# Assessment of the Quality and *In Vitro* Bioavailability of Multisourced Chlorpropamide Tablets Marketed in Nigeria

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**Abstract**

***A quality control assessment of six different brands of chlorpropamide tablets marketed in Nigeria was carried out. This was aimed at evaluating their quality and release performances as well as determining the bioequivalent brands and hence establishes the possibility of inter-brand substitution. The weight uniformity, friability and hardness of the tablets were determined. The absolute drug content, disintegration time and in vitro dissolution profiles of the six brands were evaluated in simulated intestinal fluid (SIF) without enzymes. The possible in vivo bioavailability of the brands was predicted using the concepts of dissolution efficiency and predicted availability equivalent. Three of the brands passed the assay test, and there were variations in the weight uniformity, friability, hardness, disintegration and dissolution test results. Two of the brands are bioequivalent with the innovator brand.***

**Keywords:** Chlorpropamide tablets, Bioequivalence, Interchangeability

## Introduction

Chlorpropamide hydrochloride is an oral antihyperglycaemic agent used in the management of type 2 diabetes mellitus. It acts by increasing insulin action in peripheral tissues and reducing hepatic glucose output due to inhibition of gluconeogenesis. Diabetes mellitus is a disease of high socio-economic importance and the quality of the drug products used in the management of diabetic patients is a determinant of the treatment result. Development of diabetic complications is also influenced by the quality of glycaemia control. Several quality control parameters such as tablet weight uniformity, content of active ingredient, uniformity of content, disintegration time, dissolution test, hardness test, friability test, tablet density, tablet diameter and thickness are usually applied to brands of tablets in order to assess their quality, and thus predict their efficacy. The dangers of fake, substandard or adulterated drugs are also a serious problem in every society and especially in developing nations such as Nigeria.

Innovator drugs may suddenly become unavailable or exorbitant in price for the average consumer in the Nigerian market. The substitution of one brand of drug with another is therefore common medical practice in Nigeria. If there is significant difference in the quality of the substitute brand, therapeutic goal may not be achieved and untoward effects and diabetic complications may result. Substitute brands are usually cheaper than the innovator drug, and hence attract higher patronage in developing nations. Bioinequivalence has been reported among generic tablets of metformin, ciprofloxacin and albendazole marketed in some third world countries (Osadebe et al., 2002; Osadebe and Akabogu, 2004; Galia et al., 1999).

Interchangeability is the process of dispensing a different brand or unbranded drug product in the event of absence or high cost of the prescribed brand (Bababola, 2001). The substitute brand, though containing the same active principle, is formulated differently by a different manufacturer. The binder, disintegrant and/or lubricant types, concentration and incorporation method etc, may markedly alter the bioavailability and hence therapeutic efficacy of the final product (Rubinstein, 1988). Multisourced drug product must satisfy the standards of quality, efficacy and safety as those applicable to the innovator's product (Bababola, 2001). Disintegration and dissolution tests are official *in vitro* tests that are used in predicting *in vivo* bioavailability of most oral dosage forms (Olaniyi, 2001). Since dissolution test furnishes data on the rate of drug dissolution, it ideally distinguishes between good and bad products, formulations and batches. Dissolution of certain drugs is known to correlate well with its bioavailability in the body and so provides a valuable indicator of potential *in vivo* performance (Olaniyi, 2001).

The objective of this study is to assess the quality of six brands of chlorpropamide tablets available in the Nigerian market and to use *in vitro* methods to estimate their possible *in vivo* bioavailability and bioequivalence.

## Materials and Methods

**Sample selection and storage:** Six different brands [DBN, DBK, CPM, ACC, DNI, and CMM] of chlorpropamide tablets (250 mg, label claim) were randomly obtained from patent medicine stores and pharmacies in South Eastern Nigeria. All the tablets were stored in cool dry place prior to the assay. Sampling and assay were done before their expiry dates.

**Materials:** The following analytical grade reagents were used for the tests: sodium hydroxide and methanol (Avondale, England), monobasic potassium phosphate and hydrochloric acid (BDH, England). All other reagents were freshly prepared in our laboratory.

**Preparation of dissolution media, simulated intestinal fluid (SIF):** Simulated intestinal fluid

(SIF) without enzymes was prepared by dissolving 40 g of sodium hydroxide and 34 g of monobasic potassium phosphate in 2 litres of portable water. The solution was made up to 5 litres with portable water (USP, 1980).

**Assay method:** The six brands of chlorpropamide were assayed according to the BP 2001 method. Twenty tablets of each brand were weighed and powdered. The powdered drug equivalent to 0.25 g of chlorpropamide was shaken with 40 ml of methanol for 20 minutes. Sufficient methanol was added to produce 50 ml. The resulting mixture was filtered and 5 ml of the filtrate diluted to 100 ml with 0.1M HCl. Ten ml of this solution was diluted to 250 ml with 0.1M HCl and the absorbance of the resulting solution measured at 232 nm using Uv/Vis PC spectrophotometer (UNICO 2102, USA).

**Uniformity of weight test**: Ten tablets were randomly selected and weighed singly using an analytical balance (August Sauter KG, Germany, model 404/18). Average tablet weight and standard deviations were calculated.

**Hardness Test:** Ten tablets were randomly selected from each brand. The hardness was singly determined using a Mosanto – Stokes hardness tester and the average hardness and standard deviations calculated.

**Friability Test**

Ten tablets were randomly chosen from each brand. The friability was determined using the Erweka friabilator (model TAR 50234) rotating at 25 revolutions per minute for five minutes. The initial and final weights of the tablets were determined using an analytical balance (August Sauter KG, Germany, model 404/18) and the loss calculated as abrasion resistance.

**Disintegration time test:** The Erweka dissolution rate apparatus (Erweka, Germany, model DT 55164) was used to determine the disintegration times of the brands in SIF. Chlorpropamide is an acidic drug that is insoluble in acidic media but dissolves in aqueous solutions of alkali hydroxides. Five hundred ml of SIF, maintained at 38 ± 1 °C was used. A randomly chosen tablet of the brand was dropped in the medium and the rotating paddle set at 50 rpm. The time taken for the tablet to break up into small aggregates leaving no tablet residue was noted.

**Dissolution rate test:** The paddle method was used. The *in vitro* dissolution test was performed in simulated intestinal fluid (SIF) using Erweka dissolution rate apparatus (Erweka, Germany, model DT 55164). A 500 ml volume of SIF was used in order to ensure sink conditions. Temperature was maintained at 38 ± 1 °C. One tablet each was randomly chosen from the batch for the evaluation. The tablet was placed in the dissolution medium and 2 ml samples withdrawn at intervals (5, 10, 15, 20, 30, 40, 60, 80, 100, and 120 min.). Two ml of fresh dissolution medium was used to replace the sample withdrawn. The sample withdrawn was diluted appropriately, filtered and the absorbance determined at 231 nm using a Uv/Vis PC spectrophotometer (UNICO 2102, USA). The concentration of the chlorpropamide was estimated from a standard Beer-Lambert calibration curve obtained with a pure sample of chlorpropamide. A modified calculation of dissolution efficiency (Khan, 1975) and predicted availability equivalent (Osadebe and Akabogu, 2004) were used to predict the likely *in vivo* release of the different brands of chlorpropamide tablets.

## Results and Discussion

The permitted percentage weight deviation for the 250 mg chlorpropamide tablet is 5 % (BP, 2001). The uniformity of weight test results as can be seen from Table 1 reveals that the weights of the six brands were uniform within acceptable limit. Tablet hardness greater than 5 kgf was considered acceptable for uncoated tablets (Ofoefule, 2002). All the brands passed the hardness test. They are therefore likely to withstand pressure that may be encountered between the time of production and use by the patient. Abrasion resistance (friability) of up to 1.0 % and 2.0 % may be accepted for tablets prepared by wet granulation and direct compression methods respectively (Ofoefule, 2002). Half of the brands tested (DBK, CPM, and CMM) failed the friability test. This is an indication that the brands may not retain their integrity or withstand agitations due to transportation and handling.

The disintegration time of the brands in SIF is shown in Table 1. The disintegration time increased in the order: CMM < DBK < DBN < DNI < CPM < ACC. Two brands (DBK and CMM) disintegrated within the acceptable time limit of 15 min for uncoated tablets while ACC brand disintegrated within the acceptable time of 30 min for coated tablets. ACC is a film-coated tablet. DBN, DNI and CPM failed the disintegration time test. The observed differences in the hardness and disintegration times could be related to the difference in formulation excipients, techniques and compressional force employed by the different manufacturers. Such variables are known to affect disintegration, hardness and dissolution rates (Khan, 1975). The assay of the six brands (shown in Table 1) reveals that three of the brands (DBN, CPM, and CMM) passed the assay test. They were all within the acceptable range of 92.5 – 107.5 % (BP, 2001).

The dissolution profiles of the six brands in SIF are presented in Fig 1. The curves were used to estimate the dissolution efficiency (DE) and the predicted availability equivalent (PAE) of the various brands using the equations below:

$$DE = \int_0^t y dt \quad \text{..... Equation 1}$$

$$PAE = {}_0^t[AUC]_V / {}_0^t[AUC]_{ID} \times 100\% \quad \text{..... Equation 2}$$

**Table 1: Uniformity of weight, hardness, friability, disintegration time and absolute drug content of six brands of chlorpropamide tablets**

| BRAND | Average weight (mg) ±sd | Hardness test (kgf) ±sd | Friability test (%) | Disintegration time (min) | ASSAY (%) |
|---|---|---|---|---|---|
| DBN | 452.05 ±17.4 | 5.55 ±1.74 | 1.06 | 18.0 | 94.22 ±0.05 |
| DBK | 444.94± 19.1 | 5.68 ±1.55 | 4.35 | 15.0 | 68.13 ±0.03 |
| CPM | 318.30 ±3.5 | 12.04 ±1.02 | 6.06 | 23.0 | 97.63 ±0.05 |
| ACC | 506.09 ±4.4 | 13.68 ±0.63 | 0.94 | 28.0 | 87.03 ±0.07 |
| DNI | 550.41 ±8.8 | 7.84 ±1.02 | 0.86 | 20.0 | 70.58 ±0.03 |
| CMM | 456.05 ±7.9 | 13.74 ±0.35 | 5.26 | 12.0 | 103.11 ±0.03 |

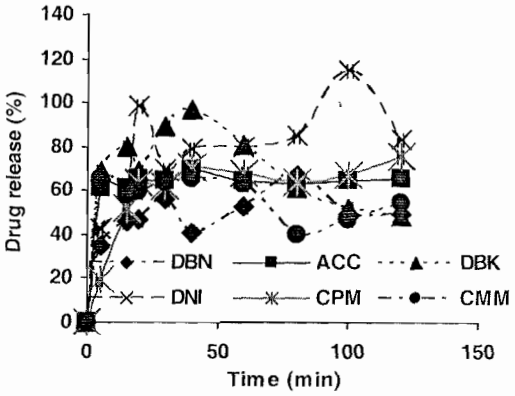


**Fig 1: Dissolution of six brands of chlorpropamide tablets in SIF**

Where ${}^{0}_{t}[AUC]_{x}$ = the area under the dissolution time curve for any particular brand and ${}^{0}_{t}[AUC]_{D}$ = the area under the dissolution time curve for the innovator product, DBN.

The area under curve ${}^{0}_{t}[AUC]$ was determined by the trapezoidal rule using the equation option in Microsoft Excel tool-pack. The area under curve at 30 min $[AUC]_{30}$, the dissolution efficiency at 30 min $[DE]_{30}$, the predicted availability equivalent (PAE) and time at which 50 % of the drug has been released ($T_{50\%}$) are shown in Table 2. The concept of dissolution efficiency was utilized in the prediction of the likely in-*vivo* availability of the brands of chlorpropamide. The concept, described by Khan, 1975 allows comparison to be made between a large numbers of formulations. At 30 min, DBK had the highest dissolution efficiency (72.58%) while DBN had the least dissolution efficiency (40.04%) among the brands compared.

**Table 2: Drug release pattern within 30 minutes of six brands of chlorpropamide tablets in SIF**

| BRANDS | $AUC_{30}$ | $DE_{30}$ | PAE (%) | $T_{50\%}$ (min) |
|---|---|---|---|---|
| DBN | 1201.25 | 40.04 | 100.00 | 30.0 |
| DBK | 2177.50 | 72.58 | 181.27 | 5.0 |
| CPM | 1397.50 | 46.58 | 116.34 | 12.0 |
| ACC | 1763.75 | 58.79 | 146.83 | 4.0 |
| DNI | 1680.00 | 56.00 | 139.85 | 7.0 |
| CMM | 1335.00 | 44.50 | 111.13 | 13.0 |

Predicted availability equivalent (PAE) of ± 20 % was used to determine bioequivalence of the brands with the innovator brand. The PAE values shown in Table 2 reveals that CPM and CMM had PAE values within ± 20 % and were therefore considered bioequivalent and interchangeable with the innovator brand, DBN.

**Conclusion:** The study showed that there are variations in the hardness, disintegration and dissolution characteristics of six brands of chlorpropamide marketed in Nigeria. Only three (DBN, CPM and CMM) out of the six generic formulations marketed in Nigeria contained the expected amount of chlorpropamide. Two of the brands (CPM and CMM) are interchangeable with the innovator drug (DBN) for the management of diabetes mellitus.

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