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+1), time taken to reach the highest concentration (Tmax), highest concentration (Cmax), T1/2, and 90% Confidence Interval (CI).

Fig. 1 shows the PRISMA flow diagram of the article selection process.
RESULTS AND DISCUSSION

A bioequivalence study is a test that compares the bioavailability profiles 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 are 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 study 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:
- 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-\infty} 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-\infty}/\lambda_e$. Where $\lambda_e$ is the drug concentration in the blood at time $t$ and $\lambda_e$ 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 $T_{1/2} = \log(2)/\lambda_e$.

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 medication 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 AUCs of the test drug: AUCs 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 AUCs of the study was 7123.32 ng·h/ml and the average AUCs of the innovator was 5318.21 ng·h/ml. The average test AUCs was 7100.74 ng·h/ml and the average of the innovator AUCs 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 mg/ml.

The average Tmax of both the test drug and innovator drug was 3 h. These parameters indicate 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>
<thead>
<tr>
<th>Design study</th>
<th>Test drug</th>
<th>Dose</th>
<th>n</th>
<th>Bioavailability profiles</th>
<th>Innovator drug</th>
<th>Bioavailability profiles</th>
<th>Bioequivalence profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC&lt;sub&gt;0-\infty&lt;/sub&gt;</td>
<td>AUC&lt;sub&gt;0-\infty&lt;/sub&gt;</td>
<td>Cmax</td>
<td>Tmax</td>
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<tr>
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<td>5080.8</td>
<td>724.1</td>
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<td>6520.7</td>
<td>6260.0</td>
<td>1110.2</td>
<td>4</td>
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<tr>
<td>Open-label, two-sequence crossover study, randomized, single-dose</td>
<td>PDC Gemigliptin/metformin [11]</td>
<td>50</td>
<td>100</td>
<td>9598.2</td>
<td>9925.3</td>
<td>1291.3</td>
<td>3</td>
</tr>
<tr>
<td>Open-label, randomized, four-periods</td>
<td>PDC saxagliptin/metformin [12]</td>
<td>25</td>
<td>500</td>
<td>7439.7</td>
<td>7491.2</td>
<td>997.9</td>
<td>3</td>
</tr>
<tr>
<td>Crossover design, open-label, randomized, two-periods, single-dose</td>
<td>PDC etertugliflozin/metformin [13]</td>
<td>18</td>
<td>25</td>
<td>6945.6</td>
<td>6746.0</td>
<td>1096.2</td>
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<td>Median</td>
<td>7123.3</td>
<td>1012.0</td>
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<td>11.04</td>
<td>5318.2</td>
<td>6696.7</td>
<td>1002.3</td>
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<tr>
<td>Min</td>
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<td>1012.0</td>
<td>2</td>
<td>11.04</td>
<td>5318.2</td>
<td>6696.7</td>
<td>1002.3</td>
</tr>
</tbody>
</table>

n=number of subjects; AUC<sub>0-\infty</sub> = ng·h/ml; AUC<sub>0-\infty</sub> = ng·h/ml; Cmax= ng/ml; Tmax= h; T<sub>1/2</sub> = 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<sub>0-5</sub>, AUC<sub>0-∞</sub>, 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<sub>0-5</sub>, AUC<sub>0-∞</sub>, Tmax, and T<sub>1/2</sub> values of the test drug Boke® had better values than the innovator drug Glucophage®. In the parameters of AUC<sub>0-5</sub>, AUC<sub>0-∞</sub>, and Cmax the test drug Boke® had higher values than the innovator drug Glucophage®. However, both drugs were declared bioequivalent because the 90% CI in the AUC<sub>0-5</sub> and Cmax parameters were in the range of 80-125%. 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<sub>0-5</sub> 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<sub>0-∞</sub> 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 range of 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<sub>0-5</sub> 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<sub>0-∞</sub> parameter was greater, the 90% CI parameter remained in the 80-125% range. Meanwhile, the AUC<sub>0-5</sub> 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].

Upneti 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<sub>0-5</sub> 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<sub>0-∞</sub> 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].

Dawn 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 co-transporter (SGLT2) inhibitor [15]. Metformin in the FDC test product has better absorption than the innovator product as evidenced by the better AUC<sub>0-5</sub>, AUC<sub>0-∞</sub>, and Cmax parameter values. The AUC<sub>0-5</sub> parameter in the 41 ng. h/ml test drug is greater than the innovator drug. The AUC<sub>0-∞</sub> 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<sub>0-5</sub> 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<sub>0-5</sub> of the test was 6495.76 ng. h/ml and the average AUC<sub>0-∞</sub> of the innovator was 6856.28 ng. h/ml. The average AUC<sub>0-5</sub> of the test was 614.95 ng. h/ml and the average AUC<sub>0-∞</sub> of the innovator was 6409.79 ng. h/ml. The average Cmax of the test drug was 183.83 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.

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

<table>
<thead>
<tr>
<th>Design study</th>
<th>Test drugs</th>
<th>Dose</th>
<th>Bioavailability profiles</th>
<th>Innovator drugs</th>
<th>Bioavailability profiles</th>
<th>Bioequivalence profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>AUC&lt;sub&gt;0-5&lt;/sub&gt;</td>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>Cmax</td>
<td>Tmax</td>
<td>AUC&lt;sub&gt;0-5&lt;/sub&gt;</td>
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<td>60.63</td>
<td>619</td>
<td>6.5</td>
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<td>5</td>
<td>5.47</td>
<td>636</td>
<td>651.4</td>
<td>5</td>
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<tr>
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<td>4950</td>
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<tr>
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<td>4877</td>
<td>4687</td>
<td>661.4</td>
<td>5</td>
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<tr>
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<td>7946</td>
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<td>14</td>
<td>5259</td>
<td>5158</td>
<td>641.7</td>
<td>3</td>
</tr>
</tbody>
</table>

n = number of subjects; AUC<sub>0-5</sub> = ng. h/ml; AUC<sub>0-∞</sub> = ng. h/ml; Cmax = ng/ml; Tmax = h; T<sub>1/2</sub> = h; CI = 90% 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-∞} 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 91.4-105.9%. 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-∞} and Cmax parameters which are in the range of 90-125%, the 500-mg metformin ER tablet 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 Sinocorp Pharmaceutical Co., China) and the innovator product Glucophage® Extended-release (Merck Serono Co., Ltd, UK). In the AUC_{0-∞} parameter, the test drug had a value of 66 ng h/ml higher than the innovator drug with a 90% CI of 96.2-105.44%. While in the Cmax parameter of the test drug had a value of 11 ng h/ml higher than the innovator drug with a 90% CI value of 96.12-105.44%. Whereas in the Tmax parameter, the test drug had a value of approximately 5 h. Based on the 90% CI in the AUC_{0-∞}, 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-∞} 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-∞} parameter, the test drug had a value 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-∞}, and Cmax parameters, 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-∞} 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-∞} 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-∞} 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-∞} 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-∞} 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-∞} 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-∞}, AUC_{0-∞} 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-∞} parameter of 96.2-111.1%, the 90% CI value of the AUC_{0-∞} 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-∞} 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 took 4 h. Based on the 90% CI in the AUC_{0-∞} and Cmax 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 a 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-∞} Parameter of the test drug was 192 ng h/ml lower than the innovator drug. In the AUC_{0-∞} 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 value of 90.58-111.92%. In the fed condition study, the AUC_{0-∞} parameter of the test drug had a significant difference, which was 567 ng h/ml lower. In the AUC_{0-∞} 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>
<thead>
<tr>
<th>Design study</th>
<th>Test drugs</th>
<th>Dose</th>
<th>Bioavailability profiles</th>
<th>AUC_{0-∞}</th>
<th>AUC_{0-t}</th>
<th>Cmax</th>
<th>Tmax</th>
<th>T_{1/2}</th>
<th>AUC_{0-∞}</th>
<th>AUC_{0-t}</th>
<th>Cmax</th>
<th>Tmax</th>
<th>T_{1/2}</th>
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</thead>
<tbody>
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<td>ertugliflozin</td>
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<td>7.5/</td>
<td>11</td>
<td>9340</td>
<td>9477</td>
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<td>9669</td>
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<tr>
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<td>/metformin</td>
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<td>8235</td>
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<td>Glucophage (Merck,US)</td>
<td>7898</td>
<td>8802</td>
<td>1888</td>
</tr>
</tbody>
</table>

n=number of subjects; AUC_{0-∞}= ng h/ml; AUC_{0-t}= 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-∞}, AUC_{0-t}, 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 AUC0-∞ 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

<table>
<thead>
<tr>
<th>Design study</th>
<th>Test drugs</th>
<th>Dose</th>
<th>Bioavailability profiles</th>
<th>Innovator drugs</th>
<th>Bioavailability profiles</th>
<th>Bioequivalence profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>AUC0-∞</td>
<td>AUC0-∞</td>
<td>Cmax</td>
</tr>
<tr>
<td>Open-label, crossover, randomized, single-dose</td>
<td>saxagliptin</td>
<td>2.5/1000</td>
<td>44</td>
<td>12400.1</td>
<td>1267.7</td>
<td>1830.1</td>
</tr>
<tr>
<td></td>
<td>Metformin</td>
<td></td>
<td>41</td>
<td>92</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

n=number of subjects; AUC0-∞= ng. h/ml; AUC0-∞= ng. h/ml; Cmax= ng/ml; Tmax= h; T1/2= 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 AUC0-∞ of the test was 12050.98 ng. h/ml and the mean AUC0-∞ of the innovator was 12040.39 ng. h/ml. The average AUC0-∞ of the test was 9106.67 ng. h/ml and the average AUC0-∞ 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

<table>
<thead>
<tr>
<th>Design study</th>
<th>Test drugs</th>
<th>Dose</th>
<th>Bioavailability profiles</th>
<th>Innovator drugs</th>
<th>Bioavailability profiles</th>
<th>Bioequivalence profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>AUC0-∞</td>
<td>AUC0-∞</td>
<td>Cmax</td>
</tr>
<tr>
<td>Open-label, crossover, randomized, two-periods</td>
<td>saxagliptin/metformin [10]</td>
<td>2.5/1000</td>
<td>30</td>
<td>1446.4</td>
<td>14618.7</td>
<td>1348.6</td>
</tr>
<tr>
<td></td>
<td>Metformin</td>
<td></td>
<td>25</td>
<td>63</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

n=number of subjects; AUC0-∞= ng. h/ml; AUC0-∞= ng. h/ml; Cmax= ng/ml; Tmax= h; T1/2= h; CI min, CI max=%; Doses= 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 AUC0-∞ parameter, the test drug had a value of 2.03 ng. h/ml lower than the innovator drug with a 90% CI of 0.85-1.028. Also, in the AUC0-∞ 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 AUC0-∞ 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 AUC0-∞ parameter was higher, the 90% CI parameter remained in the 80-125% range, which was 100.78-116.74%. Meanwhile, the AUC0-∞ parameter of the test drug had a value of 482 ng. h/ml higher than the innovator drug, and the 90% CI parameter was 100.56-106.49%. 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].

Upeti et al. [12] conducted a bioequivalence study on FDC containing saxagliptin 2.5 mg and metformin 100 mg against the innovator drug Glucophage®, the AUC0-∞ 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 AUC0-∞ 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. h/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 T1/2 values of 4 h. Based on the 90% CI values of AUC0-∞ 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

REFERENCES