Exploring the Differences: A Comparative Analysis of Pharmaceutical Quality of Different Brands of Metformin Hydrochloride Tablets

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ABSTRACT

Type 2 diabetic patients can regulate their increased blood sugar levels using metformin, an antidiabetic medicine approved by the FDA. It decreases the quantity of glucose produced by the liver, lessens the glucose absorption from the intestines, and raises insulin sensitivity. For best effects, metformin should be used in conjunction with dietary modifications and physical activity. The first-line oral hypoglycemic medication for type 2 DM(Diabetes Mellitus) is thought to be metformin. The recommended medication for obese people is MET. AMPK- Adenosine monophosphate-activated protein kinase, a liver enzyme crucial to insulin signaling, is triggered by metformin. Metformin's inhibitory effect on hepatic cell glucose synthesis necessitates AMPK activation. This study aims to compare the pharmaceutical quality of three different brands of metformin hydrochloride tablets. All the three brands were evaluated for uniformity of weight, friability, hardness, dissolution, disintegration and assay was performed. All the brands tested were within the specification, thus all the tablets passed the pharmaceutical quality test, however, variations exist between brands, which could be due to differences in excipients, pressure during compression, manufacturing procedure etc.

KEY WORDS: Metformin hydrochloride, Quality, Specification, Ultraviolet spectroscopy, IP, USP

INTRODUCTION

Medication safety is a worldwide concern. Health requires a consistent, high-quality supply of medications, but in developing nations with poor regulatory frameworks, this supply is frequently lacking. The issue of spurious, falsely-labelled, falsified, and counterfeit pharmaceuticals was initially discussed during an international conference on the responsible use of pharmaceuticals held in Nairobi (1985). The World Health Organization and other international and non-governmental organizations were advised during the meeting to investigate the viability of establishing a center for exchange in order to gather information and notify the authorities about the scope of copying. Finding and banning SFFC medications has proven to be a significant health concern since their usage can lead to unsuccessful treatment or even death, and their use or discovery could undermine public trust in the medical system. [1]It is an old herbal medicine made from the French lilac that was mentioned in 17th-century herbal literature, as having qualities that could help with the symptoms of diabetes. Metformin, namely dimethyl biguanide, was first produced in 1922. The drug metformin was first identified as Glucophage, or glucose eater, in a publication on the drug's characteristics written by French scientist Jean Sterne in

the 1950s. It has since been applied to the management of diabetes. In 1994, the use of metformin was authorized in the US.As a result of the UKPDS (United Kingdom Prospective Diabetes Study) showing improvements in type 2 diabetes morbidity and mortality, the European Association for the Study of Diabetes (EASD) and American Diabetes Association have recommended metformin for type 2 diabetes since 2009 as the first-line treatment orally. [2]

For more than five years, metformin has been a commonly used hypoglycemic medication in clinical practice to treat diabetes. For the treatment of diabetes, it can be taken either alone or in conjunction with any other hypoglycemic medication. It is both safe and effective when used alone. It is also reasonably priced, lightens, or at the very least is weight neutral. It has favorable effects on lipids, has a lower incidence of hypoglycemia than sulfonylurea and insulin, andadditional research suggests that it may provide protection against specific malignancies. [3]
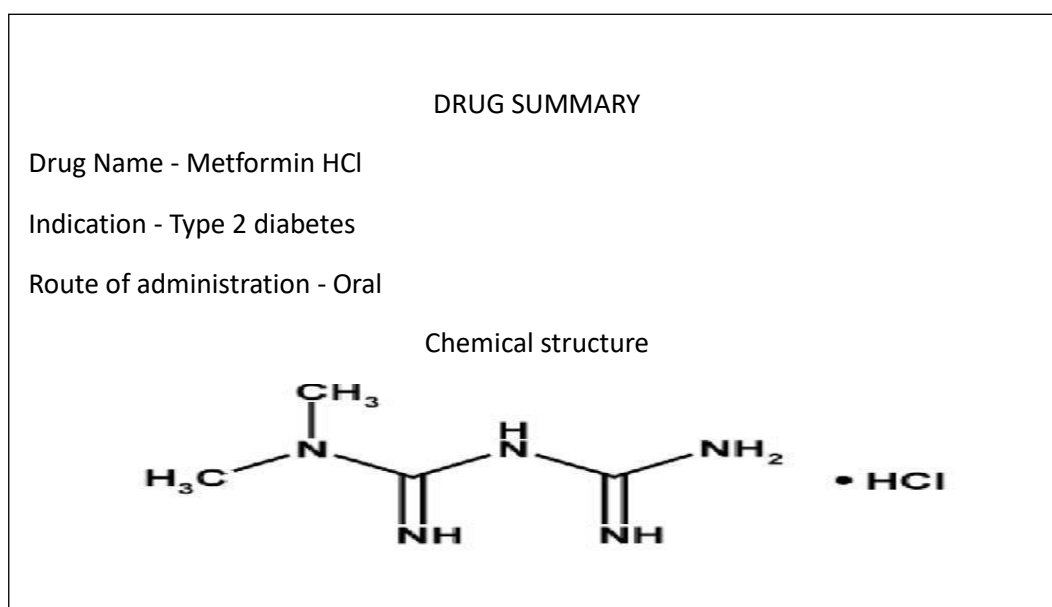
Its chemical name is N, N-dimethylimidodicarbonimidicdiamide hydrochloride, and neither its pharmacological nor chemical makeup is similar to that of any other class of oral antihyperglycemic medications. Pharmaceutical dosage forms can only be considered safe, effective, and efficacious if their quality is consistent. To verify this, assessment tests in accordance with official books such as IP, BP USP and EP must be conducted.[4] Metformin, a guanidine derivative, has a comparatively low octanol-to-water distribution coefficient (log ¼ -1.43). Metformin HCl is off white or white crystalline substance ($C_4H_{12}ClN_5$). It is practically insoluble in ether, acetone, and or chloroform and easily soluble in water.Metformin hydrochloride crystals have a melting point of 218˚C-220˚C. [5]

DIABETES MELLITUS

Diabetes was first described by the Egyptians and is distinguished by polyuria and weight loss. Aertaeus, a Greek physician, was the first to use the term diabetes mellitus. Diabetes means "to pass through" in Greek, while mellitus is derived from the Latin for honey. It is a leading cause of long-term illness and premature death, killing more people each year than HIV/AIDS, with roughly one death every 10 seconds. [6] Diabetes develops through a number of pathological processes. These include autoimmune

destruction of pancreatic beta cells, which causes insulin deficiency, as well as abnormalities that lead to insulin resistance.

Symptoms

- Polyuria
- Polydipsia
- Weight loss
- Blurred vision

Prolonged issues of diabetes include retinopathy (which can cause loss of vision), nephropathy (which can cause kidney failure), and peripheral neuropathy (which can cause foot ulcers, Charcot joint disease, and amputation). Diabetics usually have hypertension and an impaired lipid metabolism.

Type 1 DM (Diabetes Mellitus)

This type of diabetes, also known as insulin-dependent diabetes or type I diabetes (juvenile-onset diabetes), affects just 5-10% of diabetics. It is caused by an autoimmune reaction that destroys pancreatic beta cells through cellular mechanisms. [7]

Type 2 DM (Diabetes Mellitus)

Type 2 diabetes is characterized by dysfunction of protein, lipid, and carbohydrate metabolism, which can be caused by insulin resistance, reduced insulin production, or a combination of both of these factors. Its primary cause is gradually reduced pancreatic β-cell insulin release, typically in the context of already existing diabetes-related insulin resistance in the liver, skeletal muscle and adipose tissue. Many individuals with type 2 diabetes show no symptoms at diagnosis, while some have severe hyperglycemia or even diabetic ketoacidosis. [8]

HISTORY OF METFORMIN

The botanical origins of metformin can be traced back to the medieval European use of G. officinalis, often referred to as professor weed, goat's rue, and Italian fitch. The plant was brought in 1891 to North America, and now listed as a noxious weed by many US states. Galega officinalis was determined to be abundant in guanidine and similar chemicals through chemical investigations conducted in the mid-1800s. It was observed in 1918 that guanidine may lower blood glucose levels in animals. Later in the 1920s, many mono-guanidine derivatives were also found to have this effect, including galegine and diguanidines like synthalin. As insulin became more readily available, they were used less frequently in the 1930s, although initial optimism turned out to be false when toxicity was found.

Figure1. Galega officinalis, botanical origin of Metformin.

Along with being a major contributor to continuing research and training medical professionals to facilitate the introduction of metformin into clinical practice throughout Europe, Sterne proposed the term "Glucophage," which was utilized by Aron to promote the medication. The history books may be inclined to write off metformin's diabetes indication as a coincidental finding, but we have to give credit to Sterne for his tireless research, astute clinical intuition, and keen curiosity. [9] Although buformin and phenformin were initially more popular and widely used than metformin due to their potency, by the end of the 1970s, most countries had stopped using them due to their link to lactic acidosis. The combination of metformin with phenformin and buformin may have damaged the drug's reputation, but further research is confirming that metformin is an effective antihyperglycemic without producing obvious hypoglycemia or weight gain. The fact that metformin had a special range of actions that addressed insulin resistance started to become more widely recognized. Numerous biguanides and associated guanidine analogues have been investigated as possible antidiabetic drugs; however, a large portion of this research was conducted before current models of resistance to insulin were available. Nonetheless, metformin's numerous modes of action combined with its distinct pharmacokinetic and pharmacodynamic characteristics provide a favorable risk-benefit ratio that has made it a top medication for people with type 2 diabetes. [10]In 1969 a double-blind trio was conducted on female patients with normal oral glucose tolerance and refractory obesity revealed that metformin medication was linked to a significant three-month weight-loss impact. Both the oral glucose tolerance test and fasting glucose levels were unaffected by the addition of metformin, according to a 1998 study. In 2014, the study brought attention to the high risk of lactic acidosis in people using metformin who also had renal impairment. A research team did a systematic evaluation of randomized controlled trials in 2021 and found that metformin is safe to use in treating obesity, including in children and adolescents who may experience gastrointestinal (GI) adverse effects. [11]
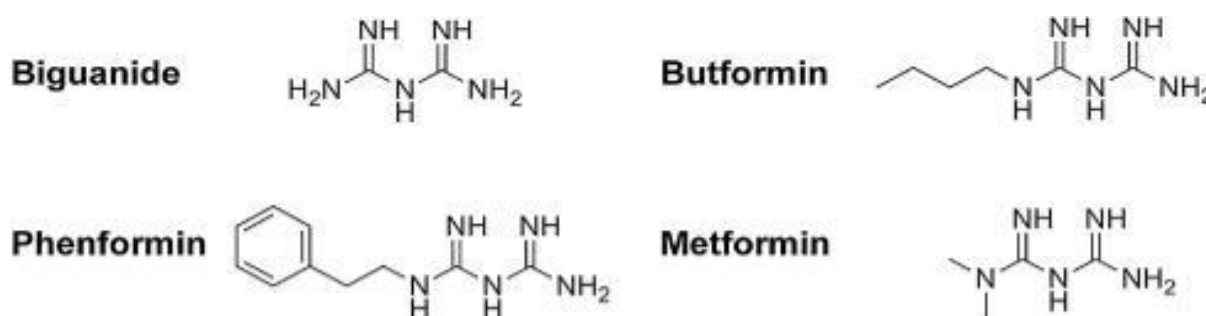

Figure2. Chemical structure of Biguanide, Buformin, Phenformin, Metformin.

PHARMACOKINETIC OF METFORMIN

Metformin is ingested orally, where it is absorbed by the intestinal enterocytes and enters the digestive system. The portal vein transports it to the liver, where the hepatocyte's cell receptors allow it to be absorbed. Since the liver does not metabolize metformin, it eventually enters the circulation, where it gets absorbed by the kidneys and then eliminated unchanged from the body through urine.

The blood concentration of metformin reaches its peak within 1–3 hours. However, this differs from individual to individual. Patients with abnormal renal function may lead to accumulation of metformin in body. [12]

MATERIAL AND METHOD

Three different brands of MetforminHCl500 mg strength were purchased from the local pharmacies in Bazpur, U. S. Nagar (Uttarakhand). Each brand were coded as M-01(Melmet-500 sr), M-02(Glycomet®-500sr), M-03(Glyciphage®).A variety of in-vitro quality control tests, including those for hardness, friability, weight variation, disintegration, and dissolution, were used in the investigation. All the tests were performed within the expiration date of each brand.

Instruments

Weighing balance, UV, Disintegration apparatus, Dissolution apparatus (basket type), Friability tester, Monsanto hardness tester.

Table1. Labelled details of sampled Metformin hydrochloride Tablets.

Coding	Brand name	Mfg. Date	Exp. Date	Manufacturer	Batch no.
M-01	Melmet-500 SR	06/2023	11/2025	Microlabs Limited	MEDSO217
M-02	Glycomet ®-500 SR	10/2023	09/2026	USV Private limited	60000760
M-03	Glyciphage®	09/2023	08/2026	Franco-Indian pharmaceuticals Pvt. Ltd.	23187

WEIGHT VARIATION

- 20 tablets were chosenrandomly and weighed separately.
- Average weight was estimated, and weight of each tablet was compared to the average.
- As to Indian Pharmacopeia, if only two out of every three individual weights depart by ± 5% and none by ± 10% from the average weight, the tablet is considered passed.

HARDNESS TEST

The nature of the formulation, dwell period, and pressure used all affect the hardness of a tablet. This represents the strength of the tablet. Five tablets was tested for hardness using a Monsanto hardness tester. [13]

FRIABILITY TEST

Friability is the propensity of the tablets to fragment, chip, or powder, and this can have an impact on the tablet's elegant look and adoption by consumers. A characteristic of the tablet that has to do with its hardness is called friability. The tablet's resistance to rattling during handling, packaging, and shipment is assessed using a device known as a friabilator. [14]

Procedure

- 20 tablets are selected randomly, dedusted and weighed.
- Then these tablets were placed in drum and allowed to rotate for 100 times/revolution.
- After completion of 100 revolutions, tablets were removed, dedusted and weighed.
- Then percentage loss of tablet weight is calculated using formula:

$$Friability\% = Wo - Wf \div Wo \times 100$$

- Wo = Initial weight, Wf = Final weight
- Limit: Friability (%) = Note more than 1.0%

DISINTEGRATION TEST

Tablet disintegration is the breakdown of a compacted tablet into numerous particles. To incorporate poorly soluble APIs, complete disintegration is recommended**. [15]**

- Six randomly chosen tablets from each of the three brands were tested for disintegration time in 900 milliliters of distilled water at a temperature of 37°C.
- The period of time during which no drug granule remained on the mesh was considered the disintegration time.[16]

DISSOLUTION TEST

- As per the US Pharmacopeia, the dissolving test was carried out in a medium that contained 6.8 pH phosphate buffer (900mL).
- The temperature was maintained at 37 ±0.5 °C, and the at a constant speed (100 rpm) the basket was rotated.
- One tablet containing 500 mg of metformin was used in each test.
- 10 ml of samples were taken at 10, 15, 20, 30, and 45 minutes.
- Then equivalent volume of 10 ml dissolving medium was added to the vessel to maintain the constant volume.
- Then samples were filtered and the drug content of the sample was determined by measuring the absorbance at maximum at 232 nm. [17,18]

ASSAY

To quantify medical substances using a spectrophotometer, prepare a solution in a clear solvent and measure its absorbance at an appropriate wavelength.[19]

- 20 tablets of Metformin HCl of each brand were weighed and powdered in mortar pestle.
- Then 0.1 g of metformin hydrochloride powder was shaken in 70 mL of distilled water for 15 minutes, then diluted to 100 mL and filtered.
- 10 mL of the filtrate was diluted to 100 mL with distilled water.
- Then 10 mL of the resultant solution was further diluted to 100 mL with distilled water to get10 µg/mL[17]
- Then absorbance of this solution was measured at maximum at 232nm, and distilled water was used as blank.
- According to monograph as A(1%) using the specific absorbance of 798the percentage content of the samples were calculated by using the formula:[20]

    $\%Metformin\ Hcl = Absorbance\ of\ sample \div A1\% \times b \times Dilution\ factor(100 \div 0.1)$[13]
- A1% = 798, b = 1,

RESULT
WEIGHT VARIATION TEST

All tablets from three brands were within the IP limit, which states that no more than two individual wei-

hts should differ from the average weight by more than ±5% and none should differ by more than ±10%.

Table2. Weight uniformity of three brands of metformin hydrochloride.

Brand	Total weight (gm)	Average weight(gm)	No. ofthe tablets deviatingby ±5%	No. of the tablets deviating by ±10%
M-01	12.97	0.648	Nil	Nil
M-02	14.43	0.721	Nil	Nil
M-03	10.99	0.549	Nil.	Nil

HARDNESS

Hardness of 5 tablets of each brand was determined by Monsanto hardness tester. The hardness of oral tablets ranges from 4 to 10 kg, whereas chewable and hypodermic tablets have a hardness of 3 kg and 10-20 kg for sustained release tablets.

Table3. Hardness of three brands of metformin hydrochloride tablets.

Brand	Hardness(kg)
M-01	14.04 kg
M-02	14.02kg
M-03	15.01kg

FRIABILITY TEST

As the limit of friability (%) is not more than 1.0% all the brands were found within the standard limit of friability, with M-03 having high %weight loss (0.36%) than the other brands.

Table4. Result of friability test of three brands of metformin hydrochloride tablets.

Brand Code	Initial weight	Fsinal weight	%weight loss
M-01	0.648	0.647	0.15%
M-02	0.721	0.720	0.13%
M-03	0.549	0.547	0.36%

DISINTEGRATION TEST

As per IP time of disintegration for uncoated tablets is 15 min and 30 min for film coated tablets, so all the brands have disintegration time according to IP. M-01 and M-03 are uncoated tablets and M-02 is film coated tablet.

Table5. DT profile of three brands of metformin HCl tablets.

Brand	% Drug release
M-01	88.6
M-02	86.9
M-03	85.3

DISSOLUTION TEST

According to the IP, all of the brands passed the dissolution requirement, which states that at least 75% of the medication should be discharged in 45 minutes.Along the three brands M-01 having the high percent release concentration.

Table6. Dissolution profile(% drug release) of three brands of metformin hydrochloride Tablets.

Brand	%Assay
M-01	95.60
M-02	103.14
M-03	99.72

ASSAY

The test limit for metformin hydrochloride tablets is usually expressed as the percentage of metformin contained in the tablets, in accordance with the Indian Pharmacopoeia (IP). According to the IP, the metformin content must fall between a particular range95.0% and 105.0% of the amount that is indicated. This range guarantees that the tablets fulfill quality standards and contain the prescribed amount of active ingredient. Every one of the three brands had values that satisfied IP criteria.M-02 having high% assay (103.14%).

Table7. Assay of three different brands of metformin HCl tablets.

Brand code	Disintegration time (min)
M-01	10.52
M-02	15.23
M-03	10.16

DISCUSSION

Three distinct brands of metformin HCl tablets were used for all pharmaceutical quality control testing. Quality control tests, including both official tests and non-official tests such as weight variation, dissolution, disintegration test, hardness, and friability test, were performed. All the tablets fall within the specification as per IP and USP.

In pharmaceutical manufacturing, weight variation testing is crucial for maintaining dose uniformity. An uneven dosage regimen could result from a weight deviation, which could have an effect on the patient's health. Following a weight variation test, all three brands passed because not one of the tablets from any of the brands deviated from ±5% as per the Indian Pharmacopeia. Hardness of the tablet is essential to prevent it from breaking during transportation, handling etc. It also influences the dissolution and disintegration rates. The friability test for tablets is important since it evaluates the ability of tablet to tolerate mechanical stress during transportation, handling, and storage. So as all the brands tested for friability passed the test and % friability was found not more than 1% of each brand that is specified in IP. Dissolution tests determine the rate at which the active pharmaceutical component is released from the tablet, assuring regulatory compliance and therapeutic efficacy. Disintegration studies determine how rapidly the medicine breaks down into smaller particles under simulated physiological settings, influencing its bioavailability and absorption in the body. These tests help to guarantee that the drug is of consistent quality and function. As per the IP, the disintegration time for an uncoated tablet is 15 minutes and 30 minutes for a film-coated tablet (M-02), so all the brands were within the specification.

The drug release of tablets was found by UV-visible spectroscopy and M-01 was found with high percent drug release. Assays quantify the concentration of active components, allowing for potency comparisons between different brands of tablets. They aid in the identification of impurities allowing for comparisons of purity levels between different brands, which is critical for safety and efficacy.

CONCLUSION

Quality control tests were performed on three different brands of metformin hydrochloride tablets (Melmet-500sr, Glycomet®-500sr, and Glyciphage®). Each brand complies with the specification; hence, each brand is effective for use in diabetes as it meets all the in vitro criteria of testing. The variation that exists between different brands may be due to different manufacturing techniques, but each brand passed the official and non-official tests as per the standards.

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