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CLINICAL TRIAL REPORT

Evaluation of Pharmacokinetics and Safety with Bioequivalence of Ibuprofen Sustained-Release Capsules of Two Formulations, in Chinese Healthy Volunteers: Bioequivalence Study

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Purpose: Ibuprofen is the first of the nonsteroidal anti-inflammatory drug (NSAID) to be used in the clinic. Our aim was to explore the pharmacokinetics (PK), bioequivalence, food effect, and safety of oral ibuprofen sustained-release capsules by two sponsors in healthy volunteers (HVs).

Methods: Two separate randomized, open-label, single-dose, crossover-design studies were conducted: a fasting study (n = 24) and a fed study (n = 24). In each study, HVs were 1:1 divided into two groups (T-R and R-T) and received 0.3-g/capsule ibuprofen with a 3-day washout. The plasma was collected for up to 24 hours at the time point after dosing on Day 1/Day 4. The plasma concentrations of ibuprofen were measured using an HPLC-MS/MS method, and PK parameters were determined by noncompartmental methods.

Results: Forty-eight healthy volunteers were enrolled. In fasting subjects, the maximum plasma concentration (C_{max}, mean ± SD) was 14.86±3.19 μg/mL at 5.0 (4.0, 7.0) hours (median [min, max]) for sponsor T, and 13.88±2.60 μg/mL at 4.5 (3.0, 8.0) hours for sponsor R. In fed subjects, C_{max} was 21.31±4.08 μg/mL at 5.6 (4.3, 10.0) hours for sponsor T, and 19.77±3.36 μg/mL at 6.0 (2.0, 8.0) hours for sponsor R. All 90% confidence intervals (CIs) for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the bioequivalence bounds (80–125%) both fasting and fed studies.

Conclusion: Ibuprofen is well tolerated and has a favorable safety profile. In both fasting and fed study, there were no serious AEs, or AEs leading to withdrawal. Bioequivalence is achieved under fasting and fed conditions, supporting the demonstration of biosimilarity.

Keywords: ibuprofen, bioequivalence, pharmacokinetics, safety, HVs

Introduction

Ibuprofen (2-arylpropionic acid derivative [(R,S)-2-(4-(4-methylpropyl) phenyl)] propanoic acid derivative) is the first of the nonsteroidal anti-inflammatory drug (NSAID) to be used in the clinic.[1,2] Ibuprofen has strong anti-inflammatory, anti-rheumatic, antipyretic and analgesic effects, and it is used to relieve pain, such as headache, joint pain, migraine, toothache, muscle pain, neuralgia, and dysmenorrhea.[3] As a cyclooxygenase (COX) inhibitor, it has a specific inhibitory effect on COX-2 to inhibit the synthesis of prostaglandins (PGs) at the inflammatory site, and then reduce tissue congestion, swelling and sensitivity to peripheral nerve pain.[4,5] In addition, due to the inhibition of PG, the regulation of body temperature is restored to the normal level, and the skin blood vessels are dilated to antipyretic.[6] Ibuprofen was rapidly absorbed. The plasma concentration reached the C_{max} 1–2 hours later. The absorption was slow down when

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taking with food, but no accumulation was observed.[7] Ibuprofen was metabolized by the liver, and then excreted by the kidney. The clearance rate was approximately 0.75±0.2 mL/(min·kg).

According to the characteristics of the ibuprofen, it is widely in demand in the postpandemic period in China. Previous literature reported, that NSAIDs could affect COVID-19 pathogenesis by modifying the expression of angiotensin-converting enzyme 2 (ACE2), regulating the replication of SARS-CoV-2, and modulating the immune response to SARS-CoV-2.[5,8,9] In addition, the advantage of ibuprofen sustained-release capsules is that the longer $t_{1/2}$ was approximately 3–4 hours, which could not only reduce the number of the administrations, but also reduce gastrointestinal AEs, having a desired effect.[10,11] Although ibuprofen has been used in China for many years,[12] it is expected to remain in high demand for a long time to come due to the impact of COVID-19. Therefore, it is necessary to develop ibuprofen generic drugs to better meet for market demand in China.

The purpose of this study was to demonstrate the bioequivalence of a generic formulation of 0.3-g/capsule ibuprofen sustained release capsules ((test formulation, T), Batch No. 22064204, ALD NED, China) in comparison with the reference formulation (R) (Fenbid®, 0.3-g/capsule, Batch No. BH2S, Tianjin SmithKline and French) in both fasting and fed conditions.

Materials and Methods

Study Design

The bioequivalence of the ibuprofen sustained-release capsules study was conducted in two separate trials. Both fasting and fed studies were single-center, open-label, randomized, single-dose, 2-cycle, and crossover designs. In each trial, 24 HVs were enrolled, and randomly divided into T-R sequences (n = 12) and R-T sequences (n = 12). HVs were administered 0.3-g ibuprofen sustained-release capsules (T/R) at the same time on days 1 and 4 in two studies. In the fasting study, the subjects fasted for at least 10 hours, and then they took the T or R formulation with 240 mL water the next morning. In the fed study, the subjects were fasted for at least 10 hours, and took the T or R formulation promptly with 240 mL water after a high-fat diet (Protein provides about 150 kcal, carbohydrates about 250 kcal, and fat about 500–600 kcal) for 30 minutes. According to the pretest, the terminal elimination half-life of ibuprofen sustained-release capsules in healthy subjects was approximately 2 hours. Therefore, the washout period was set as 3 days, and it has a half-life of more than 7 times between each single dosing[13] (Figure 1).

The trial design was approved by the Ethics Committee at the Hangzhou Red Cross Hospital, Hangzhou City, China (batch No.: 2022–007-001). The clinical study was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) principle, Chinese laws and regulations.[14] All participants signed informed consent forms. The trial was conducted at the Hangzhou Red Cross Hospital. The trial was registered at chinadrugtrials.org.cn (CTR20222480).

Inclusion Criteria

The inclusion criteria were as follows: (1) Chinese HVs of age ≥ 18 years old, weight≥50.0 kg, BMI range from 19.0 to 26.0; (2) volunteer for the clinical trial; (3) signed the informed consent voluntarily before the studies; (4) understand and comply with the requirements of this trial.

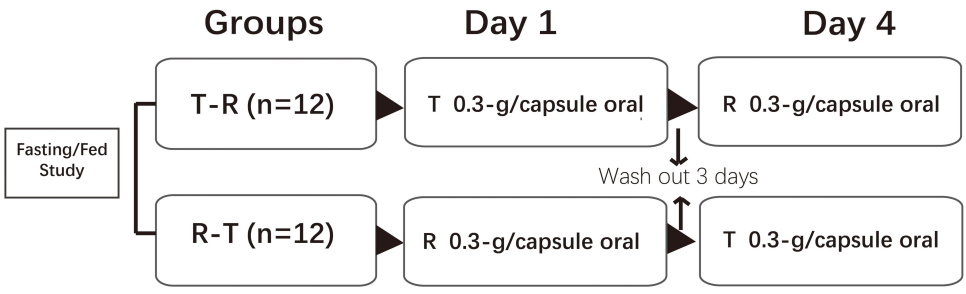

Figure 1 The flow chart of the bioequivalence study.

Exclusion Criteria

The exclusion criteria were as follows: (1) allergy to nonsteroidal drugs or other drugs; (2) any chronic or serious illness; (3) HIV, HBsAg, HBeAg, HCV or TP-Ab positivity in any test. (4) with clinically significant abnormal laboratory examination and specialist tests were abnormal; (5) had surgery within 3 months; (6) received vaccination within 2 weeks; (7) had a history of substance abuse or positive urine tests within 12 months; (8) had a history of heavy smoking, or excessive intake of alcohol in the last 3 months; (9) had a needle or blood sickness in history; (10) could not avoid using tobacco, alcohol, caffeinated beverages, or strenuous exercise for 48 hours during the trial; (11) could not tolerate high-fat meals; (12) subjects did not plan to become pregnant within 3 months from the signing of the informed consent to the final dose. (13) subjects deemed unsuitable for inclusion for other reasons.

The eligible volunteers were required to stay in the Phase I Clinical Research Center for 24 hours before agent administration and stayed 48 hours after drug administration. Subjects fasted for at least 10 hours then and took T or R drugs according to random numbers.

Estimation of Sample Size

In this crossover design study, the pharmacokinetic parameters (AUC, C_{max}) were used as the main analysis index. According to the pretest results, the geometric mean ratio of the PK parameters between T and R approximately about 1.12, the coefficient of variation (CV) was about 12.8%, and the bioequivalent interval was 80.00%~125.00%, including the boundary value. Using PASS 11.0.7 software to calculate, referring to previous research results,[15] the number of subjects was finally determined to be 24 in both fasting and fed study, and the enrolled subjects were both male and female.

Pharmacokinetic (PK) Assessment

In both the fasting and fed study, blood samples were collected for PK analysis after oral agents at the following time points: 30, 60, 90, 120, 150, 180, 210, 240, 260, 280, 300, 320, 340 mins, and 6, 7, 8, 10, 12, 24 hours. The first 1 mL of blood was discarded, and then 4 mL of blood was collected into K2-ethylenediaminetetraacetic (EDTA-K2) acid tubes, and slowly reversed up and down repeatedly 4 to 5 times to mix. Within 1 hour after blood collection, the blood samples were centrifuged at 4 °C, and 2000 * g for 10 min. Then the separated plasma was immediately placed into polypropylene tubes, and directly stored in an ultra low temperature refrigerator at −80°C.

Safety Assessment

Safety and tolerability were evaluated by the doctor during the study. The assessed items included clinical symptoms, clinical laboratory assessments (blood biochemistry, urinalysis), physical examination, 12-lead electrocardiogram (ECG), and vital signs taken at the beginning and end of each study. All AEs were recorded immediately by the clinical research physician, and the severity of each AE to the drug was assessed.

PK and Statistical Analysis

The PK parameter analysis for both studies was performed with SAS 9.4 Statistical Package (Cary, North Carolina) and using the noncompartmental analysis on Phoenix WinNonLin8.3 (Certara, Princeton, New Jersey).

The PK parameters for ibuprofen included maximum plasma concentration (C_{max}), the area under the concentration–time curve from time 0 to the last measurable plasma concentration (AUC_{0-t}), the area under the concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$), time of maximum plasma concentration (T_{max}), half-life ($t_{1/2}$), Elimination rate constant (λ_z) and percentage of residual area ($AUC_{\_\%Extrap}$, calculated by $([AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty}) \times 100\%]$. The PK parameters of ibuprofen sustained-release capsules were presented as the arithmetic mean value (mean) and standard deviation (SD). The bioequivalence between the two formulations was evaluated by the 90% confidence intervals (CIs) of the geometric mean ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. When the plasma concentration was below the limit of quantification (BLQ), the value was treated as 0 in the calculation of the mean and SD.

High Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC-MS/MS)

High performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) was used to validate the quantification and identification of ibuprofen in human plasma on ExionLC^{TM} AD and QTRAP$^{®}$5500 from SCIEX. Chromatographic separation was achieved on a ZORBAX Eclipse Plus C18 column (2.1 * 50 mm, 3.5 μm) from Agilent. Ibuprofen and ibuprofen-d_3 (internal standards, IS) were purchased from ALD NED. The mobile phase (solvent A) was 5 mM ammonium acetate solution with 0.01% formic acid, and the organic phase (solvent B) was acetonitrile. The rate of elution was 0.8 mL/min, and the total running time was 9.6 mins. In the positive ion mode, the peak area of the mass-to-charge ratio (m/z) 205.0 → 161.1 for ibuprofen was measured against the peak area of the (m/z) 208.0 → 164.1 for IS. At the lower limit of quantification (LLOQ: 0.2 μg/mL), the precision (%CV) of the LQC, MQC and HQC concentration quality control products was ≤2.9%, and the accuracy deviation range of each quality control sample was −3.0%–1.6%.

Results

Characteristics of HVs at Baseline

In both fasting and fed study, 24 subjects were enrolled and randomly assigned to the T-R or R-T group. In the fasting study, all subjects were completed the study. In the fed study, 23 subjects completed the study, and 1 subject (C021, T-R group) was withdrawn when she was unable to tolerate and could not complete the high-fat diet. The baseline characteristics and demographics of all subjects are shown in Table 1.

Pharmacokinetic and Statistical Results

The plasma concentration–time profiles of ibuprofen following a single dose in the fasting and fed study are presented in Figure 2. AUC is an important parameter that indicates the extent of absorption for a comparative bioequivalence study. In addition, C_{max} and T_{max} represent important implications for plasma drug concentration and therapeutic effect. Figure 2A and C shows that the plasma concentration reached the C_{max} and T_{max} after giving the sponsor T or R in the fasting and fed study. Figure 2B and D shows the geometric means of $t_{1/2}$ of sponsors T and R in both the fasting and fed studies.

The PK parameters derived from the T/R formulations after a single dose in the fasting and fed study are listed in Table 2, such as T_{max}, C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, λ_z and $AUC_{\_\%Extrap}$. The PK parameter analysis for both studies was conducted using the noncompartmental analysis module. In two studies, the PK parameters showed a high degree of consistency between T and R.

Bioequivalence Analysis

The 90% confidence intervals (CIs) and the geometric mean ratio of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} were used to evaluate equivalence, as shown in Table 3. All 90% CIs for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ were within the bioequivalence bounds (80–125%).

Table 1 Baseline Demographic Characteristics (Mean ± Standard Deviation) of HVs

	Fasting			Fed		
	T-R(n=12)	**R-T (n=12)**	**ALL(n=24)**	**T-R(n=12)**	**R-T (n=12)**	**ALL(n=24)**
Sex, n (%)						
Male	11 (91.67)	11 (91.67)	22 (91.67)	10 (83.33)	12 (100.00)	22 (91.67)
Female	1 (8.33)	1 (8.33)	2 (8.33)	2 (16.67)	0 (0)	1 (4.17)
Age	29.10±7.69	30.80±7.41	30.00±7.44	28.60±6.29	25.30±4.77	26.90±5.72
Height (cm)	169.53±6.68	167.33±5.76	168.43±6.20	169.18±6.06	168.08±6.97	168.63±6.41
Weight (kg)	63.34±6.85	62.20±7.09	62.77±6.84	61.22±7.08	61.43±7.96	61.32±7.37
BMI (kg/m^2)	21.99±1.57	22.18±1.77	22.09±1.64	21.36±1.87	21.75±1.85	21.52±1.83

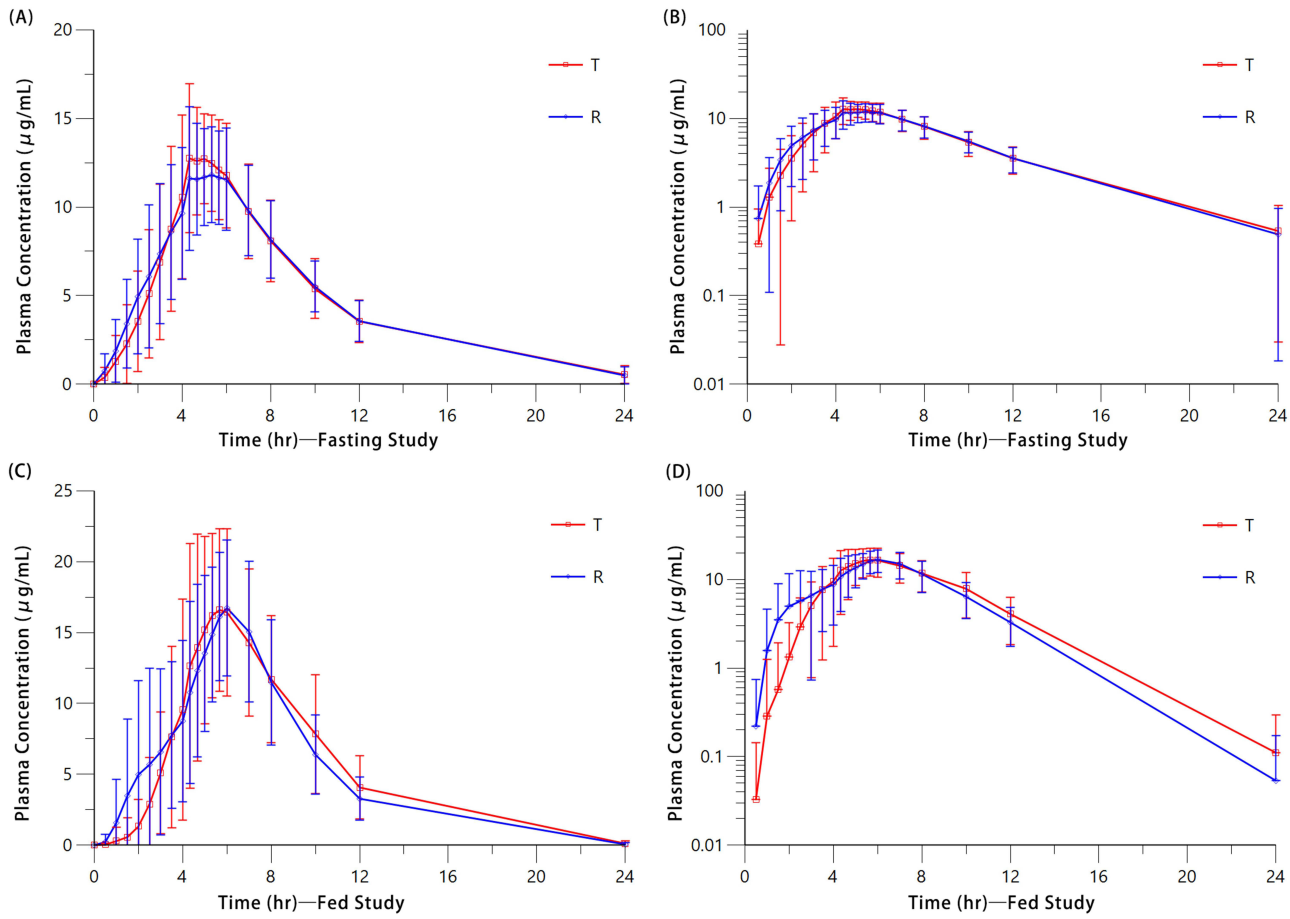

Figure 2 Mean plasma concentration-time profile. (**A**) Mean plasma concentration-time plots for ibuprofen following a single oral dose in fasting study. (**B**) Mean plasma concentration-time plots for ibuprofen following a single oral dose in fasting study (semilogarithmic scale). (**C**) Mean plasma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

Safety Analysis

Ibuprofen was generally well tolerated in both the fasting and fed study. In the fasting study, 5 AEs appeared in 4 HVs, and the ratio of AEs was 16.67% (4/24). Among the 24 subjects who took the T formulation, 2 of 24 subjects had 3 AEs (8.33%, 2/24). Moreover, 1 of 24 subjects had 2 AEs (4.17%, 1/24). After taking the R formulation, 2 subjects had 2 AEs, with an incidence of 8.33% (2/24). In the fed study, 5 subjects had 7 AEs, and the incidence of AEs was 21.74% (5/

Table 2 The Pharmacokinetic Parameters of Ibuprofen Sustained-Release Capsules in Bioequivalence Study

	Fasting		Fed	
	T (n=24)	**R (n=24)**	**T (n=23)**	**R (n=23)**
T_{max} (h)	5.00 (4.00, 7.00)	4.50 (3.00, 8.00)	5.66 (4.33, 10.00)	6.00 (2.00, 8.00)
C_{max} (μg/mL)	14.86±3.19 (21.43)	13.88±2.60 (18.75)	21.31±4.08 (19.14)	19.77±3.36 (17.01)
AUC_{0-t} (h*μg/mL)	104.93±18.07 (17.22)	105.36±21.44 (20.35)	112.72±28.40 (25.20)	107.25±21.62 (20.16)
$AUC_{0-\infty}$ (h*μg/mL)	110.80±19.87 (17.93)	110.92±22.94 (20.68)	119.87±26.13 (21.80)	114.46±20.84 (17.72)
λ_z (1/h)	0.20±0.09 (45.12)	0.20±0.08 (39.81)	0.31±0.06 (20.39)	0.32±0.05 (16.34)
$t_{1/2}$ (h)	4.13±1.63 (39.43)	3.95±1.44 (36.47)	2.35±0.49 (20.65)	2.22±0.372 (17.76)
$AUC_{\_\%Extrap}$ (%)	5.09±4.13 (81.13)	4.94±4.19 (84.86)	6.28±4.38 (69.78)	6.55±3.83 (58.65)

Notes: T_{max} was expressed by the median (minimum, maximum) (CV%). Feeding study: C021 subject failed to comply with the study protocol, withdrew from the trial during the first cycle.

Table 3 Summary of Bioequivalence Assessment

	T (Geomean)	R (Geomean)	(T/R) %	90% Confidence Interval (CI)	In vivo Variation (CV%)	Power%
Fasting (n=24)						
C_{max} (μg/mL)	14.55	13.66	106.54	99.22~114.41	14.45	98.14
AUC_{0-t} (h*μg/mL)	103.48	103.31	100.17	95.40~105.17	9.85	>99.99
$AUC_{0-\infty}$ (h*μg/mL)	109.14	108.79	100.32	96.85~103.92	7.12	>99.99
Fed (n=23)						
C_{max} (μg/mL)	20.87	19.52	106.88	100.24~113.97	12.69	99.21
AUC_{0-t} (h*μg/mL)	109.29	105.14	103.95	99.95~108.11	7.74	>99.99
$AUC_{0-\infty}$ (h*μg/mL)	115.91	112.66	102.88	99.52~106.36	5.97	>99.99

Notes: Feeding study: C021 subject failed to comply with the study protocol, withdrew from the trial during the first cycle.
Abbreviation: Geomean, geometric mean.

23). Twenty-three HVs took the R formulation, 3 AEs appeared in 2 subjects, and the ratio of AEs was 8.70% (2/23). In addition, one of the subjects had 1 AEs (4.35%, 1/23). After taking the R formulation, 4 subjects had 4 AEs, with an incidence of 17.39% (4/23). Both in fasting and fed study, there were no serious AEs, or AEs leading to withdrawal. Data are presented in Table 4.

Table 4 Adverse Events in the Study

		Fasting						Fed					
		T (N=24)			R(N=24)			T (N=23)			R(N=24)		
SOC/PT	**Grade**	**Case**	**N**	**(%)**	**Case**	**N**	**(%)**	**Case**	**N**	**(%)**	**Case**	**N**	**(%)**
AEs		3	2	8.33	2	2	8.33	3	2	8.70	4	4	16.67
SAEs		0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
AEs leading to withdrawal		0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Total AEs	**1**	1	1	4.17	2	2	8.33	3	2	8.70	4	4	16.67
	2	2	1	4.17	0	0	0.00	0	0	0.00	0	0	0.00
	3	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
	4	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
	5	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Laboratory Examination													
Low WBC	**2**	1	1	4.17	0	0	0.00	0	0	0.00	0	0	0.00
High CK	**1**	0	0	0.00	1	1	4.17	0	0	0.00	0	0	0.00
High ALT	**1**	0	0	0.00	0	0	0.00	1	1	4.35	0	0	0.00
Low Neutrophil	**2**	1	1	4.17	0	0	0.00	0	0	0.00	0	0	0.00
High eosinophil	**1**	0	0	0.00	0	0	0.00	0	0	0.00	1	1	4.17
Low blood pressure	**1**	1	1	4.17	1	1	4.17	0	0	0.00	1	1	4.17
High blood pressure	**1**	0	0	0.00	0	0	0.00	0	0	0.00	1	1	4.17
The gastrointestinal system													
Stomachache	**1**	0	0	0.00	0	0	0.00	1	1	4.35	0	0	0.00
Emesis	**1**	0	0	0.00	0	0	0.00	1	1	4.35	0	0	0.00
Heart organ													
RBBB	**1**	0	0	0.00	0	0	0.00	0	0	0.00	1	1	4.17

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: AEs, Adverse Events; SAEs, Serious Adverse Events; RBBB, right bundle branch block.

Discussion

In both the fasting and fed study, the two formulations (T and R) were assessed by the single-dose PK parameter and bioequivalence of ibuprofen sustained-release capsules in Chinese healthy volunteers. Ibuprofen of T formulation was well tolerated, and there were no deaths or SAEs in any study (Table 4). AEs were assessed by laboratory tests, vital signs, 12-lead ECG, or physical examination, and showed no significant changes.

Although ibuprofen has been used in China for many years,[12] its pharmacokinetics have been well studied in recent years. However, the development of a new generic drug, ibuprofen is necessary to ease market demand due to the impact of COVID-19 at present. Andrade mentioned that a bioequivalence study of the generic drug was a prerequisite for marketing approval.[16] The PK parameters of ibuprofen such as C_{max}, T_{max}, AUC_{0-t}, $T_{1/2,}$ and so on are shown in Table 2 and were similar to those in the previous literature.[7] In both the fasting and fed studies, the sustained-release formulation was used for investigation, so t_{max} was longer than that of the immediate-release formulations.[17] L.F. Luo et al evaluated the bioequivalence of two ibuprofen formulations after single and multiple doses in Chinese HVs,[18] considering the dose due to the different results. In each study, the 90% CIs for the C_{max}, AUC_{0-t}, and AUC_0-∞ were all within the range of 0.8–1.25. We obtained data to evaluate the two formulations by the pharmacokinetics and safety with bioequivalence of ibuprofen and demonstrated the bioequivalence of the T formulation.

In the fasting and fed study, we found that diclofenac sodium sustained-release tablets were taken with food affected absorption and systemic exposure. In our trials, compared with the fasting condition, the T_{max} of ibuprofen sustained-release capsules after a meal was delayed, and C_{max} was increased to a certain extent. Although the high-fat diet had a significant effect on the absorption rate of ibuprofen, it had little effect on the amount absorbed. The influence of food on oral drug bioavailability is related to complex interactions of drugs, preparations, food composition, and stomach and intestinal physiology (eg, gastrointestinal pH, gastric emptying, intestinal transport). Reviewing the literature, we found that there were few studies on the pharmacokinetics and bioequivalence of generic ibuprofen sustained-release capsules in fasting and fed conditions. Koenigsknecht J's study of immediate release ibuprofen, the T_{max} (4.694±1.994 hr vs 2.980 ±1.613 hr) was delayed, and the AUC_{0-24} and C_{max} (229.452±76.879 μg•hr/mL vs 241.888±88.907μg•hr/mL, 43.051 ±14.312 μg/mL vs 58.247±18.400 μg/mL) were lower in fed vs fasting subjects.[19] This is slightly different from our conclusion. Therefore, the differences in PK parameters obtained may be due to differences in subjects, management during the trial, sample size, sample instrumentation, or other unknown factors.

There were still some study limitations: ibuprofen was mainly used in patients, but the subjects were all healthy volunteers in the present study. In terms of the effects of food on the pharmacokinetics and bioequivalence of ibuprofen, we only studied high-fat diets.

Conclusions

In both the fasting and fed study, they were demonstrated the bioequivalence between the T formulation and R formulation in Chinese healthy volunteers. Clinical studies revealed that ibuprofen sustained-release capsules were well tolerated in healthy Chinese volunteers.

Data Sharing Statement

The datasets generated from the current study are available from the corresponding author, Ying Wang.

Additional Contributions

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Disclosure

All authors declare that there are no potential conflicts of interest.

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