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The Potency of Some Brands of Anti-Diabetic Medicine-Metformin Hydrochloride B.P 500 mg Tablet on the Ghanaian Market

George Louis Williams*, Dennis Agbotse**
Science Laboratory Technology Department, Accra Polytechnic, P. O. Box Gp 561, Accra. Ghana
*E-mail: glowils@hotmail.com ; **denagbo210@gmail.com

Abstract

Metformin hydrochloride tablet is a drug of choice in the treatment of diabetes mellitus type-2 especially in obese patients. It is normally given in initial doses of 500 mg tablet two or three times daily or 850 mg once or twice daily with or after meals. Recently there were numerous concerns on the increase in substandard pharmaceutical products on the market. A study was therefore carried out to determine the potency of some brands of metformin hydrochloride tablet BP 500 mg using the test method for assay as prescribed in the British Pharmacopoeia (BP) monograph. In the study, seven different brands of sample were purchased from various pharmacies in Accra and analyzed. The results indicated that all the samples analyzed passed the test for assay, dissolution rate and uniformity of weight. It is recommended that a study be carried out on other brands.

Keywords: *metformin hydrochloride, diabetes , potency claim , british pharmacopoeia (bp)*

1. Introduction

Metformin hydrochloride tablet is an biguanide anti-diabetic. It is taken orally in the treatment of Type-2 Diabetes Mellitus and it is a drug of first choice in obese patients. The initial dosage is 500 mg two or three times daily or 850 mg once or twice daily with or after meals, gradually increased if necessary to 2 to 3 g daily dose (Shashank, 2005).

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract. The absolute bioavailability of a single 500 mg dose is reported to be about 50 to 60 % although this is reduced somewhat if taken with food. Once absorbed, plasma binding is negligible, and it is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours after oral doses.

Diabetes mellitus type-2 is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency (Jayasagar *et al*. 2002). This is in contrast to diabetes mellitus type-1, in which there is an absolute insulin deficiency due to the destruction of islet cells in the pancreas. The classic symptoms are excessive thirst, frequent urination and constant hunger. Type-2 diabetes makes up about 90% of cases of diabetes with the other 10% primarily due to diabetes mellitus type-1 and gestational diabetes.

Following alerts by the Food and Drugs Authority (FDA) of Ghana on the presence of fake drugs, including some from the producers of metformin on the market on 13th of February 2013, it become necessary to

carry out an assessment of the potency (label claim) of Metformin hydrochloride 500 mg tablets sold in pharmacy shops in order to ascertain their potency.

1.1 Problem statement

Counterfeit and substandard medicines have been a serious problem facing health delivery systems developing countries. The quality of metformin hydrochloride BP 500 mg as a substandard drug or a fake is of great importance on the Ghana.

By some estimation, about 40-60% of medicines on the market are fake or substandard. Several efforts have been both proposed and undertaken to combat the problem. Systematically assaying the various drugs on the market will expose the fake and substandard ones.

1.2 Objectives

The objective was to carry out Assay, Dissolution Rate and Weight Uniformity of metformin hydrochloride tablet BP 500 mg, and compare it to the British Pharmacopoeia (BP) standards to determine their potency or otherwise.

2. Metformin

Metformin is an oral anti-diabetic drug in the biguanide class. It is the first- line drug of choice for the treatment of type-2 diabetes, in particularly, in overweight and obese people and those with normal kidney function. Metformin is the only anti diabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes. It helps to reduce LDL cholesterol and triglyceride levels, and is not associated with weight gain. As of 2010, metformin is one of the only two anti diabetic drugs in the World Health Organization model list of essential medicines (WHO, 2010).

When prescribed correctly, metformin causes few adverse effects (the most common is gastrointestinal upset) and is associated with a low risk of hypoglycemia. First synthesized and found to reduce blood sugar in the 1920's, metformin was forgotten for the next two decades as research shifted to insulin and other anti-diabetics. Interest in metformin was rekindled in the late 1940's after several reports that it could reduce blood sugar levels in people, and in 1957, French physician Jean Sterne published the first chemical trial of metformin as a treatment for diabetes. Metformin is now believed to be the most widely prescribed anti-diabetic drug in the world (Bailey, 2004).

2.1 ***Medical Uses of Metformin***

Metformin is primarily used for type-2 diabetes, but it is increasingly being used in Polycystic Ovary Syndrome (PCOS), and non-alcoholic Fatty Liver Disease, NAFLD (Marchesini *et al*., 2001). The benefit of metformin in NAFLD has not been extensively studied and may only be temporary (Nair *et al.,* 2004).

2.1.1 Type-2 Diabetes

Over 10 years of treatment in a study group, metformin reduced diabetes complications and overall mortality by 30% when compared with insulin and sulfonylurea (glibenclamide and chlorpropamide) and by about 40% when compared with the group only given dietary advice.

Metformin affords a good level of blood sugar control to insulin and sulfonylurea, it appears to decrease mortality primarily through decreasing heart attacks, strokes and other cardiovascular complications (Selvin *et al*., 2007).

2.1.2 Pre-Diabetes

Metformin treatment for people at risk for type-2 diabetes may decrease their chances of developing the disease, although intensive physical exercise and dieting work significantly better for this purpose. In a study in the United States known as Diabetes Preventive Program, participants were divided into groups and were either placed on metformin or lifestyle intervention, and they were observed for an average of three years. The intensive program of lifestyle modification included a 16-lesson training on dieting and exercise followed by monthly individualized sessions with the goals to decrease the body weight by 7% and engage in a physical activity for at least 150 minutes per week. The incidence of diabetes was 58% lower in the lifestyle group and 31% lower in those given metformin. Among younger people with a higher body mass index lifestyle modification was no more effective than metformin, and for older individuals with a lower body mass index, metformin was no better than placebo in preventing diabetes. After 10 years, the incidence of diabetes was 34% lower in the group of participants given diet and exercise and 18% lower in those given metformin (Knowler *et al*., 2009).

It is unclear whether metformin slowed down the progression of pre-diabetes to diabetes (true preventive effect), or the decrease of diabetes in treated population was simply due to its glucose-lowering action (treatment effect) (Lilly, 2009).

3. Materials and Methods

3.1 Sampling

Seven different brands of metformin hydrochloride 500 mg BP Tablets were purchased from different pharmacy shops in Accra.

3.2 Procedures

Reference Procedure: (British Pharmacopoeia, 2010)

3.2.1 Assay

Twenty tablets were weighed and grounded into powder. An amount of 0.1 g of the powdered metformin hydrochloride was added to 70 ml of water and shaken for 15 minutes. The suspension was further diluted to 100 ml with water and filtered. 20 ml of the resulting solution was discarded after settling and 10 ml of the resulting solution again diluted to 100 ml. The absorbance of the final solution was measured at a wavelength of 232 nm using the ultraviolet- visible spectrophotometer .

The content of metformin hydrochloride was then computed taking 798 as the value of A (1%, 1cm) at a peak of 232 nm.

The expression A (1%, 1cm) representing the specific absorbance of a dissolved substance refers to the absorbance of 1% w/v solution in a 1 cm cell and measured at a defined wavelength such that;

$$A\ (1\%, 1cm) = 10\varepsilon/M$$

Where M is the molecular weight of the substance being examined.

The specific absorbance is therefore the nominal absorbance of a 1cm layer of a 1% w/v solution of the absorbing solute.

3.2.2 Tablet Dissolution Rate

Six tablets were selected randomly from a brand, weighed and placed in the dissolution basket and lowered into a medium (900 ml of 0.68 % w/v solution of potassium di-hydrogen orthophosphate, pH 6.8). The chamber was then operated at 100 rpm for 45 minutes, after which a sample of the resulting solution was drawn separately from each chamber and filtered, 10 ml of the filtrate was then diluted to 100 ml. The absorbance of the filtered solutions was then determined at the peak wavelength of 233 nm using the ultraviolet-visible spectrophotometer. The total content of metformin hydrochloride in the medium was determined using 806 as the value of A (1%, 1cm) at the peak at 233 nm.

3.2.3 Weight Uniformity

Twenty tablets of each brand was selected randomly and weighed. The average weight was then evaluated, acceptable deviations are not to be more than 5 %.

4.**Results And Discussions**

4.1Assay

Table 1gives the distribution of the metformin hydrochloride content of samples of the various brands used in the study. Generally, all samples analyzed fall within the acceptable limit of **95 % ~105 %** assay. Assay is a single test carried out for the purpose of estimating the potency of a material/preparation or the pooled results of two or more such tests (BP, 2010).

4.2 Dissolution

Generally, all the samples passed the test for dissolution rate which should **not be less than 85%.** These recorded (table 2) values within the recommended values according to the British Pharmacopeia (BP 2010).

In the Pharmaceutical industry, drug dissolution testing is routinely used to provide critical *in vitro* drug release information for both quality control purposes, [to assess the batch-to-batch consistency of solid oral dosage forms such as tablets, and drug development,] to predict *in vivo* drug release profiles (Bai *et al.,* 2011). In vitro drug dissolution data generated from dissolution testing experiments can be related to in vivo pharmaco-kinetic data by means of *in vitro-in vivo* correlations (IVIVC).

A well established predictive IVIVC model can be very helpful for drug formulation design and port-approval manufacturing changes (Kortejarvi *et al*., 2006). The main objective of developing and evaluating an IVIVC is to establish the dissolution test as a surrogate for human bioequivalence studies, as stated by the Food and Drugs Administration (FDA). Analytical data from drug dissolution testing are sufficient in many cases to establish safety and efficacy of a design product without in vivo tests, following minor formulation and manufacturing changes (Qureshi, 2001).

4.3 Weight Uniformity

When 20 individuals units are taken at random and weighed, not more than two of the individual masses should deviate from the average mass by more than 5 % for 250 mg and above tablets (BP 2010), Generally, all samples passed the test for Uniformity of Weights (Table 3).

5.**Conclusion**

Inferential analysis of the analytical results proves that many brands (as sampled in the study) of metformin hydrochloride 500 mg tablet sold in various pharmacies in Accra are potent in terms of label claim, dissolution rate and uniformity in weight. This could be as a result of; the effective surveillance activities of the Food and Drugs Authority of Ghana, the proper storage of these medicines by wholesalers, retailers and pharmacies who stock these medicines, and the relatively stable nature of metformin hydrochloride compound.

These results are based on the laboratory analysis carried out on seven (7) brands of metformin hydrochloride 500 mg tablet B.P obtained from various pharmacies in Accra, namely; GLUCOPHAGE Tablet, METFORMIN-DENK Tablet, KINAMET 500 mg Tablet, METFORMIN 500 mg Tablet, DIABETMIN Tablet, GR-METFRORMIN, and BGMET Tablet.

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Table 1:Potency (Label claim) of metformin hydrochloride tablet 500mg

Name of Sample	Manufacturer	Batch Number	Expiry Date	Potency (Label claim) (%)
GLUCOPHAGE	Merck Sante s.a.s	102841	February 2016	100.63
METFORMIN-DENK	Denk Pharma GmbH & Co.	8MI	January 2016	99.96
KINAMET	Kinapharma Ltd	810	June 2016	99.96
METFORMIN-500	Bristol Labs Ltd	BUH032088	May 2016	99.01
DIABEMET	Hovid Pharma	BC12657	December 2015	99.01
GR-METFORMIN	GR Industries Ltd	MF121204	November 2015	97.34
BGMET	Bliss GVS Pharma Ltd	BG-112	November 2013	97.25

Table 2: Dissolution Rate of metformin hydrochloride tablet 500mg

Name of Sample	Manufacturer	Batch Number	Expiry Date	Dissolution Rate (%)
METFORMIN-DENK	Denk Pharma GmbH	8MI	January 2016	98.2
DIABEMET	Hovid Pharma	BC12657	December 2015	98.0
GLUCOPHAGE	Merck Sante s.a.s	102841	February 2016	96.5
BGMET	Bliss GVS Pharma Ltd	BG-112	November 2013	96.4
GR-METFORMIN	GR Industries Ltd	MF121204	November 2015	96.2
METFORMIN-500	Bristol Labs Ltd	BUH032088	May 2016	96.0
KINAMET	Kinapharma Ltd	810	June 2016	92.4

Table 3: Weight Uniformity of metformin hydrochloride tablet 500mg

Name of Sample	**Manufacturer**	**Batch Number**	**Expiry Date**	**Weight Uniformity**
METFORMIN-DENK	Denk Pharma GmbH	8MI	January 2016	**-2.2 % ~ +1.4%**
DIABEMET	Hovid Pharma	BC12657	December 2015	**-1.6% ~ +1.2 %**
GLUCOPHAGE	Merck Sante s.a.s	102841	February 2016	**-0.9% ~ +1.1%**
BGMET	Bliss GVS Pharma Ltd	BG-112	November 2013	**-1.6% ~ +1.4%**
GR-METFORMIN	GR Industries Ltd	MF121204	November 2015	**-2.2% ~ +2.6%**
METFORMIN-500	Bristol Labs Ltd	BUH032088	May 2016	**-2.0% ~ +2.6%**
KINAMET	Kinapharma Ltd	810	June 2016	**-2.9% ~ +2.8%**