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Research Article

Comparative Bioequivalence Study of 2 Fixed Dose Combinations of Ibuprofen at a Tabet Strength of 400 Mg in Moroccan Volunteers

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Abstract

This study compared ALGANTIL® 400 mg film-coated tablets, used as the test product, with BRUFEN® 400 mg film-coated tablets, used as the reference product, in healthy Moroccan volunteers. Twenty-four subjects received a single dose of each formulation in a randomized, single-blind, two-sequence, two-period crossover study conducted after an overnight fast. All randomized subjects completed both periods.

Ibuprofen exposure was characterized from serial plasma concentrations. The pharmacokinetic evaluation included Cmax, AUC_{0-t}, $AUC_{0-\infty}$, Tmax, and $t_{1/2}$. Blood was collected according to a pre-specified sampling schedule after each treatment, and ibuprofen was quantified in plasma by a validated LC–MS/MS assay meeting the applicable bioanalytical validation requirements.

Systemic exposure was similar after administration of the two products. The 90% confidence intervals for the test/reference geometric mean ratios of Cmax, AUC_{0-t}, and $AUC_{0-\infty}$ were all contained within the predefined bioequivalence interval of 80%–125%.

No adverse event, serious adverse event, or withdrawal related to safety occurred during the study, and both formulations were well tolerated.

Accordingly, the pharmacokinetic comparison under fasting conditions established bioequivalence between ALGANTIL® 400 mg and BRUFEN® 400 mg film-coated tablets, indicating comparable ibuprofen exposure after a single oral dose.

Keywords: Ibuprofen; Bioequivalence; Pharmacokinetics; Pharmacokinetic; LC–MS/MS; Generic drug; Healthy volunteers

Highlights

- Under fasting conditions, ALGANTIL® 400 mg film-coated tablets fulfilled the bioequivalence criteria relative to BRUFEN® 400 mg film-coated tablets.
- For Cmax, AUC_{0-t}, and $AUC_{0-\infty}$, each 90% confidence interval for the test/reference ratio was contained within 80%–125%.
- No tolerability concern was identified in the 24 healthy Moroccan volunteers who completed the study.

Introduction

Ibuprofen is a widely used Nonsteroidal Anti-Inflammatory Drug (NSAID) classified among the propionic acid derivatives. Its analgesic, antipyretic, and anti-inflammatory effects, together with its well-established clinical efficacy and generally favorable tolerability, have contributed to its extensive therapeutic use. Ibuprofen is commonly administered for the management of mild-to-moderate pain and a variety of acute or chronic inflammatory disorders. Its clinical applications include headache, dysmenorrhea, dental and postoperative pain, musculoskeletal conditions, osteoarthritis, and rheumatoid arthritis (Figure 1) [1,2].

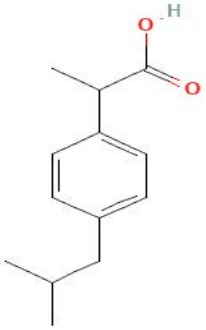


Figure 1: Structure of ibuprofen

After oral administration, ibuprofen is absorbed from the gastrointestinal tract relatively quickly, with peak plasma concentrations generally reached at about 90 minutes [3,4].

Oral ibuprofen has high systemic availability and is extensively bound to plasma proteins [5]. Biotransformation occurs mainly in the liver and yields metabolites that are not considered pharmacologically important [6]. Elimination from the circulation is rapid, with a reported half-life of roughly two hours. Renal excretion accounts for most of the administered dose as metabolites or conjugates, whereas only a small proportion is excreted unchanged [4,7].

Its pharmacological effect is largely explained by inhibition of COX-1 and COX-2, which lowers prostaglandin synthesis [8,9]. This mechanism accounts for the analgesic, antipyretic, and anti-inflammatory actions of ibuprofen, but it also contributes to adverse effects associated with NSAID therapy and therefore makes safety assessment relevant [10,11].

Moroccan requirements for generic medicines include demonstration of bioequivalence with the reference product, notably under the national bioequivalence guideline issued in 2020 and Decree No. 2-17-429 amending and supplementing Decree No. 2-12-198 [12–14]. Bioequivalence is evaluated by comparing the rate and extent of drug absorption, principally through pharmacokinetic measures such as Cmax, Tmax, and AUC [15].

Within this regulatory context, the present study compared a generic 400 mg ibuprofen formulation with its reference product in healthy volunteers. A single oral dose of each product was administered under standardized conditions. The objective was to determine whether the pharmacokinetic exposure produced by the test formulation met the accepted criteria for bioequivalence with the reference formulation.

Materials and Methods

Materials

ALGANTIL®, the test formulation, was supplied as a film-coated tablet containing 400 mg ibuprofen and was manufactured by LAPROPHAN (batch PRO-058-2644; expiry March 2025).

BRUFEN®, the reference formulation, was also a 400 mg ibuprofen film-coated tablet; it was manufactured by MYLAN under license from COOPER PHARMA (batch 220601; expiry May 2025).

Both products contained ibuprofen at the same stated strength of 400 mg per tablet.

Inclusion and exclusion criteria

Healthy Moroccan adults of either sex were eligible if they were 18–55 years old and had a body mass index between 18.5 and 30.0 kg/m². Eligibility was established from the medical history and clinical examination, vital signs, hematology, biochemistry, urinalysis, and a 12-lead ECG without clinically relevant abnormalities. Protocol-defined ECG limits included a PR interval of 120–220 ms and QTc values ≤ 450 ms in men and ≤ 470 ms in women. Women of childbearing potential had to use effective contraception during participation and for 30 days after the last dose. A negative SARS-CoV-2 PCR test was required before each period. Key reasons for exclusion were hypersensitivity to ibuprofen or another NSAID, a clinically relevant history of major disease, or absence of written informed consent [14,16].

Study design

The test and reference formulations were compared using a randomized, single-blind, two-treatment, two-period crossover design with two treatment sequences [16].

Ethical approval was obtained from the Health Science Ethics Committee at Abulcasis University, Rabat. The study also received the required authorizations from the Moroccan National Commission for Personal Data Protection and the Medicines and Pharmacy Department.

Subjects entered the Bioequivalence Study Center of the Cheikh Zaid Foundation in Rabat on the day before dosing. Randomization assigned participants equally to the two treatment sequences. After at least 10 hours of fasting, one 400 mg tablet of the assigned formulation was swallowed with 240 mL of water. The alternative formulation was given in period 2 after a 7-day washout [17].

Drug administration and sampling

Administration: Dosing and blood collection were carried out under standardized conditions at the Bioequivalence Studies Center of the Cheikh Zaid Foundation in Rabat to limit avoidable within-subject variability.

Each treatment was administered after an overnight fast of at least 10 hours as one 400 mg ibuprofen tablet with 240 mL water. Meals were standardized and served 4 and 10 hours after dosing. No water was permitted during the first 2 hours' post-dose; thereafter, water intake was unrestricted.

Blood sampling: The collection times were chosen to describe the early absorption phase as well as the terminal portion of the ibuprofen concentration-time profile [18]. In each period, 19 blood specimens of approximately 5 mL were obtained from each participant.

A predose specimen was collected at time 0, followed by samples at 0.33, 0.66, 1.00, 1.33, 1.66, 2.00, 2.33, 2.66, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, and 24.00 hours after dosing.

Blood was drawn into EDTA tubes and promptly centrifuged at 3,000 rpm for 10 minutes at 4°C. Plasma was separated into labeled sterile cryotubes and kept at −25°C or below; storage could extend to −80°C for longer-term preservation before analysis.

Chemicals and reagents: Reference ibuprofen (purity 99.6%) and the deuterated internal standard ibuprofen-D3 were obtained from Clearsynth (North America). Methanol of LC/MS and HPLC grade was supplied by Merck (Darmstadt, Germany).

Ammonium formate was purchased from HIMEDIA (Mumbai, India).

Ultrapure water with a resistivity greater than 18.0 Ω/cm was used throughout the analytical procedure.

LC-MS-MS conditions: Chromatographic analysis used an Agilent 1290 Infinity II UHPLC system comprising a quaternary pump, autosampler, and temperature-controlled column compartment (Agilent, Waldbronn, Germany) [19-21]. Separation was performed on a Phenomenex C18 column (100 × 2 mm, 4 µm) at 0.25 mL/min. Mobile phase A was 5 mM ammonium formate and mobile phase B was LC/MS-grade methanol; the working composition was 30:70 (A:B), and the column temperature was 40°C. The approximate retention times were 1.73 min for ibuprofen and 1.74 min for ibuprofen-D3.

Detection was performed on an Agilent 6420 triple-quadrupole mass spectrometer controlled with MassHunter B.09.00 [22]. Positive electrospray ionization and multiple-reaction monitoring were used, with a 200 ms dwell time per transition. The monitored transitions were m/z 205.2→161.2 for ibuprofen and 208.2→163.9 for ibuprofen-D3. The fragmentor voltage was 82 V for both compounds and the collision energy was 1 eV.

Preparation of standard stock solutions: A 1 mg/mL primary stock of ibuprofen was prepared in methanol. Methanolic dilutions yielded working solutions at 4, 20, 40, 100, 200, 400, 800, and 1,600 µg/µL for preparation of the calibration standards.

Quality-control working solutions were prepared separately from an independent 1 mg/mL ibuprofen stock in methanol, using serial dilution to obtain 4, 12, 600, and 1,200 µg/mL.

Ibuprofen-D3 served as the internal standard. Its 1 mg/mL methanolic stock was diluted in methanol to a working concentration of 40 µg/mL.

Preparation of calibration standards and QC samples: Blank human plasma was spiked with the ibuprofen working solutions to produce eight calibrator concentrations: 200, 1,000, 2,000, 5,000, 10,000, 20,000, 40,000, and 80,000 ng/mL. The 200 ng/mL calibrator constituted the Lower Limit of Quantification (LLOQ).

Independent QC samples were prepared in blank plasma at 200, 600, 30,000, and 60,000 ng/mL, corresponding respectively to the LLOQ QC (QC0), LQC, MQC, and HQC levels. These concentrations were used to assess assay performance across the analytical range.

Preparation of clinical blood samples: After informed consent, blood from six healthy adults was collected through a forearm venous cannula maintained with normal saline during serial sampling. Specimens were placed in Na_2EDTA tubes and centrifuged at 3,000 rpm for 10 minutes. The separated plasma was aliquoted into labeled polypropylene tubes and stored at −25°C until bioanalysis.

Preparation of samples prior to LC–MS-MS analysis: For extraction, 0.3 mL of plasma (calibrator, QC, or study sample) was mixed with 15 µL of internal-standard working solution and vortexed for 30 seconds. Protein precipitation was then induced with 1 mL methanol, followed by another 30-second vortex step and centrifugation at 20,000 rpm for 6 minutes at 6°C. A 0.7 mL portion of the supernatant was mixed with 0.3 mL mobile phase before LC–MS/MS injection.

Method validation

Validation of the assay followed ICH M10 and the applicable bioanalytical method-validation requirements [23,24]. The validation program addressed selectivity, matrix effects, calibration behavior, accuracy, precision, and stability under the experimental conditions used in the study.

Specificity

Selectivity was examined in blank plasma from six separate sources. Each lot was also evaluated after fortification with ibuprofen at the LLOQ and processing by the study extraction procedure. Chromatograms were reviewed for endogenous or other signals that could interfere at the retention times of ibuprofen or the internal standard.

Matrix effect

Matrix effects were examined separately for ibuprofen and ibuprofen-D3 by calculation of matrix factors. Six plasma lots were tested at LQC and HQC, with three replicates for each level in each lot. For ibuprofen, the response in post-extraction spiked plasma was compared with the response in a neat methanolic solution; the same comparison was made for the internal standard. Variation in matrix effect across plasma sources was assessed against a prespecified limit of ≤ 15%.

Hemolyzed matrix was assessed as an additional condition. Hemolyzed plasma was produced by three freeze–thaw cycles of human blood followed by centrifugation. LQC and HQC samples prepared in this matrix were analyzed in triplicate and compared with corresponding non-hemolyzed samples. Acceptance followed ICH M10 criteria: Accuracy within ± 15% of nominal concentration and precision (CV) ≤ 15%.

Calibration curves and linearity

Calibration used the ratio of the ibuprofen peak area (m/z 205.2→161.2) to that of ibuprofen-D3 (m/z 208.2→163.9) plotted against nominal plasma concentration. Weighted least-squares regression with $1/x^2$ weighting was applied. Back-calculated calibrator concentrations had to fall within ± 20% of nominal at the LLOQ and ± 15% at the other levels. A run was acceptable when at least 75% of standards, including at least six concentration levels, met these limits.

Linearity was examined with calibration curves generated on five consecutive days, with R^2 required to be >0.99. Study-sample concentrations were derived from analyte/internal-standard area ratios using the regression equation of the relevant calibration curve.

Accuracy and precision

Within-run performance was tested with four replicates at QC0, LQC, MQC, and HQC. Accuracy was evaluated relative to the nominal concentration, with limits of ± 20% at the LLOQ and ± 15% at the remaining QC levels. Precision was reported as CV% and had to be ≤ 15% at each level. Between-run accuracy and precision were also evaluated over three different days to assess reproducibility.

Carry-over

Samples above the upper limit of quantification were evaluated for dilution performance using QC material prepared in the same matrix and diluted with blank matrix into the validated range. At least five replicates were tested. Acceptance required mean accuracy within ± 15% of nominal and CV ≤ 15%. A surrogate matrix could be considered only when scientifically justified and shown not to affect analytical accuracy or precision.

Dilution integrity

For the dilution-integrity experiment, plasma was fortified with ibuprofen at 6,000 ng/mL, described as twice the HQC concentration. Five independently prepared samples were diluted 1:2 with blank plasma and analyzed with the validated procedure. Dilution was considered acceptable when mean accuracy remained within ± 15% of nominal and CV did not exceed 15%.

Reinjection reproducibility

Reproducibility was evaluated through repeated QC measurements during the accuracy and precision experiments. Where reinjection was required because of an instrument interruption or malfunction, calibration standards together with at least five replicates at low, medium, and high QC levels were reinjected after the applicable storage interval. Accuracy and precision of the reinjected QCs were reviewed to verify that analytical performance and sample integrity had been maintained; the results were documented in the validation or study report.

Stability

Ibuprofen stability in plasma was tested in triplicate at LQC and HQC under conditions intended to represent routine sample handling and analysis. The experiments covered freeze–thaw cycles, short-term room-temperature exposure, long-term storage under the specified conditions, and post-preparative residence in the autosampler. Stability of the internal standard was assessed under the relevant analytical conditions as well.

A stability condition was accepted when measured concentrations were within ± 15% of nominal and precision, expressed as CV%, was ≤ 15%.

Results

Pharmacokinetics of ibuprofen

Pharmacokinetic and statistical analyses included all 24 randomized subjects (randomization numbers 01–24) (Table 1).

Table 1: Summary of pharmacokinetic parameters of ibuprofen after a single dose of test and reference FDC tablets in healthy Moroccan volunteers

Ibuprofen		
Pharmacokinetic parameters	**Test product (n=24)**	**Reference product (n=24)**
Cmax (ng/ml)	27,014	28,724
AUC_{0}–t (ng.h/mL)	1,07,148	1,06,700
AUC_{0}–∞ (ng.h/mL)	1,04,808.60	1,04,468
Tmax (hours)	2	1
t1/2 (h)	2.07	2

Note : AUC_{0}–t: Area under the Concentration–time curve from time zero to the last measurable concentration
AUC_{0}–∞: Area under the Concentration–time curve extrapolated to infinity
Cmax: Maximum plasma concentration
Tmax: Time to maximum plasma concentration
t1/2: Elimination half-life

Table 1 summarizes the mean pharmacokinetic parameters obtained in the 24 volunteers after a single 400 mg dose of the test and reference ibuprofen formulations.

Mean ibuprofen plasma concentration-time profiles for the two treatments are displayed on linear and semilogarithmic scales in Figures 2 and 3.

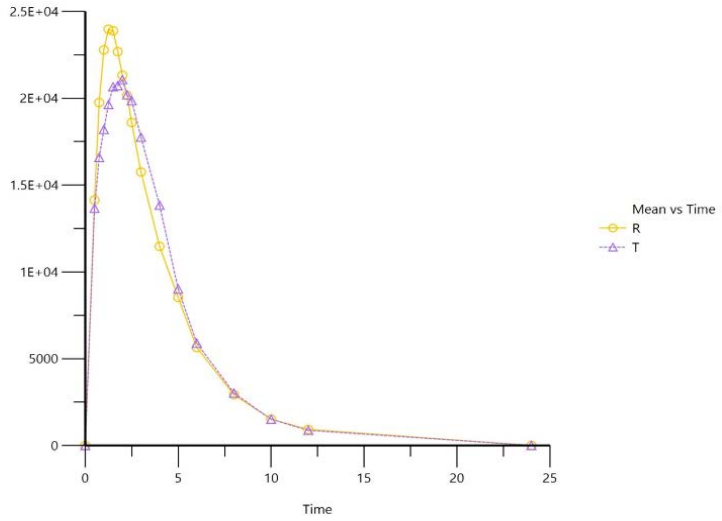


Figure 2: Mean plasma concentrations of Ibuprofen over time after a single oral dose on a linear scale

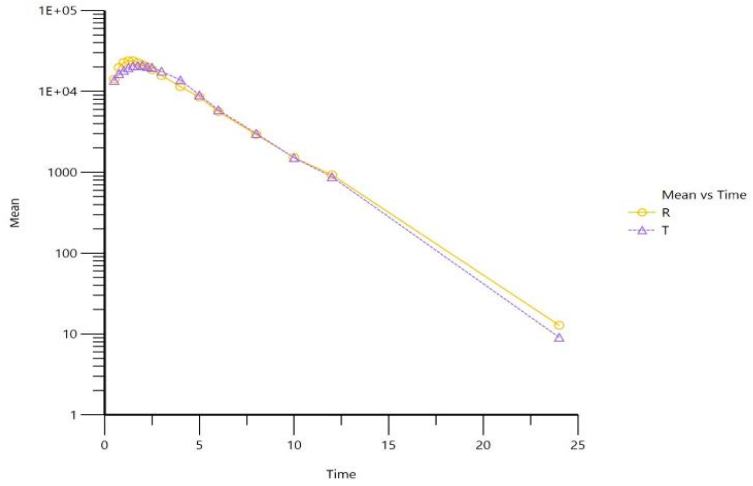


Figure 3: Mean plasma concentrations of Ibuprofen over time after a single oral dose on a linear (semilog) scale

Assessment of ibuprofen bioequivalence

The formal bioequivalence comparison is summarized in Table 2, which reports the geometric means, test/reference ratios, within-subject coefficients of variation, and 90% confidence intervals for Cmax, AUC_{0}–t, and AUC_{0}–∞.

For each of the three primary exposure measures, the 90% confidence interval for the geometric mean test/reference ratio was contained within the prespecified 80%–125% interval. The study therefore met the bioequivalence criterion for the 400 mg test and reference ibuprofen tablets under fasting conditions.

Table 2: Bioequivalence analysis of ibuprofen after single oral administration of test and reference FDC tablets in healthy Moroccan volunteers

Pharmacokinetic parameter	Geometric mean		Geometric mean ratio of test/ reference drug (%)	Within subject CV %	90% CI
	Test	Reference			
Cmax (ng/ml)	26437,41	27913,56	94.71%	9.85%	90.21 – 99.44 %
AUC_{0}–t (ng.h/mL)	104821,95	103510,86	101.27%	7.09%	97.77– 104.88 %
AUC_{0}–∞ (ng.h/mL)	102490,08	101305,31	101305.31%	7.15%	97.65– 104.82 %

Note: AUC_{0}–t: Area under the Concentration–time curve from time zero to the last measurable concentration
AUC_{0}–∞: Area under the Concentration–time curve extrapolated to infinity
Cmax: Maximum plasma concentration

Safety assessment

Both formulations were tolerated without an identified safety concern after single-dose administration. No adverse events or serious adverse events were reported, and no participant discontinued for a safety reason.

Discussion

The study compared single-dose pharmacokinetics of ALGANTIL® 400 mg and BRUFEN® 400 mg film-coated tablets in fasting healthy Moroccan volunteers, while safety observations were collected throughout both crossover periods.

The principal finding was the close agreement in ibuprofen exposure between formulations. The 90% confidence intervals for the test/reference geometric mean ratios of Cmax, $AUC_{0–t}$, and $AUC_{0–\infty}$ all remained within 80.00%–125.00%. Thus, the predefined regulatory criterion was satisfied for measures reflecting both the rate and the extent of absorption.

Absorption was rapid with both products. The observed Tmax values fall within the approximately 1–2-hour range reported for oral ibuprofen in previous pharmacokinetic studies [25]. Elimination was also similar between treatments: The estimated $t_{1/2}$ values were close to the roughly 2-hour half-life described in the literature [26,27].

The concentration-time profiles provide a visual complement to these statistical findings. Test and reference mean curves followed nearly the same course over the sampling period on both linear and semi logarithmic plots, without an evident divergence in the absorption or elimination phases.

These pharmacokinetic results establish that the test 400 mg ibuprofen tablet met the bioequivalence requirements applied to the reference product in this study and provide data relevant to the generic formulation in Morocco.

Safety observations were similarly uncomplicated. No adverse event or serious adverse event was recorded in either period, and no subject withdrew because of safety. These findings should be interpreted within the scope of a single-dose study conducted in healthy volunteers.

The timing of peak concentrations and the short elimination phase observed here are also consistent with published accounts of ibuprofen disposition after oral administration [25]. This agreement supports the plausibility of the pharmacokinetic profiles obtained in the present study.

The fasted setting was chosen to reduce variability attributable to food during gastrointestinal absorption. Published work indicates that food can postpone ibuprofen absorption, although the overall amount absorbed is often affected to a lesser degree [28-30]. Testing under fasting conditions therefore provided a sensitive setting for comparing formulation-related differences in exposure.

Overall, the statistical comparison and the observed concentration-time profiles led to the same conclusion: ALGANTIL® 400 mg and BRUFEN® 400 mg satisfied the bioequivalence criteria under fasting conditions. Tolerability was also similar during the two treatment periods.

Conclusion

In this fasting, single-dose crossover study, the 400 mg test ibuprofen tablet satisfied the prespecified bioequivalence limits relative to the reference formulation. Comparable exposure was demonstrated for the pharmacokinetic parameters used in the assessment, and no safety issue was identified during study participation. The results support comparable in vivo pharmacokinetic performance of the two formulations.

Conflicts of Interest

The authors report no conflicts of interest.

Funding

No external funding was received for this study.

Authors' Contributions

Salma Lazrak contributed to study design, data analysis, interpretation of the findings, and preparation of the manuscript.

Choukri El Khabbaz contributed to study drug administration and blood-sampling activities.

Inass Moufarraj contributed to data collection and critical review of the manuscript.

My El Abbes Faouzi contributed to conduct of the clinical study and data analysis, interpretation.

Miloud El Karbane contributed to the bioanalytical and pharmacokinetic evaluations.

Yahia Cherrah contributed to pharmacokinetic evaluation, supervised the study, and approved the final manuscript.

All authors reviewed and approved the final manuscript.

Informed Consent

Written informed consent was obtained from every participant before enrollment.

Data Availability Statement

The datasets generated and analyzed for this bioequivalence study are not publicly available because of confidentiality agreements. They may be made available by the corresponding author upon reasonable request, subject to the applicable institutional and ethical approvals.

Clinical Trial Registration

Not applicable.

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