Title: Pharmacokinetics of nifedipine sustained release tablets in healthy subjects after a single oral administration: Bioequivalence study and Food effects

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Abstract

Aim: This study has been designed to assess the bioequivalence of the newly developed delayed-release oral tablets (test) 30 mg nifedipine compared to its marketed counterpart (30 mg; reference) in healthy adult Chinese volunteers. Methods: We conducted randomized, open-label, four-period, crossover trials, including a fasting trial and a fed trial. The subjects were administered the test or reference products in a 1:1 ratio at random throughout each period with 7 days washout period. Then, in the next session, they got the alternate products. Liquid chromatography-tandem mass spectrometry and WinNonlin software were used to evaluate the bioequivalence of nifedipine peak blood concentration (Cmax) and area under the concentration-time curve (AUC). Result: A total of 46 subjects participated in the fasting trial and 48 subjects in the postprandial trial. In both cases, the 90% CI of the geometric mean ratios of Cmax, AUC0-t and AUC0-[?] were in the equivalence range (80-125%). When nifedipine was given concomitantly with a high-fat meal, tmax was approximately twofold earlier, absorption was approximately 4.8% less, and Cmax changed little compared to fasting conditions. In addition, no serious adverse events were observed in the subjects. Conclusion: This study confirms the bioequivalence of the test and reference formulations of nifedipine extended-release tablets under fasting and postprandial conditions. Food giving leads to a much earlier Tmax, which is different from the results of other studies. The effect of food effect on the pharmacokinetics of nifedipine needs to be further explored.

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Running title: N ifedipine sustained release tablets pharmacokinetics in healthy subjects

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What is already known about this subject?

Nifedipine is a short acting dihydropyridine calcium channel blocker, which can reduce myocardial oxygen consumption, diastolic and systolic blood pressure.

The bioavailability of nifedipine conventional preparations is low and the adverse reactions are serious.

The influence of food effect on the pharmacokinetics of nifedipine sustained-release preparations is uncertain.

What this study adds

We evaluated the bioequivalence of the newly developed nifedipine sustained release preparation

After eating, the T_{max} of nifedipine sustained-release preparation will be twice earlier, which is different from previous research results.

The influence of food on the pharmacokinetics of nifedipine suggests that we need to further study the causes of this phenomenon.

Abstract

Aim: This study has been designed to assess the bioequivalence of the newly developed delayed-release oral tablets (test) 30 mg nifedipine compared to its marketed counterpart (30 mg; reference) in healthy adult Chinese volunteers.

Methods: We conducted randomized, open-label, four-period, crossover trials, including a fasting trial and a fed trial. The subjects were administered the test or reference products in a 1:1 ratio at random throughout each period with 7 days washout period. Then, in the next session, they got the alternate products. Liquid chromatography-tandem mass spectrometry and WinNonlin software were used to evaluate the bioequivalence of nifedipine peak blood concentration (C_{max}) and area under the concentration-time curve (AUC).

Result: A total of 46 subjects participated in the fasting trial and 48 subjects in the postprandial trial. In both cases, the 90% CI of the geometric mean ratios of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}[?]}$ were in the equivalence range (80-125%). When nifedipine was given concomitantly with a high-fat meal, t_{max} was approximately twofold earlier, absorption was approximately 4.8% less, and C_{max} changed little compared to fasting conditions. In addition, no serious adverse events were observed in the subjects.

Conclusion: This study confirms the bioequivalence of the test and reference formulations of nifedipine extended-release tablets under fasting and postprandial conditions. Food giving leads to a much earlier T_{max}, which is different from the results of other studies. The effect of food effect on the pharmacokinetics of nifedipine needs to be further explored.

Introduction

Nifedipine (NFP) is a short-acting dihydropyridine calcium channel blocker[1]. Nifedipine can selectively block L-type calcium channels on cardiac and smooth muscle cells, organize the inward flow of extracellular calcium ions, reduce the intracellular calcium ion concentration, relieve the effect of vascular smooth muscle spasm, reduce peripheral vascular resistance, reduce myocardial oxygen consumption, and lower diastolic and systolic blood pressure in hypertensive patients[2]. At the same time, nifedipine can diastole the coronary arteries, and its application in small doses can have a very good anti-anginal effect. It is currently used clinically for the prevention and treatment of various types of coronary artery disease and angina pectoris, is also indicated for various types of hypertension, and has good efficacy in persistent and severe hypertension[3,4].

Nifedipine is almost completely absorbed from the gastrointestinal tract after oral administration and undergoes first-pass metabolism in the liver and intestinal wall, and its oral bioavailability reaches 43%-77%. Nifedipine is highly bound to plasma proteins, metabolized by the liver, and excreted primarily in the urine, with only less than 1% of the dose being excreted in its original form[5]. Regular nifedipine tablets have low and irregular bioavailability, and short-acting calcium antagonists cause increased sympathetic tone and reflex tachycardia, along with adverse effects such as headache, palpitations, flushing, and dizziness[6-78]. In contrast, nifedipine extended-release and controlled-release formulations do not have the "sudden release" phenomenon of ordinary tablets, which can reduce the gastrointestinal stimulation of the drug and avoid the adverse reactions caused by high peak blood concentrations, making the onset of nifedipine smooth and blood pressure control more stable[9]. Nifedipine extended-release tablets III, in the size of 30 mg, are capable of releasing nifedipine at a near-constant rate for 24 hours, similar to controlled-release tablets. Nifedipine extended-release tablets I and II are generally taken on an empty stomach, whereas nifedipine extended-release tablets III are not restricted by meal times because they are not affected by gastrointestinal motility or pH[10]. Therefore, the objective of this study was to investigate the pharmacokinetic properties of nifedipine extended-release formulation in the Chinese population and to evaluate the bioequivalence of the test formulation nifedipine extended-release tablets (Hunan Dino Pharmaceutical Co., Ltd.) and the reference formulation nifedipine controlled-release tablets (trade name: Baysinto®, size: 30 mg/tablet Bayer AG) to obtain regulatory approval for the test formulation.

Methods

Ethics

The study was conducted by the Declaration of Helsinki, the International Code of Practice for the Quality Management of Clinical Trials in Harmonized Meetings, and the Local Regulatory Guidelines of the State Drug Administration of the People's Republic of China. The study protocol, protocol modifications, and informed consent were approved by the Independent Ethics and Research Committee of Xiangya Hospital, Central South University before the start of the study.

Subjects

Inclusion criteria for this study included the following: healthy subjects must be 18 years of age or older (including 18 years of age). Volunteers had a body mass index (BMI) of 19.0-26.0 kg/m^2 (BMI = weight [kg]/height^2[m^2]) and weighed no less than 50 kg for men and 45 kg for women.

Exclusion criteria included: allergy to the study drug, smoking, alcohol abuse, and use of CYP-modifying drugs within 30 days before the trial; the presence of clinically significant abnormalities in the results of physical examination, vital sign monitoring, electrocardiogram examination, and laboratory tests including routine blood, urine, and blood biochemistry performed during the screening period, which was judged by the investigator to be clinically significant; the presence of clinically significant cardiovascular, hepatic, renal, endocrine digestive tract, hematological system, respiratory system, psychiatric abnormalities, or existing diseases of the above systems; those with positive hepatitis B surface antigen, or positive hepatitis C antibody, or positive syphilis spirochete antibody, or positive HIV antibody test. In addition, subjects must not have participated in another clinical study within 90 days before the start of this study. Before any study procedures, all participants provided written informed consent after being informed by the clinical investigator of the purpose, nature, procedures, and any risks of the study.

Study Design

This study consisted of two parts. The first part was conducted under fasting conditions and the second part was conducted after the consumption of a high-fat meal. Both parts of the trial were single-dose, randomized, open, two-agent, four-cycle, fully replicated crossover trials. The study was conducted at the Phase I Clinical Research Center of Xiangya Hospital, Central South University. The order in which each subject received the test preparation or the reference preparation in the study was determined by a randomization table. The randomization table was generated by Guangzhou Jingyuan Pharmaceutical Research Co., Ltd. using SAS 9.4 statistical software in 1:1 groups. 48 subjects were randomly assigned to 2 dosing order groups in a 1:1 ratio. In the fasting trial, subjects were asked to fast for 10 hours at night and take the drug in the fasted state; in the postprandial trial, subjects were to eat a high-fat meal 30 min before drug administration and finish it within 30 min, taking the drug at 30 min ± 1 min from the start of the meal. Subjects were to cross-dose the drug in the specified order (Group A: subject preparation - reference preparation - subject preparation - reference preparation; Group B: reference preparation - subject preparation - reference preparation - subject preparation). One dose of the corresponding test preparation or reference preparation was administered once per cycle with 240 mL of warm water, with a washout period of 7 days per cycle. All subjects were admitted to the Phase I clinical study center one day before dosing and underwent admission health status assessment, vital sign measurements, urine addiction drug screening, alcohol breath test, and blood pregnancy test (women of childbearing age only). Vital signs such as temperature, pulse, and sitting blood pressure were measured within 1 h before and at different times including (2, 4, 8, 24, 48, and 72 h) after dosing.

Safety Assessment

The safety of the drug was assessed by vital signs measurements, physical examination, laboratory tests, electrocardiograms, and adverse events. Adverse reactions were observed in all subjects during the trial. Coding was performed using MedDRA terminology, and categorical analysis was performed according to SOC/PT. A detailed list of adverse events, adverse reactions, and serious adverse events was tabulated by system and severity statistics of the number of cases and instances of adverse reactions.

Bioanalyses

The biological sample analysis test will be blinded, where the administered formulation is not known for each cycle during the sample analysis. Appropriate sample pretreatment methods were established based on drug properties, and a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was used to determine the blood concentration of nifedipine. The internal standard method (internal standard nifedipine d6) was used for quantification and the sample pretreatment method as protein precipitation.

Pharmacokinetic Analyses

PK analysis of plasma concentration-time curves was performed using a non-atrial model using WinNonlin version 8.2 software, and the pharmacokinetic parameters of nifedipine were calculated based on the concentration of nifedipine. After T_{max}, they were treated as missing. The linear trapezoidal method was used to calculate the area under the blood concentration-time curve (AUC) $AUC_{0\text{-}t}$ from time 0 to t. $AUC_{0\text{-}[?]}$ was calculated as the ratio of the sum of $AUC_{0\text{-}t}$ and the last measurable concentration to the elimination rate constant. C_{max} and time to peak T_{max} were obtained directly from the individual plasma concentration-time curve. The terminal elimination half-life ($t_{1/2}$) was calculated as $t_{1/2}$ = 0.693 / elimination rate constant, where 0.693 was derived from ln2.

Statistical Analyses

The main pharmacokinetic parameters of nifedipine, C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?]}$, were log-transformed and subjected to analysis of variance (ANOVA). The ANOVA model had dosing order, formulation, and period as fixed effects, formulation factors for different subjects as random effects, and the within-subject formulation repeated measures (i.e., repeated doses of subject formulation T, reference formulation R) effects were considered. The within-subject standard deviation SWR, point estimates of the geometric mean ratio,

the upper limit of the 90% confidence interval, and the one-sided 95% confidence interval of the geometric mean ratio (subject formulation/reference formulation) were calculated for the main indicators. The results of the double one-sided t-test are also presented.

Result

Subject Characteristics

A total of 48 healthy Chinese adult subjects (40 males and 8 females) were enrolled in the fasting trial. One subject withdrew from the study due to adverse events and one subject withdrew from the trial after testing positive for alcohol breath test before the start of the third cycle, while the remaining 46 subjects completed the trial. Age was 26.38+-6.03 years, height 168.30+-7.68 cm, weight 63.72+-6.52 kg, and body mass index (BMI) 22.52+-2.04 kg/m^2.

A total of 48 healthy Chinese adult subjects (38 males and 10 females) were enrolled in the postprandial trial. A total of 48 subjects completed the trial as planned. Age was 25.73+-5.48 years, height was 166.09+-8.04 cm, weight was 63.43+-8.18 kg, and body mass index (BMI) was 22.94+-1.91 kg/m2. Therefore, 46 subjects were enrolled in the fasting group and 48 subjects in the postprandial group in these two separate trials.

Pharmacokinetics

The mean blood concentration-time profiles of the two nifedipine extended-release tablets after a single oral dose of 30 mg of the test formulation and the reference formulation (under fasting conditions) are shown in **Figure 1** . The mean blood concentration-time profiles of the two nifedipine extended-release tablets after a single oral dose of 30 mg of the test formulation and the reference formulation (under postprandial conditions) are shown in **Figure 2** . The PK parameters obtained from the test results in these subjects (46 fastings and 48 postprandial) are shown in **Table 1** , and the 90% CIs for the geometric mean ratios of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?]}$, and the test efficacy are shown in **Table 2** . All the results are within the acceptable equivalent range (80% ˜ 125%).

Safety assessment

No protocol violations or serious adverse events were identified in this study. The safety profile of both the test and reference formulations was good during the conduct of the trial. A total of 50 adverse events were collected from 28 subjects in the fasting trial. These adverse events included: dizziness (n=8), headache (n=6), low back pain (n=3), inflammation of the left lower lung (n=1), positive urine red blood cells (n=6), hypotension (n=1), elevated myoglobin (n=1), elevated creatine kinase (n=1), anemia (n=2), finger burns (n=1), skin lesions on the right finger (n=1), intraventricular block (n=1), and upper respiratory tract infection (n=4), cough (n=1), skin trauma (n=1), elevated triglycerides (n=2), tachycardia (n=2), elevated cholesterol (n=1), abdominal pain (n=1), elevated blood uric acid (n=1), gastric distention (n=1), chest tightness (n=1), nosebleeds (n=1), nausea (n=1), and vomiting (n=1). None of the AEs were serious adverse events. In addition, no clinically significant changes were found in other safety assessments, including physical examination, electrocardiogram, or laboratory tests.

In the postprandial trial, one adverse event was collected in one subject before dosing and 58 subadverse events occurred in 29 subjects after dosing. These adverse events included: dizziness (n=9), headache (n=3), tachycardia (n=7), prolonged ECG P-R interval (n=2), elevated triglycerides (n=12), elevated uric acid (n=1), altered ECG T waves (n=1), gingival pain (n=2), stomach pain (n=1), decreased white blood cell count (n=1), anemia (n=1), abdominal pain (n=1), hypotension (n=10), decreased platelets (n=1), positive urine red blood cells (n=3), nasal congestion (n=1), dry throat (n=1), and skin abrasions (n=1). No serious adverse events occurred. No clinically significant changes were found in other safety assessments, including physical examination, electrocardiogram, or laboratory tests.

Discussion

This study compared the newly developed nifedipine extended-release tablets (test formulation, Qingdao Baiyang Pharmaceutical Co., Ltd.) with the marketed nifedipine extended-release tablets (reference for-

mulation, Bayer AG) for bioequivalence assessment under fasting and postprandial conditions in healthy Chinese volunteers. The controlled-release formulation of nifedipine was also found to provide a constant release of 16-18 hours in the healthy Chinese population, resulting in stable maintenance of blood levels for more than 24 hours. This is very helpful for nifedipine to control hypertension, which requires stable control.

In a domestic survey of drug utilization in the cardiovascular system published in 2007, nifedipine was one of the most frequently selected clinical species[11]. The metabolism of nifedipine as a substrate drug for CYP3A4 is highly variable in the population, and its different metabolic distribution in patients makes the adverse effects more severe in some patients. Of particular note is that nifedipine can cause some serious adverse reactions, such as severe hypotension due to sublingual nifedipine[12], severe exfoliative dermatitis, triggering cerebral ischemic attacks, cerebral infarction, and myocardial ischemia.

Therefore, the appropriate formulation can affect the metabolism and distribution of nifedipine in the patient's body, thus enabling nifedipine to exert a gentle dilating effect on the peripheral arterial vessels and lower blood pressure, as well as reducing the occurrence of adverse effects. Nifedipine controlled-release tablets need to be taken only once a day, and by reducing the number of doses and maintaining a stable blood concentration, the drug can reduce the irritation of the gastrointestinal tract and avoid the adverse reactions caused by high blood concentration[13].

Two separate studies were involved in the current study, including a fasting trial and a postprandial trial. Subjects were screened separately, with 48 subjects in the fasting group and 48 subjects in the postprandial group without crossover to each other, and after subjects were included in each of these two groups, they would undergo hospitalization, drug administration, blood collection, and discharge phases. It is necessary for subjects in both groups to be informed of the specific differences in the protocol and to obtain informed consent. The postprandial group will begin eating a high-fat, high-heat meal 30 min before dosing on the day of administration, and subjects will self-assess the menu provided by the investigator to determine that it can be consumed within 30 min. The fasting group, on the other hand, will remain fasted until the dose is administered.

The coefficient of variation for subjects was 19.37% in the fasting trial and 18.44% in the post-meal trial. The t1/2 for nifedipine was 7.12+-2.65h in the fasting trial and 6.57+-2.12h in the postprandial trial. comparing the pharmacokinetic parameters after a single fasting dose of the same dose as the subject formulation in the postprandial trial, the AUC curve area was reduced by approximately 4.8%, C_{max} was not significantly changed, but T_{max} was advanced by nearly twofold. the pharmacokinetic parameters reported in the literature for the postprandial period, absorption The postprandial pharmacokinetic parameters reported in the literature, the absorption amount was not changed significantly, and the C_{max} was also not changed significantly, but the time to peak was earlier than in the fasting state. These results indicate that food does not affect the peak plasma concentration of nifedipine extended-release tablets and has no effect on drug absorption. The pharmacokinetic data from this study showed no significant differences in PK parameters (including C_{max} and $AUC_{0\text{-}[?]}$) between the test formulation and the reference formulation under fasting and postprandial conditions. Based on the 90% confidence interval of the PK parameters obtained from the PK analysis in the range of 80%-125%, we can conclude that these data meet the regulatory requirements and that there is bioequivalence between the test formulation and the reference formulation.

In the present study, in contrast to previous findings, the effect of food factors on the pharmacokinetics of nifedipine was mainly the change in fasting and postprandial T_{max}. In our study, the T_{max} was 24h under fasting conditions and 6 h under postprandial conditions. the postprandial T_{max} in the present study was nearly twofold earlier, which is completely different from the changes in T_{max} in several previous studies on the pharmacokinetics of nifedipine extended-release tablets. In other people's studies, the value of T_{max} increases after meals, that is, eating makes the T_{max} of nifedipine sustained-release tablets push back[14]; Or there is little difference in T_{max} between fasting and postprandial[15]. Our results, on the other hand, suggest that feeding pushes forward the T_{max} of nifedipine, and the reasons for this result are complex and may be related to factors such as gastrointestinal peristalsis, visceral blood flow, altered gastrointestinal PH, and possibly population factors. The effect of food on the pharmacokinetics of nifedipine extended-release

tablets is of interest in this study, and more in-depth studies could be conducted in the future to elucidate the significance of food on nifedipine PK.

In recruiting subjects for this study, strict selection criteria were applied primarily for alcohol intake, smoking status, and other drugs that affect the nifedipine metabolizing enzyme CYP3A, as these factors may contribute to variability in nifedipine pharmacokinetic parameters.

In the safety assessment, no significant differences in the incidence of adverse reactions were observed between the tested and reference formulations, and no clinically meaningful changes were found in the physical examination, electrocardiogram, or laboratory tests.

This study has the limitation that because this trial was an open-label trial, psychological effects between subjects receiving the test and reference formulations were not completely excluded. The pharmacokinetic parameters in this study were derived from healthy Chinese subjects only, so there are limitations for other ethnicities, as well as other target populations for reference. It is hoped that more in-depth studies can be conducted to address these issues.

Conclusion

A comparative study of the fasting and postprandial plasma pharmacokinetics of nifedipine extended-release tablets demonstrated the bioequivalence of nifedipine extended-release tablets (Hunan Dino Pharmaceutical Co., Ltd.) and the reference formulation, nifedipine controlled-release tablets (trade name: Baysinto(r), size: 30 mg/tablet Bayer AG). Both drugs had a good safety profile, with no serious adverse reactions occurring throughout the study period. Notably, the high-fat diet reduced the AUC curve area by approximately 4.8%, with little change in C_{max} but an almost twofold advance in T_{max}.

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Conflicts of Interest

The authors declare no conflicts of interest.

Reference

1. Ueng KC, Lin MC, Chan KC, Lin CS. Nifedipine gastrointestinal therapeutic system: an overview of its antiatherosclerotic effects. Expert Opin Drug Metab Toxicol. 2007 Oct;3(5):769-80. DOI: 10.1517/17425255.3.5.769.
2. Noda T, Yaginuma T, O'Rourke MF, Hosoda S. Effects of nifedipine on systemic and pulmonary vascular impedance in subjects undergoing cardiac catheterization. Hypertens Res. 2006 Jul;29(7):505-13. doi: 10.1291/hypres.29.505. PMID: 17044663.
3. Di Filippo C, Lampa E, Forgione A,et al. Effects of nifedipine controlled release on blood pressure and heart rate of spontaneously hypertensive rats. Comparison with nifedipine standard and with amlodipine [J].Ital Heart J Suppl,2005,6(5):285-290.
4. Jiang S. T., Yu S. Y. Efficacy of nifedipine extended-release tablets in the treatment of hypertension combined with diabetes mellitus [J]. Shandong Medicine, 2010,50(21):67-68.
5. Murdoch D, Brogden RN. Sustained release nifedipine formulations; an appraisal of their current uses and prospective roles in the treatment of hypertension, ischaemic heart disease and peripheral vascular disorders. Drugs 1991; 41 (5): 737-79
6. Ruzicka M, Leenen FH. Relevance of 24 h blood pressure profile and sympathetic activity for outcome on short- versus long-acting 1,4-dihydropyridines. Am J Hypertens 1996; 9: 86–94.
7. Julius S. Sympathetic hyperactivity and coronary risk in hypertension. Hypertension 1993; 6: 886–93.
8. Cohn JN. Sympathetic nervous system activity and the heart. Am J Hypertens 1989; 2: 353S–356S.

9. Tang Shude, Gong Lansheng. Pharmacodynamics and pharmacokinetics of nifedipine controlled-release tablets[J]. Shanghai Medicine, 1997(01):23-24.
10. PHYSICIAN'S DESK REFERENCE:Product Information,Pfizer,Inc.Procardia(r) capsules and Procardia XL(r).Thomson Healthcare, Montvale,NJ 2002).
11. Feng L, Hou Hsiao Y, Meng L, et al. Application of drug utilization analysis of cardiovascular system in 157 hospitals in Yangtze River basin in 2005[J]. Chinese Journal of New Drugs and Clinics, 2007, 26(3):175
12. Chen Biao, Wu Shu Yue, Wang Yan Ning, et al. Case analysis of severe adverse reactions caused by short-acting nifedipine[J]. Chinese Pharmacist,2009,12(8):1136-1137.
13. Tang Shude, Gong Lansheng. Pharmacodynamics and pharmacokinetics of nifedipine controlled-release tablets[J]. Shanghai Medicine, 1997(01):23-24.
14. Li JF, Yan L, Wang XF, Li XT, Zhang SJ, Zhang LR. Effects of high-fat diet and ABCB1 gene polymorphisms on the pharmacokinetics of nifedipine in healthy subjects. Chinese Journal of Pharmacology,2014,30(04):566-569.
15. Schuger, B., Brendel, E., Werneman, et al. Dose-related food interactions observed in a marketed once-daily nifedipine formulation after a high-fat American breakfast. Euro J Clin Pharmacol 58, 119-125 (2002)

Table 1. Pharmacokinetic Parameters of nifedipine Test (T) and Reference (R) Formulations.

parameter	Fasting R(N(R1)=48,N(R2)=46)	Fasting T(N(T1)=48,N(T2)=47)	Fed R(N=48)	Fed T(N=48)
$C_{max,}$ ng/mL	26.1±12.1	29.5±13.1	29.9±10.8	32.7±12.4
T_{max}, h	24.00 (4.00,36.00)	24.00(4.00,48.00)	6.00 (4.00,24.00)	7.00(4.00,48.00)
$AUC_{0\text{-}t}$,ng[?]h/mL	686.14±372.05	744.92±410.67	657.35±340.71	736.89±368.76
$AUC_{0\text{-}[?]}$,ng[?]h/mL	695.00±388.67	772.99±426.05	673.95±349.94	732.46±358.32
$t_{1/2}$, h	7.93±3.01	7.12±2.65	7.22±3.06	6.57±2.12

$AUC_{0\text{-}[?]}$, area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to time t; C_{max}, maximum plasma concentration; t1/2, terminal elimination half-life; T_{max}, time to maximum concentration. All values are represented as the arithmetic mean +- standard deviation, except T_{max}, which is shown as the median (minimum-maximum).

Table 2 . 90%CIs for the Geometric Mean Ratios of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?].}$

parameter	Fasting Ratio % Re	Fasting 90% CIs Lower	Fasting 90% CIs Upper	Fasting Power	Fasting Intrasubject Variability (%)	Fed Ratio % Re	Fed 90% CIs Lower	Fed 90% CIs Upper	Fed Power
C_{max}	114.20	108.94	119.71	93.50	19.37	108.81	104.52	113.28	100
$AUC_{0\text{-}t}$	108.74	101.64	116.34	96.05	23.59	112.71	105.76	120.12	84.97
$AUC_{0\text{-}[?][?]}$	109.10	101.09	117.74	90.44	22.45	110.87	103.82	118.40	91.36

$AUC_{0\text{-}[?]}$, area under the plasma concentration–time curve from time 0 to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration–time curve from time0 to time t; C_{max}, maximum plasma concentration; CI, confidence interval.

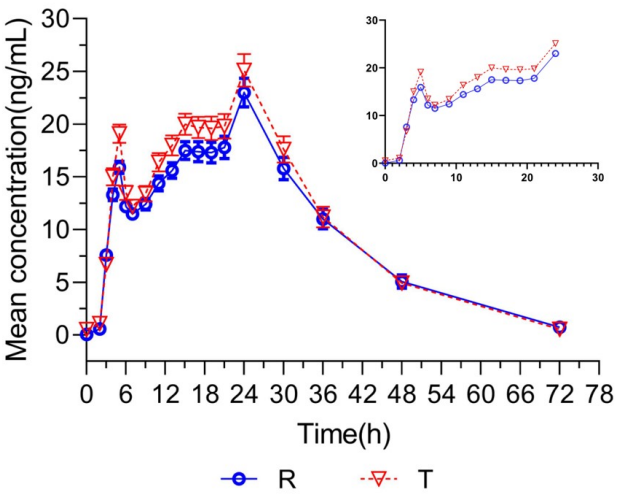

Figure 1. Plasma concentration-time profiles of nifedipine after a single oral dose of 30 mg of nifedipine test (T) or reference (R) formulation in healthy Chinese adult subjects (fasting test). Error bars represent standard errors.

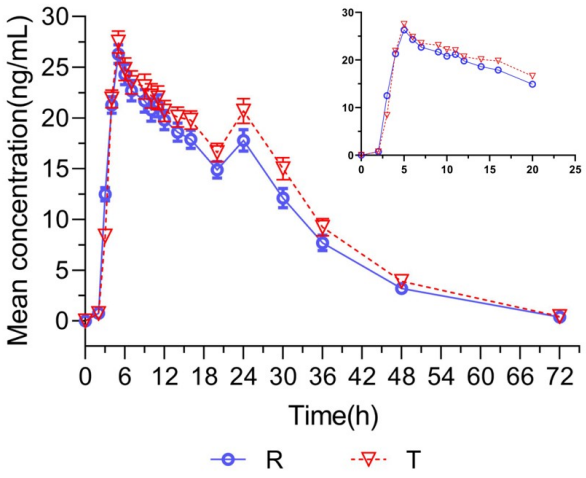

Figure 2. Plasma concentration-time profiles of nifedipine after a single oral dose of 30 mg of nifedipine test (T) or reference (R) formulation in healthy Chinese adult subjects (postprandial test). Error bars represent standard errors.

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