This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1078-6791. To subscribe, visit alternative-therapies.com

ORIGINAL RESEARCH

Bioequivalence of Levocetirizine Hydrochloride Granules (Kangzhitai) in Healthy Subjects

Hong Xiang, MM; Guoping Yang, PhD; Hongyi Tan, MM

ABSTRACT

Objective • Levocetirizine hydrochloride is the *R*-enantiomer of cetirizine, which is a new-generation histamine H1 receptor antagonist with high safety, selectivity, and affinity. As a high-efficiency non-sedating antihistamine, levocetirizine hydrochloride has been widely used in the clinical treatment of skin, respiratory, and eye allergies. However, the bioavailability of levocetirizine hydrochloride granules remains to be determined. The study examined the relative bioavailability of the test drug (levocetirizine hydrochloride granules (Kangzhitai®)) and determined whether Kangzhitai® was bioequivalent to the reference drug (levocetirizine (Xyzal®)) in healthy individuals.

Methods • Twenty eligible healthy male subjects were randomly divided into two groups. Group one received 5 mg of Kangzhitai®, followed by a 10-day wash-out period and 5 mg of Xyzal® on day 11. Group two received the same doses but in a reverse sequence. The subjects fasted for 12 h, and blood samples were collected before (blank) and after administration. The plasma concentration of Kangzhitai® was determined by HPLC-MS-MS. Pharmacokinetic parameters were analyzed using DAS 2.0 software.

Results • The main pharmacokinetic parameters C_{max}, T_{max}, $T_{1/2}$, AUC_{0-48}, and $AUC_{0-\infty}$ of the Xyzal® and Kangzhitai® groups were as follows: (218.4 ± 46.4) μg/L vs. (213.6 ± 39.3) μg/L, (0.73 ± 0.32)/h vs. (0.75±0.3)/h, (9.2 ± 2.0) h vs. (8.9 ± 2.7) h, (1594.0 ± 337.2) μg·h/L vs. (1652.6 ± 383.5) μg·h/L, and (1683.2 ± 338.5) μg·h/L vs. (1753.7 ± 445.4) μg·h/L. The two-one-sided *t* tests of C_{max}, AUC_{0-48}, and $AUC_{0-\infty}$ showed that t_h and t_1 were both higher than one-sided $t_{0.05}$. The 90% confidence intervals (CI) for AUC_{0-48} and $AUC_{0-\infty}$ of Kangzhitai® did not exceed 80%-125% of AUC_{0-48} and $AUC_{0-\infty}$ of Xyzal®. The 90% CI for the C_{max} of Kangzhitai® did not exceed 70%-143% of the C_{max} of Xyzal®. There was no significant difference in T_{max} between the two drugs. The relative bioavailability (F, assessed by AUC_{0-48}) of Kangzhitai® vs. Xyzal® was 104.4±18.5%. No adverse events occurred during the drug administration.

Conclusion • The results indicated that there was no significant difference in absorption between Kangzhitai® and Xyzal®, which confirmed the bioequivalence of the two drugs. (*Altern Ther Health Med.* 2023;29(4):205-209).

Hong Xiang, MM, Technologist-In-Charge, Center for Experimental Medicine; **Guoping Yang**, PhD, Center for Experimental Medicine; **Hongyi Tan**, MM, Technologist-In-Charge, Center of Clinical Pharmacology, The Third Xiangya Hospital, Central South University, Changsha, China.

Corresponding author: Hongyi Tan, MM
E-mail: thy_2012@126.com

INTRODUCTION

Levocetirizine hydrochloride is the *R*-enantiomer of cetirizine,[1] which is a new-generation histamine H_1 receptor antagonist with high safety, selectivity, and affinity. As a high-efficiency non-sedating antihistamine, levocetirizine hydrochloride has been widely used in the clinical treatment of skin, respiratory, and eye allergies.[2,3] Levocetirizine hydrochloride can also be used to treat cold symptoms.[2,3] It can selectively, competitively, and irreversibly bind to G-protein-coupled receptors, thus inhibiting the release of several inflammatory mediators related to allergic reactions.[4] As the *R*-enantiomer of cetirizine, levocetirizine hydrochloride has a high bioavailability and a low hepatic clearance rate. The plasma protein binding rate of levocetirizine hydrochloride reaches up to 95%. In a word, levocetirizine hydrochloride has multiple benefits, such as low tissue affinity, low cardiotoxicity, and low sedation.[5,6] Levocetirizine hydrochloride is not metabolized by the liver and has little reaction with other drugs.[7] It is also considered one of the safest antihistamines for children because of its low ability to

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1078-6791. To subscribe, visit alternative-therapies.com

penetrate the blood-brain barrier and therefore has a lower risk of affecting children's cognition.[8] Levocetirizine hydrochloride granules (Kangzhitai®, by Kangzhi Pharmaceutical Co. Ltd.) are the only granular type available. The current study evaluated the bioequivalence between the levocetirizine tablets (Xyzal®, by UCB Farchim SA, Switzerland) and levocetirizine hydrochloride granules (Kangzhitai®) for clinical use.

METHODS

Drug, reagents, and equipment

The test drug was levocetirizine hydrochloride granules (Kangzhitai®, by Kangzhi Pharmaceutical Co. Ltd., China; strength 2.5 mg; lot number: 2100704; sample volume: 99.1%, valid before June 2023) at an oral dose of 5 mg. The reference drug was levocetirizine tablets (Xyzal®, UCB Farchim SA, Switzerland; also called Xyzal® 319447X; strength 5 mg; lot number: 319447X; sample volume: 97.2%, valid before June 2023) at an oral dose of 5 mg.

The experimental reagents were acetonitrile (chromatographic-grade, Tedia Company Inc., USA), formic acid (chromatographic-grade, Tianjin Kermel Chemical Reagent Co. Ltd., Tianjin, China), pure water (self-prepared ultra-pure deionized water), and blank human plasma (Changsha Blood Center).

The experimental equipment was as follows: Agilent 6410 Triple Quadrupole LC/MS (Agilent, Santa Clara, CA, USA), AB135-S 0.01 mg balance (Mettler-Toledo Instruments (Shanghai) Co. Ltd., Shanghai, China), BS 224 S 0.1 mg Balance (Sartorius, Shanghai, China), TGL16M tabletop high-speed refrigerated centrifuge (Changsha Yingtai Instrument Co. Ltd., Changsha, China), and XW-80A Vortex Mixer (Shanghai Huxi Analysis Instrument Factory Co. Ltd., Shanghai, China).

Subjects

Twenty eligible male subjects came from The Third Xiangya Hospital of Central South University. The weight of the subjects was 50-70 kg and the height was 162-178 cm. Inclusion criteria: (1) males; (2) no drinking or smoking habits; (3) no clinical abnormalities identified by personal history, physical examination, and laboratory tests; (4) no history of drug allergy or drug dependence; (5) no history of mental illnesses and other chronic conditions; (6) not taking any medications in two weeks before the study. The study protocol was approved by the ethics committee of The Third Xiangya Hospital of Central South University. All subjects signed the written informed consent.

Dosing regimens and blood sample collection

An open-label, randomized, double-crossover, two-phase, single-dose, multi-center study was conducted. The wash-out period between the two phases lasted for ten days. Twenty subjects were randomly divided into two groups, with ten subjects in each group. Fasting 12 h before the start of the study but drinking water was allowed. However, water was also prohibited within 1 h before administration. Group one received 5 mg of Kangzhitai®, followed by a 10-day wash-out period, and 5 mg of Xyzal® on day 11. Group two received the same doses but in a reverse sequence. Before each administration, the subjects fasted for 12 h. Blank blood samples were collected in the morning before the administration. The blood was drawn from the elbow vein at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 h post-administration, respectively. The blood samples were immediately centrifuged. The plasma was separated and stored at -20°C before the detection. The plasma concentration of Kangzhitai® was determined at different time points post-administration by HPLC-MS-MS.[9] Pharmacokinetic parameters were calculated and analyzed statistically using DAS 2.0 software. The subjects were hospitalized for observation one day before administration and for 48 h after administration. All subjects were given identical low-calorie diets during the study. Qualified clinicians were responsible for on-site monitoring. The subjects were observed and inquired about any reactions after administration, and adverse events were recorded in real-time.

Determination and sample processing

Chromatographic conditions: chromatographic column: Thermo (2.1×150 mm, 5 μm, Thermo, Waltham, MA, USA); protection column core: GeminiC_{18} (4×3.0 mm, Phenomenex, St. Louis, MO, USA); mobile phase: acetonitrile-0.1% formic acid aqueous solution (55:45, v/v); flow rate: 0.2 mL·min^{-1}; column temperature: 30°C; sample size: 5 μL.

Mass spectrometry conditions: Electrospray ionization (ESI) was performed in the positive ion multiple reaction monitoring (MRM) mode. For levocetirizine, fragment ion with m/z389.2→m/z201.1 was observed at 115 V fragment voltage and 116 eV collision energy. For telmisartan as the internal standard, fragment ion with m/z515.3→m/z497.2 was observed at 135 V fragment voltage and 35 eV collision energy. The scan speed was 0.4 ms/cycle. The ion source parameters were set up as follows: Gas Temp, 325°C; Gas Flow, 8 L·min^{-1}; Nebulizer, 30 psi; Capillary, 4000 V.

Sample processing: 500 μL plasma sample and 50 μL acetonitrile aqueous solution were added to a 10 mL centrifuge tube. Then the internal standard working solution (50 μL, 332.0 μg·L^{-1}) was added precisely, and the mixture was vortexed for 10 s. Next, 500 μL trisodium citrate (pH = 6.0) was added and the mixture was vortexed for 30 s. Then 4 ml of ethyl acetate: dichloromethane (v:v = 4:1) solution was added and mixed by vortexing for 2 min. The mixture was centrifuged at 3,000 rpm for 5 min, and 3 mL of the supernatant was removed. The sample was blow-dried with the nitrogen gas at 45°C and re-dissolved with 200 μL the acetonitrile-water solution (v:v = 1:1). After the above process, 5 μL of the sample was loaded for analysis.

Methodological validation and evaluation[10]

Exclusiveness evaluation. The retention time of the test drug and the internal standard was 2.6 min and 2.3 min,

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1078-6791. To subscribe, visit alternative-therapies.com

respectively. Six blank substrates from different donors were determined. Six batches of blank samples prepared with substrates from different donors were used. The analyte and internal standard met the requirements.

Standard curve. The plasma samples were processed as described in the above methods. Sample solutions of different concentrations were prepared: 493.6, 246.8, 123.4, 61.70, 30.85, 15.425, 7.712, and 3.8560 μg/L. Linear regression was performed for the peak area ratio of the test drug to the internal standard. The standard curve was fitted using the least-squares method, and the weighting factor was $1/x^2$. The equation of the standard curve was $y = 0.0160X+0.00078058$. The linear range was 3.856-493.6 μg/L, r^2 was 0.9956, and the lower limit of quantitation was 3.856 μg/L.

Precision and accuracy. Standard plasma samples of three concentrations (7.712, 61.70, and 493.6 $\mu g \cdot L^{-1}$) were prepared. Six parallel samples were prepared for each concentration. Three batches were measured consecutively with three working days. The determined concentrations within and across the batches were 95.6-107.1% and 100.4-102.3% of the specified concentrations, respectively. The coefficients of variation for intra-batch and inter-batch precision were 2.8-7.2% and 4.4-7.5%, respectively, which satisfied the requirements of biosample test methods specified in relevant regulations and guidelines.

Yield rate. Four parallel samples were prepared for low, moderate and high mass concentrations, respectively. The yield rates for the three concentrations were estimated to be 69.5%, 67.0%, and 72.2%. The corresponding RSD was 4.3%, 4.8%, and 4.9%, respectively. The yield rate of the test drug was reproducible and not significantly dependent on the concentration.

Substrate effect. Test drug solutions of three concentrations (77.12 μg/L, 617.0 μg/L, and 4936 μg/L) were prepared with five parallels for each concentration. The substrate effect normalized by the internal standard was 96.1%, 96.5%, and 90.1%, respectively. The corresponding RSD was 6.7%, 8.4%, and 4.3%, respectively, all of which were below 15%. The above results satisfied the requirements of the biosample testing method specified in relevant regulations and guidelines.

Stability. The plasma samples were stored at room temperature for 20 h, at -20°C for 30 days, and at -20°C for at least 24 h, and subjected to three freeze-thaw cycles. The results indicated favorable stability.

Evaluation criteria

Criteria for bioequivalence evaluation. The bioequivalence was analyzed based on the area under the curve (AUC) for the plot of plasma concentration of a drug versus time after drug administration, i.e., $AUC_{0-\infty}$ and AUC_{0-t}, the maximum concentration of drug in plasma (C_{max}), and the time taken by the drug to reach the C_{max} value (T_{max}) after a single dose. The 90% CI for the ratios of the log-transformed $AUC_{0-\infty}$ and AUC_{0-t} between the two drugs were included in the bioequivalence interval of 80%-125%. The 90% CI for the ratio of the log-transformed C_{max} between the two drugs was contained in the bioequivalence interval of 70%-143%. There was no significant difference in T_{max} between the two drugs according to the nonparametric test. Thus, the test drug was considered to be bioequivalent to the reference drug.

Criteria for safety evaluation. The subjects were hospitalized for observation one day before the administration and within 48 h post-administration. They were forbidden to drink any alcoholic or caffeinated beverages or undertake vigorous physical exercise. Qualified clinicians were assigned for on-site monitoring during the study. The subjects were observed and inquired about any reactions after dosing, and adverse events were recorded in real-time.

Statistical analysis

Values of the main pharmacokinetic parameters were analyzed by logarithmic transformation and multivariate analysis of variance. Next, the bioequivalence between the two drugs was assessed using two one-sided *t* tests (at a 5% significance level), and 90% CI was calculated. $P < .05$ indicated significant difference.

RESULTS

Baseline data of patients

All patients received physical examinations before the study. The indicators including body parameters (height, weight), vital signs (heart rate, blood pressure), liver function (alanine transaminase (ALT), aspartate transaminase (AST), albumin (ALB), and total bilirubin (TBIL)), kidney function (serum creatinine (Cr), blood urea nitrogen (BUN) and uric acid (UA)), and routine blood test (red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), and hemoglobin (Hb)) were measured. The indicators determined above were normal in all subjects. The detection results are listed in Table 1.

Table 1. Baseline Data of the Subjects

Indicator	Result
Age (years)	21.85 ± 2.45
Height (cm)	171.3 ± 4.19
Body weight (kg)	60.15 ± 5.10
ALT (U/L)	14.35 ± 10.41
ALB (g/L)	47.82 ± 1.80
TBIL (μmol/L)	15.01 ± 3.98
AST (U/L)	20.40 ± 5.12
BUN (mmol/L)	3.78 ± 1.07
Cr (mmol/L)	69.05 ± 9.40
UA (μmol/L)	336.45 ± 61.38
WBC ($\times 10^9$/L)	6.51 ± 1.01
RBC ($\times 10^{12}$/L)	5.54 ± 0.31
Hb (g/L)	153.10 ± 8.98
PLT ($\times 10^9$/L)	196.45 ± 44.93

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1078-6791. To subscribe, visit alternative-therapies.com

Figure 1. Plasma Drug Concentration Curves at Different Time Points After the Administration of the Reference Drug and the Test Drug

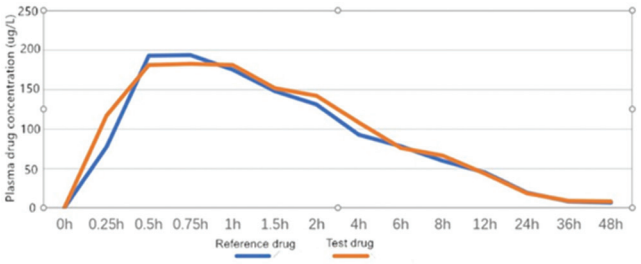

Table 2. Average Plasma Concentration-Time Curve After the Administration of the Reference Drug and the Test Drug (μg/L)

Time Post-Administration (h)	Reference Drug	Test Drug
0	0	0
0.25	77.6	116.9
0.5	193.1	181.4
0.75	193.5	182.4
1	175	181.3
1.5	147.7	151.4
2	131.3	142.3
4	92.5	108.3
6	78.3	75.8
8	59.5	66.3
12	45.1	43.7
24	19.3	18.3
36	7.7	9
48	6.8	7.9

Table 3. Comparison of Pharmacokinetic Parameters Between the Test Drug and the Reference Drug

Indicator	Reference Drug	Test Drug
C_{max} (μg/L)	218.4 ± 46.4	213.6 ± 39.3
T_{max} (h)	0.73 ± 0.32	0.75 ± 0.31
$T_{1/2}$ (h)	9.2 ± 2.0	8.9 ± 2.7
AUC_{0-48} (μg/L)	1594.0 ± 337.2	1652.6 ± 383.5
$AUC_{0-\infty}$ (μg/L)	1683.2 ± 338.5	1753.7 ± 445.4
$AUC_{0-48}/AUC_{0-\infty}$	0.95 ± 0.02	0.95 ± 0.05

Plasma drug concentration-time curve and main pharmacokinetic parameters

The average plasma drug concentration-time curves of the two drugs in 20 subjects are shown in Figure 1 and Table 2. The values of the main pharmacokinetic parameters are shown in Table 3. The two-one-sided *t* tests of C_{max}, AUC_{0-48}, and $AUC_{0-\infty}$ showed that t_h and t_1 were both higher than one-sided $t_{0.05}$. The 90% CI for AUC_{0-48} and $AUC_{0-\infty}$ of the test drug did not exceed 80%-125% of AUC_{0-48} and $AUC_{0-\infty}$ of the reference drug. The 90% CI for the C_{max} of the test drug did not exceed 70%-143% of the C_{max} of the reference listed drug. T_{max} values of the two drugs were analyzed by a nonparametric test, which did not reveal any significant difference between the two drugs ($P>.05$). The above data indicated no significant difference between the absorption of the test drug and the reference drug in healthy subjects. The relative bioavailability of the test drug vs. the reference drug was 104.4 ± 18.5%.

Adverse events

The subjects were observed during the study period by GCP-trained clinicians and experienced nurses. No adverse events were recorded.

DISCUSSION

Levocetirizine hydrochloride is the *R*-enantiomer of cetirizine and is the active component of Xyzal® tablets. Its affinity for the H_1 receptors is twice that of cetirizine. Levocetirizine hydrochloride is commonly used to treat allergies, including allergic rhinitis, pruritus, and urticaria.[11] Levocetirizine hydrochloride has many advantages, including infrequent adverse reactions, rapid onset of action, high performance, lasting efficacy, and no cardiotoxicity. Because of these advantages, levocetirizine hydrochloride has been widely used in clinical practice. The commercial formulations of levocetirizine hydrochloride in China include tablets, capsules, dispersible tablets, and oral solutions.[12] The granular formulation is the most widely used in children.[13] It has several advantages over liquid preparations, including high stability, portability, good taste, high hygroscopicity, and suitability for a wider range of applications.[14] The formulation significantly affects the time taken by the drug to reach its peak concentration. The test drug was a pellet dosage form with a faster dissolution rate in the present study. The preparation can facilitate the decomposition and absorption of drugs in clinical use. The reference drug was a tablet formulation, which was not easily absorbed before disintegrating. In this study, the time for the plasma concentration of several subjects to reach the peak was shortened compared with the referenced drug. Pellet preparations are superior to tablet preparations in terms of dissolution and absorption.

Children are susceptible to allergic diseases and require higher adaptability to drugs.[15] Pellet formulation dissolves faster, is tasteless and odorless after dissolution, and is easier to take than other formulations for children. It is also more suitable for those with dysphagia than tablets. The present study aimed to investigate the effectiveness and safety of levocetirizine hydrochloride granules in children.

The pharmacokinetic parameters, safety, and bioequivalence of Kangzhitai® granules and Xyzal® tablets were assessed. According to the relevant guiding principles,[16] the bioequivalence study helps to assess the consistency of behavior *in vivo* of different formulations containing the same active ingredient. The bioequivalence study is often used to determine the eligibility of new products to replace existing products. C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of the test drug were used as bioequivalence indicators in the present study. The bioequivalence evaluation criteria were as follows: the 90% CI of the geometric means ratio of AUC_{0-t} and $AUC_{0-\infty}$ between the two drugs was contained

This article is protected by copyright. To share or copy this article, please visit copyright.com. Use ISSN#1078-6791. To subscribe, visit alternative-therapies.com

within the interval of 80.00%-125.00%. The 90% CI of the C_{max} of the test drug did not exceed 70%-143% of the C_{max} of the reference drug. C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of the reference drug further supported the comparability of the clinical efficacy of the two drugs. The statistical analysis proved the bioequivalence of the two drugs. Thus, the effectiveness of Kangzhitai® and Xyzal® was comparable.

No adverse events were observed in any of the 20 healthy subjects recruited in the present study. According to one study,[4] 32 adverse events occurred in 20 healthy subjects in the Xyzal® group, and seven of which might be related to the drug. Therefore, the safety of Kangzhitai® was better.

CONCLUSION

In conclusion, the absorption rate and degree of Kangzhitai® and Xyzal® were similar, showing bioequivalence. Besides, the safety of Kangzhitai® granules was favorable in healthy Chinese subjects, so it can be used for the clinical treatment of pediatric patients.

AUTHOR DISCLOSURE STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this article.

ACKNOWLEDGEMENT

The authors would like to acknowledge their contributions as follows: Hong Xiang: study design; acquisition, analysis, and interpretation of data; drafting of the manuscript; Guoping Yang: analysis and interpretation of data; drafting and revision of the manuscript; Hongyi Tan: study design, interpretation of data; drafting and revision of the manuscript.

FUNDING

This work was supported by the Tianjini Health Technology Project (TJWJ2021MS024).

REFERENCES

1. Levocetirizine. In: Drugs and Lactation Database (LactMed®). *Bethesda (MD): National Institute of Child Health and Human Development*. https://www.ncbi.nlm.nih.gov/books/NBK501922/?report=reader#!po=16.6667. Published 2006.
2. Albash R, El-Dahmy RM, Hamed MIA, et al. Repurposing levocetirizine hydrochloride loaded into cationic ceramide/phospholipid composite (CCPCs) for management of alopecia: central composite design optimization, *in- silico* and *in-vivo* studies. *Drug Deliv*. 2022;29(1):2784-2795. doi:10.1080/10717544.2022.2108939
3. Ino H, Shiramoto M, Eto T, et al. Levocetirizine oral disintegrating tablet: a randomized open-label crossover bioequivalence study in healthy japanese volunteers. *Clin Pharmacol Drug Dev*. 2020;9(7):805-812. doi:10.1002/cpdd.791
4. Czapiewska M, Ciosek-skibińska P, Lenik J, et al. Testing suitability of sweeteners in masking the taste of levocetirizine dihydrochloride using the electronic tongue method. *Farmacia*. 2022;70(5):798-806. doi:10.31925/farmacia.2022.5.4
5. Kanei A, Asano K, Kanai K, Furuta A, Sasaki K, Suzaki H. Inhibitory action of levocetirizine on the production of eosinophil chemoattractants RANTES and eotaxin *In vitro* and *In vivo. in Vivo*. 2014;28(4):657-666.
6. Wen S, Wei J, Bao J, et al. Effect of levocetirizine hydrochloride on the growth of human dermal papilla cells: a preliminary study. *Ann Palliat Med*. 2020;9(2):308-317. doi:10.21037/apm.2020.01.15
7. Yurtdaş Kirimlioğlu G, Öztürk AA. Levocetirizine Dihydrochloride-Loaded Chitosan Nanoparticles: Formulation and *In Vitro* Evaluation. *Turk J Pharm Sci*. 2020;17(1):27-35. doi:10.4274/tjps.galenos.2018.34392
8. Wang XP, He GD, Zheng JZ, et al. Determination of teicoplanin in the patients' plasma by high-performance liquid chromatography-mass spectrometry. *Zhongguo Yiyuan Yaoxue Zazhi*. 2020;40(15):1616-1621. doi:10.13286/j.1001-5213.2020.15.04
9. Chinese Pharmacopoeia Commission. Chinese Pharmacopoeia Volume IV. *China Medical Science Press*. https://www.car.chula.ac.th/display7.php?bib=b2259958. Published 2015.
10. Wang WJ, Zeng SP, Jiang T, et al. Qualitative analysis of an unknown impurity in levocetirizine hydrochloride tablets by LC-MS. *Yaowu Fenxi Zazhi*. 2017;37(2):252-264.
11. Charoo NA, Abdallah DB, Ahmed DT, et al. Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Levocetirizine dihydrochloride. *J Pharm Sci*. 2022; S0022-3549(22):00584-00586. doi:10.1016/j.xphs.2022.12.021
12. Ren YM, Chen TY, Wang MY. Efficacy observation of syndrome differentiation treatment using free-frying Chinese medicine granules in upper airway cough syndrome. *Lishizhen Medicine and Materia Medica Research*. 2021;32:374-376.
13. Li N, Jiang JX, Wu YR. Research progress and prospect analysis of common dosage forms of pediatric drugs in China. *Yaowu Pingjia Yanjiu*. 2022;45:193-200.
14. Zhang Y, Lu YZ, Lin CG. Efficacy of levocetirizine oral solution combined with thymopentin in the treatment of chronic spontaneous urticaria. *J Dermatol Venereol*. 2020;42(3):435-437.
15. National Medical Products Administration. *Technical Guidelines for the Bioavailability and Bioequivalence Studies of Chemical and Pharmaceutical Products in Humans*. Published; 2005.