AN *IN VIVO* BIOEQUIVALENCE STUDY OF TWO FILM-COATED TABLET FORMULATIONS CONTAINING AMOXICILLIN (875 MG) AND CLAVULANIC ACID (125 MG)

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This was an open-label, randomized, two-treatment, two-sequence, two-period, single-dose crossover study conducted under fasting conditions in 36 healthy volunteers to assess bioequivalence of two film-coated tablet formulations containing amoxicillin 875 mg and clavulanic acid 125 mg. Participants were randomly assigned to receive either the test or the reference formulation containing 875 mg of amoxicillin and 125 mg of clavulanic acid in each study period. A washout interval of six days was applied between the two periods. Blood samples were collected prior to dosing and up to 8 hours post-administration. Plasma concentrations of amoxicillin and clavulanic acid were quantified using a liquid chromatography mass spectrometry method. For amoxicillin, the 90% confidence intervals of the test-to-reference ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 97.38–108.77%, 94.81–103.99%, and 94.66–104.03%, respectively. For clavulanic acid, the corresponding 90% confidence intervals were 96.21–115.11%, 91.31–109.26%, and 91.97–109.48%. All values fell within the accepted bioequivalence range of 80–125%. No adverse event was reported during the study. Bioequivalence and good tolerability were demonstrated between the test and reference products containing amoxicillin 875 mg and clavulanic acid 125 mg in healthy Vietnamese subjects.

Keywords: Bioequivalence, pharmacokinetics, amoxicillin, clavulanic acid.

I. INTRODUCTION

Amoxicillin, a β-lactam antibiotic of the aminopenicillin class, exerts its bactericidal activity by inhibiting the synthesis of peptidoglycan in the bacterial cell wall.[1] Clavulanic acid, a β-lactamase inhibitor, is capable of inactivating β-lactamases produced by most Gram-negative bacteria and Staphylococcus species.[2] The combination of amoxicillin with clavulanic acid results in an antibacterial formulation with an extended spectrum of activity, enabling amoxicillin to act against β-lactamase-producing organisms that are resistant to amoxicillin alone.[3] Following oral administration, the bioavailability of both amoxicillin and clavulanic acid is approximately 70%. The plasma concentrations of each component typically peak at around 1 hour, and both agents have relatively short elimination half-lives of about 1 hour.[4] Amoxicillin and clavulanic acid combination is indicated for the short-term treatment of infections, including respiratory tract infections, genitourinary tract

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infections, skin and soft tissue infections, bone and joint infections, and odontogenic infections, among others.[5]

In Vietnam, the utilization of the antibiotic combination of amoxicillin with clavulanic acid is considerable,[6-8] although the innovator product remains relatively expensive. AUGCLAMOX 1 g, a formulation containing 875 mg of amoxicillin (as amoxicillin trihydrate) and 125 mg of clavulanic acid (as potassium clavulanate), manufactured by Ha Tay Pharmaceutical Joint Stock Company, has the potential to provide greater diversity and improve accessibility in therapeutic options for patients. Moreover, according to the regulations of the Vietnamese Ministry of Health, the amoxicillin and clavulanic acid combination is classified among the substances required to undergo bioequivalence testing as a prerequisite for marketing authorization. Therefore, the present study was conducted to assess the bioequivalence of two film-coated tablet formulations containing amoxicillin 875 mg and clavulanic acid 125 mg in healthy Vietnamese volunteers under fasting conditions.

II. MATERIAL AND METHODS

1. Investigational products

The test product was AUGCLAMOX 1 g film-coated tablets (containing 875 mg of amoxicillin (as amoxicillin trihydrate) and 125 mg of clavulanic acid (as potassium clavulanate)) manufactured by Ha Tay Pharmaceutical Joint Stock Company (Vietnam), while the reference product was AUGMENTIN 1 g film-coated tablets (containing 875 mg of amoxicillin (as amoxicillin trihydrate) and 125 mg of clavulanic acid (as potassium clavulanate)) produced by SmithKline Beecham Pharmaceuticals, UK.

Study Population

The study was conducted in male volunteers aged 18-55 years with a body mass index (BMI) between 18 and 27 kg/m². Healthy volunteers enrolled in the study were required to meet all of the study's inclusion criteria. Eligible subjects underwent medical examinations and clinical laboratory tests (including biochemistry, hematology, immunology, urinalysis, and electrocardiography) to confirm that they were in good health without any clinical or laboratory abnormalities.

Subjects presenting any one of the following characteristics will not be eligible for selection: lack of legal capacity; substance abuse; a history of or current hepatic, renal, gastrointestinal, immunological, hematological, endocrine, neurological, psychiatric, or other acute illnesses; use of prescription medications within 2 weeks or over-the-counter medicines within 1 week prior to dosing; recent blood donation or blood loss exceeding 450 mL; and a history of difficult venipuncture in the antecubital vein.

2. Methods

Study Design

This was a phase I, open-label, randomized, single-dose, two-treatment, two-sequence, two-period crossover clinical trial of film-coated tablets containing amoxicillin 875 mg and clavulanic acid 125 mg. The study was conducted at the Center of Clinical Pharmacology, Hanoi Medical University, in healthy volunteers under fasting conditions. Participants were randomized in a 1:1 ratio to receive either the test or the reference formulation. A washout period of six days was applied between the two study periods.

Sample Size Calculation

Based on previously available study data, the intra-subject variability of pharmacokinetic parameters was estimated to be less than 20% for amoxicillin and approximately 27% for clavulanic acid.[9] Assuming a maximum

difference of ≤5% between the test and reference formulations, a significance level of 5%, and a statistical power of 80% for a two-treatment, two-sequence, two-period crossover design, the required sample size was calculated to be 32 subjects. Considering an anticipated dropout rate of about 12.5%, the total sample size was increased to 36 volunteers, with 18 participants allocated to each sequence.

Study Conduct and Procedures

After screening, all eligible participants were admitted to the study site in the evening prior to dosing in each period. Subjects fasted for at least 10 hours and refrained from water intake for at least 1 hour before drug administration. Each participant received a single study dose with 240 mL of warm water. For 1-hour post-dose, no additional water intake was permitted, and for 2 hours, participants were instructed to remain upright and avoid strenuous physical activity. A standardized meal was provided 4 hours after dosing.

In each study period, 15 blood samples (≈ 6 mL each) were collected into EDTA tubes at the following time points: Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3-, 4-, 6-, and 8-hour post-dose. After each sampling, a heparinized saline solution was flushed into the catheter to prevent clot formation. Blood samples were centrifuged at 4000 rpm for 6 minutes, and plasma was stored at -40 °C ± 5 °C until analysis. The mean time from blood sampling to storage of plasma samples in the freezer was 19 minutes, with a maximum recorded time of 37 minutes.

Participants were under continuous medical supervision throughout the study. On sampling days, vital signs were monitored at baseline, 4 hours, and 8 hours after dosing, or whenever subjects reported discomfort.

Sample Extraction and Analysis

Amoxicillin and clavulanic acid were extracted from plasma using a protein precipitation technique. Protein precipitation was performed by adding 100% acetonitrile to plasma at a ratio of 3:1 (v/v), followed by centrifugation at 6000 rpm for 5 minutes at room temperature. Their concentrations were determined by a validated liquid chromatography mass spectrometry method. Chromatographic separation was achieved on an RP18 column (50 × 2.1 mm, 1.8 µm) with an RP18 guard column (5 × 2.1 mm, 1.8 µm), using a mobile phase consisting of methanol and 0.1% formic acid in water under gradient conditions. Detection was performed by LC-MS/MS with electrospray ionization in the negative mode using multiple reaction monitoring (MRM) transitions of m/z 364.1 → 223.0 for amoxicillin, 198.0 → 136.1 for clavulanic acid, and 348.0 → 207.2 for ampicillin. The assay was selective for amoxicillin, clavulanic acid, and the internal standard (ampicillin). For amoxicillin, the IS-normalized matrix factor was 0.926 (CV 4.8%) at LQC and 0.970 (CV 4.4%) at HQC, indicating slight ion suppression but low variability. For clavulanic acid, the IS-normalized matrix factor was 1.313 (CV 3.8%) at LQC and 1.311 (CV 5.1%) at HQC, suggesting mild ion enhancement with acceptable variability. In all cases, CV values were ≤ 15%, demonstrating that matrix effects were consistent and adequately controlled by the internal standard. A linear correlation was established between amoxicillin concentrations and the amoxicillin-to-internal standard peak area ratio over the calibration range of 100-20,000 ng/mL, with a correlation coefficient (r) ≥ 0.99. Similarly, clavulanic acid showed a linear relationship between concentration and peak area ratio over the range of 50-5000 ng/mL, with r ≥ 0.99. The lower limit of quantification (LLOQ) was 100 ng/mL for amoxicillin and 50 ng/mL for clavulanic acid.

Intra- and inter-day accuracy and precision met acceptance criteria at Low Quality Control (LQC), Medium Quality Control (MQC), and High Quality Control (HQC) levels (within ±15% of nominal values and Coefficient of Variation (CV) < 15%). The mean recovery of amoxicillin was approximately 92% across all QC levels, while the mean recovery of clavulanic acid was 74.8%. Plasma samples were demonstrated to be stable for up to 71 days at -40 °C ± 5 °C and for up to 6 hours at room temperature. After three freeze-thaw cycles, amoxicillin demonstrated mean accuracies of 105.7% (LQC) and 106.1% (HQC), with CV values ≤ 1.9%, while clavulanic acid showed mean accuracies of 97.4% (LQC) and 97.7% (HQC), with CV values ≤ 1.7%. All values were within the predefined acceptance criteria (accuracy 85-115%, precision ≤ 15%), confirming that both analytes were stable in human plasma after three freeze-thaw cycles.

Safety Assessments

Adverse events were monitored, with details of their management recorded, and each event was assessed for its causal relationship to study medication.

Pharmacokinetic and Statistical Analyses

C_{max} and T_{max} were obtained directly from the plasma concentration-time data. The area under the curve (AUC) was calculated using the linear trapezoidal rule, and $AU_{0-\infty}$ was determined as the sum of AUC_{0-t} and the ratio of the last measurable plasma concentration (C_{last}) to the terminal elimination rate constant (λz), i.e., $AUC_{0-t} + C_{last}/\lambda z$. The terminal elimination rate constant was determined from the slope of the log-transformed concentration-time curve in the terminal elimination phase, calculated using at least three concentration data points ($r^2 \approx 0.99$).

Analysis of variance (ANOVA) was applied to the log-transformed C_{max} and AUC values. Bioequivalence was concluded if the 90% confidence intervals for the test-to-reference ratios of C_{max} and AUC fell within the acceptance range of 80-125%. T_{max} was compared using the non-parametric Wilcoxon test. All statistical analyses were performed using Phoenix WinNonlin version 5.2.

3. Ethics

The study protocol was reviewed and approved by the Hanoi Medical University Institutional Ethical Review Board, under Approval No. 1537/GCN-HMUIRB on July 1, 2024.

The trial was carried out in accordance with the principles of Good Clinical Practice (GCP), the ethical standards of the Declaration of Helsinki, and applicable Vietnamese regulations. Written informed consent was obtained from all volunteers prior to study participation.

III. RESULTS

1. Demographics

The study initially screened 48 male subjects, of whom 36 healthy volunteers were enrolled. Their mean age was 22.3 ± 2.7 years old, with an average height of 1.69 ± 0.05 m and a mean body weight of 63.9 ± 7.6 kg, resulting in a mean body mass index (BMI) of 22.3 ± 2.2 kg/m². Participants were randomized in a 1:1 ratio into two treatment sequences receiving film-coated tablets containing amoxicillin 875 mg and clavulanic acid 125 mg. Demographic characteristics were comparable between sequences, with no statistically significant difference observed (Table 1). All subjects completed the study.

Table 1. Demographic Characteristics of Subjects by Treatment Sequence

Parameters	Sequence 1 (n=18)	Sequence 2 (n=18)	p-value
Age (years)	22.22 ± 2.82	22.39 ± 2.66	0.86
Height (m)	1.69 ± 0.05	1.69 ± 0.05	0.80
Weight (kg)	62.56± 8.16	65.33 ± 7.24	0.29
BMI (kg/m^2)	21.71 ± 1.99	22.84 ± 2.36	0.13

2. Pharmacokinetic Analysis

The mean plasma concentration-time profiles of amoxicillin and clavulanic acid following administration of the test and reference products under fasting conditions are presented in Figures 1 and 2. The pharmacokinetic parameters obtained after a single oral dose of film-coated tablets containing 875 mg of amoxicillin and 125 mg of clavulanic acid are summarized in Tables 2 and 3.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amoxicillin under fast conditions.

Parameters	Unit	Test (n=36)	Reference (n=36)
C_{max}	ng/ml	11884.0 ± 2655.8	11657.1 ± 3020.9
AUC_{0-t}	h·ng/ml	38118.2 ± 6938.8	38579.9 ± 8094.5
$AUC_{0-\infty}$	h·ng/ml	38975.5 ± 7254.3	39467.8 ± 8384.8
T_{max}	hour	1.75 (0.75-4.00)	1.75 (1.25-4.00)
$t_{1/2}$	hour	1.25 ± 0.19	1.21 ± 0.27
$AUC_{0-t}/AUC_{0-\infty}$	%	97.87 ± 1.15	97.82 ± 1.46

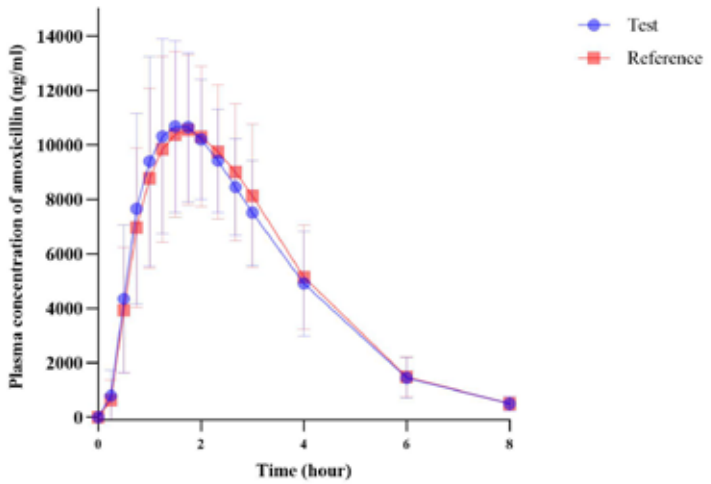

Figure 1. Mean plasma concentration- time curves of amoxicillin after a single oral dose of 875 mg amoxicillin and 125 mg clavulanic acid film-coated tablet

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clavulanic acid under fast conditions

Parameters	Unit	Test (n=36)	Reference (n=36)
C_{max}	ng/ml	2476.1 ± 1087.8	2250.9 ± 769.6
AUC_{0-t}	h·ng/ml	5733.1 ± 2157.3	5545.2 ± 1656.6
$AUC_{0-\infty}$	h·ng/ml	5902.4 ± 2149.6	5710.3 ± 1688.2
T_{max}	hour	1.25 (0.75-3.0)	1.25 (0.75-3.0)
$t_{1/2}$	hour	1.08 ± 0.13	1.07 ± 0.16
$AUC_{0-t}/AUC_{0-\infty}$	%	96.61 ± 2.22	97.04 ± 1.49

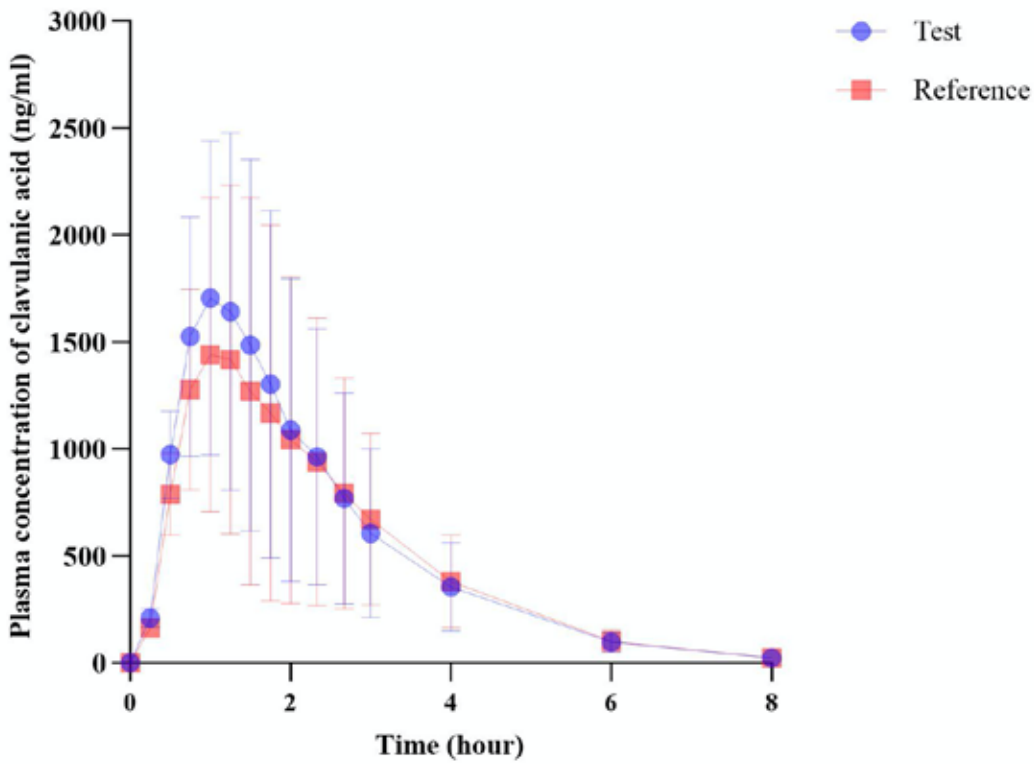

Figure 2. Mean plasma concentration- time curves of clavulanic acid after a single oral dose of 875 mg amoxicillin and 125 mg clavulanic acid film-coated tablet

Both amoxicillin and clavulanic acid were rapidly absorbed, reaching peak plasma concentrations at 1.75 hours for amoxicillin and 1.25 hours for clavulanic acid. The C_{max} values of amoxicillin for the test and reference formulations were 11,884.0 ± 2,655.8 and 11,657.1 ± 3,020.9, respectively. For clavulanic acid, the corresponding C_{max} values were 2,476.1 ± 1,087.8 for the test product and 2,250.9 ± 769.6 for the reference product. No statistically significant difference was observed in the pharmacokinetic parameters of

amoxicillin or clavulanic acid between the test and reference formulations.

3. Bioequivalence

ANOVA analysis of the pharmacokinetic parameters showed no statistically significant differences between the test and reference products, and no significant sequence or period effects were observed. Although a statistically significant subject effect was identified, this reflects normal inter-subject variability in a crossover design and does not affect the bioequivalence conclusion. The geometric mean ratios (test/reference) for amoxicillin were 102.92% for C_{max}, 99.29% for AUC_{0-t}, and 99.24% for $AUC_{0-\infty}$ (Table 3). For clavulanic acid, the corresponding geometric mean ratios were 105.23% for C_{max}, 99.88% for AUC_{0-t}, and 100.34% for $AUC_{0-\infty}$ (Table 4). According to ASEAN guidelines, the two formulations (test and reference) were concluded to be bioequivalent *in vivo*.

Table 3. Bioequivalence analysis of amoxicillin after a single oral dose of 875 mg amoxicillin and 125 mg clavulanic acid film-coated tablet

Pharmacokinetic parameters	C_{max} (ng/ml)	AUC_{0-t} (h·ng/ml)	$AUC_{0-\infty}$ (h·ng/ml)
Geometric mean value (test)	11598.3	37538.7	38358.9
Geometric mean value (reference)	11269.2	37806.5	38654.2
Geometric mean value and ratio T/R (%)	102.92	99.29	99.24
ANOVA (p value)			
Sequence	0.950	0.822	0.863
Subject	1.4E-06	1.5E-05	1.7E-05
Formulation	0.385	0.796	0.785
Period	0.910	0.852	0.926
90% confidence interval (Test/ Reference)			
Intra-subject CV (%)	13.95	11.63	11.89
POWER TOST (%)	100.00	100.00	100.00
90% CI (%)	97.38%- 108.77%	94.81%- 103.99%	94.66%- 104.03%

Table 4. Bioequivalence analysis of clavulanic acid after a single oral dose of 875 mg amoxicillin and 125 mg clavulanic acid film-coated tablet.

Pharmacokinetic parameter	C_{max} (ng/ml)	AUC_{0-t} (h·ng/ml)	$AUC_{0-\infty}$ (h·ng/ml)
Geometric mean value (test)	2231.4	5295.4	5482.8
Geometric mean value (reference)	2120.4	5301.6	5464.1
Geometric mean value and ratio T/R (%)	105.23	99.88	100.34
ANOVA (p value)			

Pharmacokinetic parameter	C_{max} (ng/ml)	AUC_{0-t} (h·ng/ml)	$AUC_{0-\infty}$ (h·ng/ml)
Sequence	0.641	0.579	0.573
Subject	3.6E-07	2.1E-05	2.0E-05
Formulation	0.343	0.983	0.947
Period	0.068	0.028	0.031
90% confidence interval (Test/ Reference)			
Intra-subject CV (%)	22.79	22.80%	22.13%
POWER TOST (%)	93.73	98.66%	99.04%
90% CI (%)	96.21% - 115.11%	91.31% - 109.26%	91.97% - 109.48%

Safety

There were no adverse event recorded during the course of the study.

IV. DISCUSSION

Bioequivalence assessment is essential to confirm that two pharmaceutical formulations containing the same active ingredient exhibit comparable absorption characteristics in terms of both rate and extent, thereby providing the basis for bridging to previously conducted studies and supporting the determination that the two products are therapeutically equivalent. Demonstration of bioequivalence helps ensure that the test product will produce the same clinical efficacy and safety profile as the reference product when administered at the same dose. Therefore, bioequivalence studies play a critical role in regulatory approval and in facilitating the development of generic medicines.

Our study was designed in accordance with the current bioequivalence recommendations of the Association of Southeast Asian Nations (ASEAN) and the European Medicines Agency (EMA).[10,11] Both guidelines specify that the 90% confidence intervals for the ratios of C_{max} and AUC must fall within the acceptance range of 80-125%, and they require a randomized, two-period crossover design with log-transformed analysis of pharmacokinetic parameters.

Amoxicillin combined with clavulanic acid enhances antibacterial efficacy by inhibiting β-lactamase enzymes produced by resistant bacteria. This combination broadens the antimicrobial spectrum of amoxicillin against both Gram-positive and Gram-negative organisms. Amoxicillin and clavulanic acid can be taken either with or without food.[4] In this study, the fasting condition was employed to minimize potential confounding factors and to facilitate the detection of any differences between the two formulations.

The sample size of the study was determined based on a reference intra-subject CV of 27% to ensure the minimum required statistical power in accordance with standard practice. The analysis results showed that the observed intra-subject CV was approximately 22% for the primary pharmacokinetic parameters, which is lower than the value used for sample size calculation. Consequently, the TOST power was high (93.73%-99.04%).

The 90% confidence intervals of the geometric mean ratios between the test and reference formulations were all within

the accepted bioequivalence limits for both amoxicillin (C_{max}: 97.38-108.77%; AUC_{0-t}: 94.81-103.99%; $AUC_{0-\infty}$: 94.66-104.03%) and clavulanic acid (C_{max}: 96.21-115.11%; AUC_{0-t}: 91.31-109.26%; $AUC_{0-\infty}$: 91.97-109.48%). These findings demonstrate that the two formulations are fully bioequivalent according to the predefined criteria. Furthermore, the AUC_{0-t}/ $AUC_{0-\infty}$ ratios for all subjects exceeded 90%, confirming that the sampling period up to 8 hours post-dose was sufficient to reliably characterize systemic exposure.[11-13] These findings are consistent with the study conducted by Abdalwali A. Saif et al. (2014), which also demonstrated bioequivalence for both active ingredients. In terms of study design, both investigations employed a crossover, single-dose, under fasting conditions in healthy volunteers, allowing direct comparison of PK outcomes. However, our study utilized a liquid chromatography mass spectrometry analytical method, which offers greater sensitivity and specificity compared with the high-performance liquid chromatography method used by Abdalwali A. Saif et al., thereby improving the accuracy of quantifying amoxicillin and clavulanic acid.[14]

Common adverse effects of amoxicillin/ clavulanic acid include gastrointestinal symptoms such as diarrhea, nausea, and vomiting, as well as skin rash and pruritus. Less frequent reactions include transient elevations in liver enzymes and, rarely, cholestatic hepatitis or anaphylaxis. Most adverse effects are mild and reversible upon discontinuation of therapy. The safety profile observed in this study was favorable, as no adverse events were reported and all participants completed the trial. This further supports the tolerability of both formulations when administered as a single oral dose in fasting healthy volunteers.

Nonetheless, since the two formulations were demonstrated to be bioequivalent, the findings support improved accessibility to the amoxicillin and clavulanic acid combination for patients in Vietnam.

V. CONCLUSIONS

The study demonstrated that the two film-coated tablet formulations containing 875 mg of amoxicillin and 125 mg of clavulanic acid are bioequivalent in healthy Vietnamese male adults under fasting conditions. Both products exhibited comparable pharmacokinetic parameters and were well tolerated.

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