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# INTERCHANGEABILITY OF MEDICINES USING METFORMIN AS A SURROGATE PRODUCT (II)

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## ABSTRACT

Interchangeability of medicines, either over-the-counter or prescription drugs is a general and wide spread practice in health institutions. In our recent publication on interchangeability, it was discovered that, cost, physical quality and full consent of the patient were major considerations while making substitution. The current investigation was aimed at undertaking a bioequivalence study of Metformin hydrochloride tablets as a surrogate medicine for general interchangeability. USP methods were used for the quality assurance assessment of the following parameters; uniformity of weight, hardness testing, identification, friability, disintegration and dissolution tests. The physicochemical evaluation of the samples showed compliance with USP specifications. All the formulations disintegrated within 15-30 minutes. Thirteen brands complied with percentage drug content specifications (95-105%), while four brands did not. Similarity factor (f2) value calculated for the brands were >50 indicating similarity with the innovator product hence can be interchanged except for the six brands (F, L, M, N, P, and Q). Fifteen of the seventeen brands including the innovator brand passed the USP 32 general specifications standard for dissolution test for immediate release tablets. Interchangeability of different brands must be based on satisfactory similarity factor (pharmaceutical equivalence), percentage drug content and dissolution rate test while cost and consent of the patient should be added advantage.

**KEYWORDS:** Metformin, generics, inter-changeability.

## INTRODUCTION

Medications are necessities and gain top priority in the list of every patient who wants to gain and maintain a healthy state, therefore whenever the need arises the patient do not have much option but to obtain whatever is available and affordable. Innovator products are usually more expensive than their generic counterparts. Interchangeability of medicines, either over-the-counter or prescription drugs is a general and wide spread practice in health institutions.[1,2] In our recent publication on interchangeability, it was discovered that cost, physical quality and full consent of the patient were employed in the substitution process.[3] Metformin hydrochloride is an oral anti-diabetic drug from the biguanide class used mainly to treat type 2 diabetes mellitus. It is the first line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function.

Generic drugs are important options that allow greater access to health care.[4,5] Generic drugs are copies of innovator drugs and are suppose to be the same (bioequivalent) as those innovator drugs with respect to safety, strength, route of administration, quality, performance characteristics and intended use. Generally, application for 'marketing approval' of a generic product must reference a corresponding product, which was approved on the basis of clinical trials.[5,6] The Nigeria Agency for Food, Drug Administration and Cosmetics (NAFDAC) like the American Food and Drug Administration (FDA) do approve some generic versions of marketed drugs on the basis of establishing bioequivalence and pharmaceutical equivalence.[7] This was aimed at providing the public with affordable medications which are therapeutically equivalent to the brand name products and also to increase access to medicines.[8,9] Innovator medicines are generally expensive particularly when the patent rights are still on. The Food and Drug Administration (FDA) approved generic versions of marketed innovator medicines on the basis of established bioequivalence and pharmaceutical equivalence. The Act was aimed at providing the public with affordable medications which are therapeutically equivalent to the innovator products and also to increase access to medicines.[8] Generic drugs tend to imitate

innovator products in safety, efficacy, strength, route of administration, and quality.[10,11] Regulatory authorities therefore demand for studies to prove adequate comparison according to their specifications. As the word implies any generic drug that is bioequivalent to its brand named counterpart may be interchanged with it. Hence they can be defined as drugs that contain the same amount of the same active ingredients and the same dosage forms.[12,13] It is therefore, paramount for the physician and the pharmacist to be familiar with drugs on the interchange-ability list (Essential Drug List). Also the pharmacists need to have knowledge of the cost, safety, efficacy and patients specific differences. In our recent publication, we found that, 82.35% of the respondents base their selection of generic medicines on cost and 96.8% considered availability as priority. Also, 68% used bioequivalence data available while 44.2% of the respondent based selection on product popularity, local demands and company's reputation. Finally, 63.5% based their substitution on patients consent or demand.[3]

In vitro dissolution specifications for generic drug products are used to simulate in vivo bioavailability profile and to establish bioequivalence along with other quality assurance parameters.

The study is a follow-up to our earlier report on interchangeability of metformin in a tertiary hospital.[7] This is to undertake bioequivalence study of metformin products that is mostly interchanged in Nigeria.

## MATERIALS AND METHODS

### Materials

The following equipment/apparatus were used in the course of evaluating the different brands of Metformin hydrochloride (500 mg) tablet; Roche friabilator, Monsator hardness tester, Disintegration apparatus, Shimadzu UV-2650PC double beam spectrophotometer (Shimadzu, 1620 Japan) and RC -6 Dissolution test apparatus, 1L per vessel (Tianjin,China).

### Product Selection'

Available brands of Metformin hydrochloride (500 mg) tablets were purchased from registered Pharmacy stores within Jos metropolis and coded as shown in Table I (Not arranged in any particular order: Gluformin, Dibinorm Vpl Metformin, Degluco, Diabetmin, Guamet, Glyformin, Chantformin, Aurobindo, Glucophage, Sandos Metformin, Grakkophage, Juformin, Betaform, Exadea, Pontal Metformin, Biophage,).

### Quality Assurance Parameters examined

### Uniformity of thickness and Diameter

The thickness and diameter of ten (10) tablets selected randomly from each brand were measure by the use of a veneer calliper. The standard deviation values for all tablet brands were calculated.

### Uniformity of weight

Twenty tablets (20) were selected randomly from each brand and weighed on an electronic weighing balance (Metler P165). Their average weights were calculated for all tablets brands

### Friability test

Ten (10) tablets from each brand were weighed and carefully placed in a friabilator (Roche friabilator).The friabilator was operated at a rate of 25 revolutions per minute for 4min, with the tablet falling through a height of 6 inches at each turn. The tablets were de-dusted, final weight taken, and the percentage loss in weight calculated. The percentage loss in weight was calculated by using the formula.

$$\text{Friability} = \frac{(\text{Weight before test} - \text{Weight after test}) \times 100}{\text{Weight before test}}$$

The percentage weight loss was then compared with the official specification (0.5 to 1%).

### Hardness test

The hardness test was determined at room temperature by diametrical compression using monsator hardness tester. The tablet was placed between the platen of the tester and the adjustable knob was screwed, to make contact with the tablet. Enough pressure was applied to cause tablet breakage and pressure at which the tablet cracked was recorded in $Kg/cm^3$.

### Disintegration test

Tablet disintegration was determined at 37°C using ERWEKA (Heusenstamm Germany) disintegration apparatus. Six tablets from each brand were subjected to disintegration test. One tablet was placed in each of the six tubes of the basket .The disintegration time was taken to be the time no granule of any tablet was left on the mesh.

### Dissolution test and Assay of Metformin hydrochloride tablet

This was determined using RC-6 dissolution apparatus (basket method) in 6 replicates for each brand. The dissolution medium was 1000 ml phosphate buffer ph 6.8 which was maintained at 37°C at 100 revolutions per minute. In all the experiments, 5 ml of dissolution sample was withdrawn at 5, 10, 15, 30, 45 and 60 minutes and replaced with equal volume to maintain sink condition. Samples were filtered with syringe of 0.45um.The filtrate was diluted to $10^{-5}$ by serial dilution using phosphate buffer ph6.8 and assayed by ultraviolet spectrophotometer at 233nm. The % drug released was then plotted to obtain the dissolution-time profile.

$$\%\ \text{drug released} = \frac{\text{Concentration in mg/ml at a given time} \times 100}{\text{Final concentration}}$$

The test for Metformin is done to find out the actual amount of active ingredients present in the tablet and whether it is the same as the labelled amount.

Twenty (20) tablets from each brand was weighed and finely powdered, an accurately weighed portion of powder equivalents to A 100 mg quantity Metformin hydrochloride was transferred to a 100 ml volumetric flask and 70 ml of distilled water added. This was shaken mechanically for 15 minutes and the volume made up to 100 ml and filtered. 10 ml of the filtrate was transferred to a 100 ml volumetric flask and further diluted to 100 ml with distilled water, 10 ml of this was transferred to another 100 ml volumetric flask and further madeup to 100 ml with distilled water.

100 mg of the reference sample (RS) powder was added to 1000 ml volumetric flask and made up to volume with distilled water, 10 ml of the solution was transferred to a 100 ml volumetric flask which was made up to 100 ml with distilled water to get 10µg/ml concentration.

The absorbance of the standard preparation and assay preparation were concomitantly determined at λmax 232nm with UV-1650PC SHMADZU spectrophotometer using water as a blank. The quantity in mg of Metformin hydrochloride in the portion of the tablet taken was calculated by the formula.

**10C (Au/As)**

In which C is the concentration of Metformin HCl RS in $\mu g/ml$ and Au and As are the absorbance obtained from preparation and the standard preparation respectively.

## RESULTS

### Physicochemical properties of Metformin hydrochloride tablets

The samples have good to high quality package/labels with manufacturing and expiry dates. They are all registered in Nigeria as each one has NAFDAC number, a parameter which is highly considered when purchasing medicines in Nigeria.

Weight variation, hardness, friability, disintegration time, thickness and diameter test results are shown in Table 2. All the samples passed the uniformity of weight test in each group as justified by the narrow SDs. Hardness test showed a wide range (5 to 15Kg/cm$^2$) of hardness from one set of products to another. The Diameter and thickness tests complied with the USP specification and the ranges within the group of products are tolerable as indicated by the SDs. Disintegration time ranged from 4 min to 19 min., which falls within the USP specification. The percent drug content ranged from 63.4% to 102%. With this result, four products are out of USP specification (see Table 2).

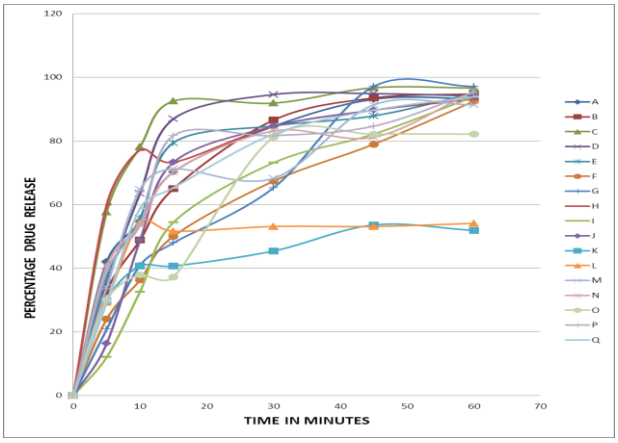


**Figure 1: Dissolution profile for Seventeen (17) brands of Metformin HCl (500 mg) tablets.**

**Table 1: Similarity factor (F2) the seventeen brands of Metformin HCl 500 mg (arrangement is not in any specific order).**

| S/N | Code | | F2 |
|---|---|---|---|
| 1 | A | Glucophage (innovator) | 100 |
| 2 | B | | 56 |
| 3 | C | | 57 |
| 4 | D | | 51 |
| 5 | E | | 58 |
| 6 | F | | 42 |
| 7 | G | | 74 |
| 8 | H | | 58 |
| 9 | I | | 64 |
| 10 | J | | 71 |
| 11 | K | | 64 |
| 12 | L | | 0 |
| 13 | M | | 0 |
| 14 | N | | 34 |
| 15 | O | | 65 |
| 16 | P | | 45 |
| 17 | Q | | 41 |

**Table 2: The results of official and unofficial methods of tablet evaluation.**

| Code | Uniformity of weight (g)±SD | Hardness (kg/cm²) | Disintegration time (min) | Assay (%) | Diameter (mm) | Thickness (mm) | Friability (%) |
|---|---|---|---|---|---|---|---|
| A | 0.5601±0.008 | 15 | 8 | 102.0 | 0.1661±0.030 | 0.050±0.004 | 0.09 |
| B | 0.5601±0.008 | 15 | 10 | 98.9 | 0.1529±0.002 | 0.065±0.002 | 0.17 |
| **C** | 0.6322±0.016 | 10 | 11 | 100.1 | 0.1894±0.002 | 0.0657±0.007 | 0.03 |
| D | 0.5601±0.008 | 5 | 7 | 100.9 | 0.1495±0.001 | 0.0668±0.0025 | 0.40 |
| E | 0.5601±0.008 | 7 | 7 | 99.0 | 0.1475±0.001 | 0.0505±0.002 | 0.50 |
| F | 0.5259±0.003 | 6 | 12 | 96.0 | 0.1495±0.001 | 0.0572±0.003 | 0.06 |
| G | 0.5831±0.149 | 7 | 9 | 99.4 | 0.1532±0.001 | 0.05511±0.004 | 0.02 |
| H | 0.6796±0.005 | 10 | 15 | 95.8 | 0.1838±0.001 | 0.0558±0.001 | 0.07 |
| I | 0.5973±0.006 | 5 | 14 | 98.3 | 0.1830±0.001 | 0.0668±0.002 | 0.57 |
| J | 0.6714±0.011 | 7 | 4 | 101.5 | 0.1633±0.002 | 0.0714±0.002 | 0.25 |
| K | 0.589±0.030 | 15 | 15 | 99.0 | 0.1207±0.001 | 0.1373±0.005 | 0.04 |
| L | 0.5431±0.042 | 6 | 5 | 63.4 | 0.1403±0.033 | 0.0815±0.004 | 0.37 |
| M | 0.5922±0.032 | 12 | 17 | 68.2 | 0.1745±0.003 | 0.1663±0.005 | 0.22 |
| N | 0.6432±0.103 | 14 | 9 | 98.0 | 0.1875±0.001 | 0.0852±0.005 | 0.62 |
| O | 0.5721±0.412 | 5 | 11 | 93.7 | 0.1644±0.025 | 0.0575±0.002 | 0.50 |
| P | 0.6012±0.322 | 11 | 8 | 97.0 | 0.1582±0.003 | 0.0754±0.004 | 1.04 |
| Q | 0.5431±0.007 | 13 | 19 | 94.0 | 0.1937±0.006 | 0.0677±0.004 | 0.30 |

## DISCUSSION

Seventeen brands of Metformin hydrochloride tablets which are commercially available in Jos, capital city of plateau state were subjected to a number of quality control test in order to assess their biopharmaceutical equivalence. The assessments involved the evaluation of uniformity of weight, friability, hardness, disintegration and dissolution test as well as chemical content determination. All the brands used were within their shelf life as at the time of study.

The weight uniformity for the seventeen brands of the Metformin hydrochloride tablets gave values that comply with the USP specification with a deviation less than 5% from the mean value (i.e. maximum deviation value 0.016) Table 2.

Using ERWEKA hardness tester, the strength of the tablets was tested. All the tablets failed this non official test according to USP specifications (4-6 kg).

The friability test is mostly important criteria for uncoated tablets during and after manufacturing to examine that the tablets have a good capacity to withstand stress during transportation, packaging, shipping and coating. The friability was tested for all the seventeen brands and it was seen that nine of the brands had values $>$0.2% while the remaining eight including the innovator drug passed the test. The values of $<$1% are considered to be highly satisfactory evaluation characteristics.

The observed disintegration time for all the tablets investigated was less than the 30 minutes limit prescribed by the official compendium (Table 2). All tablets of the different generic brands passed the disintegration test. The fastest disintegrated tablets were of the J brand, while the least were of the C brand. The various brands could have employed different disintegrants to improve the penetration of aqueous liquids. It should also be noted that the products with high hardness test results also have long disintegration time.

### Percentage content determination (Assay)

The assessment of percentage content of the active ingredient of the seventeen metformin tablets showed values within the monograph specification of 95% to 105%, while some fell outside this range of the stated amount of metformin hydrochloride as demonstrated in Table 5. Four brands gave values below 95% which includes L, M, O, and Q.

### Dissolution testing and Similarity factor (2)

Dissolution of drug from oral solid dosage forms is an important aspect for drug bioavailability (i.e. the drug must be solubilized in the aqueous environment of the gastrointestinal tract to be absorbed).[14] Accordingly, dissolution testing of solid oral drug products has emerged as one of the most important control test for assuring product uniformity and batch-to-batch equivalence.[15,16]

In the present investigation, the release of metformin hydrochloride from all the tablets was immediate and the percentage of drug released at 45 minutes was more than 70% except in the case of L and M as shown in Figure 1. The results obtained from this study revealed that fifteen out of the seventeen brands including the innovator brands passed the USP 32, general specifications standard for dissolution rate test for conventional release tablets.

Similarity factor analysis between eleven of the marketed tablets and the innovator brand A for the release of

metformin hydrochloride showed an f2 factor greater than 50 (Table 1). The remaining six brands which includes brand F, L, M, O, and Q showed f2 values less than 50. The higher the f2 values, the more similar the dissolution profiles, so f2 $<$50 represented non-similar profiles, while f2$>$50 denoted a similarity between eleven of the marketed brands and the innovator product (Table 1 and 2). Even though the similarity factors were low, they were not too far from the 50 mark they can as well be used as pharmaceutical equivalents; interchanged.

## CONCLUSION

Medicines inter-changeability is desirable if the basic requisite need of safety, quality, and efficacy are met in addition to cost effectiveness and availability of the' medicines. Out of the seventeen products compared, thirteen can be interchanged based on the result of the quality assurance parameters examined, similarity factor F2 and the dissolution testresult.

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