RESEARCH ARTICLE

IJBCS
Indones J Basic Clin Stud. 2026; 1(1): 76-82
doi: 10.21705/ijbcs.v1i1.709

Comparative Pharmacokinetic of Two Levofloxacin Film-Coated Tablet Formulations: A Bioequivalence Study

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Background: Levofloxacin is a broad-spectrum antibiotic used to treat respiratory, soft tissue, and urinary tract infections. Generic formulations aim to reduce healthcare costs and improve accessibility but must demonstrate equivalent bioavailability to the originator drug. It remains unclear whether the new generic drug shares the same pharmacokinetic profile as the originator. Therefore, a bioequivalence study was conducted to evaluate the 500 mg generic Levofloxacin formulation against the reference product.

Methods: The study was an single blind open-label, randomized, single-dose, two-periods, two-sequences crossover study under fasting conditions, with a one-week washout period with total subjects 16 healthy adults. Levofloxacin in plasma was measured using HPLC-VWD. The main parameters of bioavailability were assessed. AUC0-t, C_{max}, and AUC0-inf were analyzed with ANOVA and their 90% confidence interval of the geometric mean ratio between test and reference product were calculated. Meanwhile, T_{max} and T1/2 were compared nonparametrically using the Wilcoxon matched-pair test.

Results: The value of 90% CI for C_{max} and AUC0-t were 92.10%-111.74% and 101.63%-108.58, respectively. The median T_{max} of test and reference drug were 1.00 and 0.88 hours, respectively. Meanwhile, the mean half-life of test and reference drug were 6.73±0.74 hours and 6.93±1.29 hours, respectively. The 90% confidence intervals for C_{max} were (92.10–111.74%) and AUC0-t were 101.63–108.58% fell within the 80–125% acceptance range, demonstrating bioequivalence between formulations.

Conclusion: The 90% confidence intervals for C_{max} and AUC0–t were within the accepted range, with similar T_{max} and half-life values, confirming that the generic Levofloxacin 500 mg is bioequivalent to the reference product.

Keywords: bioequivalence, levofloxacin, pharmacokinetics

Introduction

Levofloxacin, the levorotatory isomer of Ofloxacin, is categorized as fluoroquinolone (FQ) bacterial agent. It is also classified as one of broad-spectrum antibiotics which can affect a wide range of microbes.[1,2] Levofloxacin is commonly indicated for lower and upper respiratory tract, skin and soft tissue, and urinary tract infections. Levofloxacin was developed because of its antimicrobial potency and exhibits higher efficacy than Ofloxacin. Like other fluoroquinolones. Fluoroquinolones act by inhibiting bacterial DNA gyrase and topoisomerase IV, enzymes essential for introducing transient single-strand breaks and maintaining DNA supercoiling during replication. By stabilizing the enzyme–DNA complex, they prevent resealing of the DNA strands, thereby blocking replication and transcription, which results in bacterial cell death. This leads to the blockade of bacterial DNA replication and transcription, resulting in cell death.[3,4]

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Submitted: July 5, 2025
Last Revised: December 10, 2025
Accepted: December 12, 2025

Generic antibiotics are produced to reduce the cost and help healthcare facilities. However, it must have a similar rate and extent of absorption as the brand-name product.[5,6] The correct dosage must provide the efficacy to eliminate microorganisms. To cure the infection, the antibiotics must achieve minimum inhibitory concentration (MIC).[7] A lower dose below MIC cannot eradicate the infection and the risk of developing drug resistance might increase. On the other hand, if the dose is higher than maximum tolerated dose, the drugs become toxic and leads to adverse event reaction.[8,9]

Differences in manufacturing processes, excipient types, formulations and dosage technologies can lead to variations in bioavailability in drugs that have the same active substance. These variations, particularly in antibiotics, have the potential to affect their therapeutic effectiveness and safety profile.[5,10,11] Therefore, the Indonesia Food and Drugs Authority requires supporting data to ensure the quality and consistency of branded generic products on the market. The supporting data is in the form of bioavailability information that is obtained through pharmacokinetic studies in healthy subjects in the form of bioequivalence tests. Because of the characteristics of Levofloxacin, a bioequivalence study must be conducted. It is necessary to compare the generic product to its reference containing the same active substances. Furthermore, some generic products may have a few alternate fillers or inactive ingredients. Two medicinal products are considered bioequivalent if they have identical therapeutic effects and safety profiles.[11] The aim of the present study was to compare the pharmacokinetics profile of Nislev® (test drugs) with Cravit® (references drugs) and to assess the bioequivalence of the two formulations.

Materials and methods

Study Design

This is a single-dose, randomized, single blind, two periods, one week washout period, two-sequences, cross-over design, and under fasting condition.[12] The study was conducted in Econolab Clinical and BABE (Bioavailability and Bioequivalence) Laboratory, Jakarta, Indonesia. The protocol was reviewed and approved by The Ethics Committee of Faculty of Medicine, University of Indonesia - Cipto Mangunkusumo Hospital and Indonesian Food and Drug Authority with approval number KET-464/UN2.F1/ETIK/PPM.00.02/2021. The study involved 16 healthy subjects who were assigned to receive the test drug and reference drug in different dosing sequences in cross over design.

Investigational Products

The 500 mg Levofloxacin Tablet (Nislev®, batch number D0K486G PT Prima Medika Laboratories, Tangerang, Indonesia) as test product, 500 mg Levofloxacin Tablet (Cravit®, batch number KTCRVK93248, PT Kalbe-Farma, Jakarta, Indonesia) as reference product. Reference standard (Levofloxacin BPFI 113019) and internal standard (Moxifloxacin HCl BPL B0116494) were purchased from Indonesian Food and Drug Authority, Jakarta. The tools used in this study were High Performance Liquid Chromatography with Variable Wavelength Detector (HPLC-VWD) instrument (Agilent 1200, Waldbronn, Germany) and Purospher Star RP-18e (5um, 250 x 4,6 mm) as the column. The materials used in this study were blood collection tube with sodium citrate anticoagulant (ArkanMedical, Bogor, Indonesia).

Clinical Subjects

The subjects were healthy Indonesian males or females aged 18–55 years who had provided written informed consent. Subjects were required to have a body mass index (BMI) between 18 and 25 kg/m², normal vital signs (heart rate 60–100 bpm, respiratory rate 12–20 breaths/min, systolic blood pressure 90–120 mmHg, and diastolic blood pressure 60–90 mmHg), and normal results from routine clinical laboratory tests. Before participating in the study, subjects signed the informed consent and undertook an initial medical screening and clinical laboratory test. Subjects enrolled in this study must be able to communicate well with the investigators and have normal clinical laboratory test result. The physician was responsible for giving medical justification regarding the clinical laboratory test results, if necessary.

Pregnant or lactating women, hypersensitive to the product, heavy smokers, and those participating in a previous study within 3 months before the dosing day of the first period, were excluded from this study. Other exclusion criteria were those who had a history of any prior allergic drug rash, bleeding or coagulation disorders, or any surgical or medical condition that might significantly alter the pharmacokinetics of the study drug.

Pre-study Conditions and Subject Restrictions

From a week before until the end of the clinical phase, the subjects were not allowed to take any drug, including Over-the-Counter (OTC) products, food supplements, and herbal medicine. Smoking or consuming xanthine-containing food or beverages and fruit juices was prohibited within 24 hours before and during all sampling days. The subjects underwent quarantine a night before drug administration. They were required to fast from 9 pm until 4 hours after taking the study drug on the next day. Water intake was not allowed from one hour before dosing until two hours after dosing.

Drug Administration and Dosing Procedures

The responsible physician instructed subjects to take 1 film-coated tablet of either test or reference product with 240 mL of water. The responsible physician ensured that each subject swallowed the product. Subjects were instructed to maintain an upright position (sitting or standing) from right after until 4 hours after dosing. Food intake was not allowed until 4 hours after drug administration. Water intake was allowed ad libitum except from an hour before until 2 hours after dosing. Standardized meals were served at 4, 8, 12, and 24 hours after dosing. After a week of washout period, subjects underwent the second period of the study. The procedure of the second period was carried out with the same steps as the first period, except the drug administered to the subjects was the alternative to the first period.

Blood Collection and Safety Monitoring Procedures

Blood sampling from each subject were collected at pre-dose (control), 0.16, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-dosing and carried out under yellow monochromatic light. Blood samples were collected using disposable syringes and transferred into sodium citrate vacuum tubes, with a total of 6 ml of blood collected.The separation of plasma from the blood cells was done with centrifugation at 3000 rpm for 15 minutes and kept in a freezer at (-15)-(-25)ºC until analysis.

Vital signs monitoring (body temperature, blood pressure, pulse, and respiratory rate) and side effects were done during the pre-dose, 0.16 (first sampling), 1, 2, 4, 6, 12, and 24 hours post-drug administration. All adverse events were recorded regardless of the causal relationship with the drug.

Plasma Sample Analysis and Validation Method

Levofloxacin concentration in plasma was determined with HPLC-VWD. Some amount of plasma sample was added to the microtube with internal standard Moxifloxacin HCl. The sample was extracted using cold acetonitrile and centrifuged. The organic layer was moved to the new microtube and evaporated with nitrogen gas. The supernatant was separated, put in the injection vial, and injected into a liquid chromatography system to be analyzed. The lower limit of quantification (LLOQ) was set at 50 ng/mL. The bioanalytical method has been validated for selectivity, carry-over, LLOQ, calibration range, within and between run accuracy and precision, dilution integrity, and stability. Long-term stability of the samples under frozen condition (-15)-(-25)ºC, short-term stability of the analyte in the plasma at room temperature (20-30ºC), freeze and thaw stability, stock solution stability of Levofloxacin under a refrigerated condition (2-8ºC), and the stability at autosampler were determined.

Statistical Analysis

Pharmacokinetic parameters were applied based on the actual time of sampling. The parameters to determine the bioequivalence of drugs were area under curve before dosing until the last time of sampling (AUC0-t) and maximum concentration (C_{max}). Additional parameters to be estimated are the a under the curve before dosing until the infinite time (AUC0-inf), time to peak plasma concentration (T_{max}), and half-life (T1/2).

The linear trapezoidal method was used to calculate AUC0-t. The elimination constant rate was used to calculate AUC0-inf by determining three of timepoints in the elimination phase and calculating the slope. The calculation of T1/2 was 0.693/ke while C_{max} and T_{max} were acquired from the analytical data. The statistical method for testing bioequivalence is ANOVA for 2-periods, 2-sequences, cross-over design, comparing AUC0-t and C_{max} on log-transformed value using R Statistical Software. The error variance (s2) obtained from ANOVA will be used to calculate a 90% confidence interval (CI). The test product is bioequivalent to the reference product if the 90% CI for AUC0-t, and C_{max} are between 80.00%-125.00%.

Depending on their data distribution, T_{max} and T1/2 were compared parametrically or non-parametrically by employing a Wilcoxon matched pair test without

logarithmic transformation of the original data. The power of the study is 80% with 5% alpha. The statistical analysis was done using R statistical software (version 4.1.2).

Results

Clinical Characteristic

Sixteen healthy Indonesia adult male and female enrolled and no drop out during this study. All of them were qualified to fulfill the inclusion criteria and had good medical results, and all the subjects completed the study according to the protocol. The mean of demographic and clinical characteristics of the subjects can be seen in **Table 1**.

Bioanalytical Validation

The calibration range was linear over the concentration range of 50 to 20,000 ng/mL with a mean correlation coefficient of 0.9968. LLOQ (Lower Limit of Quantification) and quality control samples at low, medium, and high levels were used to analyze the accuracy and precision of the instrument. The acceptable criteria of precision are if the CV value of each QC point was ≤ 15% while for the LLOQ was ≤ 20%. The within and between run accuracy and precision is shown in **Table 2**, indicating that the bioanalytical method was accurate and precise. The fully validated bioanalytical method was used to measure the plasma concentration in this study.

The mean concentration of Levofloxacin in plasma after 24-hour blood sampling is shown in **Figure 1**. The concentration was increased after 30 minutes of dosing and constantly decreased after 6 hours post-drug administration. The graph showed test and reference products were almost superimposable because two lines were overlapping.

To assess bioavailability, analysis of pharmacokinetic parameters was done. The 90% CI of the geometric mean ratio (GMR) was acquired from the inversed in of the equation. Data analyses were conducted in compliance with the regulation of the Indonesian Food and Drug Authority. The result of statistical analysis of Levofloxacin is presented in **Table 3.** Both Levofloxacin formulations were well tolerated, and no adverse events were observed during the study.

Discussion

In this study, 90% CI of Cmax and AUC0-t met the criteria for bioequivalence (80.00-125.00%) with a low intra-subject coefficient of variation (CV) value (≤15%). The participation of 16 subjects in this study was adequate and had enough power to confirm statistical conclusion. The point estimate and Geometric Mean Ratio (GMR) between the test drug and the reference were close to one (1) for both C_{max} and AUC, indicating that the test drug is bioequivalent to the reference. This bioequivalence range is also used by the

Table 1. Subjects demographic and clinical characteristics.

Characteristic	Value
Age (year)	32.12 ± 9.79
BMI (kg/m^2)	23.21 ± 2.72
Systolic blood pressure (mmHg)	117 ± 5.47
Diastolic blood pressure (mmHg)	77.5 ± 5.15
Respiratory rate (x/min)	19.4 ± 1.0
Heart rate (x/min)	83 ± 9.15
Body temperature (^{o}C)	36.33 ± 0.20
Hemoglobin (g/dL)	14.6 ± 1.80
Leucocyte (µL)	7.249 ± 2.64
Eritrocyte (10^6/µL)	5.04 ± 0.60
Thrombocyte (µL)	272.800 ± 47.85
Serum creatinine (mg/dL)	0.77 ± 0.09
SGOT (U/L)	16.188 ± 4.27

Table 2. Accuracy and precision of Levoflaxcin in HPLC-VWD instrument.

Concentration (ng/mL)	Accuracy Deviation (%)		Precision Coefficient of Variation	
	Within Run (n=6)	Between Run (n=6)	Within Run (n=6)	Between Run (n=6)
50	13.39	9.92	3.24	5.39
150	2.90	2.33	1.27	2.53
10000	2.73	3.29	3.20	3.35
15000	1.56	4.83	2.00	4.83

Indonesian Food and Drug Authority as a standard for generic drug approval. Pharmacokinetic parameters such as half-life (T1/2) and T_{max} showed similar values in both formulations, as reflected by the overlapping pharmacokinetic curves.[8,11]

The median T_{max} of Levofloxacin was 1.00 and 0.88 hours for test and reference products. The result indicates that both formulations of Levofloxacin were rapidly absorbed. Moreover, when compared non-parametrically, there was no significant difference in T_{max} between the products.

The half-life of Levofloxacin for the test and reference products were 6.73- and 6.93-hour post-dose, respectively. No significant difference was found in T1/2 when compared non-parametrically. Levofloxacin was eliminated relatively slowly from the body. Therefore, a one-week washout period was appropriate to be applied in this study.

This study showed that there was low inter-subject variability in both preparations (test and reference), indicating that Levofloxacin bioavailability levels were not influenced by subject sexual characteristic. This finding is in line with the results of other bioequivalence trials involving male and female subjects with similar characteristics.[13,14] This low inter-variability was also due to the characteristics of the subjects which is a healthy, normal body mass index (BMI), and there were no pathological conditions that could cause changes in the pharmacokinetic profile, such as impaired renal function, impaired liver function, hemodynamic disorders (*e.g.*, interstitial oedema, blood pressure disorder), and disorders of the digestive system.[13,14] This is confirmed from previous pharmacokinetic studies that special populations showed significant differences in Levofloxacin blood concentration in groups with characteristics, such as: geriatric, obesity, sepsis, chronic kidney disease, pregnancy and liver failure.[15–18]

Levofloxacin bioequivalence test was conducted under fasting conditions because the drug has optimal absorption when there is no food in the digestive tract. Fasting conditions allow drug absorption to take place more quickly and efficiently, thus providing a more accurate picture of drug bioavailability.4,6,8 The results of this test are also in line with previous pharmacokinetic studies that demonstrated variability in bioavailability in patients who consumed

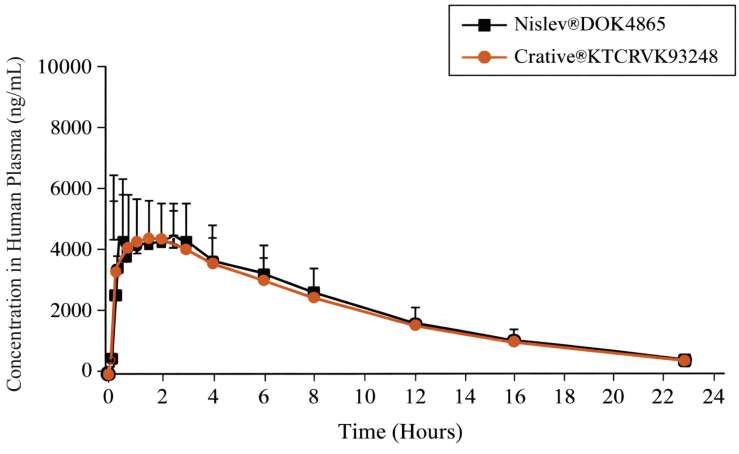

Figure 1. Mean plasma concentration–time profile of Levofloxacin (500 mg) following single-dose oral administration of the test and reference products in 16 healthy subjects (semilog plot).

Table 3. Statistics summary of Levofloxacin.

Parameters	Test (n=16)	Reference (n=16)	Geometric Mean Ratio (90% CI)	Intra-subject Coefficient of Variation (%)
C_{max} (ng/mL)	5517.90 ± 1492.38	5526.66 ± 2014.18	101.45 (92.10 – 111.74)	15.69
AUC_{0-t} (ng/mL.h)	50204.80 ± 13649.64	47873.12 ± 13433.62	105.05 (101.63 – 108.58)	5.33
AUC_{0-inf} (ng/mL.h)	55033.44 ± 14389.45	52634.39 ± 13990.19	104.62 (101.77 – 107.54)	4.45
T_{max} (h)	1.00 (0.33-3.00)	0.88 (0.33 – 4.00)	-	-
$T_{1/2}$ (h)	6.73 ± 0.74	6.93 ± 1.29	-	-

food prior to drug administration. The presence of food was shown to decrease and affect the consistency of peak blood levels of the drug, making fasting a more reliable condition to objectively assess the bioequivalence of Levofloxacin.[19]

The bioequivalence test results in this study showed that the drug concentration in the blood plasma of the test product was comparable to that of the reference product. This equivalence reflects that both products have similar bioavailability profiles, which is one of the main criteria in determining the appropriateness of a drug for distribution in Indonesia in order to maintain therapeutic quality and effectiveness. The C_{max} value achieved by both products was recorded at test product: 5517.90 ± 1492.38 ng/mL vs references product 5526.66 ± 2014.18 ng/mL. These concentrations indicate that both products have plasma drug levels that are above the MIC value, so can be considered to have adequate antimicrobial activity against bacteria sensitive to the antibiotic Levofloxacin. This supports the conclusion that both products have the potential to provide equivalent clinical effectiveness in the treatment of infections caused by the target bacteria.[20,21] Both products were well tolerated by the subjects as there was not any adverse event reported during the study. Moreover, the vital signs monitoring did not show any out of normal range data.

Conclusion

Based on the results of this study, the test product was determined to be bioequivalent to the reference product, as demonstrated by comparable pharmacokinetic parameters C_{max}, AUC, T_{max}, and T1/2 all of which fell within the accepted bioequivalence range of 80–125%. These findings indicate that the test drug (Nislev) delivers the active ingredient in a manner like the originator product (Cravit).

Acknowledgment

The authors would like to acknowledge PT Prima Medika Laboratories for providing financial support for this study.

Authors' Contribution

CG, AL and NMDW contributed to the conception and planning of the research. AZ and AYR drafted the manuscript and designed the figures. CAS served as the medical supervisor of the study. AI performed the statistical analysis. YC and RA conducted the PK analysis. AYR and NMDW contributed to data interpretation and provided critical revisions to the manuscript. All authors participated in the critical revision of the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Conflict of Interest

The authors declare no conflict of interest.

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