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CLINICAL TRIAL REPORT

Pharmacokinetics and Safety with Bioequivalence of Isosorbide Mononitrate Sustained-Release Tablets in Chinese Healthy Volunteers: Bioequivalence Study

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Purpose: Isosorbide mononitrate was recommended for controlling anginal symptoms in patients with cardiovascular disease. We aimed to compare the pharmacokinetics, bioequivalence and safety of two formulations of oral isosorbide mononitrate sustained-release tablets in healthy Chinese volunteers.

Subjects and Methods: A randomized, open-label, two-period, single-center, single-dose clinical trial with crossover design was conducted in Zhejiang Hospital. Subjects received single dose 40-mg/tablet isosorbide mononitrate in each period with a 5-day washout. Serial blood samples were collected over 36 hours post-dose (Days 1 and 6). The plasma concentrations of isosorbide mononitrate were measured using a high-performance liquid chromatography-tandem mass spectrometry method, and pharmacokinetic parameters were determined using noncompartmental methods.

Results: Fifty-six healthy subjects were enrolled. In the fasting group, the maximum plasma concentration (C_{max}, mean ± SD) was 487.54 ± 69.17 ng/mL at 3.75 (1.50, 6.00) hours (median [min, max]) for test formulation, and 529.76 ± 84.64 ng/mL at 4.00 (2.50, 5.50) hours for reference formulation. In the fed group, C_{max} was 501.46 ± 68.80 ng/mL at 4.50 (1.50, 6.50) hours for test formulation, and 535.14 ± 69.89 ng/mL at 4.00 (1.50, 9.00) hours for reference formulation. All 90% confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ fell within the 80–125% bioequivalence range under both fasting and fed conditions. No drug-related serious adverse events were observed throughout the trial.

Conclusion: The isosorbide mononitrate sustained-release tablet demonstrated bioequivalence to the reference formulation (Ismo® retard) under both fasting and fed conditions, with comparable safety profiles. Both formulations were well tolerated.

Keywords: isosorbide mononitrate, bioequivalence, pharmacokinetics, safety, Chinese healthy volunteers

Introduction

Isosorbide mononitrate is a venous and arterial vasodilator used for reducing symptoms in patients with stable coronary artery disease (CAD), acute and chronic congestive heart failure and acute coronary syndromes.[1,2] The mechanisms underlying vasodilation involve a release of nitric oxide after oral administration. Nitric oxide activates the enzyme guanylate cyclase, accelerating the generation of cyclic guanosine monophosphate (cGMP).[3] Acting through cGMP-dependent protein kinase, accumulating cGMPs cause vasodilation by decreasing intracellular calcium.[4] Isosorbide mononitrate decreases myocardial oxygen consumption by decreasing preload and afterload. Isosorbide mononitrate can enhance endothelial-independent vascular function, decrease reactive oxygen species (ROS) levels, and simultaneously increase nitric oxide levels in the aortic rings.[5] In addition, it causes the relaxation of the epicardial coronary arteries thereby increasing myocardial oxygen supply.[6] Isosorbide mononitrate was rapidly absorbed. The plasma concentration reached the maximum plasma concentration (C_{max})

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within an hour with no significant first-pass metabolism.[7] Isosorbide mononitrate exhibits nearly complete oral bioavailability (≈100%) and the pharmacokinetics are not altered in elderly subjects or in patients with CAD,[8] renal failure[9] or hepatic dysfunction.[10] Recent studies have shown that isosorbide mononitrate may also reduce the recurrence of stroke, dependence and cognitive impairment after lacunar infarction.[11] Moreover, Isosorbide mononitrate combined with Chinese materia medica preparation improved treatment efficacy and was well tolerated.[12]

Isosorbide mononitrate is widely in demand due to the huge number of patients with cardiovascular disease (CVD) in China. There were approximately 2.4 million deaths from atherosclerotic CVD in 2016, representing a rapid and substantial increase from 1990.[13] Ischemic heart disease is likely to become the leading cause of death in China in the near future. In addition, a rapid and consistent increase in the aging population contributed greatly to the CVD burden.[14,15] Sustained-release preparations of isosorbide mononitrate allow once-daily administration, producing significant improvements in total exercise duration.[16,17] Results of a double-blind randomized study indicated that a single oral dose of isosorbide mononitrate sustained-release tablet was effective in the treatment of effort angina and its effectiveness could last more than 10 hours without evident side effects.[18] Given the convenience and effectiveness of sustained-release formulation and the need to reduce costs of the Chinese health care system, it is of great necessity to develop isosorbide mononitrate sustained-release tablet generic drugs to better meet market demand.

According to the requirements of the China Food and Drug Administration, any generic drug before adopting the new regulatory measures must be reassessed for comparable quality to the branded drug. Meanwhile, in terms of bioequivalence criteria (with the 90% confidence interval falling within the range of 80% to 125%), trial design (two-period crossover, and with healthy subjects as the default population), and statistical methods (Two One-Sided Tests), the study was aligned with the FDA bioequivalence guidelines. Therefore, we carried out the clinical trial to testify the bioequivalence of a generic formulation of 40-mg/tablet isosorbide mononitrate sustained-release tablets ((test formulation, T), Batch No. Y22103006, content: 99.0%, expiration date: 2024.08, Nanjing Easeheal Pharmaceutical Co., Ltd, Nanjing, China) in comparison with the reference formulation (R) (Ismo® retard, 40-mg/tablet, Batch No. S001, content: 97.7%, expiration date: 2024.03, Kern Pharma, SL) in both fasting and fed conditions.

Materials and Methods

Study Design

This Phase I clinical trial evaluating the bioequivalence of the isosorbide mononitrate sustained-release tablets was conducted in two separate groups from February 24, 2023 to March 26, 2023. Both fasting and fed groups were open-label, randomized, single-center, single-dose, two-period and crossover design. 26 healthy Chinese volunteers were enrolled in the fasting group while 30 healthy volunteers were enrolled in the fed group. Subjects were randomly 1:1 divided into T-R sequence and R-T sequence and orally administered 40-mg isosorbide mononitrate sustained-release tablets (T/R) on Day 1/Day 6 under fasting or fed condition. The study protocol was approved by the Ethics Committee of Zhejiang Hospital, Hangzhou City, China. The study was completed at the Phase I Clinical Trial Center of Zhejiang Hospital and was carried out in accordance with the Declaration of Helsinki,[19] Good Clinical Practice principle[20] and relevant laws and regulations in China. All participants signed written informed consent forms prior to the commencement of the study.

According to the requirements of the sponsor, the clinical trial was registered at chinadrugtrials.org.cn (CTR20230050, January 12, 2023), which was well-known and widely acknowledged by Chinese laws and regulations. Owing to the website not yet acknowledged by the World Health Organization, we conducted a retrospective registration at chictr.org.cn (ChiCTR 2400092394, November 15, 2024), aiming at bringing novel researches and current progress to clinicians. The trial starts on January 31, 2023, and no protocol modifications occurred before the retrospective registration.

Inclusion Criteria

Volunteers who met all the following criteria were included: (1) Chinese healthy volunteers of age between 18 and 60 (inclusive); (2) body weight above 50.0 kg (for male) or body weight above 45 kg (for female); (3) body mass index range from 19.0 to 26.0 kg/m^2 (inclusive); (4) voluntarily signed the written informed consent prior to the study; (5) understand and comply with all requirements of this trial.

Exclusion Criteria

The exclusion criteria in the study were as follows: (1) a history of allergies or contraindications to isosorbide mononitrate or its excipients; (2) systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg in the screening period or orthostatic hypotension in history; (3) a history of swallowing difficulties or glaucoma; (4) any chronic or serious illness or acute illnesses prior to clinical trial; (5) clinically significant abnormities in laboratory examination and specialist tests; (6) had surgery within 3 months prior to drug administration or plan to undergo surgery in the study period; (7) a loss or a donation of more than 400 mL of blood within 3 months before drug delivery; (8) received vaccination within 28 days; (9) positive urine tests or had a history of substance abuse; (10) a history of drug use that may affect liver drug-metabolizing enzymes 14 days prior to drug delivery; (11) had a history of heavy smoking or consumed excessive amounts of alcohol within 3 months; (12) excessive intake of tea, coffee or any other caffeinated beverages; (13) had a history of needle or blood sickness; (14) a participation in other drug clinical trial in the last 3 months; (15) special requirements on diet or could not tolerate high-fat meals; (16) female subjects in pregnancy or lactation period; (17) participants deemed unsuitable for inclusion for other reasons.

Estimation of Sample Size

Using PASS software (version 11.0.7) to calculate the sample size, the area under the concentration (AUC) and C_{max} were the main analysis indexes in our study design. The parameters were established as follows: The unilateral $\alpha = 0.05$, $\beta = 0.2$, and intra-CV = 15% (based on the previous completed bioequivalence trials of Isosorbide Mononitrate Sustained-release Tablets), the geometric mean ratio (GMR) of T and R was 0.90–1.10, the default bioequivalence interval was 80%~125%. Following EMA CHMP recommendations, we selected a statistical power of 90% (exceeding the minimum requirement of 80%) to minimize type II error risk (false negatives). The minimum sample size of the two-period crossover study was 44 cases. Considering an approximate 20% dropout rate, the number of participants was 56 finally in both fasting and fed groups, and a total of 212 volunteers were included in the screening period.

Pharmacokinetic Assessment

In both fasting and fed groups, blood samples were collected for pharmacokinetic analysis after oral drug administration at the following time points: 0h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 4.5h, 5h, 5.5h, 6h, 6.5h, 7.5h, 9h, 12h, 15h, 24h, 36h. Blood samples were collected into K2-ethylenediaminetetraacetic (EDTA-K2) acid tubes, reversed up and down to mix and then centrifuged at 4 °C, and 1700 * g for 10 min within 60 minutes after collection. EDTA-K2 acid tubes were transferred and stored in a refrigerator at −60°C within 1 hour after centrifugation.

Safety Assessment

The adverse events (AEs) after taking isosorbide mononitrate sustained-release tablets were recorded according to clinical symptoms, physical examination results, clinical laboratory assessments (blood routine, blood biochemistry, urinalysis), 12-lead electrocardiogram (ECG) and other indicators. All AEs were recorded in detail by the research physician and the severity of AEs to the drug was determined according to the NCI-CTCAE version 5.0.[21]

Pharmacokinetic and Statistical Analysis

In both fasting and fed groups, the pharmacokinetic parameter analysis was performed with SAS software (version 9.4) and the non-compartmental analysis model was conducted with Phoenix WinNonLin8.2 (Certara, Princeton, New Jersey). The main pharmacokinetic parameters for isosorbide mononitrate included C_{max}, AUC – time curve from time 0 to the last measurable plasma concentration (AUC_{0-t}), AUC–time curve from time 0 to infinity ($AUC_{0-\infty}$), half-life ($t_{1/2}$), time of maximum plasma concentration (T_{max}) and elimination rate constant (λ_z). The above parameters of isosorbide mononitrate sustained-release tablets were reported as the arithmetic mean value and standard deviation (SD) while T_{max} values are presented as the median, maximum and minimum values. The bioequivalence between T and R, considered the acceptance range of 80–125%, was evaluated by the 90% confidence intervals (CIs) of the GMR of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Analytical Method

Using isosorbide mononitrate-$^{13}C_6$ as the internal standard (IS), plasma isosorbide mononitrate concentrations were determined using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS). Chromatographic separation was achieved on an ACE Excel 3 Super C18 column (50 * 2.1 mm, 3.0 μm) from ACE. Isosorbide mononitrate was provided by the China National Institutes for Food and Drug Control and isosorbide mononitrate-$^{13}C_6$ was purchased from TLC. The mobile phase (solvent A) was 1 mM ammonium acetate solution and the organic phase (solvent B) was acetonitrile. The rate of elution was set at 0.3 mL/min and the total running time was 4.5 minutes. HPLC-MS/MS chromatograms of isosorbide mononitrate and isosorbide mononitrate-13C6 are presented in Figure 1. Detected in the multiple reaction monitor mode, the peak area of the mass-to-charge ratio (m/z) 250.1→ 59.0 for isosorbide mononitrate was measured while the peak area of the (m/z) 256.1→ 59.0 for IS. The linear range of

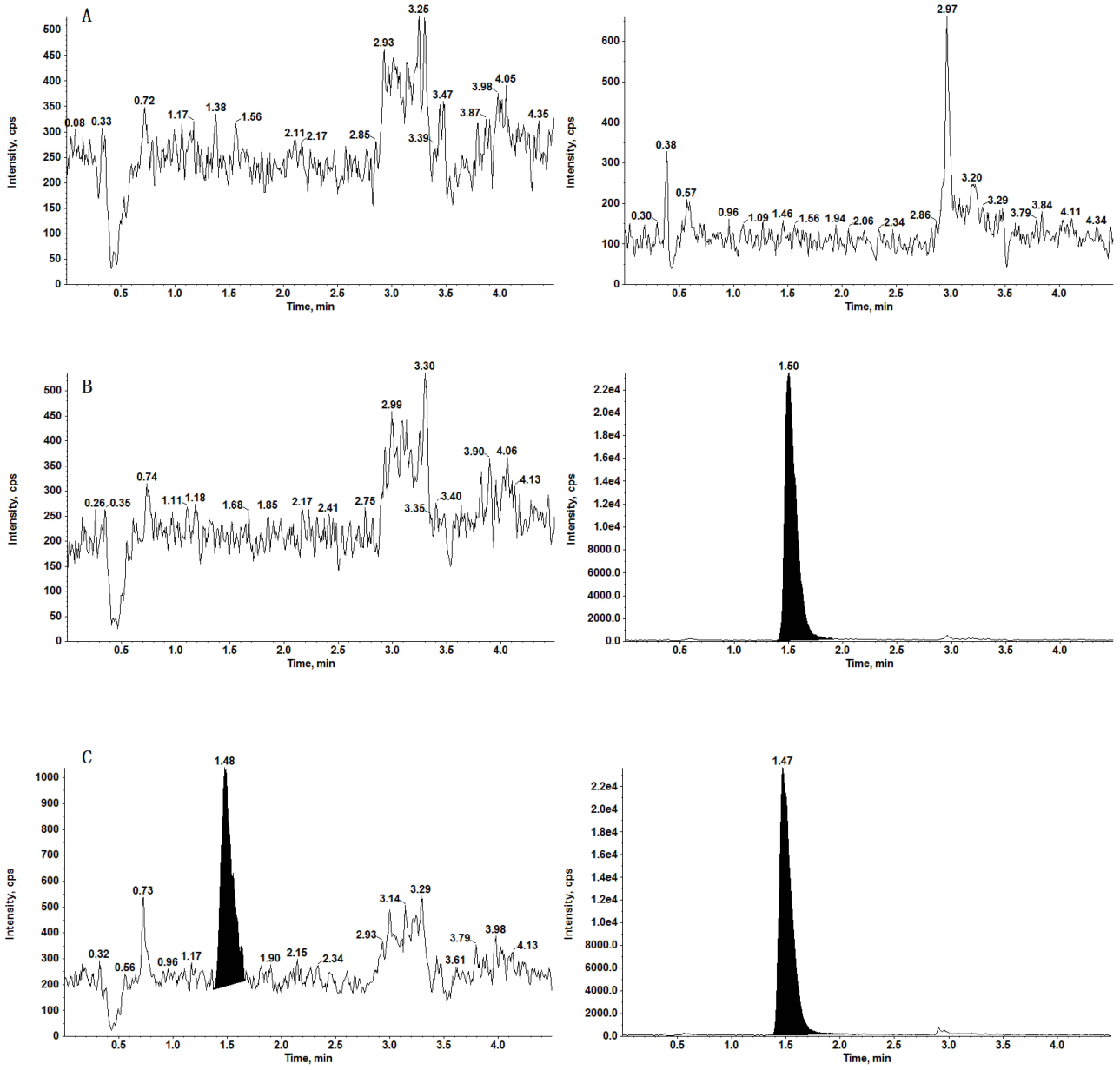

Figure 1 HPLC-MS/MS chromatograms of isosorbide mononitrate and isosorbide mononitrate-13C6. (**A**) HPLC-MS/MS chromatograms of blank plasma sample. (**B**) HPLC-MS/MS chromatograms of 0h point plasma sample. (**C**) HPLC-MS/MS chromatograms of lower limit of quantification standards.
Notes: Left: isosorbide mononitrate. Right: internal standard isosorbide mononitrate-13C6.

isosorbide mononitrate concentration was 8.00–800 ng/mL and the lower limit of quantification was 8.00 ng/mL. The precision (%CV) of the low-quality control sample, middle-quality control sample and high-quality control sample concentration quality control products was ≤ 5.7%, and the accuracy deviation range of each quality control sample was −2.0% ~ 4.3%. Analyst software (version 1.6.3) was used to process the data.

Results

Baseline Demographics

Fifty-six healthy Chinese adults were included and randomized into T/R or R/T subgroups. In the fasting group, 25 subjects completed the study. 1 subject (K003, T-R group) was withdrawn voluntarily before drug delivery in the second period. In the fed group, 28 subjects completed the study. 1 subject (C005, T-R group) vomited after drug administration within 24 hours in the first period. Another subject (C014, R-T group) was withdrawn when she could not complete the high-fat diet in the second period and so failed to meet the requirements of the protocol. In the fasting group, the minimum age was 19 years and the maximum age was 54 years; the minimum weight was 51.0 kg and the maximum weight was 77.4 kg. In the fed group, the minimum age was 18 years and the maximum age was 49 years; the minimum weight was 56.0 kg and the maximum weight was 83.7 kg. The baseline characteristics of all subjects are presented in Table 1.

Pharmacokinetic Results

The plasma concentration–time profiles of isosorbide mononitrate sustained-release tablets after oral administration in both the fasting and fed groups are presented in Figure 2. AUC represents the extent of drug absorption in a bioequivalence study while C_{max} and T_{max} indicate implications for plasma concentration and therapeutic effect. The plasma drug concentration and geometric means of $t_{1/2}$ after giving the T or R in the fasting and fed groups are presented in Figure 2A–D, respectively.

The main pharmacokinetic parameters, such as T_{max}, C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{–}\infty}$, λ_z, and $t_{1/2}$, derived from the T/R formulations after oral administration in both fasting and fed groups are listed in Table 2. Using the noncompartmental analysis module, the mean values of the above parameters (median value for T_{max}) were similar between the two treatments under both fasting and fed conditions.

Bioequivalence Analysis

The 90% CIs and the GMR of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were used to evaluate bioequivalence, as presented in Table 3. All 90% CIs of above pharmacokinetic parameters in both fasting and fed groups were within the acceptable bioequivalence bounds (80–125%).

Table 1 Baseline Demographics Characteristics

	Fasting			Fed		
	Total (n = 26)	**TR (n = 13)**	**RT (n = 13)**	**Total (n = 30)**	**TR (n = 15)**	**RT (n = 15)**
Age (years)	31.00 (10.37)	26.31 (5.45)	35.69 (12.10)	28.03 (7.44)	30.00 (8.40)	26.07 (5.98)
Female, n (%)	21 (80.77)	11 (84.62)	10 (76.92)	25 (83.33)	12 (80.00)	13 (86.67)
Race						
Han, n (%)	23 (88.46)	12 (92.31)	11 (84.62)	26 (86.67)	12 (80.00)	14 (93.33)
Other, n (%)	3 (11.54)	1 (7.69)	2 (15.38)	4 (13.33)	3 (20.00)	1 (6.67)
Height (cm)	168.56 (8.15)	170.69 (6.84)	166.42 (9.03)	168.63 (6.48)	168.30 (5.64)	168.97 (7.42)
Weight (kg)	63.39 (6.02)	63.78 (6.11)	62.99 (6.16)	63.35 (6.57)	61.73 (4.51)	64.98 (7.96)
BMI (kg/m²)	22.33 (1.72)	21.88 (1.61)	22.77 (1.77)	22.26 (1.51)	21.83 (1.55)	22.70 (1.40)

Note: Data were shown in mean (SD) or otherwise specified.
Abbreviations: T, test formulation; R, reference formulation; BMI, body mass index.

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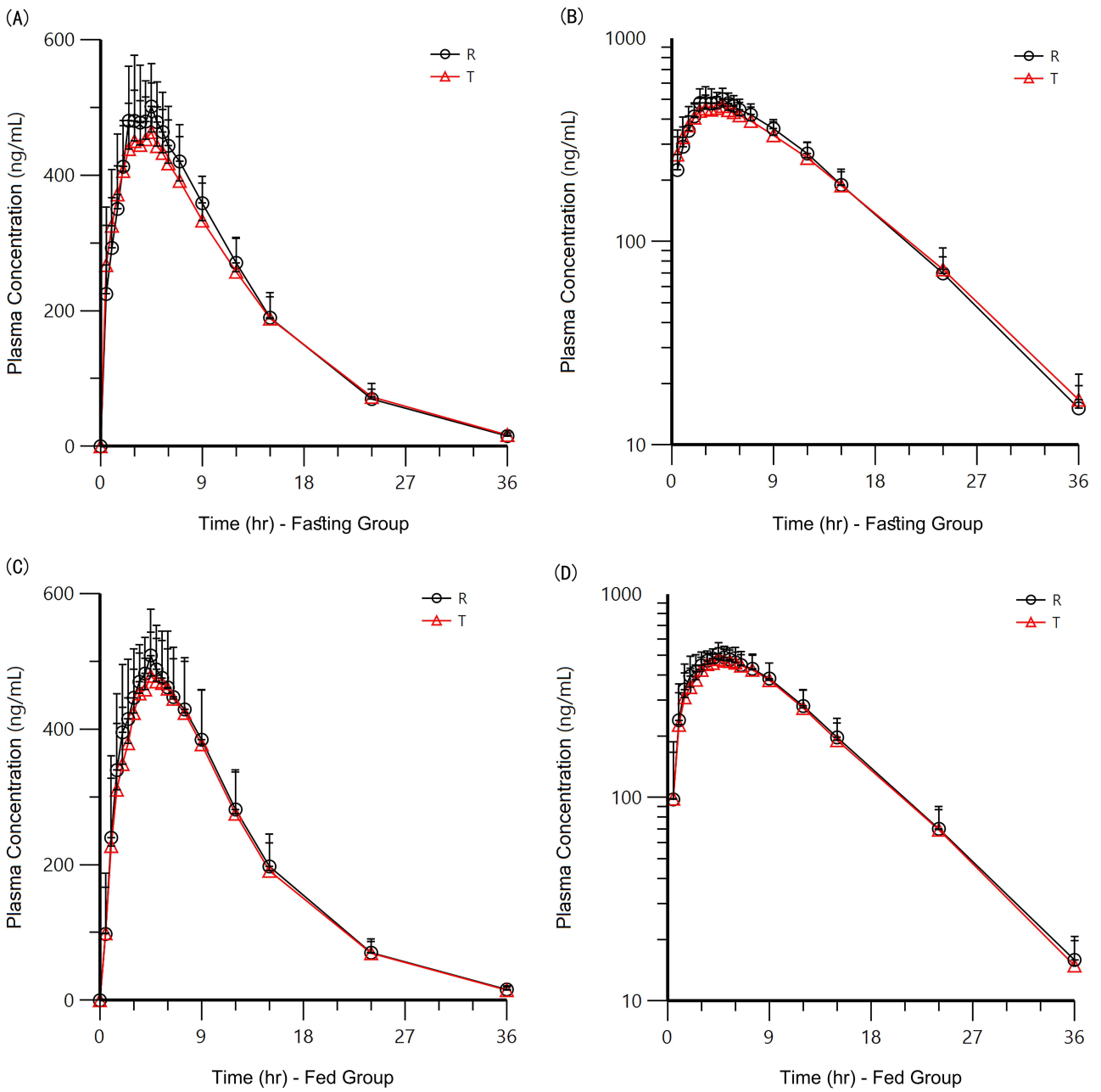

Figure 2 Mean plasma concentration-time profile. (**A**) Mean plasma concentration-time plots for isosorbide mononitrate following a single oral dose in the fasting group. (**B**) Mean plasma concentration-time plots for isosorbide mononitrate following a single oral dose in the fasting group (semilogarithmic scale). (**C**) Mean plasma concentration-time plots for isosorbide mononitrate following a single oral dose in the fed group. (**D**) Mean plasma concentration-time plots for isosorbide mononitrate following a single oral dose in the fed group (semilogarithmic scale).
Note: Error bars are standard deviation (SD).

Safety Analysis

Subjects (n = 56) who received assigned tablets were included in the safety analysis (Table 4). When taking medications under the fasting condition, 25 participants reported 123 AEs, of which 23 (88.46%) reported the events after taking the T formulation and 24 (96.00%) in the R treatment. When taking medications under the fed condition, 25 participants reported 82 AEs, of which 21 (72.41%) participants reported after taking the T formulation and 18 (62.07%) reported in the R treatment. In the fasting group, all AEs were grade 1 except six AEs were grade 2, which were "dizziness" and "low blood pressure". In the fed group, all AEs were grade 1 except three AEs were grade 2, which were "dizziness", "epistaxis" and "low blood pressure". One AE led to withdrawal in the fasting group due to a positive result of blood

Table 2 The Pharmacokinetic Parameters of Isosorbide Mononitrate Sustained-Release Tablets in Bioequivalence Study

	Fasting		Fed	
	T (n = 26)	**R (n = 25)**	**T (n = 28)**	**R (n = 29)**
T_{max} (h)	3.75 (1.50, 6.00)	4.00 (2.50, 5.50)	4.50 (1.50, 6.50)	4.00 (1.50, 9.00)
C_{max} (ng/mL)	487.54 ± 69.17 (14.19)	529.76 ± 84.64 (15.98)	501.46 ± 68.80 (13.72)	535.14 ± 69.89 (13.06)
AUC_{0-t} (h·ng/mL)	6704.69 ± 1116.92 (16.66)	6937.00 ± 828.00 (11.94)	6767.00 ± 1067.21 (15.77)	6928.00 ± 1051.31 (15.17)
$AUC_{0-\infty}$ (h·ng/mL)	6879.24 ± 1121.49 (16.30)	7071.89 ± 852.06 (12.05)	6912.36 ± 1070.81 (15.49)	7106.57 ± 1020.28 (14.36)
λ_z (1/h)	0.12 ± 0.01 (9.14)	0.12 ± 0.01 (8.34)	0.12 ± 0.01 (9.91)	0.12 ± 0.01 (7.46)
$t_{1/2}$ (h)	6.02 ± 0.59 (9.84)	5.72 ± 0.49 (8.53)	5.66 ± 0.60 (10.67)	5.61 ± 0.41 (7.28)

Notes: 1. T_{max} was expressed by the median (minimum, maximum); Other data were shown in mean±SD (CV%). 2. Fasting study: K003 subject (T-R group) was withdrawn voluntarily before drug delivery in the second period; Feeding study: C005 subject (T-R group) vomited after drug administration within 24 hours in the first period and withdrew from the trial. C014 subject (R-T group) was withdrawn when she could not complete the high-fat diet in the second period.

Table 3 Summary of Bioequivalence Assessment

	N		Geometric mean and Ratio			In vivo Variation (CV%)	90% Confidence Interval (CI)	Power %
	T	**R**	**T**	**R**	**(T/R) %**			
Fasting (n = 26)								
C_{max} (ng/mL)	26	25	482.85	525.76	91.84	7.42	88.6–95.19	>99.99
AUC_{0-t} (h·ng/mL)	26	25	6612.58	6942.02	95.25	5.24	92.8–97.70	>99.99
$AUC_{0-\infty}$ (h·ng/mL)	26	25	6790.40	7073.00	96.00	4.94	93.73–98.33	>99.99
Fed (n = 29)								
C_{max} (ng/mL)	28	29	496.60	531.10	93.50	8.18	90.10–97.04	>99.99
AUC_{0-t} (h·ng/mL)	28	29	6732.02	6849.32	98.29	7.14	95.15–101.53	>99.99
$AUC_{0-\infty}$ (h·ng/mL)	28	29	6881.41	7034.61	97.82	6.29	95.06–100.66	>99.99

Notes: Fasting study: K003 subject (T-R group) was withdrawn voluntarily before drug delivery in the second period; Feeding study: C005 subject (T-R group) vomited after drug administration within 24 hours in the first period and withdrew from the trial. C014 subject (R-T group) was withdrawn when she could not complete the high-fat diet in the second period.

Table 4 Adverse Events in the Study

	Fasting						Fed					
	T (n = 30)			**R (n = 30)**			**T (n = 34)**			**R (n = 34)**		
	Case	**N**	**(%)**	**Case**	**N**	**(%)**	**Case**	**N**	**(%)**	**Case**	**N**	**(%)**
AEs	51	23	88.46	62	24	96.00	46	21	72.41	39	18	62.07
SAEs	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
AEs leading to withdrawal	1	1	3.84	0	0	0.00	0	0	0.00	0	0	0.00
Total AEs	50	23	88.46	57	24	96.00	45	20	68.97	37	18	62.07
	1	1	3.84	5	3	12.00	1	1	3.45	2	1	3.45
	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Symptoms												
Headache	0	0	0.00	4	4	16.00	5	4	13.79	4	4	13.79
Dizziness	5	5	19.23	9	7	28.00	5	5	17.24	5	5	17.24
Excessive sweating	0	0	0.00	1	1	4.00	0	0	0.00	0	0	0.00
Epistaxis	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00
Nausea	0	0	0.00	2	2	8.00	0	0	0.00	0	0	0.00
Vomiting	0	0	0.00	0	0	0.00	1	1	3.45	1	1	3.45

(*Continued*)

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Table 4 (Continued).

Laboratory Examination													
Low WBC		1	1	3.85	0	0	0.00	0	0	0.00	0	0	0.00
High WBC		0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00
Low Neutrophils		2	1	3.85	0	0	0.00	0	0	0.00	0	0	0.00
High Neutrophils		0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00
High ALT		0	0	0.00	1	1	4.00	0	0	0.00	0	0	0.00
		Fasting						**Fed**					
		T (n = 26)			**R (n = 25)**			**T (n = 29)**			**R (n = 29)**		
	Grade	**Case**	**N**	**(%)**	**Case**	**N**	**(%)**	**Case**	**N**	**(%)**	**Case**	**N**	**(%)**
High triglycerides	–	3	3	11.54	0	0	0.00	0	0	0.00	1	1	3.45
HCG (+)	–	1	1	3.85	0	0	0.00	0	0	0.00	0	0	0.00
Urinary leukocytes (+)	–	1	1	3.85	1	1	4.00	0	0	0.00	2	2	6.90
Urinary red blood cells (+)	–	1	1	3.85	1	1	4.00	1	1	3.45	0	0	0.00
Urinary leukocyte esterase (+)	–	0	0	0.00	1	1	4.00	0	0	0.00	0	0	0.00
Urinary squamous epithelial cells (+)	–	0	0	0.00	0	0	0.00	0	0	0.00	1	1	3.45
Electrocardiogram													
Prolonged QT interval	–	1	1	3.85	0	0	0.00	0	0	0.00	1	1	3.45
Prolonged QRS duration	–	0	0	0.00	1	1	4.00	0	0	0.00	0	0	0.00
Significant counterclockwise rotating	–	1	1	3.85	0	0	0.00	1	1	3.45	0	0	0.00
Inferior ST segment mild change	–	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00
Ectopic Rhythm	–	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00
Vital Signs													
Low blood pressure	–	34	20	76.92	36	21	84.00	27	16	55.17	23	15	51.72
Low heart rate	–	1	1	3.85	5	3	12.00	0	0	0.00	1	1	3.45

Notes: Grade 1: asymptomatic or mild, there is no treatment; Grade 2: Moderate; minor, local or non-invasive treatment is required; Grade 3: Serious, but not immediately life-threatening, hospitalization or prolonged hospitalization is resulted; Grade 4: Life-threatening, urgent treatment is required; Grade 5: deaths associated with AEs.

Abbreviations: T, test formulation; R, reference formulation; AEs, Adverse Events; SAEs, Serious Adverse Events.

human chorionic gonadotrophin, considered probably not related to the medication. No severe AEs or deaths were recorded throughout the study period. All AEs were followed up until recovery naturally or improvement.

Discussion

Isosorbide mononitrate was clinically widely applied for controlling anginal symptoms of CVD patients. Owing to a rapid and consistent increase in the Chinese aging population with CVD and the heavy financial burden of the healthcare system, there has been an urgent need to develop a new generic drug to ease market demand and reduce costs. It is well acknowledged that generic drugs are bioequivalent to the original drug is a prerequisite for its marketing approval.[22] Therefore, an open-label, randomized, single-center, single-dose study with two-period crossover was designed to compare the bioavailability of isosorbide mononitrate of two formulations (T and R) in healthy Chinese adult subjects under both fasting and fed conditions.

Both the immediate-release and sustained-release formulation of pharmacokinetics for isosorbide mononitrate have been well studied.[23,24] Zhang et al[25] evaluated the bioequivalence of two isosorbide mononitrate formulations after single and multiple doses in Chinese healthy volunteers. Jin et al[26] compared the pharmacokinetic properties and relative bioavailability of two isosorbide mononitrate sustained-release drugs in healthy Korean subjects under fasting and fed conditions. They have shown the corresponding 90% CIs of AUClast and Cmax for the test/reference geometric mean ratio were 90.75–98.44% and 92.28–98.33%, respectively, under fasting conditions. In the fed state study, the 90% CIs for the geometric mean ratio of test to reference drugs were 94.79–103.33% for AUClast and 99.86–108.02% for Cmax. The

single-dose pharmacokinetic parameters of isosorbide mononitrate sustained-release tablets in this study including C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$ were similar to those in the previous study.[27] The results showed that 90% of CIs for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ in both fasting and fed groups were all within the acceptable range of 80% −125%. We assessed the two formulations by the pharmacokinetics with bioequivalence of isosorbide mononitrate and certificated the bioequivalence of the T formulation, providing a new choice for clinicians and CVD patients. The new generic drug helps reduce the costs for supplies of brand-name formulation and alleviates the contradiction between supply and market demand.

Isosorbide mononitrate of T and R formulation in this study was well tolerated, with nervous symptoms and laboratory results abnormalities being the primary AEs. AEs were assessed by vital signs, physical examination, laboratory tests and 12-lead ECG. The most commonly solicited adverse reactions of T and R were "low blood pressure", "dizziness" and "headache", mainly related to its vasodilation. All reported AEs were of mild to moderate severity, and no deaths or severe AEs throughout the study period (Table 4). Most AEs did not require special treatment apart from close observation until the subjects recovered naturally. In previous similar studies,[26] the sustained-release tablets of isosorbide mononitrate also demonstrated good tolerance. The reported adverse events were similar to those in this study. In clinical application, this drug is used in patients with coronary artery disease, most of them with hypertension and coronary atherosclerosis, the adverse events (such as low blood pressure, headache) reported in this paper are for a healthy population, and tend to provide a good antihypertensive and vasodilator effect in patients.

There were some limitations in our study. First of all, the isosorbide mononitrate sustained-release tablet was mainly used in CVD patients, but the participants were all healthy volunteers in the study. More detailed pharmacokinetics are needed in CVD patients including the elderly. Secondly, the homogeneous Chinese cohort may limit extrapolation to other ethnic populations. Furthermore, in the field of the effects of food on the pharmacokinetic parameters of isosorbide mononitrate, food effects were evaluated solely with high-fat meals. Lastly, three subjects withdrew during the study period; however, we fully considered this possibility before the commencement of the study and included an additional 20% of subjects.

Conclusion

The study demonstrated isosorbide mononitrate sustained-release tablets (40 mg/tablet) were bioequivalent to branded formulation (40 mg/tablet) in a population of Chinese healthy volunteers under both fasting and fed conditions. Both formulations were safe and well tolerated.

Data Sharing Statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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