In vitro Bioequivalence Analysis of Generic Metformin Hydrochloride Film-coated Tablets

Zsarie P. Buenavidez,[1] Althea Kathleen P. Brum,[1] Krizia Marie T. Manzo,[1] Zenia Luisa M. Mora,[1]
Perlita M. Crucis, RPh, MS Pharm,[1,2] April Mergelle R. Lapuz, MS Pharm,[1]
Kevin Jace A. Miranda, PhD[1] and Rogie Royce Z. Carandang, PhD[1,3]

[1]*Adamson University, Manila, Philippines*
[2]*Graduate School, Centro Escolar University, Manila, Philippines*
[3]*Department of Public Health Sciences, University of Connecticut School of Medicine, Connecticut, USA*

ABSTRACT

Background and Objectives. The *in vitro* bioequivalence assessment using a dissolution apparatus, as specified by the United States Pharmacopeia (USP), is a critical parameter in the formulation and development of generic pharmaceutical products. This study is crucial for evaluating the interchangeability of generic drugs with their reference innovator counterparts. Post-market surveillance of generic drugs ensures consistent quality after distribution in the market. Metformin hydrochloride, a widely prescribed oral hypoglycemic agent for managing type 2 diabetes, is among the most utilized medications globally.

In the Philippines, there is a growing need to assess the bioequivalence of various generic formulations of metformin HCl film coated tablets to ensure compliance with regulatory requirements. The Philippine Food and Drug Administration (FDA) mandates *in vivo* or *in vitro* bioequivalence including, dissolution profile comparison, as a prerequisite for the registration of generic drugs. This study aims to evaluate the quality and *in vitro* bioequivalence of metformin HCl film-coated tablets available in the Philippine market by comparing their dissolution profiles against the innovator, Glucophage. This research seeks to provide insights into the interchangeability, therapeutic equivalence, and overall quality of these generic formulations, thus contributing to public health and regulatory standards.

Methods. Generic metformin HCl film-coated tablets were subjected to quality control tests, including weight variation, thickness and diameter, hardness, friability, and disintegration tests, in accordance with USP guidelines. To assess *in vitro* bioequivalence, dissolution testing was performed, and the concentration of the dissolved drug was determined using a microplate assay reader to measure absorbance. Dissolution profiles of the generic metformin HCl film-coated tablets were compared to that of the innovator drug, Glucophage to evaluate bioequivalence.

Results. All tested generic metformin HCl film-coated tablets complied with USP specifications for quality control tests, except for the hardness test, where three brands failed to meet the required standards. While for dissolution testing, five out of six generic brands demonstrated acceptable dissolution profiles and were bioequivalent to the innovator drug Glucophage. However, one brand (Brand A) failed to meet the bioequivalence criteria, exhibiting a dissolution profile outside the acceptable limits.

Conclusion. This study demonstrates that most generic metformin HCl film-coated tablets available in the Philippine market meet the United States Pharmacopeia (USP) quality control requirements and exhibit *in vitro* bioequivalence with the innovator drug. However, the failure of three brands to meet the hardness specifications and the lack of bioequivalence in one brand highlight the need for stringent quality assurance and

Paper presentation – 6th South Manila Educational Consortium (SMEC) Congress, February 23, 2024, The Manila Prince Hotel, Ermita, Manila, Philippines.

eISSN 2094-9278 (Online)
Published: January 30, 2026
https://doi.org/10.47895/amp.vi0.10375

Corresponding author: Perlita M. Crucis, RPh, MSPharm
College of Pharmacy
Adamson University
900 San Marcelino St., Ermita, Manila 1000, Philippines
Email: pcrucis@adamson.edu.ph
ORCiD: https://orcid.org/0009-0006-9135-0269

regulatory oversight. Ensuring compliance with these standards is critical to maintaining the safety, efficacy, and therapeutic interchangeability of generic drugs. These findings emphasize the importance of continuous post-market surveillance to uphold the quality of generic medications in the market, to safeguard public health.

Keywords: in-vitro bioequivalence, metformin hydrochloride, United States Pharmacopeia (USP), disintegration tests, dissolution, thickness and diameter, weight variation

INTRODUCTION

Generic medicines are pharmaceutical products designed to be interchangeable with innovator drugs, typically marketed after the expiration of patent protections.[1] They are more affordable alternatives to branded drugs and must meet stringent regulatory requirements to ensure bioequivalence, including similarity in active ingredient, strength, quality, dosage form, and intended use.[2] One of the key prerequisites for the registration of specific generic medicines is the conduct of bioequivalence (BE) studies, which are performed to confirm that the generic drug exhibits no significant difference in the rate and extent of absorption compared to the reference drug. BE studies act as surrogate markers for the clinical safety and efficacy of generic products, replacing the need for full-scale clinical trials.[3]

The price of medications is a major factor contributing to rising healthcare costs, making generic medicines a crucial solution for cost-effective treatment. Despite their proven efficacy and safety, consumer and healthcare professional perceptions of generics remain a challenge. Studies, such as one conducted in New Zealand, reveal that patients often perceive generics as less effective and more prone to adverse effects, particularly when transitioning from branded drugs.[4] In the Philippines, the Generics Act of 1988 highlighted similar concerns. Surveys indicate limited public understanding of generics, with some physicians also doubting their bioequivalence due to prior experiences with unrelieved patient outcomes after using generics.[5] Addressing these misconceptions through public education and strengthened regulatory oversight is essential to enhancing confidence in generic medicines and maximizing their potential to reduce healthcare costs.

Adding to these challenges is the prevalence of substandard or counterfeit drug products, particularly in low- and middle-income countries, where regulatory enforcement and quality assurance mechanisms are inadequate.[6] According to the World Health Organization, up to 10% of drug products in these regions may be falsified or of poor quality, posing serious risks to public health and decreasing trust in both branded and generic medicines.[6] Bioequivalence studies, both *in vitro* and *in vivo*, play an important role in ensuring the therapeutic equivalence of generics. These studies assess the rate and extent of drug absorption, with relative bioavailability often used to compare the systemic availability of generic and reference drugs.[7] Addressing the issues of counterfeit products, improving public education, and strengthening regulatory frameworks are important to ensure the safety, efficacy, and acceptance of generic medicines.

Diabetes is a major global health concern, accounting for approximately 7.5% of all deaths worldwide in 2021, with an estimated 4.2 million deaths attributed to the disease.[8] Type 2 diabetes, which represents over 90% of all diabetes cases, is primarily associated with lifestyle factors such as diet and physical activity, as well as genetic and environmental influences. The condition significantly increases the risk of comorbidities, including heart disease, stroke, kidney failure, and vision loss. In the Philippines, diabetes affected an estimated 4.7 million adults in 2019, with an additional 2.4 million cases undiagnosed, according to the International Diabetes Federation.[9] If current trends persist, diabetes prevalence in the country could rise to 6.2 million by 2045, emphasizing the urgent need for effective interventions and anti-diabetic medications.

Metformin or metformin hydrochloride is used in the management of type 2 diabetes, widely prescribed as a first-line treatment worldwide due to its efficacy and safety profile. It works by reducing hepatic glucose production and enhancing cellular insulin sensitivity, effectively lowering blood glucose levels without significantly increasing the risk of hypoglycemia.[10] Globally, metformin is the most prescribed anti-diabetic drug, as supported by data from Austria, where it accounts for 51.3% of anti-diabetic prescriptions.[11] Despite its widespread use, the bioequivalence of generic metformin formulations relies heavily on manufacturers' studies rather than independent evaluations by regulatory bodies like the Food and Drug Administration (FDA). This highlights the need for research to ensure the bioequivalence of generic metformin products in the after distribution as part of the post market surveillance study, providing reassurance of their efficacy and therapeutic equivalence to innovator drugs. Moreover, Metformin HCl has a variety of brands that are available and accessible, medical professionals and pharmacists may face challenges when deciding which brand to choose or whether alternative options should be considered. This study intends to assess the quality as well as the bioequivalence of metformin HCl tablets available and sold in the Philippine market.[12]

A comparative *in-vitro* bioequivalence analysis of metformin HCl tablet formulations was conducted in Nigeria. The results indicated that all tested brands conformed to 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, based on the UV analysis at 10 µg/ml. The study concluded that all brands of metformin HCl met the regulatory standards for identification, weight uniformity, hardness and thickness, disintegration, and dissolution.[13] Similarly, an *in-vitro* bioequivalence study of metformin HCl tablets conducted

in Iran which resulted in confirming the presence of bio-equivalence of the 7 brands out of 8 brands tested in comparison to the reference product.[14]

This study evaluated the quality and *in vitro* bioequivalence of metformin HCl film-coated tablets available in the Philippine market. With the wide availability of generic formulations of metformin HCl, healthcare professionals and pharmacists often encounter challenges in selecting the most appropriate generic brand or considering alternative options. This research aims to establish the *in vitro* bioequivalence through comparison of dissolution results or % dissolved of the generic drugs of metformin HCl film-coated tablets ensuring that these drug products meet the necessary standards for interchangeability. By demonstrating that innovator and generic metformin HCl film-coated tablets provide *in vitro* bioequivalence, this study seeks to support the rational use of generic drugs. The findings aim to encourage the adoption of generic drugs as cost-effective alternatives to innovator drugs, thereby reducing healthcare expenses without compromising treatment efficacy or patient safety.

METHODS

Study Design

This quantitative experimental *in vitro* study of the generic brands of metformin HCl film-coated tablets were subjected to quality control and *in-vitro* bioequivalence tests. The data obtained were statistically analyzed and evaluated. All tests were conducted in triplicates.

Materials

The study utilized materials and equipment from the Pharmacy Laboratory of Adamson University College of Pharmacy (Table 1). The ortho-phosphoric acid used in the buffer solution were from RCl Labscan Limited in Bangkok, Thailand. The NaOH pellets and di-potassium hydrogen phosphate used in the buffer solution were from HiMedia Laboratories in Mumbai, India.

Metformin 500 mg film-coated tablets available in the Philippine market with approved Certificate of Product Registration (CPR) by the FDA were procured for this research. The generic drugs were collected by narrowing down the list of all available metformin HCl film-coated tablets in the market. The researchers utilized the FDA verification portal and listed all available brands of metformin that have a CPR. The samples were then narrowed down by considering the expiry date of the samples' CPR. Furthermore, the list was narrowed down to the samples that have different manufacturers. The tablets tested were purchased from community pharmacies in Manila, where the medication is readily available.

Quality Control Tests

Weight Variation

To guarantee dosage unit consistency, a weight variation test was carried out; each unit in a batch should contain a drug substance within a limit specified. Ten individual tablets of the innovator, Glucophage, and the six generic brands of metformin HCl film-coated tablets were weighed accurately. The acceptance value was then calculated using the formula below to determine the weight variation of each tablet. The USP specification for the tablets to be accepted is 90 - 110% of the average weight.[15] Below is the formula used to calculate the % weight variation of the tablets.

$$\text{Where, } \%\ \text{weight variation} = \frac{\text{actual weight of the tablet}}{\text{average weight of the tablet}} \times 100$$

Thickness and Diameter

The thickness and diameter of the tablets were also measured using J.P. Selecta RS Pro 150 mm Digital Vernier Caliper. Ten tablets, each of the innovator, Glucophage, and the six generic brands of the metformin HCl film-coated tablets were tested.

Hardness Test

A hardness test was performed to test for the crushing strength and the resistance of the tablet to chipping and abrasions. Monsanto HT-30/50 hardness tester was used for this test. The ten sample tablets, each of the innovator, Glucophage, and the six generic brands of the metformin HCl film-coated tablets, were subjected to thickness and diameter tests prior to the hardness test. After that, the ten film-coated

Table 1. Analytical Instruments and Quality Control Equipment

Instrument	Brand	Model	Institution
Analytical Balance	A&D	HR250AZ	Pharmacy Laboratory, Adamson University (Ermita, Manila)
Digital Vernier Caliper	J.P Selecta	RS Pro 150mm	
Dissolution Tester	Pharma Test	PharmaTEst PTWS 820D	
Disintegration Tester	Thermonik Tablet Disintegration Tester of Campbell Electronics	TD-20S	
Friability Tester	Copley Scientific	Copley FRV2000	
Hardness Tester	Monsanto Hardness Tester	HT-30/50	
Microplate Assay Reader	BMG Labtech	FLUOstar Omega	

tablets were placed between the two jaws of the instrument and were compressed until they broke.[16] The strength was shown and recorded. Oral tablets have a hardness of 4-10 kg.

Friability Test

The friability test was performed using a Copley FRV2000 friability tester wherein 10 each of the innovator, Glucophage, and the six generic brands of the metformin HCl film-coated tablets, were placed in the friabilator's drum and were rotated one hundred times at the speed of 25 rotations per minute (rpm) for four minutes. They were taken out, and the percentage loss was computed using the formula below. The USP specifications for the tablets were <1%.[17] Below is the formula used to calculate the friability of the tablets.

$$\text{Where,} \qquad \%\ \text{loss} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

Disintegration Test

The disintegration test for both the innovator, Glucophage, and the six generic brands of the metformin HCl film-coated tablets was performed using a TD-20S tablet disintegration tester. The tablets were settled in the tablet disintegration tester containing distilled water, and the temperature was maintained at 37±0.5°C. After all the tablet particles passed through the wire mesh, the tablets were considered as completely disintegrated.[18] The time it takes for the tablets to disintegrate was recorded.

Dissolution Test

A dissolution test to measure the *in vitro* bioequivalence was performed to be able to measure the release of drugs in the solution or the % dissolved. PharmaTest PTWS 820D dissolution tester was used for this test. Six tablets, each of the innovator, and generic drugs of the metformin HCl film-coated tablets were subjected to a paddle dissolution apparatus with a rotation speed of 100 rpm.[19] The medium used was 1000 milliliters of phosphate buffer solution at a pH of 6.8 and at a controlled temperature of 37±0.5°C. The filtered samples were diluted (100 dilutions), and their absorbance was measured at a wavelength of 232 nm using a microplate assay reader. A dissolution medium was used to prepare the metformin HCl working standard, and with the use of blank, which is the phosphate buffer, its absorbance was measured. A calibration curve was used to quantify the concentration of each sample, and the percentage of the drug release at each time point was determined. Below is the formula used to calculate the dissolution of the tablets.

$$\text{Where,} \qquad \%\ \frac{\text{Test}}{\text{Reference}}$$

Data Analysis

The data gathered from the tests done were analyzed using descriptive statistics such as mean and standard deviation. Further evaluation and analysis were made using the analysis of variance (ANOVA) test and Dunnett's test. Analysis of variance (One-way ANOVA) test was performed to compare the dissolution profile of the different products' tablets. The significant difference will be considered if the p-value is <0.05. All statistical analyses were performed using STATA version 17 (StataCorp, College Station, TX USA). Dunnett's test is a post hoc test performed after ANOVA to statistically determine the significant differences between the generic brands and the innovator brand.

Research Implications

The results of this study will help in providing additional data about the bioequivalence of the innovator and generic equivalents of Metformin HCl available in the market, aside from the bioequivalence studies done by the manufacturers of the drug.

Ethical Considerations

The manuscript underwent ethics review by the University Ethics Review Committee of Adamson University. The study did not involve any human participants, and it is purely laboratory experiments. Therefore, it is exempted from ethical considerations.

RESULTS

Weight Variation Test

According to the USP, tablets weighing more than 250 mg have a standard % deviation difference of ±5%.[15] The mean results of weight variation for the innovator, Glucophage and the six brands of metformin HCl film-coated tablets obtained were in the following order: Innovator (0.53) < Brand D (0.55) < Brand E, Brand F and Brand A (0.56) < Brand C (0.58) < Brand B (0.59). All generic brands of metformin HCl film-coated tablets passed the weight variation test with a range of 0%-0.06% deviation.

The innovator drug, Glucophage, and the six generic brands of metformin HCl film-coated tablets met the specifications with the percent deviation ranging from 0%-0.6%, with the highest weight variation seen in Brand B and the lowest in the Innovator (Table 2). A weight variation test was performed to ensure the drug distribution's uniformity.[20] According to the USP, the tablets must have a percent deviation difference of ±5% to pass the USP specifications.[15]

Thickness and Diameter

The thickness and diameter of the tablets were measured, and the average results were also recorded. The results showed that the tablet's thickness ranged from 4.68 mm - 5.86 mm, while the diameter ranged from 6.09 mm - 13.01 mm.

The mean results of thickness for the innovator drug, Glucophage, and the six generic brands of metformin HCl film-coated tablets showed that Brand C (4.68) < Brand F (4.75), Brand D (4.89) < Brand B (5.14) < Brand A (5.60) <

Glucophage (Innovator) (5.63) < Brand E (5.86). The mean results of diameter for ten brands show that Brand D (6.09) < Glucophage (Innovator) (11.00) <Brand E (11.02) < Brand F (11.09) < Brand A (11.49) < Brand B (12.96) < Brand C (13.01).

One brand did not pass the diameter test, while the rest met the specifications for these tests (Table 2).[21] The results vary due to the different formulations of the companies. The size of the tablet influences esophageal transit, irrespective of patient factors and administration of techniques.[22] As stated in the FDA guidelines, the diameter of tablets must be greater than 8 mm.[23] The thickness of the tablets should be controlled within a ± 5% variation of the standard value.[23] The size of the tablets also affects the disintegration time. The larger the tablet showed, the faster the disintegration time. When the tablets were smaller, the released drug significantly decreased.[24]

Hardness Test

The tablets went through a hardness test using the Monsanto HT-30/50 hardness tester. Ten tablets were crushed using the instrument, and the average results were recorded.

The mean results of hardness for the innovator drug, Glucophage, and the six generic brands of metformin HCl film-coated tablets obtained were in the resulting order: Brand F (8.12 kg) < Brand B (8.74 kg) < Glucophage (Innovator) (8.76 kg) < Brand E (9.66 kg) < Brand C (10.09 kg) < Brand A (10.48 kg/) < Brand D (11.30 kg).

The results ranged from 8.12 kg – 11.30 kg. Three out of six generic brands of metformin HCl film-coated tablets failed the hardness test (Table 2). Tablets need to possess a specific level of hardness to endure the physical impacts they encounter during the manufacturing, packaging, and shipping processes.

Several factors can affect the hardness of film-coated tablets such as the quantity of binder in addition to the proper force of compression when compressing the tablets.[13] Moreover, tablets should be able to withstand reasonable consumer mishandling levels. The hardness of tablets can be attributed to the varying properties of the ingredients used to produce different brands. As stated in the USP, oral tablets must obtain a hardness ranging from 4-10 kg to pass the specifications.

Friability Test

The average friability values obtained for the innovator drug, Glucophage, and the six generic brands of metformin HCl film-coated tablets followed a specific order, indicating their varying degrees of durability. Brand D and E (0.07%) < Brand A (0.08%) < Brand B and Glucophage (Innovator) (0.09%) < Brand C (0.15%) < Brand F (0.23%).

Table 2. Characterization of the Innovator (Glucophage) and Six Generic Brands of Metformin HCl Film-coated Tablets

Tablet Brands	Weight Variation (mg)	Thickness (mm)	Diameter (mm)
USP Specifications	Percent deviation difference of ±5%	–	–
Glucophage (Innovator)	0.53 (0.00%)	5.63 (0.01)	11.00 (0.01)
Brand A	0.56 (0.00%)	5.60 (0.01)	11.49 (0.00)
Brand B	0.59 (0.00%)	5.14 (0.03)	12.96 (0.00)
Brand C	0.58 (0.00%)	4.68 (0.01)	13.01 (0.01)
Brand D	0.55 (0.00%)	4.89 (0.01)	6.09 (0.00)
Brand E	0.56 (0.00%)	5.86 (0.02)	11.02 (0.00)
Brand F	0.56 (0.00%)	4.75 (0.02)	11.09 (0.00)

Tablet Brands	Hardness (kg)	Disintegration (mins.)	Friability (%)	% Dissolved
USP Specifications	4-10 kg	<30 mins.	<1%	80-125%
Glucophage (Innovator)	8.76 (0.20)	8:05 (0.00)	0.09 (0.01)	111.37 (0.00)
Brand A	10.48 (0.60)	7:00 (0.01)	0.08 (0.04)	91.15 (0.00)*
Brand B	8.74 (0.46)	11:05 (0.00)	0.09 (0.02)	119.27 (0.01)
Brand C	10.09 (0.23)	6:24 (0.00)	0.15 (0.04)	105.69 (0.01)
Brand D	11.30 (0.35)	10:32 (0.00)	0.07 (0.03)	105.53 (0.02)
Brand E	9.66 (0.14)	10:55 (0.01)	0.07 (0.04)	106.32 (0.01)
Brand F	8.12 (0.07)	11:24 (0.06)	0.23 (0.03)	118.64 (0.00)

Data are presented as mean (standard deviation) (n=3).
Data inside the parentheses are the standard deviation of all 3 trials.
Data presented are the average of all 3 trials.
**p<0.05 when compared to the innovator*

The average results ranged from 0.07%-0.23%. According to USP, the tablets must have a friability value of <1% to pass the specifications for this test.[21] Based on the results, all brands have passed the USP specifications for this test (Table 2).

Friability test is used to determine the content uniformity as well as the variation in the weight of the tablets which may involve several factors that may affect the drug's uniformity and overall appearance such as its tendency to chip, powder, or fragment.[20] It has significant importance to ensure that the tablets can withstand mechanical stress during the process of its manufacturing processes and consumer handling.

Disintegration Test

The tablets were placed in a disintegration tester containing distilled water, and the temperature was maintained at 37±0.5°C. The mean results of DT for ten brands obtained show that Brand C (6:24 min) < Brand A (7 min) < Glucophage (Innovator) (8:05 min) < Brand D (10:32 min) < Brand E (10:55 min) < Brand B (11:05 min) < Brand F (11:24 min). Based on the results, Brand F took the longest to disintegrate; while Brand C took the shortest time to disintegrate. Brand C has the fastest disintegration time at 6 minutes and 24 seconds; while Brand F has the slowest disintegration time at 11 minutes and 24 seconds.

The innovator drug, Glucophage, and the six generic brands of metformin HCl film-coated tablets dissolved within 30 minutes, ranging from 6 – 11 min. Disintegration plays a vital role as it is directly linked to the dissolution process, and consequently, the bioavailability of a drug. This test determined the drug's therapeutic efficacy and guaranteed its quality. According to the USP, film-coated tablets must be dissolved in under 30 minutes to pass the test. The disintegration time for the innovator drug, Glucophage, and the six generic brands of metformin HCl film-coated tablets was under 30 minutes which signifies that all passed the test (Table 2).

Dissolution Test

Dissolution testing is necessary to identify the bioequivalence of the Glucophage (innovator) and the six generic brands of metformin HCl film-coated tablets. All tablets were subjected to dissolution using a paddle disk dissolution apparatus. The phosphate buffer solution was also utilized with a pH of 6.8. Six tablets per batch were analyzed, the average result was recorded, and the % drug release or % dissolve was computed and recorded.

The average results were obtained for the seven brands in a specific order; Brand A (91.15%) < Brand D (105.53%) < Brand C (105.69%) < Brand E (106.32%) < Glucophage (Innovator) (111.37%) < Brand F (118.64%) < Brand B (119.27%).

The result ranged from 91.15% – 119.27%, the innovator drug, Glucophage, and the five generic brands of metformin HCl film-coated tablets passed the (USP) specifications, except for Brand A (Figure 1).

The % drug release profile of the different generic brands of metformin HCl film-coated tablets was compared to the innovator brand, Glucophage, to determine bioequivalence using ANOVA. Based on the results, all metformin hydrochloride tablets do not have significant differences ($p>0.05$) with the innovator except for Brand A (95% CI -39.99 - -1.46; $p<0.05$). This suggests that Brand A is not bioequivalent with the innovator.

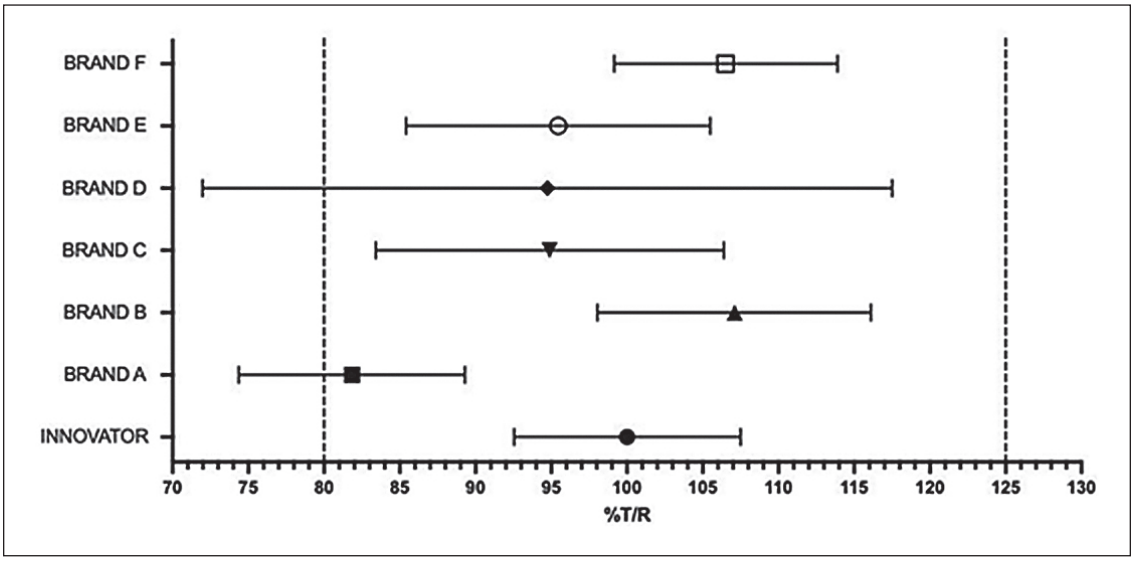

Figure 1. *In vitro* bioequivalence of the Innovator and Six Generic Brands of Metformin Hydrochloride Film-coated Tablets [where %T/R is based on the Mean (Standard error)].

DISCUSSION

The results confirmed that the innovator drug, Glucophage, and the six generic brands of metformin HCl film-coated tablets met the required friability and disintegration standards, and three out of six generic brands met the specifications for hardness test which may be due to many reasons such as the quantity of binder in addition to the proper force of compression when compressing the tablets. Enforcing quality control standards is a method to ensure uniformity in batch-to-batch production of pharmaceutical products. These various factors affect drug absorption, bioavailability, and related outcomes.[25] Moreover, five generic brands of metformin HCl film-coated tablets met the acceptable limits for dissolution as specified in the United States Pharmacopeia (USP) except for Brand A which exhibited non-bioequivalence to the innovator. For some generic alternatives, they may require a higher degree of bioequivalence to the original brand. While these generics can still be utilized, they may not be interchangeable with the innovator product.[23]

According to a study conducted in Iran wherein they also tested generic metformin HCl brands to the innovator, significant differences were not observed in both parameters, and this confirmed similarity between all brands formulations compared with innovator product and indicated that the release of metformin from all formulations were similar to reference. However, comparison of the two dissolution curves shows that Brand C couldn't release 80% of the drug during 30 minutes. Therefore, taking all results into account, all formulations are comparable with reference and there is essential similarity between all formulations with reference product except brand C.[14]

The release of drug in solution of the generic brands is important to determine its bioequivalence to the innovator. The concentration or the % drug dissolved in the dissolution medium was measured using microplate assay reader in this study. One-way ANOVA and Dunnett's post-hoc tests compared the concentrations of the six generic brands of metformin HCl film-coated tablets to the innovator, Glucophage, used in the study. It showed that Brand A is the only brand with a significant difference, to the innovator having a p-value of >0.03. In contrast, the other five generic brands of metformin HCl film-coated tablets have shown no significant difference compared to the innovator. This concludes that Brand B to Brand F can be used interchangeably and can be interchangeable with the innovator drug, while Brand A cannot be used as a substitute for the innovator drug.

Any generic drugs that is comparable and bioequivalent with the innovator brand may be interchangeable with it, given that bioequivalence tests are done, which may prove that the drugs have comparable bioavailability.[26] This shows that these generic drugs can be safely used as substitutes for the innovator as they are all equally effective. According to the FDA, a drug is considered bioequivalent to the innovator if it is within the limit of 80-125%.[26] The non-bioequivalent drug, however, can still be used even if it is not bioequivalent with the innovator brand since it is still able to pass the USP specifications. However, they may not be used as the Innovator's substitute or may not be used interchangeably with the Innovator.[26] These non-bioequivalent drugs may still be used if their therapeutic use is proven through clinical trials or pharmacodynamics.[27] Further analysis may also be done to determine if there are any deviations during the development of the drug.[28] Regular review and updates regarding the bioequivalence data may also be needed to ensure that the drug is safe and effective for use.[29]

A drug's non-bioequivalence may be affected by several factors. This may include the excipients or the inactive ingredients during the drug formulation or its composition, as well as the drug's particle size distribution or physical properties. Differences during the manufacturing process can also be one of the factors that may affect the drugs' non-bioequivalence.[30] The non-bioequivalent drug is recommended to undergo additional studies to further understand its pharmacokinetics and pharmacodynamics that will help in determining if it can be used safely and effectively with adjustments.

The presence of non-bioequivalent drugs in the market can lead to concerns, especially regarding the difficulties in substituting generic drugs. Since these drugs may not generate the same desired treatment outcomes, there is a potential risk to patient health. As a result, the potential cost savings associated with using these medications may be outweighed by the potential harm they can cause.

CONCLUSION

This study evaluated the quality and bioequivalence of the innovator drug, Glucophage, and six generic brands of metformin hydrochloride film-coated tablets available in the Philippine market as part of the post market surveillance. All tested brands met the United States Pharmacopeia (USP) specifications for weight variation, friability, and disintegration tests, indicating uniformity and adequate physical properties. However, three generic brands failed the hardness test, which is essential for withstanding physical handling during production and distribution. These variations may be attributed to differences in manufacturing processes, binder quantities, and compression forces.

In dissolution testing, five out of six generic brands demonstrated bioequivalence to the innovator drug, Glucophage, with drug release profiles falling within the acceptable 80–125% range specified by the FDA. However, Brand A exhibited significant deviation, indicating non-bioequivalence and thus cannot be interchanged for the innovator. Non-bioequivalence may result from factors such as differences in excipients, particle size distribution, or production methods. While non-bioequivalent drugs may still comply with USP quality standards, they cannot be used interchangeably with the innovator product without

additional evidence of therapeutic efficacy through clinical trials. This study highlights the importance of quality control and *in-vitro* bioequivalence testing to ensure the safety, efficacy, and interchangeability of generic drugs and innovator, safeguarding public health and supporting cost-effective treatment options.

Recommendations

This study can provide information about the drugs and their compliance with the pharmacopeial standard once released in the market. This study has shown that generic counterparts are comparable with the innovator. Thus, this study can be used as reference for future research to further explore the bioequivalence of the drugs by using different dissolution parameters to compare the results of the dissolution test of the drugs and the innovator.

Strengths and Limitations

The study aimed to assess the bioequivalence of metformin HCl tablets by comparing six different brands obtained from various local pharmacies in Manila, Philippines, with the innovator product. One strength of the study was acquiring the required working standard from a manufacturing company through a donation, ensuring the use of authentic and reliable reference standards. This contributed to the credibility and accuracy of the research findings. A microplate assay reader was also used to determine the concentration of metformin HCl tablets after undergoing dissolution tests, which have higher specificity and sensitivity for determining drug concentrations.

However, the limitation of the study is that it only tested the 500 mg film-coated tablets of Metformin HCl. Metformin also comes in Extended-Release tablets as well as 850 mg and 1 g tablets. Another limitation is that the study only performed *in-vitro* analysis. In-vivo analysis can also be performed in this study to further test for the bioequivalence.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

The study was funded by Adamson University - Center for Research and Development.

REFERENCES

1. Shargel L, Kanfer I. editors. Generic Drug Product Development: Solid Oral Dosage Forms, 2nd ed. CRC Press; 2013. doi: 10.1201/b15569
2. Food and Drugs Authority. Guidelines for Registration of Biosimilar Products [Internet]. 2019 Mar 15 [cited 2022 Feb 5]. Available from: https://www.fdaghana.gov.gh/img/organisation/GUIDELINES%20FOR%20REGISTRATION%20OF%20BIOSIMILAR%20PRODUCTS.pdf
3. Estole-Casanova LA, Tolosa EN, Pacaro LB, Jimeno, CA, Cagayan, M, Yabes, AM, et al. A Feasibility Study on Re-establishing the Bioavailability/Bioequivalence Unit of the Department of Pharmacology and Toxicology, College of Medicine-University of the Philippines Manila. Acta Med Philipp. 2024 Mar;58(4):26-39. doi: 10.47895/amp.vi0.6685
4. Kleinstäuber M, Colgan S, Petrie KJ. Changing understanding, perceptions, pain relief of and preference for generic medicines with patient education: An experimental intervention study. Res Social Adm Pharm. 2021 July;17(7), 1288–1299. doi: 10.1016/j.sapharm.2020.09.014
5. Wong JQ, Baclay JRM, Duque RG, Roque PMS, Serrano GKT, Tumlos JOA, et al. How effective has the Generics Act Been? Think Asia [Internet]. 2016 Aug 2 [cited 2022 Oct 30]. Available from: https://think-asia.org/handle/11540/6426
6. Sweileh, W.M. Substandard and falsified medical products: bibliometric analysis and mapping of scientific research. Global Health. 2021 Sep;17:114 doi: 10.1186/s12992-021-00766-5
7. Price G, Patel DA. Drug Bioavailability. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan [cited 2023 Jun 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557852/
8. World Health Organization, Diabetes. [Internet]. 2023. [cited 2023 Mar]. Available from: https://www.who.int/health-topics/diabetes#tab=tab_1
9. IDF Diabetes Atlas. International Diabetes Federation: Philippines Diabetes report 2000 - 2045. [Internet]. 2020. [cited 2023 Mar]. Available from: https://diabetesatlas.org/data/en/country/157/ph.html
10. Corcoran C, Jacobs TF. Metformin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan [cited 2023 Jun 17]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK518983/
11. Engler C, Leo M, Pfeifer B, Juchum M, Chen-Koenig D, Poelzl K, et al. Long-term trends in the prescription of antidiabetic drugs: Real-world evidence from the Diabetes Registry Tyrol 2012–2018. BMJ Open Diabetes Res Care. 2020 Sep;8(1). doi: 10.1136/bmjdrc-2020-001279
12. Nipun TS, Debnath D, Miah MSUH, Hossain MK, Hossen SMM. COMPARATIVE IN VITRO DISSOLUTION STUDY OF LOSARTAN POTASSIUM MARKETED TABLETS IN FOUR DIFFERENT DISSOLUTION MEDIA BY VALIDATED ANALYTICAL METHOD. Int. Res. J. Pharm. 2017 Feb;8(1):8-13. doi: 10.7897/2230-8407.08012
13. Ebiere, D., Samuel J.B., & Ikoi A.I. Comparative In-Vitro Bioequivalence Analysis of Metformin Hydrochloride Tablet Formulations Available in Yenagoa Metropolis, Bayelsa State, Nigeria. [Internet]. 2023 [cited 2024 Nov]. https://jcras.com/uploads/archivepdf/8832JCRA_Vol_03_June_2022_04.pdf
14. Zakeri-Milani P, Nayyeri-Maleki P., Ghanbarzadeh S, Nemati M, & Valizadeh H. In-vitro bioequivalence study of 8 brands of metformin tablets in Iran market. J. appl. pharm. sci. 2012 Aug; 2(8). doi: 10.7324/JAPS.2012.2834
15. United States Pharmacopeia. <1216> Tablet Friability. [Internet]. 2016 [cited 2023 Jan]. Available from: https://www.usp.org/sites/default/files/usp/document/harmonization/gen-chapter/g06_pf_ira_32_2_2006.pdf
16. United States Pharmacopeial Convention. <1217> Tablet Breaking Force [Internet]. 2012 [cited 2023 Jan 10] Available from: https://www.drugfuture.com/Pharmacopoeia/usp35/PDF/0868-0870%20%5B1217%5D%20TABLET%20BREAKING%20FORCE.pdf
17. United States Pharmacopeia. <905> Uniformity of Dosage Units. [Internet]. 2016 [cited 2023 Jan]. Available from: https://www.usp.org/sites/default/files/usp/document/harmonization/gen-method/q0304_pf_30_4_2004.pdf
18. United States Pharmacopeia. <701> Disintegration. [Internet]. 2019 [cited 2023 Jan]. Available from: https://www.usp.org/sites/default/files/usp/document/harmonization/gen-chapter/april-2019-m99460.pdf
19. United States Pharmacopeia. Metformin Hydrochloride. [Internet]. 2012 [cited 2023 Jan]. Available from https://www.drugfuture.

com/Pharmacopoeia/usp35/PDF/3830-3831%20Metformin%20Hydrochloride%20Tablets.pdf
20. Gupta MM, Khoorban A, Ali A, Ramlogan O, Talukdar D. Comparative Quality Control Study of Different Brands of Diclofenac Sodium Tablet Available in Local and Government Pharmacies by In-Vitro Testing. Cureus. 2020 Nov;12(11) doi: 10.7759/cureus.11348
21. Kumar D, Singh J, Antil M, Kumar V. Quality Control of Tablets: A Review. Int. J. Univers. Pharm. Bio Sci. 2016 Aug;5(3):13-20. ISSN: 2319-8141
22. Food and Drug Administration. Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules [Internet]. 2022 [cited 2023 Jun 23]. Available from: https://www.fda.gov/media/161902/download
23. Smith Marsh. Bioequivalence and Interchangeability of Generic Drugs. MSD Manual [Internet]. 2023 [cited 2023 Jun 21]. Available from: https://www.msdmanuals.com/home/drugs/brand-name-and-generic-drugs/bioequivalence-and-interchangeability-of-generic-drugs
24. Molavi F, Hamishehkar H, Nokhodchi A. Impact of Tablet Shape on Drug Dissolution Rate Through Immediate Released Tablets. Adv Pharm Bull. 2020;10(4):656–661. doi: 10.34172/apb.2020.079
25. Wen H, Jung H, Li X. Drug Delivery Approaches in Addressing Clinical Pharmacology-Related Issues: Opportunities and Challenges. The AAPS Journal. 2015 Nov;17(6):1327-1340. doi: 10.1208/s12248-015-9814-9 PMID: 26276218; PMCID: PMC4627459
26. Gozzo L, Caraci F, Drago F. Bioequivalence, drugs with narrow therapeutic index and the phenomenon of Biocreep: A critical analysis of the system for Generic Substitution. Healthcare. 2022 July;10(8):1392. doi: 10.3390/healthcare10081392
27. Marcheva M, Manigault A, Peasah SK. Insights Into Effective Generic Substitution. U.S. Pharmacist [Internet]. 2016 Jun 16 [cited 2023 Jun 28]. Available from: https://www.uspharmacist.com/article/insights-into-effective-generic-substitution
28. U.S. Department of Health and Human Services. Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products -General Considerations. [Internet]. 2003 [cited 2024 Nov 24]. Available from: https://ipqpubs.com/wp-content/uploads/2020/12/BioStudies_OralDosageProducts_March.2003.GUIDANCE.pdf.pdf
29. European Medicines Agency. Research and Development: Scientific guidelines. [Internet]. 2008 [cited 2024 Nov 24]. Available from: www.ema.europa.eu. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-guidelines
30. European Medicines Agency. Non-inferiority and equivalence comparisons in clinical trials - Scientific guideline. [Internet]. 2024 [cited 2024 Nov 24]. Available from: https://www.ema.europa.eu/en/non-inferiority-equivalence-comparisons-clinical-trials-scientific-guideline