Hindawi
Journal of Clinical Pharmacy and Therapeutics
Volume 2024, Article ID 9200636, 9 pages
https://doi.org/10.1155/2024/9200636

Research Article

Pharmacokinetics and Bioequivalence of Two Combination Metformin/Glipizide Tablets under Fasting and Fed Conditions in Chinese Healthy Subjects: A Randomized, Open-Label, Crossover Study

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Received 15 December 2023; Revised 26 March 2024; Accepted 27 March 2024; Published 10 April 2024

Academic Editor: Irina B. Bondareva

Metformin/glipizide tablets are a compound formulation composed of metformin hydrochloride and glipizide. This study aimed to assess the pharmacokinetics and bioequivalence of two fixed-dose combination (FDC) tablets of metformin/glipizide (500 mg/2.5 mg) in healthy Chinese subjects. We conducted a single-center, open-label, randomized, two-way crossover study with a total of 48 subjects enrolled (24 in each dietary group). The test or reference formulations were given to the subjects at random at a ratio of 1 : 1, with a seven-day washout period. Blood samples, collected at prearranged intervals before and up to 24 hours after dosage, were analyzed using validated LC-MS/MS technology to ascertain plasma concentrations of metformin and glipizide. Finally, 23 subjects completed the fasting and fed studies, respectively. In both studies, the 90% confidence intervals for the geometric mean ratios (test/reference) of the C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ were all found to fall within the acceptable range for bioequivalence (80%–125%). The exposure of metformin/glipizide FDC tablets in vivo was not significantly affected by food. No serious adverse events were observed. In conclusion, this study demonstrated that both the test and reference metformin/glipizide tablets exhibited bioequivalence and were well tolerated under both fasting and fed conditions. This trial is registered with CTR202686.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder marked by chronically elevated blood glucose levels and varying degrees of protein, lipid, and carbohydrate metabolism dysfunction [1]. The prevalence of DM is on the rise, leading to severe complications and significant metabolic issues [2]. Among diabetes, type 2 diabetes mellitus (T2DM) is the most common metabolic disease with the highest incidence rate, and its main causes are insulin resistance and impaired insulin secretion [3, 4]. Clinical studies suggest that employing single dosing in diabetic patients may not be ideal; instead, double or multiple combination dosing proves more effective [5]. A rational treatment strategy for T2DM involves using an insulin sensitizer and an insulin secretagogue, taking into account the underlying pathophysiology. For example, common treatment methods include the use of metformin to enhance insulin sensitivity in peripheral tissues and the liver, effectively reducing fed glucose absorption. Simultaneously, the use of the second-generation

sulfonylurea antidiabetic drug gliclazide can effectively induce pancreatic beta cells to secrete insulin and lower blood glucose levels. The combination of metformin and glipizide at lower concentrations is more effective than monotherapy in regulating glycated hemoglobin (HbA1c), fasting plasma glucose, and fed plasma glucose in T2DM patients [6]. Notably, the metformin/glipizide combination tablet does not increase fasting insulin or body weight nor does it significantly affect lipid profiles [7]. Hence, it stands as a safe, effective, and cost-efficient therapeutic alternative for T2DM patients not responding well to monotherapy.

A fixed-dose combination (FDC) has the potential to simplify therapy, enhance medication adherence, and reduce medication errors in diabetic patients compared to the administration of two individual tablets [8]. Although there have been some pharmacokinetic (PK) studies conducted individually on metformin and glipizide, there is a lack of PK studies on the combination of these two medications. Teva Pharmaceuticals IND. LTD. has developed and marketed the branded formulation of metformin/glipizide (METAGLIP®, 500 mg/2.5 mg) FDC. This research aims to assess the bioequivalence between the newly developed metformin/glipizide FDC tablet and the branded formulation in healthy Chinese subjects by comparing their PK characteristics.

2. Methods

2.1. Study Drugs. The test drug was a metformin/glipizide FDC tablet manufactured by Beijing SHKB Pharmaceutical Co., Ltd., Beijing, China (500 mg/2.5 mg tablet, batch number: BN20200919, expiration date: September 2022). The reference drug was a metformin/glipizide FDC tablet manufactured by Teva Pharmaceuticals IND. LTD., America (500 mg/2.5 mg tablet, batch number: G23335, expiration date: October 2021).

2.2. Ethical Statement. The trial was registered at the Chinese Clinical Trial Registry website (https://www.chinadrugtrials.org.cn/index.html#CTR202686). The trial received approval from the Clinical Trial Research Ethics Committee of the Second People's Hospital of Nanning City in December 2020 (approval no: 2020025). The trial was conducted at the Phase I Clinical Research Center, Second People's Hospital of Nanning, following Good Clinical Practice (GCP), the Helsinki Declaration, and relevant legislation and regulations of China's National Medical Products Administration (NMPA). Before their participation, the subjects furnished with thorough information about the study, encompassing both the potential advantages and disadvantages. They voluntarily provided written informed consent. Subjects were granted the autonomy to discontinue their involvement in the research at any given moment.

2.3. Study Selection. In this study, we recruited healthy Chinese subjects with an age requirement of 18 years or older. Females had a minimum body weight of 45 kg and males had a minimum of 50 kg. Furthermore, subjects' body mass index (BMI) ranged from 19 to 26 kg/m^2. All subjects had their vital signs measured objectively, their medical histories reviewed in detail, and a complete physical examination performed. In addition, a battery of diagnostic lab tests was conducted to determine their overall health.

The exclusion criteria were as follows: the exclusion criteria include current or past history of severe diseases, drug allergies, glucose-6-phosphate dehydrogenase (G6PD) deficiency, vaccination within 3 months prior to the study, surgery performed within 28 days prior to the study or planned during the study, medication use within 14 days prior to the study, participation in any clinical trial within the preceding 3 months, potential liver metabolism inhibiting or inducing drug therapy within 30 days, consumption of grapefruit within 14 days prior to the first dose, excessive daily intake of coffee, tea, or any caffeinated beverages, smokers, abnormal alcohol breath test, positive screening test for drug abuse (morphine, methamphetamine, ketamine, ecstasy, and cannabis), abnormal vital signs, abnormal physical examination, abnormal electrocardiogram or clinically significant laboratory results (as determined by the physician), irregular bowel movements, inability to use effective contraception, and unwillingness to consume provided meals. Pregnant women or breastfeeding women with positive pregnancy tests are also excluded.

2.4. Study Design. This is a single-center, randomized, open-label, single-dose, two-formulation, two-period, two-sequence crossover study, which includes two parts focusing on fasting and fed administration. It consists of two three-day treatment periods separated by a seven-day abstinence period. The study recruited a total of 48 subjects, with 24 subjects in the fasting study and 24 subjects in the fed study. Within a crossover design, subjects are allocated to one of two treatment sequences in each group; receiving the reference formulation before the test formulation or the test formulation followed by the reference formulation.

Fasting bioequivalence study: all 24 eligible subjects were enrolled one day before the study and fasted for at least 10 hours before the dose. A single dose of the reference or test formulation was administered orally on the day of dosing in the morning, on an empty stomach, along with 240 mL of a 20% glucose solution. Subsequently, 60 mL of a 20% glucose solution was to be consumed at 1, 1.5, 2, 2.5, 3, 3.5, and 4 hours after dosing.

Fed bioequivalence study: all 24 eligible subjects were enrolled one day before the study and fasted for at least 10 hours (excluding a high-fat, high-calorie meal). On the day of dosing, they initiated the consumption of a high-fat, high-calorie meal in the morning (providing approximately 150 kcal from protein, 250 kcal from carbohydrates, and 500–600 kcal from fat, with a total of roughly 800–1000 kcal, of which about 50% of the calories came from fat). Following the high-fat, high-calorie meal, a single dose of the test or reference formulation was orally administered with 240 mL of a 20% glucose solution, followed by the consumption of 60 mL of a 20% glucose solution at 1, 1.5, 2, 2.5, 3, 3.5, and 4 hours after dosing. The composition of the test meal was to be consistent between the two test periods in the fed condition.

Subjects were not allowed to drink water for 1 hour before or after dosing (except for the 20% glucose solution). They were provided with a regular light lunch and dinner four and ten hours after their dosage.

2.5. Blood Sample. Venous blood samples of approximately 3 mL were collected under fasting and fed conditions at the following time points following dosing: predose (0 hours), 0.25, 0.5, 1, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 12, and 24 hours later. Blood samples were obtained in anticoagulant containers containing K2EDTA and were centrifuged within sixty minutes of the collection process commencing. Following centrifugation, the specimens were swiftly prefrozen for 120 minutes in a refrigerator set to −10°C (−20°C). After achieving absolute freezing, the specimens were transferred to a freezer set at −70°C (≤−60°C) to preserve them.

2.6. Sample Size. According to previous clinical studies, the within-subject variability of metformin was 22.4% [9]. The sample size was calculated using PASS version 15.0 based on the following conditions: within-subject variability = 22.4%, significance level (α) = 0.05, type II error rate (β) = 0.2, equivalence margin (δ) = ln (1.25), and the point estimate (θ) = ln(1.05). Considering a 20% risk of dropout, the final number of subjects required for either fasting or fed studies was determined to be 24.

2.7. Analytical Methods. The concentrations of metformin and glipizide in the plasma were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The protein precipitation procedure involved acetonitrile containing stable isotope-labeled internal standards, namely, metformin-d6 and glipizide-d11.

For metformin detection, an ACQUITY UPLC BEH Amide column (2.1 × 50 mm, 1.7 μm, Waters, Milford, USA) was used with a binary gradient elution system. Mobile phase A consisted of a 10 mM ammonium acetate aqueous solution, and mobile phase B was 100% acetonitrile. The autosampler temperature was set at 10°C, and the column temperature was maintained at 40°C. The flow rate was set to 0.30 mL/min. Mass spectrometry analysis was performed using a Sciex Triple Quad 6500+ instrument (AB SCIEX, USA) with electrospray ionization in the positive ion mode. Multiple reaction monitoring transitions for metformin and metformin-d6 were m/z 130.0-70.9 and m/z 136.1-77.0, respectively. Data collection and processing were conducted using Analyst 1.6.3 software (Waters, Milford, USA). The linear range for metformin quantification was 5.000–2500.000 ng/mL, with a lower limit of quantification of 5.000 ng/mL. Precision, accuracy, and recovery met the acceptance criteria.

For glipizide detection, an ACQUITY UPLC HSS T3 column (2.1 × 50 mm, 1.8 μm, Waters, Milford, USA) was employed with a binary gradient elution system. Mobile phase A consisted of a 10 mM ammonium acetate aqueous solution, and mobile phase B was 100% acetonitrile. The autosampler temperature was set at 10°C, and the column temperature was maintained at 40°C. The flow rate was set to 0.40 mL/min. Mass spectrometry analysis was conducted using a Xevo TQ-S instrument (Waters, Milford, USA) with electrospray ionization in the positive ion mode. Multiple reaction monitoring transitions for glipizide and glipizide-d11 were m/z 446.13-321.08 and m/z 457.19-320.99, respectively. Data collection and processing were carried out using Unifi 1.8.0.0 software (Waters, Milford, USA). The linear range for glipizide quantification was 1.000–500.000 ng/mL, with a lower limit of quantification of 1.000 ng/mL. Precision, accuracy, and recovery met the acceptance criteria.

2.8. PK Parameters and Statistical Analysis. All participants who were randomized and treated, and who had valid test or reference concentration findings that were appropriate for calculating PK parameters, were included in the PK concentration population. This population was used to calculate PK parameters. The participants who were randomized, received therapy, and had measurable PK parameters of main interest during at least one phase of the study made up the group that was analyzed for PK parameter assessment.

The PK parameters (C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, and T_{max}) for metformin and glipizide were determined using noncompartmental methods, assisted by Phoenix WinNonlin software version 8.1 (Pharsight Corporation, Sunnyvale, CA, USA). Descriptive statistics in SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) were primarily employed for data analysis. Multivariate analysis of variance (ANOVA) examined logarithmically transformed PK parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$), while the Wilcoxon signed-rank test evaluated T_{max}. The two-sided t-test calculated the 90% confidence interval (CI). Bioequivalence between test and reference preparations was assessed when the 90% CI of the geometric mean ratio (GMR) of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ fell within the range of 80%–125%.

The primary endpoints, C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$, in both the fasting and fed groups, will be log transformed, and a mixed-effects model will be applied. The model will include fixed effects for sequence, treatment, and period, and a random effect for subjects nested within the sequence. Differences in treatment on the log scale will be estimated for the parameters, along with their 90% CIs. Point estimates and CIs will be back transformed to the original scale for presentation, i.e., ratios of geometric means and corresponding 90% CIs for T/R. The intrasubject CV estimated from the model will also be presented.

2.9. Safety Assessment. Safety was evaluated through a series of assessments, including the measurement of vital signs (temperature, blood pressure, and heart rate), fingertip blood glucose testing, physical examinations, laboratory tests (hematology, biochemistry, and urine analysis), and 12-lead electrocardiograms. Vital signs were recorded at check-in, before drug administration (0 hours), and at 1, 4, 8, 12, and 24 hours postdose. Fingertip blood glucose testing

was conducted before administration (0 hours) and at 1, 2, 3, 4, and 6 hours postdose. Physical examinations, laboratory tests, and 12-lead electrocardiograms were carried out at the beginning of the treatment and repeated 24 hours after treatment completion. All adverse events (AEs), encompassing clinical symptoms, onset and end times, severity, duration, treatment measures, and their association with the drug, were diligently recorded. Patients experiencing adverse events were monitored unless they returned to a normal or stable condition or were not accessible. Observations of adverse effects were continued until patients returned to a normal or stable condition or could no longer be accessed.

3. Results

3.1. Participants. 48 subjects were assigned to the research treatment, with 24 subjects in each of the fasting and fed studies. The study was completed by 46 of the original 48 subjects (23 for the fasting study and 23 for the fed study). In the fasting trial, one subject dropped out before period 2 without ingesting the test formulation because of acute pharyngitis, as decided by the investigator in the subject's best interests. In the fed trial, one subject withdrew from the study before period 2 due to personal circumstances, without taking the test formulation, and could not continue participating in the study. Table 1 presents the baseline demographic and physical parameters.

3.2. PK Parameters and Plasma Concentration-Time Curve. In this study, two subjects (treatment sequence: reference test) withdrew in the second period before dosing. Only the PK data from the first period were included in the PK concentration set (PKCS), PK parameter set (PKPS), and bioequivalence set (BES). The remaining 46 subjects completed the trial and were included in the PKCS, PKPS, and BES analyses. Figures 1 and 2 depict the mean plasma concentration-time curves of glipizide and metformin acquired following a single oral administration of the test and reference FDC products during fed and fasting settings. The curve in Figure 1 demonstrates how quickly metformin was absorbed. In contrast to the fed study, Figure 2 shows that glipizide absorption is delayed in the fasting phase. Table 2 summarizes the key PK parameters of glipizide and metformin under fed and fasting conditions.

3.3. Bioequivalence. The 90% confidence intervals for the geometric mean ratios of the PK parameters of metformin/glipizide (test or reference) were within the 80% to 125% range for both fasting and fed conditions (Table 3). The study findings demonstrate that after a single oral dose of tablets containing 500 mg of metformin and 2.5 mg of glipizide, healthy subjects exhibited bioequivalence between the test and reference formulations when exposed to both fasting and fed studies.

3.4. Safety Assessment. Throughout the entire study period, no serious adverse events (SAEs) occurred, and both the test and reference formulations exhibited good tolerability. In the fasting group, one subject experienced an adverse event of acute pharyngitis after taking the investigational drug in the first period, leading to withdrawal from the study (severity: grade 2, possibly related to the drug). No other adverse events leading to withdrawal were reported. After medication administration, six subjects reported adverse events (AEs) of hypoglycemia (severity: grade 2, definitely related to the drug). All hypoglycemia AEs resolved after taking a glucose solution. At the end of the trial, all adverse events had either resolved or remained stable. Details of AEs in fasting and fed conditions are shown in Table 4.

4. Discussion

To our knowledge, this is the first study assessing the bioequivalence of the metformin/glipizide FDC under both fed and fasted conditions. We have confirmed the bioequivalence of the test and reference medications, metformin/glipizide FDC, in both scenarios. Throughout the trial, every participant demonstrated good tolerance to the metformin/glipizide FDC. The plasma concentrations of glipizide and metformin were measured, considering that 99% of metformin is excreted by the kidneys in its unaltered form [10] and glipizide is hydrolyzed to produce inactive metabolites [11]. The newly approved commercialization of metformin/glipizide FDC (500 mg/2.5 mg) tablets in China is supported by the study's findings.

The fasting PK results of metformin and glipizide in this study align with previous research [12, 13]. However, the conclusion regarding the impact of food on metformin is only partially consistent. This study found that although food decreased the C_{max} of metformin, its impact on AUC and T_{max} was nominal. Other studies have shown that food decreased both C_{max} and AUC of metformin, delaying T_{max}, which signifies that a high-fat, high-calorie diet decreased the extent and rate of metformin absorption and slowed down this process [12, 14]. Factors such as gastrointestinal permeability, age, and body weight significantly influence metformin PK [15–17], potentially contributing to variations in its PK parameters across studies. There need to be more research on the effects of food on glipizide. In our study, we observed that food accelerates the absorption of glipizide (T_{max} decreased from 4 to 2.5 hours) with little impact on C_{max} and AUC. It is noteworthy that in some subjects, the plasma concentration-time curve of glipizide exhibited two peaks, consistent with previous studies [13, 18]. The study concludes that dietary intake has minimal effect on the bioavailability of metformin and glipizide. In clinical practice, the metformin/glipizide FDC will be taken with food. Some studies have found that the I^2 test results for pooled $AUC_{0\text{-}\infty}$ and C_{max}showed quite heterogeneous. These findings suggest that it may be necessary to increase the dosage of metformin when administering it following a high-fat, high-calorie diet to maintain the same therapeutic effect [14].

Table 1: Demographics of healthy subjects.

	Fasting $N = 24$	Postprandial $N = 24$
Gender, *n* (%)		
Male	18 (75.0)	16 (66.7)
Female	6 (25.0)	8 (33.3)
Age (years)		
Mean ± SD	27.0 ± 5.8	26.2 ± 6.7
Min-max	19–40	18–45
Height (cm)		
Mean ± SD	165.1 ± 8.4	166.2 ± 9.8
Min-max	152.0–181.0	150.5–184.0
Weight (kg)		
Mean ± SD	61.3 ± 8.3	63.2 ± 10.1
Min-max	50.1–76.7	51.7–81.7
BMI (kg/m^2)		
Mean ± SD	22.4 ± 1.9	22.8 ± 2.0
Min-max	19.3–25.8	19.1–25.9

N: number of subjects; SD: standard deviation; BMI: body mass index.

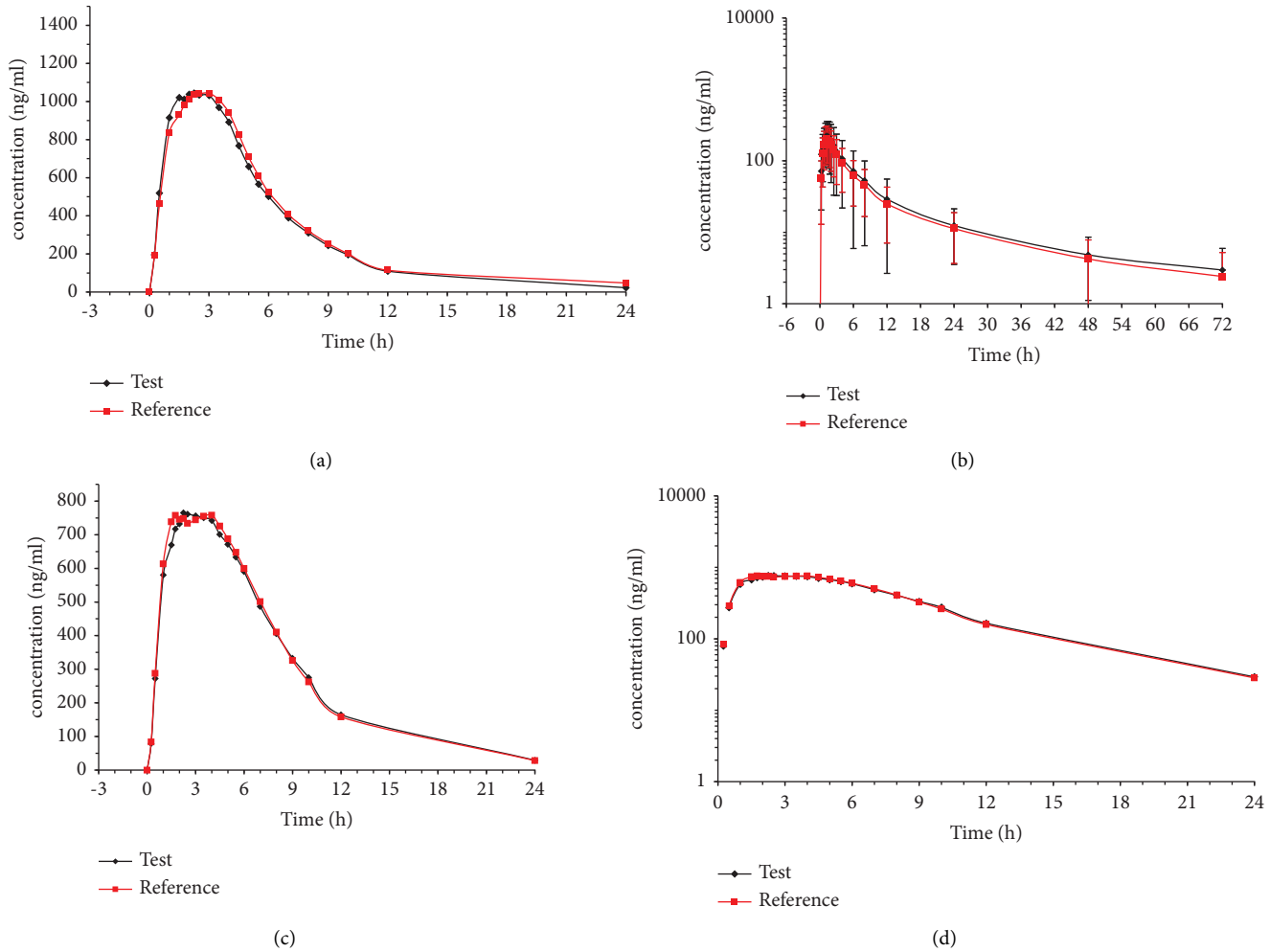

Figure 1: Mean plasma concentration-time curves (a) and semilogarithmic curves (b) of the test and reference drugs of metformin in healthy subjects under fasting conditions. Mean plasma concentration-time curves (c) and semilogarithmic curves (d) of the test and reference drugs of metformin in healthy subjects under fed conditions.

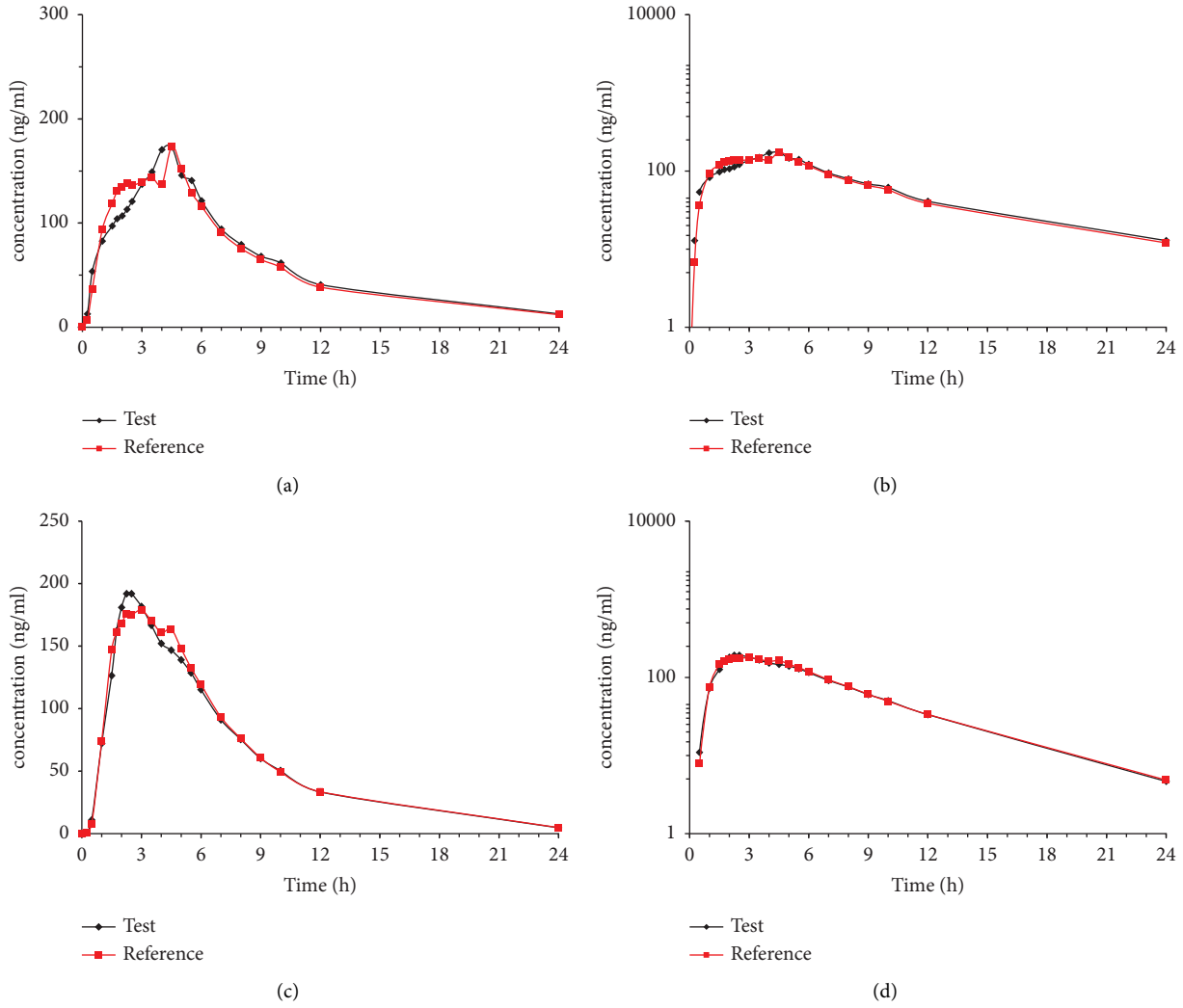

Figure 2: Mean plasma concentration-time curves (a) and semilogarithmic curves (b) of the test and reference drugs of glipizide in healthy subjects under fasting conditions. Mean plasma concentration-time curves (c) and semilogarithmic curves (d) of the test and reference drugs of glipizide in healthy subjects under fed conditions.

Table 2: Main pharmacokinetic parameters of metformin and glipizide after a single dose of the test drug or reference drug under fasting and fed conditions.

PK parameter	Fasting		Fed	
	Test ($N = 23$[a])	Reference ($N = 24$[a])	Test ($N = 23$[b])	Reference($N = 24$)
Metformin				
C_{max} (ng/mL)	1227 ± 335	1251 ± 298	928 ± 278	947 ± 298
T_{max} (h)[c]	2.50 (0.50, 4.00)	2.38 (0.50, 4.00)	2.25 (1.00, 6.00)	2.75 (1.50, 7.00)
$t_{1/2}$ (h)	4.4 ± 0.7	4.4 ± 0.6	4.3 ± 0.5	4.3 ± 0.7
$AUC_{0\text{-}t}$ (h∗ng/mL)	7198 ± 1630	7469 ± 1826	7041 ± 1800	7070 ± 1540
$AUC_{0\text{-}\infty}$ (h∗ng/mL)	7340 ± 1651	7357 ± 1416	7222 ± 1847	7253 ± 1572
Glipizide				
C_{max} (ng/mL)	226 ± 50	196 ± 42	234 ± 65	245 ± 57
T_{max} (h)[c]	4.00 (0.50, 5.50)	4.50 (1.50, 6.00)	2.50 (1.00, 5.50)	2.50 (1.50, 8.00)
$t_{1/2}$ (h)	4.0 ± 0.6	4.0 ± 0.6	3.9 ± 0.7	3.9 ± 0.8
$AUC_{0\text{-}t}$ (h ∗ ng/mL)	1474 ± 946	1442 ± 865	1396.5 ± 288.7	1416 ± 353
$AUC_{0\text{-}\infty}$ (h ∗ ng/mL)	1318 ± 332	1302 ± 298	1426.8 ± 316.3	1447 ± 387

N, number of subjects; C_{max}, maximum observed drug concentration in the plasma; T_{max}, the time to attain C_{max} following dose; $t_{1/2}$, terminal half-life of the analyte in the plasma; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last sampling time; $AUC_{0\text{-}\infty}$, area under the plasma concentration-time curve from time 0 to infinity. [a]One subject withdrew from the period 2 without taking the test drug. [b]One subject withdrew from the period 2 without taking the test drug. [c]T_{max} (hour) is expressed as median (minimum, maximum).

Table 3: Bioequivalence analysis of metformin and glipizide after a single dose of the test drug or reference drug under fasting and fed.

Parameters	Fasting			Fed		
	Test/Reference (%)	Intra-CV (%)	90%CI of ratio (%)	Test/Reference (%)	Intra-CV (%)	90%CI of ratio (%)
Metformin						
C_{max} (ng/mL)	97.9	13.0	91.7~104.5	96.8	11.8	91.2~102.7
$AUC_{0\text{-}t}$ (h ∗ ng/mL)	96.6	10.1	91.8~101.7	97.5	10.9	92.2~103.0
$AUC_{0\text{-}\infty}$ (h ∗ ng/mL)	98.2	8.9	93.8~102.8	97.5	10.5	92.5~102.8
Glipizide						
C_{max} (ng/mL)	115.7	12.4	108.7~123.2	94.3	20.8	85.0~104.6
$AUC_{0\text{-}t}$ (h ∗ ng/mL)	101.4	6.8	98.0~105.0	99.6	7.0	96.1~103.2
$AUC_{0\text{-}\infty}$ (h ∗ ng/mL)	101.4	7.2	97.7~105.3	99.5	7.6	95.8~103.5

CV%, within-subject coefficient of variation; C_{max}, maximum observed drug concentration in the plasma; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last sampling time; $AUC_{0\text{-}\infty}$, area under the plasma concentration-time curve from time 0 to infinity.

Table 4: Summary of drug-related AEs.

AEs, *n* (%)	Fasting		Fed		All ($N = 48$)
	Test ($n = 23$[a])	Reference ($n = 24$)	Test ($n = 23$[b])	Reference ($n = 24$)	
Total AEs	7 (30.4)	13 (54.2)	10 (43.5)	11 (45.8)	41
AEs related to drugs	3 (13.0)	5 (20.8)	4 (17.4)	7 (29.2)	19
Hypoglycemia	1 (4.3)	2 (8.3)	2 (8.7)	1 (4.2)	6
Total bile acid increased	0	1 (4.2)	0	0	1
Acute pharyngitis	0	1 (4.2)	0	0	1
Head and neck pain	0	1 (4.2)	0	0	1
Dizziness	1 (4.3)	0	0	0	1
Hypertension	1 (4.3)	0	1 (4.3)	1 (4.2)	3
Diarrhea	0	0	1 (4.3)	3 (12.5)	4
Urine WBC count increased	0	0	0	1 (4.2)	1
Upper respiratory tract infection	0	0	0	1 (4.2)	1
AEs not related to drugs	4 (17.4)	8 (33.3)	6 (26.1)	4 (16.7)	22
Hypertriglyceridemia	1 (4.3)	3 (12.5)	1 (4.3)	0	5
Hypercholesterolemia	0	1 (4.2)	0	0	1
LDL increased	0	1 (4.2)	0	0	1
Hyperuricemia	1 (4.3)	1 (4.2)	1 (4.3)	0	3
Eosinophilia	1 (4.3)	0	1 (4.3)	0	2
ST-T change	0	1 (4.2)	0	0	1
Right lower limb soft tissue contusion	1 (4.3)	1 (4.2)	0	0	2
T-wave change	0	0	2 (8.7)	0	2
CK-MB increased	0	0	0	1 (4.2)	1
Urine occult blood	0	0	1 (4.3)	2 (8.3)	3
Neutropenia	0	0	0	1 (4.2)	1
At least grade three adverse reactions	0	0	0	0	0
SAE	0	0	0	0	0
Drug-related death	0	0	0	0	0

[a]One subject withdrew from the period 2 without taking the test drug. [b]One subject withdrew from the period 2 without taking the test drug.

Based on the recommendations of the draft guidelines for assessing metformin bioequivalence by the US FDA and reference to other studies [9, 12, 19], the subjects in this study consumed 20% glucose water concurrently with oral administration of metformin/glipizide FDC to mitigate the potential impact of adverse hypoglycemic events on PK outcomes. It is worth mentioning that due to the small impact of food on the safety of metformin [14], subjects in the fed study also took 20% glucose water together with the metformin/glipizide FDC.

In this study, the AE observed in the test and reference formulation were similar and mild. In this study, adverse events observed in the test and reference formulations were similar and mild. Three cases of hypoglycemic adverse reactions were recorded in the fasting study. Among them, one case (4.3%) was attributed to the test formulation, while the remaining two cases (8.3%) were associated with the reference formulation. Similarly, three cases of hypoglycemic adverse reactions were observed in the fed study. Among these, two cases (8.7%) were linked to the test formulation, while one case (4.2%) was connected to the reference formulation. These reactions were successfully treated by the researchers using a 20% glucose solution. We found that food did not cause a change in the incidence of hypoglycemic adverse reactions. Given that metformin does not induce hypoglycemia [20], the similarity in the AUC of

glipizide between fasting and fed studies may account for the comparable incidence of hypoglycemic adverse reactions in both studies. However, it should be noted that since the study subjects were healthy, the incidence of hypoglycemic adverse events cannot be equated to that in diabetic patients. Overall, the combination of metformin/glipizide exhibited good tolerance among the healthy Chinese subjects in this study.

However, this study has certain limitations. First, it was designed as a single-center clinical trial with a limited sample size. Second, as life expectancy in the general population increases, the number of elderly individuals with T2DM is also on the rise [21]. Notably, the study subjects were aged between 18 and 45. While the bioequivalence of the metformin/glipizide FDC product has been established in this age group, it has not been established in individuals over the age of 45. Although some studies indicate that age has a minimal impact on the pharmacokinetics of glipizide [22, 23], other research involving elderly participants has shown higher C_{max} and AUC values for metformin compared to younger subjects [24]. Therefore, treating this age group may present unique challenges.

5. Conclusions

This study was based on data from healthy Chinese subjects, and the results indicated that under fasting and feeding conditions, the absorption rate and degree of metformin/glipizide FDC tablets (experimental and reference drugs) were similar. They exhibited bioequivalence and similar safety. Meanwhile, the research found that food had almost no effect on the exposure of metformin/glipizide FDC tablets in vivo.

Data Availability

The data used to support the findings of this study are currently under embargo while the research findings are commercialized. Requests for data, 6/12 months after publication of this article, will be considered by the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

We would like to gratefully acknowledge all the volunteers for their contribution to this clinical trial. This work was supported by grants from the Hunan Key Laboratory for Bioanalysis of Complex Matrix Samples (2017TP1037), the International Scientific and Technological Innovation Cooperation Base for Bioanalysis of Complex Matrix Samples in Hunan Province (2019CB1014), the Nature Science Foundation of Hunan Province (2022JJ80100), the Hunan Science and Technology Youth Talent Support Program (2023TJ-N20), and the Science and Technology Innovation Program of Hunan Province (2023RC3232).

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