.2.6.1 Disintegration Test

The tablet disintegration was determined at 37℃ using a Veego model $VTDH_3$ disintegration testing apparatus (Rutartek, India).

2.2.6.2 Weight uniformity

Tablets of each brand were weighed individual using a digital analytical balance (Adventure Ohaus) and the mean calculated. The percentage deviation of the individual tablets from the mean was determined.

2.2.6.3 Tablet hardness test

The crushing strength of the tablets was determined using a Monsanto tablet hardness tester at 25 per/min.

2.2.6.4 Assay/Chemical content

Twenty tablets of each six of the brands were weighed separately and crushed in a mortar. The powdered drug product of glibenclamide were weighed and an amount equivalent to 5mg was weighed in triplicate into conical flasks and dissolved in methanol to produce 50µg/ml of glibenclamide. The sample was injected into the chromatographic system and analyzed at 229.5nm. The mobile phase for the determination was monobasic ammonium phosphate and acetonitrile (45:55) and flow rate, 1.0ml/min.

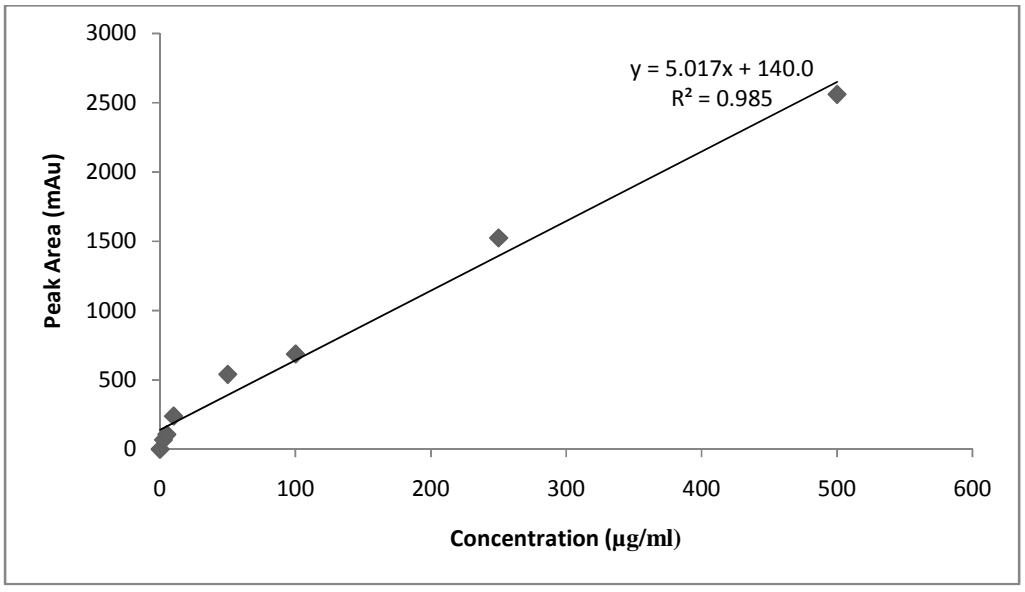

Fig. 1. Calibration curve and regression equation of pure glibenclamide powder

2.2.6.5 Dissolution test

Dissolution test was performed using an Erweka DT-6 dissolution tester according to dissolution tests protocols. The dissolution medium was 900ml comprising of monobasic potassium phosphate buffer at 37±0.5℃ and the speed of rotation 100 rpm. At time 5, 15, 30, 45, 60 and 90 min, 5ml aliquot samples were withdrawn and replaced with equal amounts of fresh medium to maintain a constant volume. The withdrawn samples were analyzed using the HPLC system. The T_{70} (average time for 70% of the active drug to be released and C_{45} (concentration at 45 minutes) were determined.

2.2.6.6 Hypoglycemic performance evaluation

The study was performed in July, 2013.Thirty six volunteers (21 males, 15 females), mean ± SD age of 34.5±2.6 years, mean body weight ± SD of 59.4±5.8 kg and body mass index (BMI) ± SD of 23.1±1.2 Kg/m^2 oral hypoglycaemic users from hospitals in the neighbourhood were recruited into the study after obtaining their written informed consents, administrative approval from the community pharmacy management where the study was carried out and the study protocols approved by the ethics committee of Faculty of Pharmacy, University of Uyo. The volunteers' fasting blood sugar (FBS) were taken at 7am on the first day of study and referred to as study entry point (SEP) value. The volunteers were randomized into six groups containing six members. Each group was given a particular brand of glibenclamide as a twice daily dosing for 21 days and the change in fasting blood sugar (SEP - FBS) values per volunteer every day recorded.

2.3 Statistical Analysis

Statistical significant differences in the daily values for the change in blood sugar levels for group members of each brand of drug with respect to the SEP were assessed, compared with other members of each brand and analyzed using one sample hypothesis and one tailed at α=0.05. The difference between the six brands was evaluated using a two sample hypotheses to test for differences in the reductions of fasting blood sugar levels achieved by the various brands. Other parameters were statistically analyzed using SPSS ver. 17 for significant differences at $P<0.05$ [13].

3. RESULTS

The randomly selected brands of glibenclamide were all within the shelf life and authorized for sale in the country. The brands were also available in the leading drug retail outlets in the study area. The physicochemical parameters evaluated for the brands of glibenclamide gave satisfactory outcomes. The tablet hardness was within 3.5 – 4.8 KgF and weight uniformity (maximum deviation from the mean) was 4.5% for the brand with the highest value. The lowest C_{45} value was 78% while the maximum time for 70 % of active content release was 38min. The chemical content for the brands lay between 92.4 -105.5%w/w (Table 2). There was no preference for one than the other with respect to buyers or prescribers. The volunteers were aged 34.5±2.6 years and body weight 59.4±5.8 kg` with no other known metabolic disease.

4. DISCUSSION

The drug glibenclamide has been advocated for effective control of blood sugar in Type 2 diabetes. Some physicians present the idea that twice daily dosing of glibenclamide together with controlled evening meal adequately regulates FBS. We set out to evaluate the practicality of the idea in a small group of out-patients in the locality. Upon the increasing number of generic products of the drug, there was the need to assess the quality of the available brands before evaluating the performance of some of the products. The brands employed were all registered products (Table 1) in the country and they all complied with the quality control parameters investigated. The quality indices of the various brands were satisfactory with respect to the parameters analyzed. The circulating products are therefore regarded as pharmaceutical equivalents (Table 2). Whether these products can be used interchangeably will depend on the outcome of in-vivo performance. The widespread peddling of substandard drugs makes the investigation of the quality control parameters expedient before further investigation on performance. Performances of drugs have been demonstrated to be closely associated with the quality indices of drugs [14] (Fig. 2 and Table 2). Glibenclamide is Biopharmaceutics Classification system (BCS) class 2 drug with low aqueous solubility. Manufacturing protocols from different producers are expected to circumvent this problem and these may be responsible for the variations in the dissolution characteristics, if any exists. The dissolution outcome however did

not show marked variations as to suggest an indictment on the performance of the various brands. Buffer of pH 8 was used to assess the dissolution characteristics of the brand as this gives the optimum dissolution properties with respect to the acidic nature of the drug and the pH nature of the intestinal milieu where maximum absorption is expected. Since drug dissolution affects the bioavailability of the brands the outcome of the dissolution assessment will predict the in-vitro performance. The volunteers willingly accepted their allotted medications and complied with the routine of reporting for FBS checks to the extent of over 90% responsiveness. This was owed to the fact that the enlightenment on the need to achieve a stable FBS was well understood by the volunteers. The expected FBS projected for the group was 5.0. This value was designed as a FBS value ideal for effective drug performance. One sample hypothesis and two tail statistical analyses for the observed MFBS in each group with data collection for 21 days determination was analyzed to assess if there was difference in the MFBS of the groups compared with the postulated FBS. There was no significant difference in the MFBS of the individual group with the projected FBS at $P<0.05$ and 0.01 for brands GL1, GL2, GL3, GL4 and GL5. GL6 was however satisfactory at $\alpha=0.01$ (Table 3). The drugs therefore at the dosing and the feeding condition will not produce a FBS value of about 5mmol/L [15,16]. There was however a significant reduction in MFBS when paired T-test was used to evaluate the group MSEP values and the group MFBS values for the six brands.

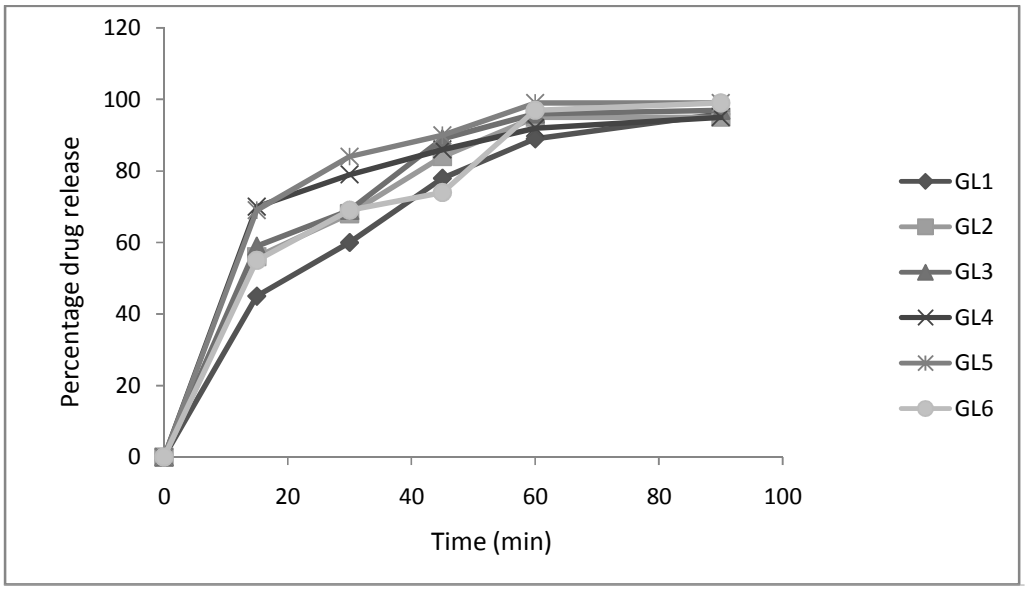

Fig. 2. Dissolution profile of the six brands of glibenclamide drug products in dissolution medium (pH 8)

Table 1. The details of the drugs used in the study

Name	Code	Manufact Urer	Manufacturing/ Expiry Date	Nafdac Reg. number	B. No.
Daonil	GL1	May and Baker	08 – 2011/08-2014	04-0744	T028
Glanil	GL2	Nig German chemical	03 – 2011/03-2014	04-2450	W228
Solimide	GL3	Solidum Pharm	03 – 2009/02-2012	04-8751	9C-27
Gliben J	GL4	Juhel	05 – 11/04-2014	04-5735	0019
Clamide	GL5	Hovid	06 – 11/06-2014	04-4015	BB06596
Diabeta	GL6	Greenlife	11 – 10/10-2013	04-3856	DB-02

Table 2. The physicochemical analysis of the brands of glibenclamide in the study

Drugs	Tablet hardness	Weight uniformity MDM%	Chemical content (%w/w)	Disinte-gration time (min)	Friability (%)	Dissolution profile (SIF)	
						C_{45} (%)	T_{70} (min)
GL1	3.5±0.3	3.2	98.5±0.2	4.5±0.2	0.03	80	38
GL2	4.4±0.5	1.5	99.4±0.2	4.0±0.2	0.04	78	36
GL3	3.9±0.2	2.4	101.3±0.5	3.0±0.1	0.03	83	30
GL4	4.8±0.8	4.5	105.5±0.6	5.0±0.2	0.02	85	17
GL5	4.8±0.2	2.8	92.4±0.2	4.0±0.2	0	83	17
GL6	4.0±0.4	3.1	99.6±0.5	4.2±0.1	0.01	82	30

Key: MDM- Maximum deviation from the mean

Table 3. The statistical analysis of the hypoglyceamic drug effect of the drug products

Brands	Number of sample	MFBS (Mmol/L)	MSEP (Mmol/L)	Statistical			Analysis
				$T_{calc.}$	$T_{critical}$ α=0.05	$T_{critical}$ α=0.01	Remark
GL1	105	6.2	7.9	1.65	0.64	1.62	Not satisfactory
GL2	111	5.7	8.9	1.97	0.12	1.34	Not satisfactory
GL3	106	4.8	7.8	3.41	0.12	1.19	Not satisfactory
GL4	94	5.2	10.3	1.19	0.71	1.14	Not satisfactory
GL5	101	4.5	9.6	1.94	0.98	1.59	Not satisfactory
GL6	89	6.7	8.9	1.49	1.43	1.97	Satisfactory at α= 0.01

Key: MFBS- Mean fasting blood sugar; MSEP- Mean Study Entry Point (mmol/L)

5. CONCLUSION

The study revealed that the various brands of glibenclamide marketed in the country imported from different sources have comparable quality characteristics. The postulated MFBS was however not met by any of the brands which is an indication that a supportive therapy may be needed to achieve this value. Failure to meet the projected value may not be drug production factor as the quality parameters of the employed brands were satisfactory in this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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