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Review Article

BIOEQUIVALENCE OF METFORMIN AS AN ORAL ANTIDIABETIC: A SYSTEMATIC REVIEW

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ABSTRACT

Metformin is the first line in type 2 Diabetes Mellitus (DM). Metformin is available as an innovator drug and copy drug. The high price of innovator drugs makes it difficult for patients to obtain the required drugs. Therefore, many pharmaceutical industries have developed a copy of the innovator drug. To obtain .a distribution license, the pharmaceutical industry must conduct a bioequivalence test on metformin copy tablets to ensure that the copy drug has the same efficacy, safety, and quality as the innovator drug. However, several surveys show that most patients believe that the effectiveness of copy drugs is not equivalent to the innovator drug. This study aims to determine the bioavailability profile and bioequivalence profile of Metformin copy tablets to Glucophage® (Merck) innovator tablets so that it can provide an overview of the effectiveness of copy drugs with innovator drugs and the public no longer hesitate to use copy drugs. Metformin copy tablets are declared bioequivalent to the innovator drug if they provide a Confidence Interval (CI) value of 90% in the 80-125% range. All 500 mg, 850 mg, and 1000 mg doses of metformin copy tablets, both fasting and eating conditions, gave bioequivalent results to the innovator Glucophage® based on 90% CI.

Keywords: Bioequivalence, Bioavailability, Pharmacokinetics, Glucophage®, Metformin

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by elevated blood glucose levels due to impaired insulin secretion and/or impaired insulin sensitivity. According to the International Diabetes Federation (IDF), approximately 10.5% of the world's population lives with diabetes at the age of 20-79 y old [1]. The first line of pharmacologic therapy used in type 2 DM is metformin. Metformin is mainly used because it has a low risk of side effects of hypoglycemia and has no impact on body weight. To achieve maximum blood glucose-lowering effect, metformin is commonly combined with other blood glucose-lowering agents, such as thiazolidinediones [2].

Metformin is a medicine used to treat type 2 DM. Metformin is a derivative of Galegin, a compound from the Galega officinalis plant that was used for herbal medicine in Europe. In the 1920s, Galegine was tested as a glucose-lowering agent in humans, but the results were found as toxic to humans. At the same time, synthetic derivatives of Galegine were synthesized, namely Metformin and Phenformin. However, phenformin is no longer widely used due to side effects such as lactic acidosis [3].

Metformin is widely used as an antidiabetic, followed by sulfonylureas and insulin [4]. Metformin is available in the form of an innovator drug and copy drug. The high price of the innovator drug makes it difficult for patients to obtain the drug they need, so the pharmaceutical industry develops a copy of the innovator drug. To be approved for distribution, a copy drug must be bioequivalent to the comparator drug as proven through a bioequivalence study [5]. A bioequivalence study is a test that compares the bioavailability profile between a test drug and a comparator drug [1]. Even though they have passed bioequivalence tests, some surveys show that most patients believe a copy drug's effectiveness is not equivalent to the innovator drug [6].

The main objective of this review was to determine the bioequivalence profile of Metformin copy tablets to Glucophage® (Merck) as innovator tablets so it can provide an overview of the effectiveness of copy drugs with innovator drugs and the public no longer hesitate to use copy drug.

Methods

Research article search on reputable databases, which are PubMed, ScienceDirect (Elsevier), John Wiley and Sons, and Springer Verlag collected in December 2022-January 2023. The inclusion criteria for articles are research articles on the bioequivalence study of metformin copy tablets, research articles with metformin copy tablets with doses of 500 mg, 850 mg, and 1000 mg, research articles published in the last 10 y (2013-2023), and articles written in Indonesian or English. Articles excluded have criteria that do not discuss the bioequivalence study of metformin. The extracted data are the main author's name, year of publication, study design, number of participants, doses, test and innovator drug data, Area Under Curve (AUC0-∞ and AUC0-t), time taken to reach the highest concentration (Tmaks), highest concentration (Cmaks), T1/2, and 90% Confidence Interval (CI). Fig. 1 shows the PRISMA flow diagram of the article selection process.

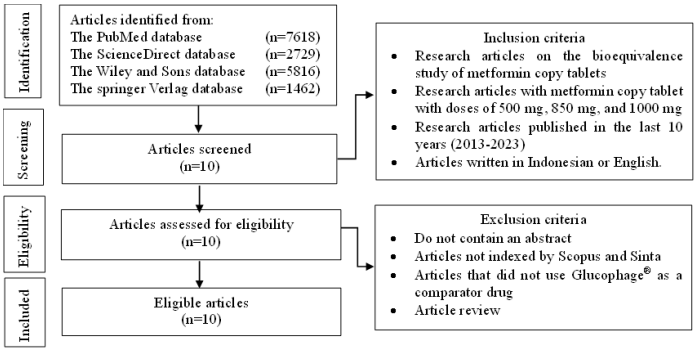

Fig. 1: PRISMA flow diagram of article research

RESULTS AND DISCUSSION

A bioequivalence study is a test that compares the bioavailability profile between a test drug and a comparator drug. The bioavailability study is one of the documentation requirements to apply for a copy drug distribution license. In general, the bioequivalence study aims to ensure the safety, efficacy, and quality of the test drug, in this case, the copy drug is equivalent to the innovator drug. Meanwhile, the specific objective is to obtain a distribution license for the copy drug [1].

A copy drug is a medicine that contains the same active components as registered and circulated medicines. A comparator drug is a medicine that serves as a comparison in the equivalence test to prove the equivalence of a test drug. Meanwhile, one of the comparator drugs uses innovator medicine. Innovator drugs a medicines that were first licensed for distribution and were patented [5].

Before conducting a bioequivalence study, the bioequivalence study organizer must develop a bioequivalence study protocol that will be submitted to the ethics committee. This must be carried out because the subjects are humans. In addition, this is also required to obtain informed consent from the subjects involved. The subjects who participate in the bioequivalence study must meet the inclusion and exclusion criteria.

After determining the subjects, the study conditions are standardized to reduce the variability that may affect the test results. Generally, bioequivalence study conditions are conducted under fasting and eating conditions. Fasted condition is considered the most sensitive condition so it is commonly performed in the bioequivalence study.

After the subject consumed the drug, blood samples were taken. Blood sampling at certain times can indicate the absorption, distribution, and elimination phases. The required blood samples are usually 12-18 samples, each of which represents [5]:

- Before drug administration (at time zero) as much as 1 sample
- Before reaching the maximum level (Cmax) as many as 2-3 samples
- Around Cmax 4-6 samples
- After Cmax 5-8 samples until at least 3 times the elimination half-life of the drug.

Determination of pharmacokinetic parameters was done by mapping the concentration of metformin against time to form a concentration-time curve. The AUC_{0-t} parameter was determined by calculating the area under the curve with the trapezoidal method. Then, the $AUC_{0-\infty}$ parameter was determined using the formula $AUC_{0-\infty} = AUC_{0-t}+C_t/\lambda_e$. Where Ct is the drug concentration in the blood at time t and λ_e is the elimination constant obtained from the slope value of the concentration curve against time. Cmax and Tmax are determined directly on the concentration-time curve by determining the highest concentration (Cmax) and the time taken to reach the highest concentration (Tmax). Meanwhile, the parameter $T_{1/2}$ was determined using the formula $T_{1/2}=0,693/\lambda_e$.

Tests on the test drug and innovator drug are separated by a time interval known as the washout period. The washout period is the time that separates the two testing periods and considers the drug administered in the first period to be eliminated from the body before the second period of medicine administration [7].

Most type 2 DM patients use metformin and sitagliptin as monotherapy, which is in India [8]. Metformin tablets copy with Glucophage tablets are bioequivalent if [5]:

1. The average ratio of the AUC_{0-t} of the test drug: AUC_{0-t} of the comparator drug = 1.00 with a 90%CI= 80.00-125.00%.

2. The average ratio of the Cmax of the test drug: Cmax of the comparator drug = 1.00 with a 90% CI = 80.00-125.00%.

Table 1 presents the bioavailability and bioequivalence profiles of 500 mg Metformin copy and innovator tablets tested under fasted conditions. From the five bioequivalence studies under fasted conditions with a metformin dose of 500 mg, the average AUC_{0-t} of the study was 7123.32 ng. h/ml and the average AUC_{0-t} of the innovator was 5318.21 ng. h/ml. The average test $AUC_{0-\infty}$ was 7100.74 ng. h/ml and the average of the innovator $AUC_{0-\infty}$ was 6696.78 ng. h/ml. Then, the average Cmax of the test was 1043.89 ng/ml and the average Cmax of the innovator was 1002.52 ng/ml. The average Tmax of both the test drug and innovator drug was 3 h. These parameters interpret the level and speed of metformin reaching the subject's body circulation. It can be seen that the average metformin level in the test drug is higher than the innovator drug with the same average Tmax. Therefore, the 500 mg fasted dose of metformin copy drug in this study can be a therapeutic substitution for the innovator drug.

Table 1: Bioavailability and bioequivalence profiles of 500 mg Metformin copy and innovator tablets under fasting conditions

Design study	Test drug	Dose	n	Bioavailability profiles					Innovator drug	Bioavailability profiles					Bioequivalence profiles	
				AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$		AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$	90% CI	
															AUC_{0-t}	Cmax
Single-centre, open-label, two-sequence crossover study, randomize, two-periods, single-dose	Boke® [9]	500	48	5203.8	5080.6	724.14	4	10.38	Glucophage® (BMS, USA)	5099	4999.6	697.54	4	10.23	97.36-108.3	96.76-111.37
Open-label, two-sequence, crossover study, randomize	Glucophage® [10]	500	26	6520	6260	1110	2	4.38	Glucophage® (Merck, French)	6410	6280	1110	2	4.9	92.84-107.2	92.69-106.77
Open-label, two-way crossover study, randomized, single-dose	FDC Gemigliptin/metformin [11]	50/1000	40	9598.36	9925.88	1291.33	4	14.2	Glucophage® (Merck, Korea)	897.1	8667.3	1203.59	4	13.7	102.73-116.81	98.25-115.49
Open-label, randomized, four-periods	FDC saxagliptin/metformin [12]	2.5/500	44	7349.43	7491.2	997.97	3	12.03	Glucophage® (BMS, USA)	7280.93	7175.98	989.45	3	9.87	96.4-108.8	93.9-108.4
Crossover design, open-label, randomize, two-periods, single-dose	FDC ertugliflozin/metformin [13]	2.5/500	18	6945	6746	1096	2	14.21	Glucophage® (Merck, US)	6904	6361	1012	2	8.67	96.17-118.61	95.69-122.5
Mean				7123.32	7100.74	1043.89	3	11.04		5318.21	6696.78	1002.52	3	9.47	97.1-111.94	95.46-112.91
Median				6945	6746	1096	3	12.03		6410	6361	1012	3	9.87		
Max				9598.36	9925.88	1291.33	4	14.21		7280.93	8667.3	1203.59	4	13.7		
Min				5203.8	5080.6	724.14	2	4.38		897.1	4999.6	697.54	2	4.9		

n=number of subjects; AUC_{0-t}= ng. h/ml; $AUC_{0-\infty}$= ng. h/ml; Cmax= ng/ml; Tmax= h; $T_{1/2}$= h; CI min, CI max=%; Dose= mg

Sun *et al.* [9] reported the bioequivalence study of two sustained-release tablets of metformin hydrochloride. The study was conducted on 48 subjects, with 36 male and 12 female subjects. In the parameters of AUC_{0-t}, $AUC_{0-\infty}$, and Cmax, female subjects are known to have higher values than male subjects. This is due to women having a longer small intestine than men. Based on the research that has been done, it is known that women have a small intestine that is±30 cm longer than men [14]. 47 out of 48 subjects were of Han ethnicity, but the pharmacokinetic profile showed no significant difference between the two. The AUC_{0-t}, $AUC_{0-\infty}$, Cmax, Tmax, and $T_{1/2}$ values of the test drug Boke® showed better values than the innovator drug Glucophage®. In the parameters of $AUC_{0-\infty}$, $AUC_{0-t,}$ and Cmax the test drug Boke® had greater values than the innovator drug Glucophage®. However, both drugs were declared bioequivalent because the 90% CI in the AUC_{0-t} and Cmax parameters were in the range of 85-125%. The test drug Boke® is, therefore, bioequivalent to the innovator Glucophage®[9].

Hu *et al.* [10] reported a bioequivalence study between the test drug Glucophage® produced in China and the innovator drug Glucophage® produced in France. Both dosage forms are immediate-release or immediate-release tablets. The study was conducted on 26 subjects. In the $AUC_{0-\infty}$ parameter, the test drug had a higher 110 ng. h/ml, but the 90% CI parameter was in the range of 80-125%. While in the AUC_{0-t} parameter, the test drug had a smaller value of 20 ng. h/ml, but the 90% CI parameter was in the range of 80-125%. In the Cmax parameter, the test drug has the same value as the innovator drug so the 90% CI is in the 80-125% range. Therefore, the test drug Glucophage® produced in China is bioequivalent to the innovator drug Glucophage® produced in France based on the 90% CI [10].

Jin *et al.* [11] reported a bioequivalence study between a Fixed-Dosed Combination (FDC) containing gemigliptin and metformin compared to the innovator loose combination of Glucophage® with gemigliptin. In the $AUC_{0-\infty}$ parameter, metformin in the gemigliptin/metformin FDC test drug had a value of 954 ng. h/ml greater than the innovator drug Glucophage®. Although the $AUC_{0-\infty}$ parameter was greater, the 90% CI parameter remained in the 80-125% range. Meanwhile, the AUC_{0-t} parameter of the test drug has a value that is not much different, which only has a value of 81 ng. h/ml higher than the innovator drug, and the 90% CI parameter is in the 80-125% range. The Cmax parameter of the test drug had a similar value compared to the innovator drug, and the 90% CI parameter was in the range of 80-125%. Therefore, the gemigliptin/metformin FDC is bioequivalent to the innovator drug Glucophage®[11].

Upreti *et al.* [12] reported a bioequivalence study between a FDC test drug containing saxagliptin and metformin against the innovator loose combination product Glucophage® with Onglyza™. In the $AUC_{0-\infty}$ parameter, the test drug had a value of 210 ng. h/ml greater than the innovator drug with 90% CI in the range of 80-125%. Then, the AUC_{0-t} parameter has a significant difference, where the test drug has a value of 173 ng. h/ml higher than the innovator drug. However, the 90% CI parameter remains in the 80-125% range. While the parameter has an insignificant difference, the 90% CI parameter is in the range of 80-125%. Therefore, the saxagliptin/metformin FDC test product is bioequivalent to the innovator product Glucophage®[12].

Dawra *et al.* [13] reported a bioequivalence study between a FDC test product containing ertugliflozin 2.5 mg and metformin 500 mg compared to an innovator loose combination of Glucophage® and ertugliflozin. Ertugliflozin is a drug with an indication of antidiabetic, which is classified as a Sodium-glucose cotransporter (SGLT2) inhibitor [15]. Metformin in the FDC test product has better absorption than the innovator product as evidenced by the better AUC_{0-t}, $AUC_{0-\infty}$, and Cmax parameter values. The $AUC_{0-\infty}$ parameter in the 41 ng. h/ml test drug is greater than the innovator drug. The AUC_{0-t} parameter has a significant difference from the innovator drug, which is 430 ng. h/ml higher than the innovator drug. However, the 90% CI parameter value is in the range of 80-125%. While the Cmax parameter of the test drug has a value of 84 ng/ml greater than the innovator drug, from the 90% CI in the AUC_{0-t} and Cmax values are in the range of 80-125% so that the ertugliflozin/metformin FDC test drug is bioequivalent to the innovator drug Glucophage®[13].

Table 2 presents the bioavailability and bioequivalence profiles of 500 mg Metformin copy and innovator tablets tested under fed conditions. From all seven bioequivalence studies under fed conditions with a 500 mg metformin dose, the average AUC_{0-t} of the test was 6495.76 ng. h/ml and the average AUC_{0-t} of the innovator was 6856.28 ng. h/ml. The average $AUC_{0-\infty}$ of the test was 6149.56 ng. h/ml and the average $AUC_{0-\infty}$ of the innovator was 6409.78 ng. h/ml. Then, the average Cmax of the test drug was 813.83 ng/ml and the average Cmax of the innovator was 848.63 ng/ml. The average Tmax of the test drug was 4.02 h, while that of the innovator drug was 3.77 h.

Table 2: Bioavailability and bioequivalence profiles of 500 mg Metformin copy and innovator tablets under fed conditions

Design study	Test drugs	Dose	Bioavailability profiles						Innovator drugs	Bioavailability profiles					Bioequivalence profiles	
			n	AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$		AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$	90 % CI	
															AUC_{0-t}	Cmax
Open-label, crossover, randomize, two-periods, single-dose	500-mg metformin-Er [16]	500	8	6627	6563	619	6.5	4.8	Gluco-phage® (Merck, Germany)	6828	6753	570	5.5	5	91.4-105	101.2-119.4
Single-centre, open-label, crossover, randomize, two-sequence, single-dose	Yuantang® [17]	500	36	6434	6366	651.41	5	4.7	Gluco-phage® (Merck Serono, UK)	6367	6305	640.29	5	4.81	96.12-105.4	98.42-105
Open-label, two-sequence, crossover study, randomize	Gluco-phage® IR [10]	500	18	5070	4950	711	2.75	4.23	Gluco-phage® (Merck, Franch)	5160	5020	700	2.75	4.16	91.25-106.69	93.72-109.92
Single-centre, open-label, four-period crossover study, randomize	FDC acarbose/ metformin [18]	50/ 500	33	4877.24	4687.44	661.44	5	4.82	Gluco-phage® (BMS, USA)	6548	6437	997.311	3	4.305	92.44-101.94	93.13-104.48
open-label, four-period, randomize	FDC saxagliptin/ metformin [12]	2.5/ 500	44	7449.8	7375.98	1007.76	4	8.61	Gluco-phage® (Merck, US)	7147.97	7076.48	974.8	4	8,62	98.6-110.2	98.1-110.8
Two-period crossover study, single-dose, randomize	metformin tablet [19]	500	21	9753.3	7946.5	1404.5	1.91	4.74	Glucophage ®(Merck, Germany)	10858	8049	1425.5	2.12	5.97	92.72-107.37	92.14-110.95
Crossover design, open-label, randomize, two-periods, single-dose	FDC Ertugliflozin/ Metformin [13]	2.5/ 500	14	5259	5158	641.7	3	15.44	Glucophage (Merck, US)	5085	5228	632.5	4	13.06	92.79-106.40	97.54-105.52
Mean				6495.76	6149.56	813.83	4.02	6.76		6856.28	6409.78	848.63	3.77	6.56	94.46-106.55	97.17-109.42
Median				6434	6366	661.44	4	4.8		6548	6437	700	4	5		
Max				9753.3	7946.5	1404.5	6.5	15.44		10858	8049	1425.5	5.5	13.06		
Min				4877.24	4687.44	619	1.91	4.23		5085	5020	570	2.12	4.16		

n=number of subjects; AUC_{0-t}= ng. h/ml; $AUC_{0-\infty}$= ng. h/ml; Cmax= ng/ml; Tmax= h; $T_{1/2}$= h; CI min, CI max=%; Dose= mg

Zhou *et al.* [16] reported a bioequivalence test between the test product metformin tablets in extended-release (ER) form against the innovator product Glucophage®. In the $AUC_{0-\infty}$ parameter, the innovator drug has a value of approximately 201 ng. h/ml higher than the test drug, with a 90% CI value of 91.3-104.7%. Similarly, in the AUC_{0-t} parameter, the innovator drug had a value of approximately 190 ng. h/ml higher with a 90% CI value of 91.4-105%. Whereas in the Cmax parameter, the test drug had a value of 49 ng/ml higher than the innovator drug with a 90% CI of 101.2-119.4. The Tmax parameter of the test drug was 1 h longer than the innovator drug. The $T_{1/2}$ parameter in the test drug occurred slightly faster than the innovator drug. From the 90% CI values in the AUC_{0-t} and Cmax parameters which are in the range of 90-125%, the 500-mg metformin ER tablet test product is bioequivalent to the innovator drug Glucophage®[16].

Sun *et al.* [17] conducted a bioequivalence study between the test product Yuantang® sustained release (Guangdong Sinocorpd Pharmaceutical Co., China) and the innovator product Glucophage® Extended-release (Merck Serono Co., Ltd, UK). In the $AUC_{0-\infty}$ parameter, the test drug had a value of 66 ng. h/ml higher than the innovator drug with a 90% CI of 96.22-105.54. The AUC_{0-t} parameter of the test drug has a value of 60 ng. h/ml higher than the innovator drug with a 90% CI value of 96.12-105.44%. While the Cmax parameter of the test drug had a value of 11 ng/ml higher than the innovator drug with a 90% CI of 98.42-105%. Both drugs have the same Tmax value, which is 5 h. Based on the 90% CI in the AUC_{0-t} and Cmax parameters, the Yuantang® test product is bioequivalent to Glucophage® [17].

Hu *et al.* [10] reported bioequivalence studies between the test product Glucophage® IR produced in China and Glucophage® IR produced in France. The $AUC_{0-\infty}$ parameter of the test drug was 90 ng. h/ml lower than the innovator drug with a 90% CI of 91.61-105.21%. In the AUC_{0-t} parameter, the test drug has a of 70 ng. h/ml lower than the innovator drug with a 90% CI of 91.25-106.69%. Whereas in the Cmax parameter, the test drug had a higher value than the innovator drug. In the $T_{1/2}$ parameter, the two drugs have a slight difference. Based on the 90% CI in the AUC_{0-t}, $AUC_{0-\infty}$, the test product Glucophage® produced in China is bioequivalent to Glucophage® produced in France [10].

Kim *et al.* [18] reported a bioequivalence study conducted on FDC containing acarbose 50 mg and metformin 500 mg compared to Glucophage®. In the $AUC_{0-\infty}$ parameter, the test drug had a significant difference in value, which was 1670 ng. h/ml lower than the innovator drug with a 90% CI value of 94.97-102.99%. The AUC_{0-t} parameter also has a significant difference; the test drug has a value of 1750 ng. h/ml lower than the innovator drug. Whereas in the Cmax and Tmax parameters, the test drug had a better value than the innovator drug. In the $T_{1/2}$ parameter, both drugs have a slight difference. Although the parameters of the test drug and innovator have significant differences, the 90% CI in the parameters AUC_{0-t} and Cmax are in the range of 90-125%. Therefore, the acarbose/metformin FDC test product is bioequivalent to Glucophage® [18].

Upreti *et al.* [12] conducted a bioequivalence study on FDC containing saxagliptin 2.5 mg and metformin 500 mg compared to the innovator drug Glucophage®. In the $AUC_{0-\infty}$ parameter, the test drug had a value of 302 ng. h/ml higher than the innovator drug with a 90% CI of 96.2-111.1%. Similarly, the AUC_{0-t} parameter, the test drug, had a value of 299 ng. h/ml higher than the innovator drug with a 90% CI of 98.6-110.2%. The Cmax parameter of the test drug had a value of 25 ng/ml higher than the innovator drug, with a 90% CI of 98.1-110.8%. Both drugs had similar Tmax values of 4 h and slightly different $T_{1/2}$ values. Based on the 90% CI of AUC_{0-t} and Cmax, the saxagliptin/metformin FDC test drug is bioequivalent to Glucophage® [12].

Valizadeh *et al.* [19] conducted a bioequivalence study on the test drug metformin tablets against the innovator drug Glucophage®. The AUC_{0-t}, $AUC_{0-\infty}$, and Cmax parameters of the innovator drug had better values than the test drug. However, the 90% CI in the three parameters is in the range of 80-125%, with each 90% CI value of the $AUC_{0-\infty}$ parameter of 96.2-111.1%, the 90% CI value of the AUC_{0-t} parameter of 98.6-110.2%, and the 90% CI value in the Cmax parameter of 98.1-110.8%. Therefore, the test drug metformin tablet (Exir Pharmaceutical Company) is bioequivalent to Glucophage® (Merck) [19].

Dawra *et al.* [13] documented the bioequivalence test between the FDC test drug containing ertugliflozin 2.5 mg and metformin 500 mg against Glucophage. the AUC_{0-t} parameter of the test drug has a lower value than the innovator drug with a 90% CI value of 92.79-106.4%. In the Cmax parameter, the test drug had a higher value than the innovator drug, with a 90% CI value of 97.54-105.52%. The test drug reached Cmax faster, which took 3 h while the innovator drug took 4 h. Based on the 90% CI in the $AUC_{0-\infty}$ and AUC_{0-t} parameters, which are in the range of 80-125%, the ertugliflozin/metformin FDC test drug is bioequivalent to Glucophage [13].

Table 3 presents the bioavailability and bioequivalence profiles of 850 mg Metformin copy and innovator tablets tested under fasted and fed conditions. Dawra *et al.* [13] documented a bioequivalence test between an FDC test product containing ertugliflozin 2.5 mg and metformin 500 mg compared to Glucophage. In addition, the bioequivalence study was conducted on different doses, namely ertugliflozin 7.5 mg and 850 mg. Under fasted conditions, the $AUC_{0-\infty}$ Parameter of the test drug was 192 ng. h/ml lower than the innovator drug. In the AUC_{0-t} parameter, the test product also had a lower value than the innovator drug with a 90% CI of 91.88-106.40%. Whereas in the Cmax parameter, the test drug had a higher value than the innovator drug with a 90% CI of 90.58-112.92%. In the fed condition study, the $AUC_{0-\infty}$ parameter of the test drug had a significant difference, which was 567 ng. h/ml lower. In the AUC_{0-t} parameter, the test drug had a value of 1059 ng. h/ml higher than the test drug, with a 90% CI value of 95.99-116.62%. In the Cmax parameter, the test drug and the innovator drug had a slight difference with a 90% CI value of 91.50-106.40. So the ertugliflozin/metformin FDC test drug is bioequivalent to the Glucophage innovator based on the 90% CI value, which is in the range of 80-125% [13].

Table 3: BE profiles of 850 mg metformin copy and innovator tablets under fasting and fed conditions

Design study	Test drugs	Dose	Bioavailability profiles						Innovator drugs	Bioavailability profiles					Bioequivalence profiles	
			n	AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$		AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$	90% CI	
															AUC_{0-t}	Cmax
Open-label, crossover, randomize, two-periods, single-dose, fasted condition	FDC ertugliflozin /metformin [13]	7.5/ 850	18	9340	9477	1453	2	16.69	Glucophage (Merck, US)	9446	9669	1437	2.01	16.54	91.88-106.40	90.58-112.92
Open-label, crossover, randomize, two-periods, single-dose, fed condition	FDC ertugliflozin /metformin [13]	7.5/ 850	14	8357	8235	1073	3.53	16.05	Glucophage (Merck, US)	7898	8802	1088	2.52	22.03	95.99-116.62	91.50-106.40

n=number of subjects; AUC_{0-t}= ng. h/ml; $AUC_{0-\infty}$= ng. h/ml; Cmax= ng/ml; Tmax= h; $T_{1/2}$= h; CI min, CI max=%; Dose= mg

Table 4 presents the bioavailability and bioequivalence profiles of 1000 mg Metformin copy and innovator tablets tested under fasted conditions. Upreti *et al.* [12] reported a bioequivalence study with FDC test drug containing saxagliptin 2.5 mg and metformin 1000 mg against the innovator drug Glucophage®. Bioavailability parameters including AUC_{0-t}, $AUC_{0-\infty}$, Cmax, and

Tmax of the innovator drug, had better values than the test drug. Although the bioavailability parameters of the innovator drug are better, the 90% CI in the parameters AUC_{0-t} and Cmax are in the range of 80-125%. Therefore, the saxagliptin/metformin IR FDC test drug is bioequivalent to Glucophage® (BMS, USA) based on the 90% CI [12].

Table 4: Bioavailability and bioequivalence profiles of 1000 mg Metformin copy and innovator tablets under fasted conditions

Design study	Test drugs	Dose	Bioavailability profiles						Innovator drugs	Bioavailability profiles					Bioequivalence profiles	
			n	AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$		AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$	90% CI	
															AUC_{0-t}	Cmax
Open-label, crossover, randomize, four-periods, single-dose	FDC saxagliptin / Metformin IR [12]	2,5/ 1000	44	12400.41	12677.92	1830.76	2.98	10.58	Glucophage® (Bristol-Myers Squibb Co., USA)	13238.43	13363.46	2004.99	2	8.43	90.6-102	86.4-101.6

n=number of subjects; AUC_{0-t}= ng. h/ml; $AUC_{0-\infty}$= ng. h/ml; Cmax= ng/ml; Tmax= h; $T_{1/2}$= h; CI min, CI max=%; Doses= mg

Table 5 presents the bioavailability and bioequivalence profiles of 1000 mg Metformin copy and innovator tablets tested under fed conditions. From the three bioequivalence studies under fed conditions with 1000 mg metformin dose, the mean AUC_{0-t} of the test was 12050.98 ng. h/ml and the mean AUC_{0-t} of the innovator was 12040.39 ng. h/ml. The average $AUC_{0-\infty}$ of the test was 9106.67 ng. h/ml and the average $AUC_{0-\infty}$ of the innovator was 11797.86 ng. h/ml. Then, the average Cmax of the test was 1340.81 ng/ml and the average Cmax of the innovator was 1323.11 ng/ml. The average Tmax of the test drug was 4.68 h, while that of the innovator drug was 4.67 h.

Table 5: Bioavailability and bioequivalence profiles of 1000 mg metformin copy and innovator tablets under fed conditions

Design study	Test drugs	Dose	Bioavailability profiles						Innovator drugs	Bioavailability profiles					Bioequivalence profiles	
			n	AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$		AUC_{0-t}	$AUC_{0-\infty}$	Cmax	Tmax	$T_{1/2}$	90% CI	
															AUC_{0-t}	Cmax
Open-label, crossover, randomize, two-periods,	Xigduo (dapagliflozin/ metformin) XR [20]	10/ 1000	40	8858.5	9408.5	1030.8	4	11.95	Glucophage Long 500-mg	9286.9	9612.2	986.9	4	12.43	89.5-102.8	98.5-110.6
Open-label, two-way crossover study, randomized, single-dose	FDC gemigliptin/metformin [11]	50/ 1000	30	14464,63	14618,25	1348,73	6,04	7.47	Glucophage XR® (Merck and Co., Inc., Korea)	13982,36	13982,36	1315,87	6	8.2	100.58-106.49	99.66-105.57
Open-label, randomized, four-periods	FDC saxagliptin/ Metformin IR [12]	2.5/ 1000	44	11996.88	12126.19	1642.90	4	7.63	Glucophage® (Bristol-Myers Squibb Co., USA)	12124.31	12357.87	1666.55	4	11.78	92-103.2	89.1-104.2
Mean				12050.98	9106.67	1340.81	4.68	9.02		12040.39	11797.86	1323.11	4.67	10.80	94.03-104.16	95.75-106.79
Median				12126.19	11996.88	1348.73	4	7.63		12357.87	12124.31	1315.87	4	11.78		
Max				14618.25	14464.63	1642.9	6.04	11.95		14151.09	13982	1666.55	6	12.43		
Min				9408.5	858.5	1030.8	4	7.47		9612.2	9286.9	986.9	4	8.2		

n=number of subjects; AUC_{0-t}= ng. h/ml; $AUC_{0-\infty}$= ng. h/ml; Cmax= ng/ml; Tmax= h; $T_{1/2}$= h; CI min, CI max=%; Dose= mg

Khomitskaya *et al.* [20] conducted a bioequivalence study of the test product Xigduo which is an FDC containing dapagliflozin 10 mg and metformin 1000 mg against the innovator drug Glucophage®. Dapagliflozin and metformin combination is known to be safe and effective for controlling blood glucose levels [21]. In the $AUC_{0-\infty}$ parameter, the test drug had a value of 203 ng. h/ml lower than the innovator drug with a 90% CI of 89.5-102.8. Also, in the AUC_{0-t} parameter, the innovator drug had a higher value of 428 ng. h/ml than the test drug. However, the Cmax value was achieved higher in the test drug with a 90% CI of 98.5-110.6%. Therefore, the test drug Xigduo is bioequivalent to Glucophage Long 500-mg based on 90% CI [20].

Jin *et al.* [11] reported a bioequivalence study between a FDC test drug containing gemigliptin and metformin against the innovator loose combination drug Glucophage® with gemigliptin. The $AUC_{0-\infty}$ parameter of metformin in the gemigliptin/metformin FDC test drug was 467 ng. h/ml greater than that of the innovator Glucophage®. However, although the $AUC_{0-\infty}$ parameter was higher, the 90% CI parameter remained in the 80-125% range, which was 100.78-106.74%. Meanwhile, the AUC_{0-t} parameter of the test drug had a value of 482 ng. h/ml higher than the innovator drug, and the 90% CI parameter was 100.58-106.49%. The Cmax parameter of the test drug has a value that is not significantly different from the innovator drug, and the 90% CI parameter is 99.66-105.57. Therefore, based on the 90% CI, gemigliptin/metformin FDC is bioequivalent to the innovator drug Glucophage®[11].

Upreti *et al.* [12] conducted a bioequivalence study on FDC containing saxagliptin 2.5 mg and metformin 100 mg against the innovator drug Glucophage®. the $AUC_{0-\infty}$ parameter of the test drug had a value of 231 ng. h/ml lower than the innovator drug with a 90% CI of 91.5-102%. The AUC_{0-t} parameter, the test drug, had a value of 127 ng. h/ml lower than the test drug with a 90% CI of 92.0-103.2%. The Cmax parameter of the test drug had a value of 23.65 ng/ml lower than the innovator drug with a 90% CI of 89.1-104.2%. Both drugs had the same Tmax value of 4 h and different $T_{1/2}$ values of 4 h. Based on the 90% CI values of AUC_{0-t} and Cmax, the FDC test drug saxagliptin/metformin is bioequivalent to Glucophage®[12].

CONCLUSION

All 500 mg, 850 mg, and 1000 mg doses of metformin copy tablets, both fasted and fed conditions, gave bioequivalent results to the innovator Glucophage® based on 90% CI.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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