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Comparative *in-vitro* bioequivalence analysis of metformin hydrochloride tablet formulations available in Yenagoa Metropolis, Bayelsa State, Nigeria

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ABSTRACT

Aim: This study was aimed to use biopharmaceutical analysis and UV/visible spectroscopy to investigate the physicochemical attributes and in-vitro bioequivalence of metformin tablets.

Method and Materials: Glucophage and five other brands of metformin hydrochloride tablets were bought from selected authorized pharmacies in Yenagoa, Bayelsa State, and were all traditional, instantaneous-release oral dose forms. They were coded (M1 - M5), and pharmacopeia assays such as weight uniformity, friability, disintegration, hardness and assay were employed to demonstrate physicochemical equivalency, while percentage purity was determined using UV-spectroscopy.

Results: Based on the UV analysis at 10µg/ml, all brands gave percentage compositions that were within the monograph specifications ranging from 100.21%w/w (M1), 100.23%w/w (M3), 100.34% w/w (M4), 101.26% w/w (M5), and 104.26% w/w (M2), respectively. The metformin content in every brand was optimal from the other physicochemical analysis.

Conclusion: It was concluded that all of the brands of metformin hydrochloride tablets tested founds as per regulatory standards for identification, dissolution, weight uniformity, disintegration, hardness and thickness.

Keywords: Metformin, diabetes mellitus, biguanide, bioequivalence, UV/visible spectroscopy.

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Introduction

Diabetes mellitus (DM) is a group of metabolic disorders with clinical manifestation by high blood glucose levels (hyperglycemia) caused by defects in insulin secretion, insulin action, or both (American Diabetes Association, 2003). DM is classified into types 1 and 2, with other rare variations. Insulin insufficiency induced by pancreatic beta cell loss distinguishes type 1 DM, also known as insulin-dependent DM. Type 2 DM, on the other hand, presents as a spectrum of metabolic disorders characterized by significant resistance to insulin and an associated insulin shortage(American Diabetes Association, 2009; Solis-Herrera *et al.*, 2018). DM affects over 347 million individuals throughout the world. Fasting and high blood sugar levels were projected to be responsible for 3.4 million fatalities in 2004 (Kharroubi & Darwish, 2015).

Data on DM prevalence in Nigeria is few and unreliable. However, a previous study discovered a significant prevalent incidence of 6.3% (Uloko *et al.*, 2018).

Oral hypoglycemic medications like sulfonylureas and biguanides are used in the pharmacotherapeutic management of DM (Ganesan et al., 2022; Craig, 1994). Metformin (N, N-dimethylimidodicarbonimidic diamide hydrochloride), a biguanide, is used in the initial therapy and management of Type 2 DM, particularly in overweight and obese individuals (Nasri and Rafieian-Kopaei, 2014).

It is highly soluble, has a low permeability in the intestinal tract, and has a bioavailability of 50-60%. Metformin hydrochloride 500 mg tablet has an absolute bioavailability of 50 to 60% when administered during a fasting state (Gong *et al.*, 2012). Metformin may impede lactic acid metabolism in the liver due to its inhibition of gluconeogenesis. Biguanides accumulate in people with kidney disease, raising the risk of acidosis

caused by lactic acid, which appears to have a dose-dependent impact (Blough *et al.*, 2015; Rahman and Tuba, 2022).

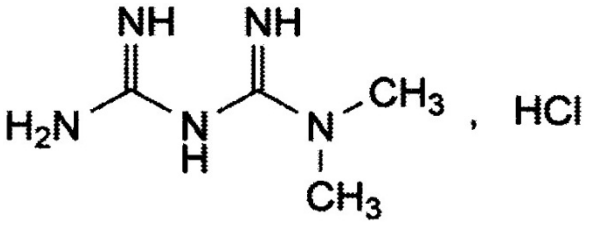

Fig 1.Metformin hydrochloride

Following the trademark expiration of the originator brand, Glucophage, different generics of metformin hydrochloride tablets are now accessible throughout the global healthcare system, and also in Nigeria. Only when the pharmacological and clinical properties of generic and innovator medications are identical may they be interchanged. The first stage in evaluating a pharmaceutical product's therapeutic equivalency is to identify its chemical and biological equivalence (Akinleye et al., 2012). The inclusion of generic medications from a range of sources in many developing countries' healthcare delivery systems attempts to enhance the usage of life-saving medications in these nations (Adegbolagun et al., 2007). The global incidence of counterfeit medications has reached epidemic proportions with developing nations being disproportionately affected (Ozawa et al., 2018). The prevalence estimates are not precise due to the difficulty of recognizing counterfeit pharmaceuticals, but they provide vital insight into the scale of the problem. According to the World Health Organization, counterfeit medicines account for 10% of the global pharmaceuticals market, while this proportion rises to 25% in developing countries and may exceed 50% in extreme situations (Board on Global Health, 2013; Glass, 2014).

Counterfeiting is possible with both innovator and generic products and might involve the wrong ingredient, products without an active component, products with the insufficient active ingredient, or products with phony packaging (Almuzaini et al., 2013; WHO, 2018). Substandard pharmaceuticals are genuine medicinal commodities that do not meet the quality and specifications specified by their makers following laboratory testing (Johnston and Holt, 2014). The goal of this study was to use biopharmaceutical analysis and UV/visible spectroscopy to investigate the physicochemical attributes and in-vitro bioequivalence of metformin tablets.

Materials and Methods

Sampling of metformin hydrochloride tablets

Five (5) different brands of metformin tablets (500 mg), alongside the innovator brand, were procured from licensed pharmacies in Yenagoa, Bayelsa State. Each location provided a balanced selection of amenities. The products were coded for research purposes, and the investigation was conducted before the expiration dates of the products. All studies were carried out following the British Pharmacopoeia's standard guidelines (BP, 2007).

Weight uniformity test

Twenty (20) tablets of the M1 brand were chosen at random and weighed individually, with their weights recorded. Each tablet's mean weight and percentage deviation were then computed (British Pharmacopoeia, 2007). This procedure was done with the remaining brands.

$$\% \text{ deviation} = \frac{A-B}{B} * 100$$

A= tablet weight, B = Average weight (20 tablets)

Friability test

Exactly 10 tablets were chosen at random from the M1 group, pulverized, weighed, and loaded in the friabilator machine. For 4 minutes, the friabilator was rotated at 25 rpm. The tablets were thoroughly cleaned and weighed again. The percent of weight loss was then calculated (British Pharmacopoeia, 2007). This procedure was repeated for the other brands. The following percentage weight loss was calculated:

$$\% \text{ weight loss} = \frac{Wi-Wf}{Wi} * 100$$

Wi= initial weight, Wf = final weight

Hardness test

Another 10 tablets were obtained from each brand for the hardness test, and the hardness of the samples was measured using a DKB hardness tester. The calibrated scale was reset to zero when a tablet was put between the tester's spindle and anvil. The tablet was squeezed, and the location on the calibrated scale where it broke was measured in kgf units. For each brand, the mean hardness with standard deviation was computed.

Disintegration test

Six tablets of each brand were individually placed into each of the disintegration equipment's six (6) cylindrical tubes. The bottom of the basket rack

was placed at least 15 millimeters beneath the surface of distilled water, and the experiment was conducted at 37°C. The moment when no granule of any tablet remained on the mesh was described as the disintegration time. This process was performed for each of the remaining brands. The average disintegration time for each brand was calculated using two estimates.

UV/Visible determination of metformin hydrochloride tablets: For UV/visible analysis, 20 tablets from each brand were weighed and powdered. After shaking for 15 minutes with 70 ml of distilled water, 0.1 g of metformin powder was diluted to 100 ml with water and filtered, discarding the first 20 ml. Distilled water was used to dilute 10 ml of the filtrate to 100 ml, and the solution was then distilled to 100 ml. The resulting solution's absorbance was measured at 232 nm. The process was then repeated for the remaining brands. Each brand's purity percentage was calculated.

Table 1. Samples of Metformin hydrochloride

Brand	Batch Number	Manufacturer Date
M1	E201597	08/18
M2	1508	12/15
M3	BJ04582	04/18
M4	FBH080118	08/18
M5	A181108	06/18

Results and Discussion

The completion of the necessary procedure on the selected brands of metformin hydrochloride pills, results were obtained and recorded. Test for Weight uniformity, Friability The hardness and disintegration time and UV/Visible analysis were done and data were tabulated.

The study employed five distinct types of metformin tablet formulations (Table 1). Without packaging, all of the samples were coded and evaluated. Quality characteristics that can be altered by drug product formulation include disintegration time, weight uniformity, hardness, friability, and dissolution time (Gupta et al., 2020). Furthermore, quality control criteria are powerful tools for guaranteeing consistency in batch-to-batch manufacture and should be applied to all pharmaceutical products. All of these variables interact and influence drug absorption, bioavailability, and other consequences (Wen et al., 2015). The requirement for equal drug dosage among different tablets within the same batch is a fundamental quality characteristic for all pharmaceutical formulations. Minor variances between particular preparations are permissible in practice, and the limits for these variations are established as standards in pharmacopeias (Jakubowska, & Ciepluch, 2021).

The weight of all metformin tablet brands was greater than 500 mg (Table 2). As a result, it is necessary for a batch of these tablets to pass the weight uniformity test, no more than two of their weights must be more than 5% off of the average weight. Furthermore, no tablet should deviate from the permissible percentage fluctuation more than twice (United States Pharmacopoeia, 2007). As a consequence, the weight uniformity test was passed by all brands. It could be attributed to the granules' good flow characteristics, the uniform compression force used in tablet compression, and consistent motion of bottom punch, which results in tablets' constant weight distribution (Aulton, 2002). M5 showed best weight variation homogeneity, with lowest standard deviation value of 0.021. M2 had greatest dispersion in tablet weight from mean weight, resulting in least consistent tablet weights, with a standard deviation (SD) of 0.069 (Table 2).

The friability test assesses a tablet's resistance to abrasion caused by handling, packaging, and distribution. For pharmaceutical goods, weight loss of not more than one percent of the weight of the tested tablet is deemed acceptable; values greater than 1% are regarded as undesirable (British Pharmacopoeia, 2007). The friability test was passed by all brands (Table 3).

During the tablet production process, hardness (crushing strength) tests are performed to identify the need for pressure change on the tablet machine. If the tablet is too firm, it may not disintegrate rapidly enough to meet dissolution standards; if the tablet is too soft, it may not withstand handling during later processing, such as coating, packaging, and transportation. Tablet hardness determines resistance to capping, friction, or breakage during transportation, storage, and handling before use. The power of compression, as well as the kind and amount of binder employed, determine the hardness of a tablet. For a decent tablet, a diametric crushing force of 4 Kgf was required or regarded as the bare minimum. All brands could withstand breakage, with M4 having the highest hardness parameter (14.5 Kgf), whereas M1 had the lowest (4.01 Kgf). This could be due to the use of the accurate quantity of binder in addition to the proper force of compression when compressing the tablets (Table 4).

Table 2. Uniformity of weight of the different brands of metformin hydrochloride tablets

Brands	The total weight (g)	Mean weight ±SD (g)	No. of tablets deviating by ±5%	No. of tablets deviating by ±10%
M1	10.757	0.538±0.034	Nil	Nil
M2	11.550	0.578±0.069	Nil	Nil
M3	11.240	0.562±0.052	Nil	Nil
M4	11.300	0.565±0.057	Nil	Nil
M5	10.211	0.5106±0.021	Nil	Nil

SD – Standard deviation

Table 3: Friability of the metformin hydrochloride tablets

Brands	Initial weight (g)	Final weight (g)	Weight Loss(g)	Percentage Weight Loss (%)
M1	3.254	3.228	0.026	0.805
M2	3.471	3.470	0.001	0.029
M3	3.441	3.414	0.027	0.790
M4	3.400	3.395	0.005	0.147
M5	3.083	3.082	0.001	0.032

Table 4. The hardness and disintegration time of the metformin hydrochloride tablets

Brands	The mean force applied (Kgf)	Average disintegration time(min)
M1	4.30	7.12
M2	6.01	8.43
M3	8.45	8.07
M4	14.5	11.59
M5	7.30	8.53

Table 5.UV/Visible analysis of metformin hydrochloride tablets

Brands	Concentration (µg/ml)	Mean absorbance	Assay (%w/w)
M1	10	1.004	100.21
M2	10	1.036	104.26
M3	10	1.020	100.23
M4	10	1.005	100.34
M5	10	1.016	101.26

The British Pharmacopoeia (BP) recommends that tablets without coatings disintegrate in less than 15 minutes and film-coated tablets disintegrate in less than 30 minutes. All of the film-coated and uncoated brands passed the test, according to the data because their disintegration times were shorter than thirty minutes.

The ultraviolet-visible spectroscopy was used to test all brands of metformin hydrochloride pills. According to British Pharmacopoeia standards, an assay of a metformin hydrochloride product should be between 95%w/w and 105%w/w of the label claim. Based on the UV analysis at 10µg/ml, all brands gave percentage compositions that were within the monograph specifications ranging from 100.21%w/w (M1), 100.23%w/w (M3), 100.34% w/w (M4), 101.26% w/w (M5), and 104.26% w/w (M2), respectively (Table 5). The metformin content in every brand is considered optimal because effective *in-vivo* release ensures therapeutic concentration and thus greater therapeutic response.

Conclusion

It was concluded that all the brands of metformin hydrochloride tablets tested fulfilled regulatory standards for identification, dissolution, weight uniformity, disintegration, hardness and thickness. All brands used in the analysis had contents that are within the British Pharmacopoeia's assay standard range. Thus, they are biopharmaceutical equivalents.

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