Comparative Study of Evaluation of Generic and Branded Metformin HCl (500mg) Tablets

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ABSTRACT: The use of generic or branded drugs is gaining attention globally, with governments promoting the use of generics over branded ones. Metformin hydrochloride, a first-line anti-diabetic drug, is used for treating type II diabetes, particularly in obese patients. Various brands of metformin are available, making it challenging to select an effective and economical option. This research aimed to compare and evaluate the performance of different marketed brands of generic and branded metformin tablets. Two 500 mg tablets were selected and evaluated for their physical and chemical parameters. The physicochemical equivalence of all brands was determined using official standards, including thickness, hardness, weight variation, friability, disintegration time, standard calibration curve, dissolution study, and drug content. The results showed that all brands were within acceptable range, following IP specifications. It is recommended that further research be conducted in different formulations to ensure product quality.

Keywords: **Generic drugs, patent, metformin, evaluation, quality.**

INTRODUCTION:

Generic Drug

According to FDA "a drug product that is comparable to branded product is dosage form strength route of administration, quality and performance, characteristics, and intended use [1]. It is a copy of branded drug whose patent has expired which has no longer exclusive rights to produce and distribute medicines [2]. On expiration of the originator product's patent term protection, other manufacturing companies may file submissions to regulatory authorities for approval to market generic versions of the originator medicine [3]. Generic medicine works in the same way and provides the same clinical benefit as the brand-name medicine. In other words, you can take a generic medicine as an equal substitute for its brand-name counterpart [4]. Generic medicines have the same active ingredient as brand-name medicines and work in the same way, but may look different and contain different non-active ingredients. Generic alternatives are often cheaper than brand-name medicines. This is because the company that produces the medicine did not need to invest money in developing and marketing it [5]. They can cost up to 95% less than the brand name drugs and can be afforded by almost all the sections of the society. They are cheaper because after the expiry of the patent many manufacturers compete with each other for their generic version which results in decrease in prices [6].

Branded Drug

It is the original product that has been developed by pharmaceutical company. It has sole right to manufacture and distribution for a period of time (patent). Brand name medicine is approved by FDA by submitting a New Drug Application along with data regarding proof of characteristics of dosage form, manufacturing, chemistry, stability, efficacy, safety, labelling and packaging. After approval by FDA only, the innovatory company can exclusively market this brand name medicine for a period of patent protection (about 20years or as specified) [1].

Similarities between Generic and Branded Drug

1. Generic medicines use the same active ingredients as brand-name medicines and work the same way, so they have the same risks and benefits as the brand-name medicines [4].
2. It must contain the same active ingredients (the chemical substance that makes the drug work)
3. It must have the same dosage form (that is, it needs to be available in the same form as the original-for example. As a liquid, pill, etc)
4. It must have the same dosage strength (the amount of active ingredient, for example the amount of active ingredient, for example 20mg or 40mg)
5. It must have the same route of administration (the way the medication is introduced into the body)
6. It must deliver similar amounts of the drug to the bloodstream(that is,it needs to deliver a comparable amount of the drug into the bloodstream within a similar time period as the brand name drug) [7].
7. Generic drugs are safe as branded drug.
8. It has same bioavailability [5].

Differences in Generic and Branded Drug

Table 1: Difference in generic and branded drugs.

Generic drugs	Feature	Branded drugs
Off patent	Patents	Patent protect
Marketed under the generic name of the drug	Trade name	Marketed under the unique proprietary name given by the company
Manufacture by several pharmaceutical companies after patents expiration of the relevant brand name drug	Manufactured by	Developed and manufactured by an innovator company
Not required to perform	Animal and clinical study	Essential to perform
Cheaper	price	Costly than generic drugs
Look different from relevant brand name drug	Appearance (colour, shape, size)	Unique look as design during product development
Same generic drug name in any country	Name variation	Same or different brand name in different countries
Same or altered but acceptable excipients	Excipient	Uses acceptable excipients
Same expiration of patent and exclusivities	Availability	From product launch after proving the safety and effectiveness

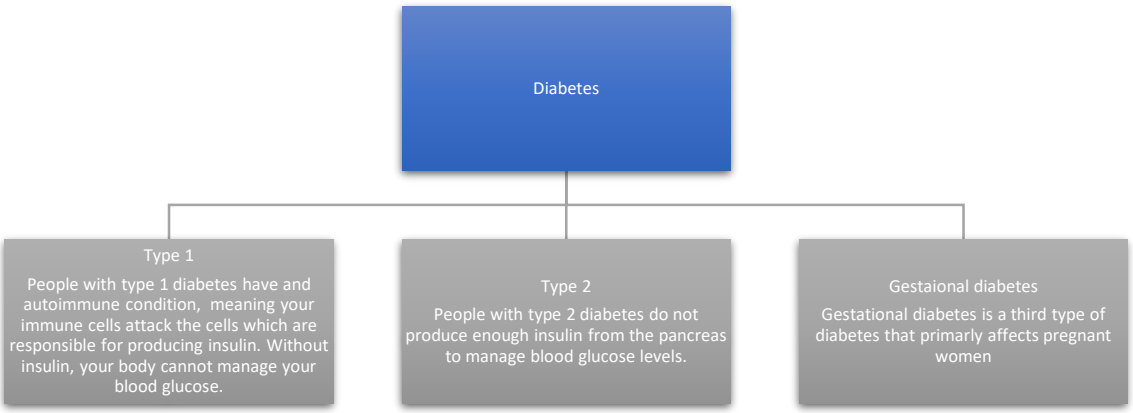
Cost effectiveness of generic drug in comparison to branded drugs.

The generic drugs have and immense advantage of being much cheaper with no compromise on the quality and efficacy as compared to their branded counterparts. The utmost reason behind this is that these do not require the cost expenses on the research and development of the drug. The costly clinical trials are also not required to be repeated again which surely make these drugs cheaper [8]. The reduction in upfront research costs means that, although generic medicines have the same therapeutic effect as their branded counterparts, they are typically sold at substantial discounts, an estimated 80 to 85% less, compared with the price of the brand-name medicine [4]. According to the FDA, drug makers must prove that generic medications can be substituted for brand-name drugs and offer the same benefits as their brand-name counterparts [8].

Diabetes:

Diabetes is a chronic condition that affects the body's ability to process blood sugar, leading to high blood sugar levels and potential damage to various body parts. Glucose, the body's main energy source, is produced by the body and comes from food. Insulin, a hormone produced by the pancreas, helps glucose enter cells for energy. In diabetes, the body lacks insulin or doesn't use it properly, resulting in glucose staying in the blood and not reaching cells. Diabetes increases the risk of damage to the eyes, kidneys, nerves, and heart, and is linked to certain types of cancer. Preventing or managing diabetes can lower the risk of developing diabetes health problems [9].

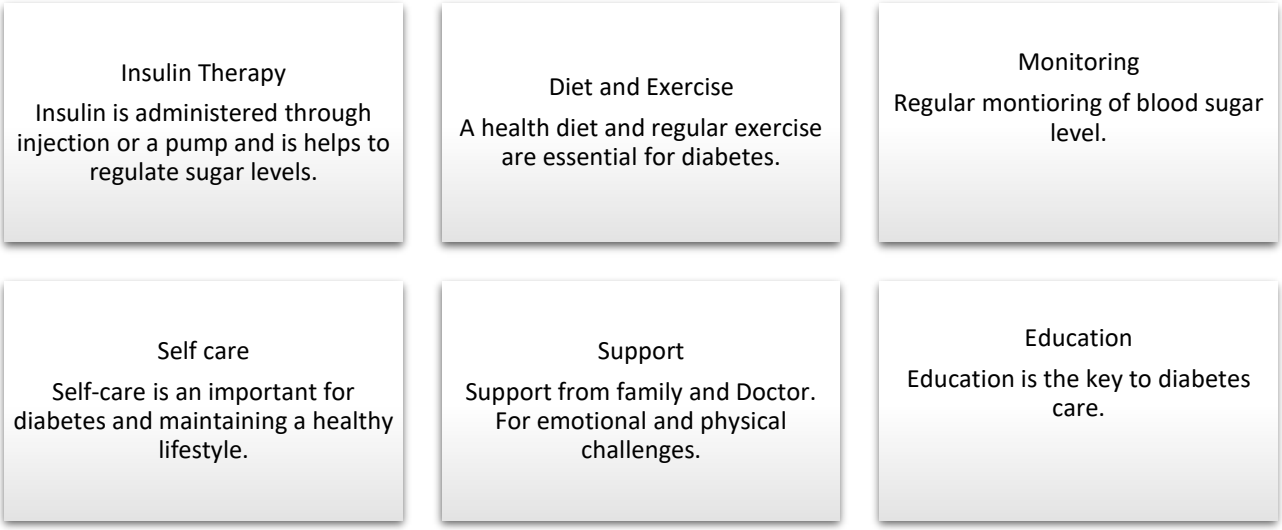
Types of diabetes:



Symptoms:

- Feeling more thirsty than usual.
- Urinating often.
- Losing weight without trying.
- Presence of ketones in the urine. Ketones are a byproduct of the breakdown of muscle and fat that happens when there's not enough available insulin.
- Feeling tired and weak.
- Feeling irritable or having other mood changes.
- Having blurry vision.
- Having slow-healing sores.
- Getting a lot of infections, such as gum, skin and vaginal infections. [10].

Treatment and Care of diabetes:



MATERIAL AND METHODS:

Branded (Glycomet500 USV and Glyciphage500 Franco India) and Generic (okamet500 Cipla and Walcephase500SR Wallace) Metformin hydrochloride tablets having label strength 500 mg were purchased from local market. The detailed descriptions for these products are presented in Table 2. All tests were performed within product expiration dates. All the samples were collected for the local pharmacy stores.

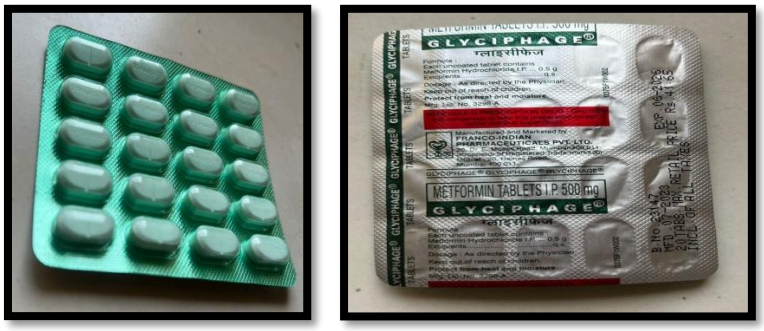
Table 2: Details of sample

Code	Sample Type	Brand Name	Name of Company	Batch No.	Manufacture date	Expiry date	Price for 20 Tabs
B1	Branded	**Glycomet**	USV	28024438	Jul 23	Jun 26	**Rs. 37.40**
B2	Branded	**Glyciphage**	Franco-India	23147	Jul 23	Jun 26	**Rs. 41.65**
G1	Generic	**Okamet**	Cipla	E728801	Nov 22	Oct 25	**Rs. 24.62**
G2	Generic	**Walcephase**	Wallace	WBW2002	Feb 22	Jan 24	**Rs. 42.60**

Drug Name:

1) Glycomet500

2) Glycophage500



3) Okamet500

4) Walcephase500SR

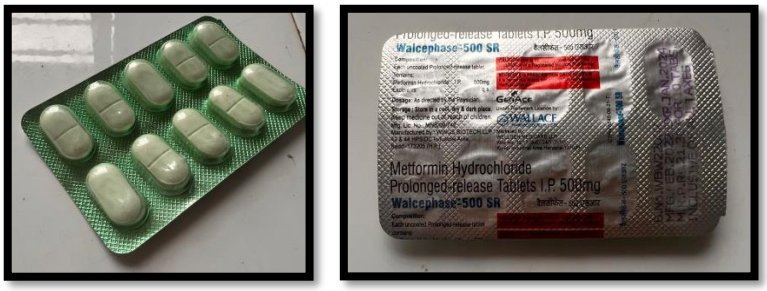


Fig 1: Sample of tablets from the local market as mentioned above.

Drug Profile:

Table 3: Drug profile

Synonyms	Metformin Hydrochloride
Chemical Formula	C4H11N5.HCl
IUPAC Name	1,1-dimethylbiguanide hydrochloride.
Half-life	6.2 hours in the plasma
Shelf life	3 years from the date of manufacture. Store at or below 25°C. Protect from heat, light and moisture.
Molecular weight	165.62 g/mol
Pka value	12.4
Bioavailability	50–60%
Excretion	Urine (90%)

Mechanism of Action:

The centre of metformin mechanism of action is the alteration of the energy metabolism of the cell. Metformin exerts its prevailing, glucose-lowering effect by inhibiting hepatic gluconeogenesis and opposing the action of glucagon. The inhibition of mitochondrial complex I results in defective cAMP and protein kinase A signalling in response to glucagon. Stimulation of 5'-AMP-activated protein kinase, although dispensable for the glucose-lowering effect of metformin, confers insulin sensitivity, mainly by modulating lipid metabolism.

Structure:

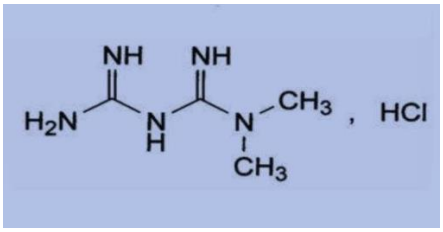


Fig 2: Structure of Metformin HCL [14]

Uses:

Metformin is used to treat high blood sugar levels that are caused by a type of diabetes mellitus or sugar diabetes called type 2 diabetes. With this type of diabetes, insulin produced by the pancreas is not able to get sugar into the cells of the body where it can work properly.

Side effect:

Nausea, vomiting, stomach upset, diarrhea, weakness, or a metallic taste in the mouth may occur. Stomach symptoms that occur after the first days of your treatment may be signs of lactic acidosis. Metformin does not usually cause low blood sugar (hypoglycemia). Low blood sugar may occur if this drug is prescribed with other diabetes medications. Symptoms of low blood sugar include sudden sweating, shaking, fast heartbeat, hunger, blurred vision, dizziness, or tingling hands/feet.

Overdose

Symptoms of overdose may include severe drowsiness, severe nausea/vomiting/diarrhea, rapid breathing, slow/irregular heartbeat [11].

Evaluation Tests of Tablets:

A. Visual Inspection:

The shape, size, and colour of the different formulations of tablets were examined visually. At least 10 tablets were unpacked and inspected. They should be undamaged, smooth, and usually of uniform colour. Evidence of physical instability is demonstrated by:

a) Presence of excessive powder and/or pieces of tablets at the bottom of the container (from abraded, crushed, or broken tablets);

b) Cracks or capping, chipping in the tablet surfaces or coating, swelling, mottling, discoloration, fusion between tablets; and the appearance of crystals on the container walls or on the tablets.

c) The appearance of crystal on the container walls or on the tablets. The results are shown in **Table no 4.**

B. Thickness (in cm):

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. The thickness and of the tablets were determined by using Vernier calipers. 5 tablets were randomly selected and thickness was determined using a Vernier caliper. The results are shown in **Table no 5.**

C. Hardness:

Hardness of the tablet was determined using the Monsanto hardness tester. The observed results showed that all the selected brands of metformin have an acceptable crushing strength or hardness. [23] The results are shown in **Table no 6.**

D. Weight Variation:

20 Tablets were taken, weighed and their average weight was calculated. The test stated that all the four brands of metformin hydrochloride have passed the weight variation uniformity test which complied with the IP specifications for weight uniformity as none of the brands deviated by up to±5% from the mean value. The results are shown in **Table no 7.**

E. Friability:

Ten tablets of each brand were weighed and subjected to abrasion using a Roche Friabilator at 100 revolutions for four min. The tablets were deducted and weighed again then percentage of weight loss was recorded. The friability of the tablets was then calculated using the following expression: The results are shown in **Table no 8.**

F. Disintegration:

The process of breakdown of a tablet into smaller particles is called as disintegration. The in vitro disintegration time of 6 tablet were determined using disintegration test apparatus as per IP specifications. This test is useful to know about the disintegration time under experimental conditions as it is correlated with dissolution profile of sample. Six tablets of each sample were placed in disintegration apparatus. The volume of disintegration medium was 900 ml of water maintained at 37 ± 0.5°C. The time taken to break each tablet into small parts and pass through the mesh was recorded and average time was calculated in minutes. This process was repeated for all four different brands of metformin tablets. The results are shown in **Table no 9.**

G. Standard Calibration Curve:

For standard calibration curve different solution of increasing concentration of standard Metformin were prepared. The solution concentration of 5, 10, 15, 20, 25, 30µg/ml were prepared by proper dilution. The results are shown in **Table no 10.**

H. Dissolution:

Dissolution test of four brands of metformin hydrochloride was carried out using single flask dissolution apparatus. Dissolution medium used was 0.68 % w/v solution of potassium dihydrogen phosphate, adjusted to pH 6.8 by the addition of 1 M sodium hydroxide. One tablet (500 mg) was put in the basket which rotates in the vessel filled with 900 mL of phosphate buffer medium at 37±0.5°C. The basket was rotated at 100 rpm for 45 minutes. A volume of 10 ml of sample was drawn at intervals of 5, 15, 25, 35, 45 minutes with 10 mL bulb pipette. A fresh 10 ml dissolution medium was replaced after each sampling to maintain the sink conditions. Each of the withdrawn sample was filtered and the filtrate diluted. The absorbance of the resulting solution was measured at λ max 232nm using UV visible double beam spectrophotometer. The % drug release of each brand of metformin hydrochloride tablet was calculated by using standard calibration curve method. The results are shown in **Table no 11.**

I. Assay:

This test is done to find out the actual amount of active ingredient present in the tablet and whether it is the same as the labeled amount. Twenty tablets from each brand were weighed and finely powdered then an accurately weighed portion of powder equivalent to 100 mg metformin hydrochloride were transferred to 100 ml volumetric flask, 70 ml of distilled water then was added and shacked mechanically for 15 min then diluted to the volume and filtered. 10 ml of the filtrate was transferred to 100 ml volumetric flask and further diluted to 100 ml with distilled water. Then, 10 ml was transferred to another 100 ml volumetric flask and the volume was completed with distilled water. The absorbance of assay preparation was determined at λ max 232 nm with UV-visible spectrophotometer using water as a blank [12]. The results are shown in **Table no 12.**

RESULT:

A. Visual Inspection:

Table 4: Data of visual inspection

Sample	Shape	Colour
B1	Circle	White
B2	Rectangular	White
G1	Rectangular	White
G2	Rectangular	White

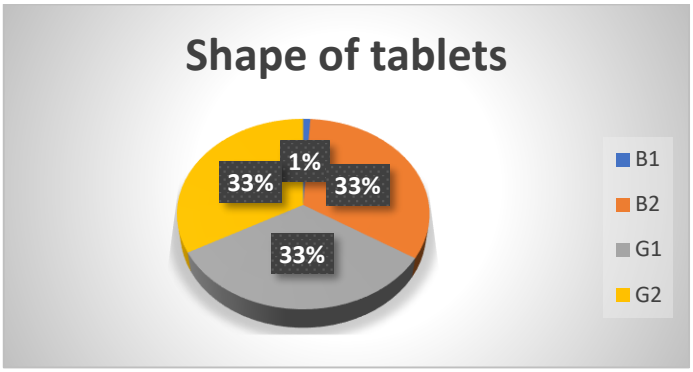


Fig 3: Shape of tablet.

B. Thickness (in cm):

Table 5: Data of thickness of tablets.

Sample	1	2	3	4	5	Average
B1	0.2±0.10	0.3±0.12	0.3±0.11	0.2±0.14	0.3±0.16	0.2625
B2	0.3±0.15	0.3±0.13	0.3±0.12	0.3±0.16	0.2±0.11	0.2875
G1	0.3±0.17	0.2±0.12	0.3±0.13	0.3±0.15	0.3±0.18	0.275
G2	0.2±0.11	0.3±0.13	0.3±0.14	0.3±0.16	0.3±0.15	0.275

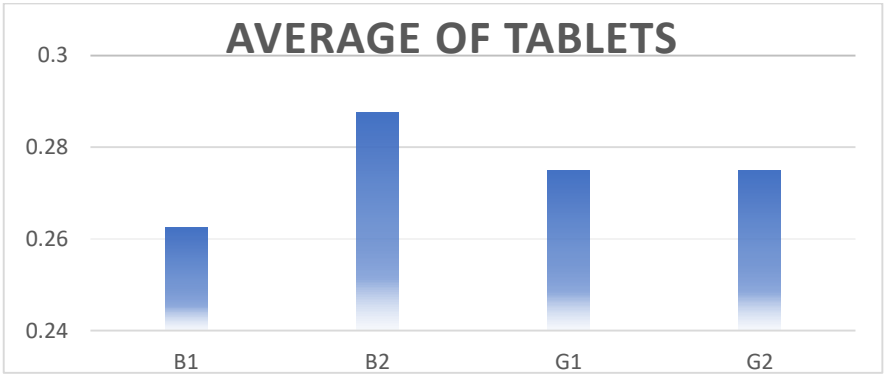


Fig 4: Average of tablets

C. Hardness:

Table 6: Data of hardness of tablets.

Sample	1	2	3	4	5	Average	Acceptance Criteria
B1	4.2±0.02	4.5±0.0.4	4.6±0.03	4.1±0.05	4.8±0.03	4.44	
B2	5.1±0.04	5.5±0.05	5.3±0.07	5.7±0.08	5.3±0.06	5.38	**4-10**
G1	5.4±0.07	5.8±0.05	5.6±0.04	5.2±0.06	5.7±0.03	5.54	**kg/cm^2**
G2	6.9±0.09	6.2±0.07	6.5±0.02	6.7±0.04	6.1±0.05	6.48	

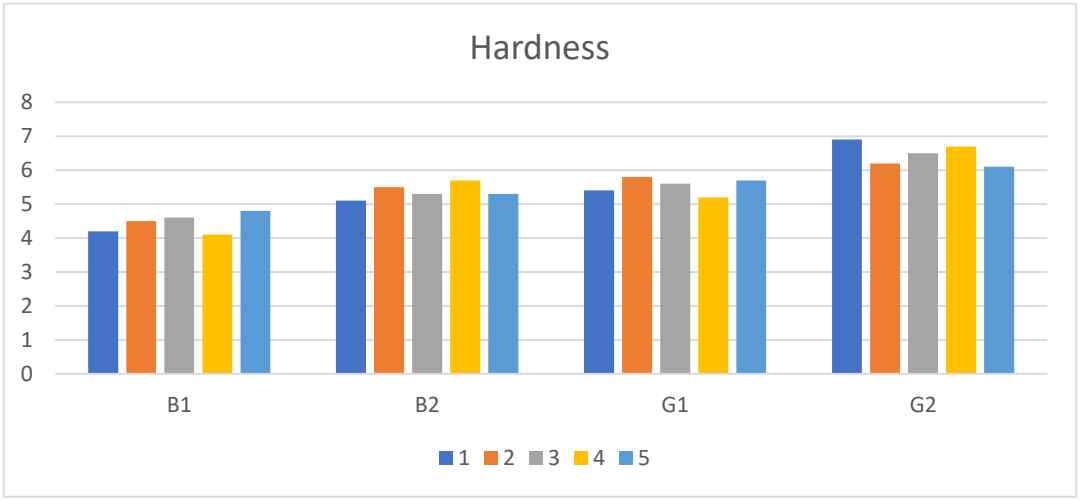


Fig 5: Hardness of tablets

D. Weight Variation:

Table 7: Data of weight variation of tablets

NUMBER OF TABLETS	SAMPLE B1 (GM)	SAMPLE B2 (GM)	SAMPLE G1 (GM)	SAMPLE G2 (GM)	ACCEPTANCE CRITERIA
1	0.5	0.5	0.5	0.6	
2	0.6	0.4	0.4	0.7	
3	0.5	0.5	0.5	0.7	
4	0.6	0.6	0.6	0.7	
5	0.6	0.6	0.6	0.7	
6	0.6	0.6	0.6	0.7	
7	0.5	0.5	0.5	0.7	
8	0.6	0.6	0.6	0.7	
9	0.6	0.6	0.6	0.7	
10	0.6	0.6	0.6	0.7	
11	0.6	0.6	0.6	0.7	±5%
12	0.6	0.5	0.5	0.7	
13	0.5	0.6	0.6	0.6	
14	0.5	0.5	0.5	0.6	
15	0.6	0.6	0.6	0.7	
16	0.6	0.5	0.5	0.7	
17	0.5	0.6	0.6	0.6	
18	0.6	0.6	0.6	0.7	
19	0.6	0.6	0.6	0.6	
20	0.6	0.6	0.6	0.6	
Average Wt.	0.575±0.24	0.56±0.21	0.56±0.21	0.67±0.27	
% DEVIATION	**0.13%**	**0.10%**	**0.10%**	**0.30%**	

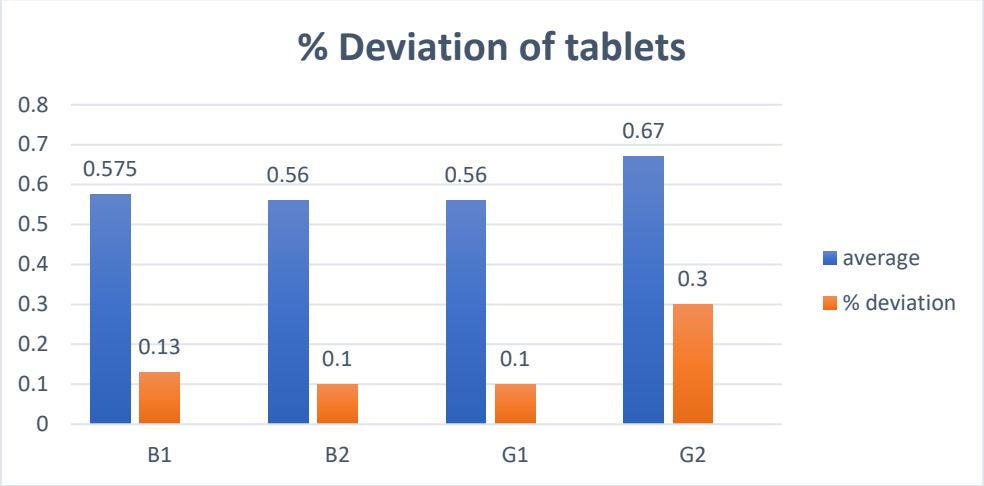


Fig 6: % Deviation of tablets

E. Friability:

Table 8: Data of friability of tablets

Sample Code	B1	B2	G1	G2	Acceptance Criteria
Initial weight (W0)	6.013	5.517	5.32	7.332	Not lose 1% of their initial weight
Weight after revolution (W)	5.978	5.486	5.297	7.327	
% Loss (%F)	0.03%	0.03%	0.02%	0.06%	

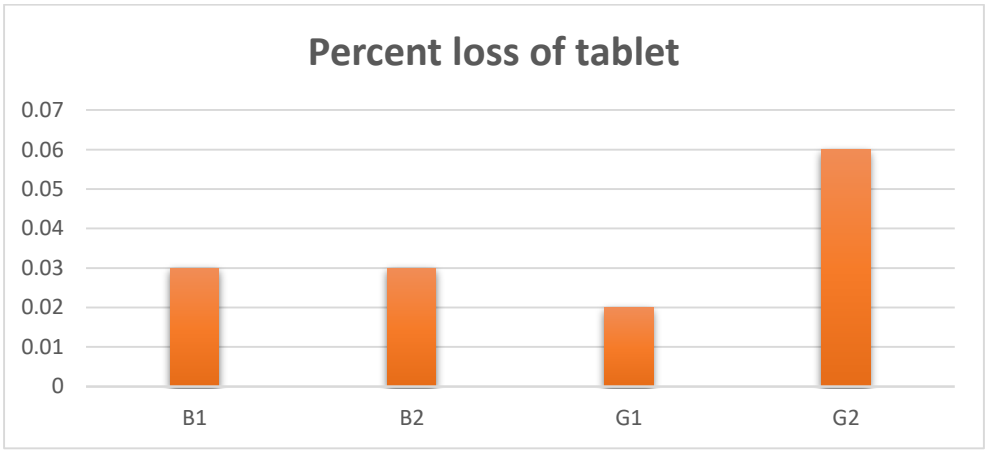


Fig 7: Percent loss of tablet

F. Disintegration:

Tablet 9: Data of the disintegration of tablets

Number of Tablets	Sample B1 Time in Min.	Sample B2 Time in Min.	Sample G1 Time in Min.	Sample G2 Time in Min.	Acceptance Criteria
1	6.3±0.04	5.7±0.03	6.2±0.03	7.6±0.05	
2	5.7±0.07	5.2±0.02	7.1±0.07	8.4±0.03	
3	5.2±0.02	6.8±0.09	7.5±0.08	8.2±0.02	Not More
4	6.4±0.05	6.1±0.07	7.6±0.08	7.9±0.06	Than 15
5	5.8±0.06	7.1±0.08	6.4±0.04	7.3±0.04	minutes
6	6.5±0.02	6.3±0.06	6.7±0.05	8.5±0.07	
Average	**5.98**	**6.2**	**6.91**	**7.98**	

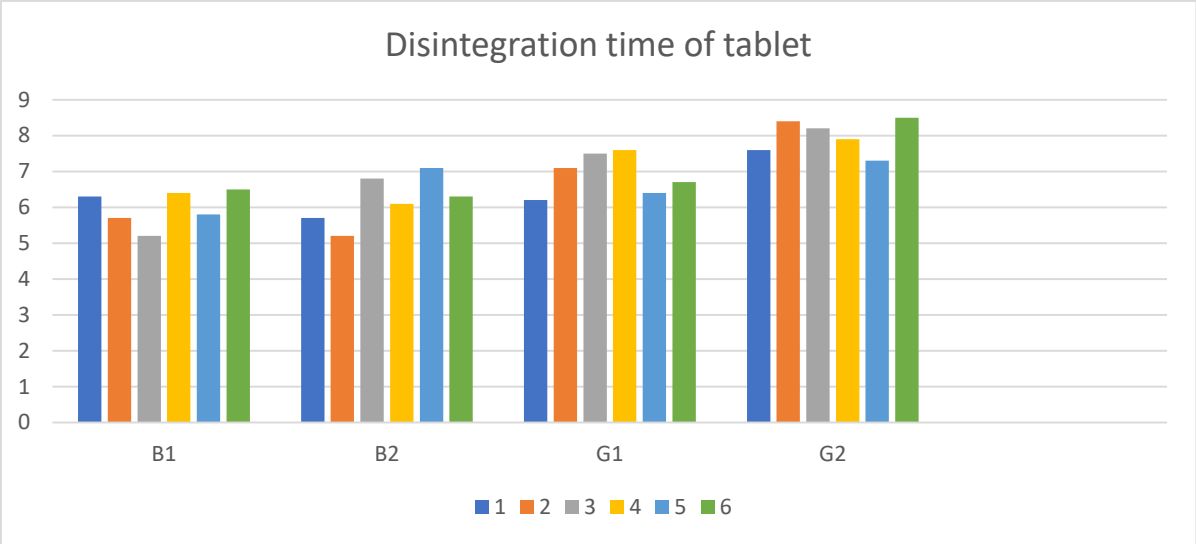


Fig 8: Disintegration time of tablets.

G. Standard Calibration Curve

Table 10: Data of standard Calibration Curve

Sr. No.	Concentration (µg/ml)	Absorbance (nm)
1	5	0.168
2	10	0.332
3	15	0.469
4	20	0.625
5	25	0.784
6	30	0.898

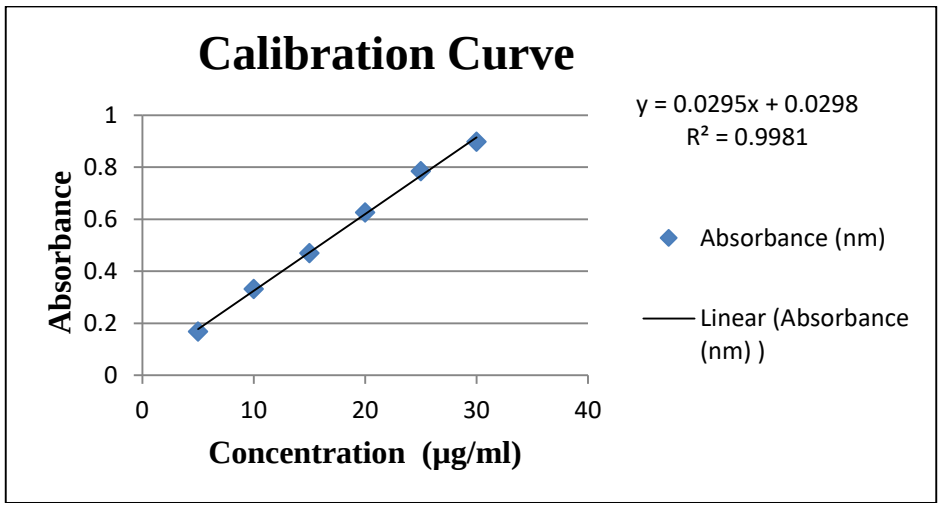


Fig 9: Calibration curve

H. Dissolution:

Table 11: Data of dissolution of tablets

Sr. No.	Time in Min.	% Drug Release				Acceptance Criteria
		Sample B1	Sample B2	Sample G1	Sample G2	
1	5	21.4±0.05	20.8±0.02	22.5±0.01	21.6±0.03	
2	15	39.7±0.03	36.2±0.04	38.9±0.08	37.2±0.05	Not less
3	25	62.3±0.02	59.6±0.05	64.8±0.06	58.4±0.01	than 75 %
4	35	77.5±0.06	75.1±0.01	82.6±0.05	79.9±0.02	
5	45	98.4±0.07	97.8±0.09	98.1±0.03	97.3±0.04	

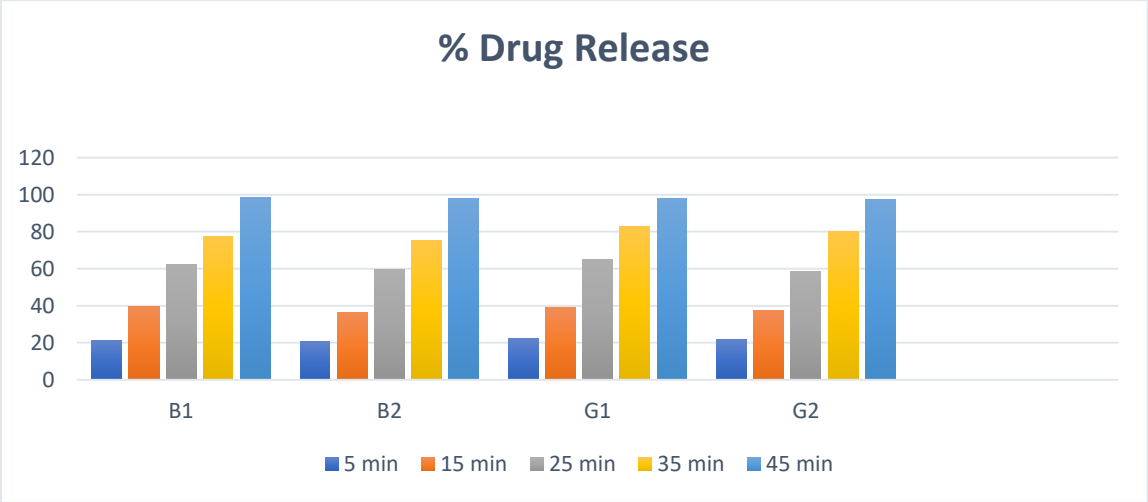


Fig 10: % Drug release.

I. Assay:

Table 12: Data of assay of tablets

Drug Assay (%)				Acceptance Criteria
Sample B1	Sample B2	Sample G1	Sample G2	
98.6±0.45	100.2±0.32	102.5±0.71	99.3±0.83	±5%

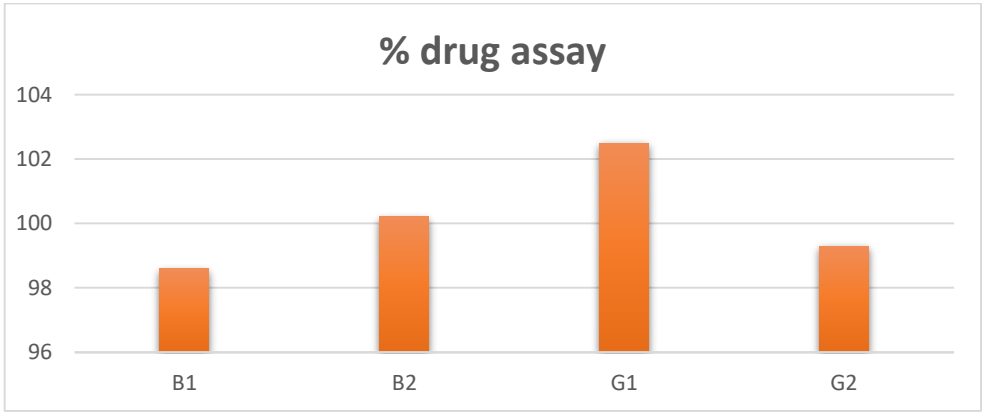


Fig 11: % Drug assay

Conclusion:

The government of developing countries are now focusing on the use of generics. This study was aimed to assess quality as well as physicochemical equivalence of Branded and Generic metformin hydrochloride tablet. The study confirmed that the generic and branded metformin hydrochloride tablets complied with the official specification for weight variation, hardness, friability, disintegration, assay and dissolution. From the obtained result we were conclude that the selected generic and branded metformin hydrochloride tablet taken for comparative evaluation of their quality assessment to assure its efficacy and potency gives different results from each other but not a single brand crosses the limits given in official books. The result indicated that the entire selected brand fulfilled the required official specification and thus assures that these brands although manufactured by different pharmaceutical companies it can be used interchangeably. The economic benefits of the use of Generic medicines cannot be denied; and in many countries their use is essential to control healthcare spending. Suitable changes in the drug price policy may be made to have lower prices for Generic medicines. The government and healthcare professionals must take up generic promotional schemes, general awareness programs on quality of generics to build confidence among prescribers, pharmacists, and consumers.

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