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A Bioequivalence Study of Benidipine Tablets Based on the Pharmacokinetics of Benidipine Enantiomers in Healthy Male Subjects Under Fed Conditions

Gökçe Demiray[1],* Nesrin Yüzüak Okatan[1], Emel Doğan Kurtoğlu[1], Merve G Sarıkaya[1], Berrak Güney[1], Onursal Sağlam[1], Muradiye Nacak[2], Mustafa Köktürk[3], Ayten Ellialtı[3] & Dilara Ulaş[3]

[1]Novagenix Bioanalytical Drug R&D Centre, Ankara, Türkiye
[2]FARMAGEN-Good Clinical Practice Center, Gaziantep, Türkiye
[3]Biofarma Ilaç San ve Tic. AS, Istanbul, Türkiye

***Corresponding author:** Gökçe Demiray, Novagenix Bioanalytical Drug R&D Centre, Ankara, Türkiye.

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Abstract

This study aimed to evaluate the bioequivalence of two benidipine formulations by analyzing the pharmacokinetics of individual benidipine isomers ((−)-alpha benidipine and (+)-alpha benidipine) in healthy male human volunteers under fed conditions. Plasma concentrations of benidipine isomers were quantified using a specific and sensitive liquid chromatography–tandem mass spectrometry (LC–MS/MS) validated method. Acquisition was performed in multiple reaction monitoring (MRM) mode, by monitoring the transitions: m/z 506.3>174.2 for (−)-alpha benidipine and (+)-alpha benidipine and m/z 511.2>179.2 for (+)-alpha benidipine d5 and (−)-alpha benidipine d5 511.2>179.3 as IS. The method was validated over the concentration range of 30–10000 ng/ml for (−)-alpha benidipine and 50–10000 ng/ml for (+)-alpha benidipine in human plasma. Based on the conducted bioequivalence study, it was concluded that the benidipine hydrochloride test and reference formulations are bioequivalent under fed conditions

Keywords: Benidipine Enantiomers, Bioequivalence, Lc-Ms/Ms, Pharmacokinetics.

Introduction

The dihydropyridine calcium antagonist, benidipine hydrochloride is a racemate, containing the (−)-alpha and (+)-alpha isomers. Benidipine is chemically named as 3 - [(3RS)-1 -Benzylpiperidin-3-yl] 5-methyl (4RS)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylatemonohydrochloride. Benidipine is an orally active drug for the treatment of hypertension and angina pectoris. Benidipine is a potent calcium channel blocker characterized by marked antihypertensive activity and a prolonged duration of action. In vitro studies have demonstrated that its effect on vascular smooth muscle closely resembles that of nifedipine, albeit with a comparatively lower negative inotropic potency.

It exerts its action through competitive inhibition of the nitrendipine receptor, with its antagonistic effect persisting even after washout. Preclinical studies have shown that the pharmacokinetic profiles and pharmacodynamic responses of benidipine stereoisomers differ significantly [1–4]. Because the hepatic intrinsic clearance rate for (−)-alpha benidipine is greater than that for (+)-alpha benidipine, plasma concentrations of (+)-alpha benidipine are greater than those of (−)-alpha benidipine following the administration of a benidipine racemate to rats [5]. In addition, the hypotensive effect of (+)-alpha benidipine was between 30-and 100-fold the effect of (−)-alpha benidipine in spontaneously hypertensive rats [1]. These findings imply that, following oral administration of the racemic mixture of benidipine, competitive metabolic processes among its stereoisomers lead to enantiomer-specific pharmacokinetic profiles. Although multiple pharmacokinetics studies have been conducted by measuring plasma concentrations of benidipine, data on the enantioselective pharmacokinetics of its stereoisomers in humans in a large population remain unpublished [6–9].

Following a single oral administration of 8 mg benidipine tablets to healthy volunteers, mean peak plasma concentration was

3.89 ng/ml after 0.8 hours and AUC was 6.70 ng.h/ml. Plasma protein binding of benidipine is approximately 98%. In healthy volunteers receiving a single oral dose of 8 mg benidipine, 35% of the dose is excreted unchanged in the urine and up to 36% in the faeces [10]. In a pharmacokinetic study involving ten healty volunteers who received a single oral dose of 8mg benidipine, a mixture of 4mg of (-)- and (+)-alpha isomer, under fasting conditions, Cmax values were found 0.75 ng/ml and 1.47 ng/ml for (-)-alpha and (+)-alpha isomers respectively. The mean time to reach peak plasma concentrations was 0.85 h for (-)-alpha isomer and 0.71 h for (+)-alpha isomers [11].

In healthy volunteers, oral administration of benidipine (8 mg) taken 30 minutes after a meal resulted in slower absorption but higher plasma concentrations compared to when the drug was taken on an empty stomach [12]. Consequently, co-administration of the drug with meals is recommended to optimize its absorption and plasma levels.

In human blood plasma, from metabolites detected in the urine and the research on metabolism in animals, metabolic reaction in humans generally is considered to be elimination of benzyl group in the 3rd level side chain (N-dealkylation), hydrolysis of 3rd level 1-benzyl-3-piperidyl ester and 5th level methyl ester, oxidation of dihydropyridine ring, and oxidation of 2nd level methyl group.

Bioequivalence assessment is necessary for orally administered generic drugs, as stipulated by certain health authorities [13,14]. According to regulatory guidelines, achiral bioanalytical methods are generally acceptable; however, chiral analysis becomes necessary when enantiomers exhibit distinct pharmacokinetic or pharmacodynamic behaviors, or when variations in absorption affect their AUC ratio. Enantiomer-specific quantification is also advised if these conditions are present or cannot be ruled out. The objective of the present research is to analyze and compare the pharmacokinetic profiles of a generic formulation and the reference product of which efficacy and safety have been established in clinical trials and to confirm that the products are bioequivalant with respect to the rate and extent of absorption of the stereoisomers of benidipine under fed conditions in healthy male subjects.

Subjects and Methods

Ethical Statement

The clinical trial was performed at FARMAGEN-Good Clinical Practice Center, Gaziantep, Türkiye, under the regulatory framework of the Turkish Ministry of Health, in conformity with the Declaration of Helsinki and GCP guidelines [15]. The protocol and informed consent form were approved by an independent ethics committee (Erciyes University, Bioavailability- Bioequivalence Research Ethics Commitee, Kayseri, Türkiye, Approval Date: 07.06.2023) and Turkish Medicines and Medical Devices Agency (Approval Date: 07.07.2023). All participants provided voluntary, written informed consent.

Study Population and Study Design

All subjects were healthy adult males aged between 18 and 55 years, with body weight within the normal range as defined by body mass index (BMI). Individuals with a known history of drug hypersensitivity—particularly to the active or inactive components of benidipine formulations—or intolerance to any form of sugar were excluded. Additionally, subjects with a history or clinical evidence of any significant cardiovascular, renal, hepatic, pulmonary, metabolic, endocrine, hematological, gastrointestinal, neurological, psychiatric, or other systemic disorders were not eligible for participation. Clear inclusion and exclusion criteria were defined, along with the conditions for subject withdrawal. All eligible participants voluntarily signed a written informed consent form after being fully informed about the study, and were made aware of their right to withdraw at any point without the need to provide justification. The study was conducted as a single centre, open-label, randomised, single oral dose, crossover, two-sequence, two-period study in 48 healthy, Caucasian, adult, male, subjects under fed conditions. The study was conducted at FARMAGEN-Good Clinical Practice Center, Gaziantep, Türkiye. The standard laboratory examinations in blood and urine were done consistent with the study protocol and the volunteers were checked for presence of HBsAg, HCV-Ab and HIV-Ab in serum. They were requested to provide a urine sample for a drug screen which include “amphetamines, cannabinoids, benzodiazepines, cocaine, opioids and barbiturates” and an alcohol breath test on entry examinations. All laboratory tests were carried out in a certified local laboratory. A total of 48 subjects have been randomised and all subjects completed the clinical study. Under fed conditions, subjects fasted for 10 hours prior to consuming a high-fat breakfast. Water intake was restricted from 1 hour before until 1 hour after dosing—except during drug administration—and subjects remained in a fasted state for 4 hours post-dose. Immediately after pre-dose sampling,1 tablet of the test drug (containing 8 mg benidipine hydrochloride) or 1 tablet of the reference drug (8 mg benidipine hydrochloride), were taken by the subjects with 240 mL of water. After the washout period (at least 3 days); in Period II, the subjects were administered the other drug they did not take in the Period I.

Investigational Medicinal Products

The test drug used was Biodipin 8 mg Film Kaplı Tablet, Biofarma Ilaç , Türkiye (Batch No: 22-XB04-FT-8-P02; Expiry Date:03.2024); the reference drug used was CONIEL® 8 mg Tablet, Kyowa Kirin Co. Ltd. - Japan (Batch No: 703ABH; Expiry Date: 08.2025).

Blood Sampling and Study Assessment

The samples were drawn by a short intravenous catheter predose and 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00 hours post-dose in each clinical study period, and they were collected into polypropylene tubes using K2 EDTA as anti-coagulating agent. Volunteers were hospitalized at FARMAGEN-Good Clinical Practice Center. An evening meal was provided at hospitalization days (total caloric value of approximately 1200 kcal). In the study a high-fat, high-caloric breakfast (total of approximately 900 to 1000 kcal) was served before dosing of each period. The standardised lunch was served 4 hours and the standardised dinner was served 10 hours post dosing in each period.

Following blood collection, the samples were promptly refrigerated at approximately 2–8°C and stored under these conditions for no longer than 20 minutes. Subsequently, the samples were centrifuged at 1500 × g for 10 minutes at 4°C. The resulting

plasma was carefully separated and aliquoted into two 3.5 mL transparent polypropylene tubes per sample. All plasma aliquots were immediately flash-frozen and the flash frozen samples (aliquoted plasma samples) were transferred to a deep-freezer and stored at -70°C until they were transported to the bioanalytical center.

Determination of Plasma Concentrations and Bioanalytical Methods

The bioanalytical phase of the study has been run at Novagenix Bioanalytical R&D Center, Ankara, Türkiye. In order to avoid bias, the analytical studies were operated as analytically blinded. The validated LC-MS/MS method according to the guidelines was used to determine benidipine enantiomers in plasma samples generated during the clinical phase of this study [16, 17].

(+)-alpha-Benidipine HCl and (-)-alpha-Benidipine HCl, (+)-alpha-Benidipine D5 HCl (Internal Standard) and (-)-alpha-Benidipine D5 HCl (Internal Standard) were provided by BioOrganics&Applied Materials Pvt. Ltd, India. Methanol, ammonium formate, diethyl ether was purchased from Merck, ammonium acetate was purchased from Sigma-Aldrich, blank human plasma (K2EDTA) was sourced from Bioivt (UK) and Gaziantep University Farmagen GCP Centre, (Türkiye).

Benidipine enantiomers were extracted from plasma by liquid liquid extraction using diethyl ether. The analytes were separated on a chiral Supelco Astec CHIROBIOTIC® V column (15cmx-4.6mm, 5 µm) with isocratic mobile phase of methanol containing 2mM ammonium formate and 2 mM ammonium acetate together. LC-MS/MS analysis was carried out using Shimadzu Liquid Chromatograph Mass Spectrometer LCMS-8060 System, controlled by LabSolutions Software. Acquisition was performed in multiple reaction monitoring (MRM) mode, by monitoring the transitions: m/z 506.3>174.2 for (−)-alpha benidipine and (+)-alpha benidipine and m/z 511.2>179.2 for (+)-alpha benidipine d5 and (−)-alpha benidipine d5 511.2>179.3 as IS.

Validation of the analytical method was successfully achieved across all required parameters, including selectivity, linearity, precision, accuracy, dilution integrity, matrix effects (haemolysis and lipemia), drug–drug interactions, carry-over, recovery, reinjection reproducibility, and batch size. The method was validated in the range of 50-10000 pg/mL for (+)-alpha-benidipine and 30-10000 pg/mL for (-)-alpha-benidipine.

Pharmacokinetic and Statistical Analyses

According to in-house study, the intra-subject variability of maximum plasma concentration (Cmax) for benidipine was estimated approximately 33%. In order to demonstrate bioequivalence with a power of 80% and a test/reference parameter ratio of 0.95 for a 2x2 crossover design, 48 subjects were enrolled into the study.

Cmax and area under the curve from time 0 to the last measurable concentration (AUC0-tlast) were considered as the primary target variables; area under the curve from time 0 to the infinite time (AUC0-∞), time to reach the peak concentration (tmax), terminal half life (t½), terminal disposition rate constant (λz) and mean residence time (MRT) were declared as the secondary target variables in this bioequivalence study.

Cmax and tmax for benidipine enantiomers were obtained directly by plasma concentration-time curves. AUC0-tlast was calculated using the linear-log trapezoidal rule. AUC0-∞was calculated by summing AUC0-tlast and extrapolated area. The latter was determined by dividing the last measuredconcentration by λz which was estimated byregression of the terminal log-linear plasma concentration time points.

Cmax and AUC0-tlast were tested for statistically significant differences by means of the Analysis of Variance (ANOVA) test procedure after logarithmic transformation (ln). The effects of ANOVA were treatment, period, sequence and subject within the sequence and tested at 5% level of significance.

In the assessment of bioequivalence of benidipine enantiomers [(+)-alpha-Benidipine hydrochloride and (-)-alpha-Benidipine hydrochloride], confidence intervals approach was used. The two one-sided hypothesis at the 5% level of significance were tested by constructing the 90% confidence intervals (90% CIs) for the geometric mean ratios of test/reference products. The two formulations were considered as bioequivalent if the 90% CIs were within 80.00-125.00% for Cmax and AUC0-tlast of benidipine enantiomers [(+)-alpha-Benidipine hydrochloride and (-)-alpha-Benidipine hydrochloride]. Difference in tmax was evaluated non-parametrically using Mann–Whitney U test.

All statistical analysis were done using Phoenix WinNonlin (Version 8.3.5, Certara L.P.). Also, ANOVA and determination of 90% CIs were applied to non-logaritmic transformed data of tmax, t1/2, λz and MRT and to ln transformed data of AUC0-∞.

Results

57 subjects were screened. 48 subjects were randomised and included into the study. The subjects were divided into two groups according to the randomisation table. There has been one dropout. Subject 01 was dropped out due to adverse event (urticaria) in Period I. He has not been replaced in accordance with the Clinical Study Protocol. 47 subjects completed the clinical phase of the study. All of the subjects were Caucasian. For completed subjects, mean age was 27.62 years (±6.51 years), mean weight was 76.89 kg (±11.39 kg) and mean height was 173.28 cm (±6.49cm). The demographic data of subjects are presented in Table 1.

Table 1: Demographic Data of Completed Subjects.

n* = 47	Age (Years)	Weight (kg)	Height (cm)	BMI (kg/m²)
Mean	27.62	76.89	173.28	25.57
SD	6.51	11.39	6.49	3.24
Minimum	20.00	55.00	158.00	19.38
Maximum	45.00	100.00	189.00	29.86

Actual time of sampling was used in the estimation of the pharmacokinetic parameters. In period II, there was observed no pre-dose drug concentrations, which indicates that the washout period of 3 days was sufficient.

The pharmacokinetic parameters for test and reference products are summarised in Table 2, the geometric least square means, ratios and 90% CIs are summarised in Table 3. Average plasma concentration-time curves and average ln plasma concentration-time curves of test and reference products for single dose of benidipine enantiomers are displayed in Figure 1 and 2, respectively.

For [(+)-alpha-Benidipine hydrochloride:
The mean±sd of Cmax for Test and Reference product were 2729.156±1738.766 pg/mL and 2807.627±1532.946 pg/mL, respectively. The mean±sd of AUC0-tlast for Test and Reference product were 5849.698±3017.044 hr.pg/mL and 5835.613±3163.051 hr.pg/mL, respectively (Table 2).

The primary target variables data demonstrate the bioequivalence of test and reference products with regard to 90% CI for Cmax of 88.61 - 108.28% and for AUC0-tlast of 97.58-106.33%, which are within acceptance limits (80.00-125.00%) [4]. The geometric mean ratios were found as 97.95% and 101.86% for Cmax and AUC0-tlast, respectively. The intra-subject variabilities of Cmax and AUC0-tlast have been found as 29.54% and 12.45%, respectively (Table 3).

For the secondary target variables, the median (min-max) of tmax for Test and Reference products were 1.250 (0.500-5.000) hr and 1.500 (0.500-5.000) hr, respectively. tmax was analyzed using a nonparametric approach by Mann–Whitney U test. There was found no significant difference between the two formulations in regard to tmax (p=0.5104>0.05). The mean±sd of t1/2 for Test and Reference product were 5.293±2.687 hr (ranged from 2.155 hr to 12.565 hr) and 5.417±2.811 hr (ranged from 2.509 hr to 14.162 hr), respectively.

For [(-)-alpha-Benidipine hydrochloride:
The mean±sd of Cmax for Test and Reference product were 1649.493±892.259 pg/mL and 1722.925±983.801 pg/mL, respectively. The mean±sd of AUC0-tlast for Test and Reference product were 3223.184±1492.546 hr.pg/mL and 3197.757±1502.798 hr.pg/mL, respectively (Table 2).

The primary target variables data demonstrate the bioequivalence of test and reference products with regard to 90% CI for Cmax of 90.36 - 108.23% and for AUC0-tlast of 97.25 - 106.84%, which are within acceptance limits (80.00-125.00%) [4]. The geometric mean ratios were found as 98.89% and 101.93% for Cmax and AUC0-tlast, respectively. The intra-subject variabilities of Cmax and AUC0-tlast have been found as 26.48% and 13.62%, respectively (Table 3).

For the secondary target variables, the median (min-max) of tmax for Test and Reference products were 1.250 (0.500-5.000) hr and 1.500 (0.750-5.000) hr, respectively. tmax was analyzed using a nonparametric approach by Mann–Whitney U test. There was found no significant difference between the two formulations in regard to tmax (p=0.4237>0.05). The mean±sd of t1/2 for Test and Reference product were 3.531±1.873 hr (ranged from 1.117 hr to 10.019 hr) and 3.413±1.889 hr (ranged from 1.322 hr to 13.321 hr), respectively (Table 2).

Table 2: The arithmetic mean±sd of pharmacokinetic parameters of single oral dose of 8 mg benidipine hydrochloride in test drug (Biodipin 8 mg Film Kaplı Tablet, Biofarma-Turkiye) and reference drug (CONIEL® 8 mg Tablet, Kyowa Kirin Co. Ltd. - Japan) in healthy adult male subjects under fasting conditions.

(+)-alpha-Benidipine Hydrochloride		
Parameters (Units)	**Test (T) Arithmetic Mean ± SD (n=47)**	**Reference (R) Arithmetic Mean ± SD (n=47)**
C_{max} (pg/mL)	2729.156±1738.766	2807.627±1532.946
$AUC_{0\text{-}tlast}$ (pg.hr/mL)	5849.698±3017.044	5835.613±3163.051
$AUC_{0\text{-}\infty}$ (pg.hr/mL)	6441.143±3213.169	6449.880±3398.614
t_{max} (hr) *	1.250 (0.500-5.000)	1.500 (0.500-5.000)
t½ (hr)	5.293±2.687	5.417±2.811
(-)-alpha-Benidipine hydrochloride		
C_{max} (pg/mL)	1649.493±892.259	1722.925±983.801
$AUC_{0\text{-}tlast}$ (pg.hr/mL)	3223.184±1492.546	3197.757±1502.798
$AUC_{0\text{-}\infty}$ (pg.hr/mL)	3434.250±1562.689	3397.085±1585.094
t_{max} (hr) *	1.250 (0.500-5.000)	1.500 (0.750-5.000)
t½ (hr)	3.531±1.873	3.413±1.889

Table 3: Geometric Least Square Means, Ratio and 90% Confidence Intervals for benidipine enantiomers of test drug (Biodipin 8 mg Film Kaplı Tablet, Biofarma-Turkiye) and reference drug (CONIEL® 8 mg Tablet, Kyowa Kirin Co. Ltd. - Japan) in healthy adult male subjects under fasting conditions.

(+)-alpha-Benidipine Hydrochloride						
Parameter	**TEST GeoLSM**	**REF GeoLSM**	**Ratio**	**90% CI**	**CV (intra)%**	**Power%**
ln (C_{max})	2373.0311	2422.6907	97.9502	88.6077 - 108.2778	29.5439	94.6267
Ln (AUC0-$_{tlast}$)	5262.8834	5166.6953	101.8617	97.5762 - 106.3354	12.4520	100.0000
(-)-alpha-Benidipine Hydrochloride						
Parameter	**TEST GeoLSM**	**REF GeoLSM**	**Ratio**	**90% CI**	**CV (intra)%**	**Power%**
ln (C_{max})	1456.6304	1472.8900	98.8961	90.3642 - 108.2335	26.4841	98.3477
ln (AUC0-$_{tlast}$)	2949.9191	2893.9926	101.9325	97.2546 - 106.8354	13.6198	100.0000

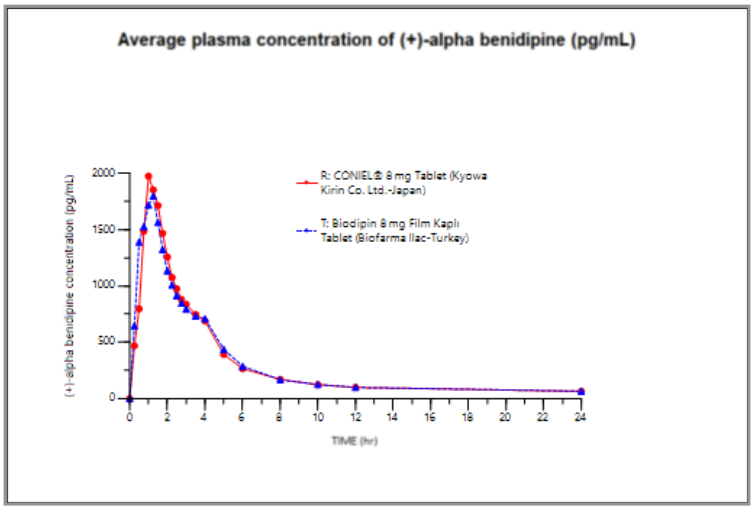

Figure 1: Mean plasma concentration-time curves after a single dose of a test drug (Biodipin 8 mg Film Kaplı Tablet, Biofarma-Turkiye) and reference drug (CONIEL® 8 mg Tablet, Kyowa Kirin Co. Ltd. - Japan) of (+)-alpha benidipine hydrochloride in healthy adult male subjects (n = 47) under fasting conditions.

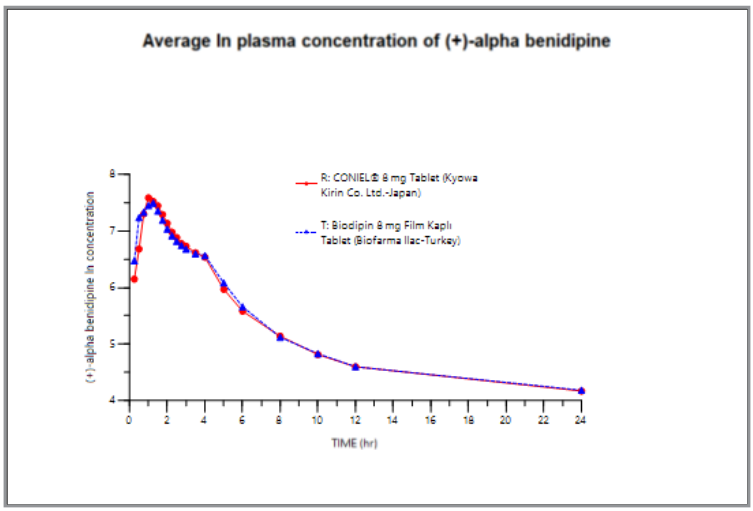

Figure 2: Average ln plasma concentration-time curves after a single dose of a test drug (Biodipin 8 mg Film Kaplı Tablet, Biofarma-Turkiye) and reference drug (CONIEL® 8 mg Tablet, Kyowa Kirin Co. Ltd. - Japan) of (+)-alpha benidipine hydrochloride in healthy adult male subjects (n = 47) under fasting conditions.

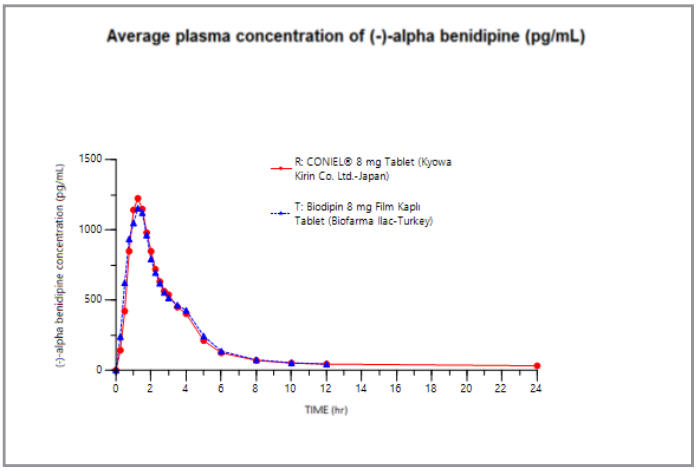

Figure 3: Mean plasma concentration-time curves after a single dose of a test drug (Biodipin 8 mg Film Kaplı Tablet, Biofarma-Turkiye) and reference drug (CONIEL® 8 mg Tablet, Kyowa Kirin Co. Ltd. - Japan) of (-)-alpha benidipine hydrochloride in healthy adult male subjects (n = 47) under fasting conditions.

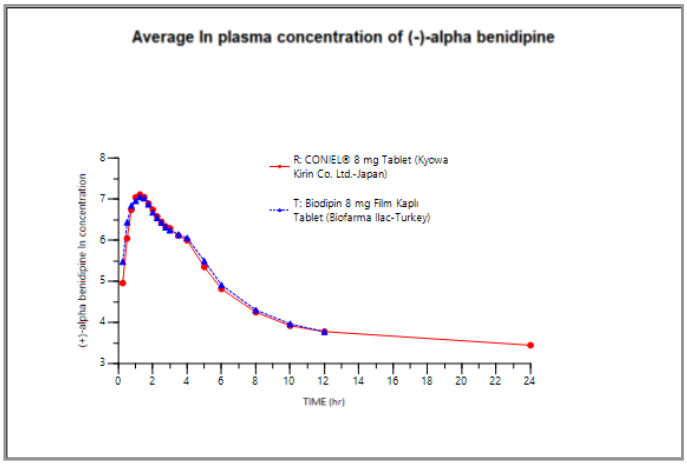

Figure 4: Average ln plasma concentration-time curves after a single dose of a test drug (Biodipin 8 mg Film Kaplı Tablet, Biofarma-Turkiye) and reference drug (CONIEL® 8 mg Tablet, Kyowa Kirin Co. Ltd. - Japan) of (-)-alpha benidipine hydrochloride in healthy adult male subjects (n = 47) under fasting conditions

Conclusions

In this study, a robust and sensitive LC-MS/MS method was successfully developed and validated for the quantification of benidipine enantiomers in human plasma. The method demonstrated high precision, accuracy, and linearity within the calibration range. This bioequivalence study has shown that the test and reference products met the required bioequivalence criteria. Besides, both products were well tolerated and safe.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Conflict of Interest

Authors declare no conflict of interest.

References

1. Muto, K., Kuroda, T., Kawato, H., Karasawa, A., Kubo, K., & Nakamizo, N. (1988). [Article title not provided]. Arzneimittelforschung, 38, 1662.
2. Muto, K., Kuroda, T., Kawato, H., Karasawa, A., Kubo, K., & Nakamizo, N. (1988). [Article title not provided]. Arzneimittelforschung, 38, 1666.
3. Ishii, A., Nishida, K., Oka, T., & Nakamizo, N. (1988). [Article title not provided]. Arzneimittelforschung, 38, 1677.
4. Yamada, S., Nakajima, M., & Kusaka, T. (2002). [Article title not provided]. Life Sciences, 70, 1999.
5. Kobayashi, H., & Kobayashi, S. (1999). [Article title not provided]. European Journal of Drug Metabolism and Pharmacokinetics, 24, 121.
6. Yun, H.-Y., Yun, M.-H., Kang, W., & Kwon, K.-I. (2005). Pharmacokinetics and pharmacodynamics of benidipine using a slow receptor-binding model. Journal of Clinical Pharmacy and Therapeutics, 30(6), 541–547. https://doi.org/10.1111/j.1365-2710.2005.00683.x.
7. Yao, K., Nagashima, K., & Miki, H. (2006). Pharmacological, pharmacokinetic, and clinical properties of benidipine hydrochloride, a novel, long-acting calcium channel blocker. Journal of Pharmacological Sciences, 100(3), 243–261. https://doi.org/10.1254/jphs.CRJ06001X.

8. Kang, W., Yun, H., Liu, K.-H., Kwon, K., & Shin, J.-G. (2004). Determination of benidipine in human plasma using liquid chromatography-tandem mass spectrometry. Journal of Chromatography B, 805, 311–314. https://doi.org/10.1016/j.jchromb.2004.02.007.
9. Kang, W. K., Yun, H.-Y., & Kwon, K.-I. (2005). Assessing the bioequivalence of 4 and 8 mg benidipine tablets in healthy volunteers after a single oral dose. Journal of Clinical Pharmacy and Therapeutics, 30(1), 85–90. https://doi.org/10.1111/j.1365-2710.2004.00607.x.
10. Coniel Tablet. (2019). Summary of product characteristics (Japanese Standard Product Classification No. 872179, translated version).
11. Kang, W., Lee, D.-J., Liu, K.-H., Sunwoo, Y. E., Kwon, K., Cha, I.-J., & Shin, J.-G. (2005). Analysis of benidipine enantiomers in human plasma by liquid chromatography–mass spectrometry using a macrocyclic antibiotic (vancomycin) chiral stationary phase column. Journal of Chromatography B, 814, 75–81. https://doi.org/10.1016/j.jchromb.2004.10.054.
12. Yao, K., Nagashima, K., & Miki, H. (2006). Pharmacological, pharmacokinetic, and clinical properties of benidipine hydrochloride, a novel, long-acting calcium channel blocker. Journal of Pharmacological Sciences, 100(3), 243–261. https://doi.org/10.1254/jphs.CRJ06001X.
13. European Medicines Agency (EMA). (2010, January 20). Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr.). https://www.ema.europa.eu.
14. U.S. Food and Drug Administration (FDA). (2022, April). Bioavailability and bioequivalence studies submitted in NDAs or INDs: General considerations. https://www.fda.gov.
15. Ministry of Health of Turkey. (2015, November 13). Guidance for good clinical practice.
16. U.S. Food and Drug Administration (FDA). (2013). Bioanalytical method validation: Guidance for industry. https://www.fda.gov.
17. European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP). (2011). Guideline on bioanalytical method validation. https://www.ema.europa.eu.