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# Comparative Bioavailability Study of Two 81 mg Coated Tablet Formulations of Acetylsalicylic Acid in Fasting Healthy Volunteers

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## Abstract

**Introduction:** Low-dose acetylsalicylic acid is used as antithrombotic agent and the enteric-coated formulations are widely used to minimize the gastrointestinal side effects.

**Aim:** To compare the bioavailability of two acetylsalicylic acid formulations (Ecasil-81®, 81 mg coated tablet) in fasting healthy volunteers.

**Methods:** Healthy volunteers (n=16) were recruited to a monocentric, open label, randomized, two-way crossover pharmacokinetic study, with seven days washout period between the treatments. They received a single 81 mg oral dose of a test (new formulation) or a standard reference formulation of acetylsalicylic acid (Ecasil-81®) after about 8 h fasting. Blood samples were collected over a period of 36 h. The salicylic acid plasma concentration was evaluated by high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS). Noncompartmental pharmacokinetic analysis was performed using the WinNonlin program.

**Results:** The maximum plasma concentration ($C_{max}$) of salicylic acid was 5433 and 5719 ng/mL reached in 3.66 and 4.02 h ($t_{max}$) for the test and the reference formulation, respectively. The 90% confidence interval of the ratios of geometric means of $C_{max}$ and area under curve of plasma concentration until the last concentration observed ($AUC_{0-last}$) were within the interval 80-125%.

**Conclusion:** The new acetylsalicylic acid formulation has a bioavailability equivalent to the reference formulation for the rate and the extent of absorption.

**Keywords:** Acetylsalicylic acid; Salicylic acid; Bioavailability; Pharmacokinetics; HPLC-MS/MS.

**Abbreviations:** HPLC-MS/MS: High-performance Liquid Chromatography Coupled to Tandem Mass Spectrometry; $C_{max}$: Maximum Plasma Concentration; $t_{max}$: Time to Reach the Maximum Plasma Concentration; $AUC_{0-last}$: Area under Curve of Plasma Concentration Until the Last Concentration Observed; $AUC_{0-\infty}$: Area under the Plasma Concentration versus Time Curve from Time 0 Extrapolated to Infinity; $t_{1/2}$: Elimination Half-life; COX: Cyclooxygenase; GI: Gastrointestinal; CI: Confidence Interval; CV: Coefficient of Variation; °C: Degree centigrade; ECG: Electrocardiogram; LOQ: Lower Limit of Quantification; QC: Quality Control; IS: Internal Standard; MRM: Multiple Reaction Monitoring; MFN: Matrix Factor Normalized by IS; g: Gram; ng/mL: Nano Gram/Millilitre; h: Hour; s: Second; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; HBsAg: Hepatitis B Virus; Anti-HBc: Hepatitis B Surface Antigen

## Introduction

Acetylsalicylic acid is one of the most widely used drug as an anti-inflammatory, analgesic, and antipyretic drug. Moreover, in low-dose it is also used as antithrombotic agent to inhibit cyclooxygenase-dependent platelet aggregation responsible for the formation of thrombi, which may be related to myocardial infarction and stroke [1-3].

Acetylsalicylic acid also inhibits Cyclooxygenase (COX) in the Gastrointestinal (GI) tract, which may lead to significant side effects including dyspeptic symptoms, peptic ulcers, as well as serious upper GI ulcer-related complications such as peptic ulcer bleeding or perforation, even when acetylsalicylic acid is given at low doses [4-6]. Enteric-coated formulations are widely used to minimize the GI side effects of acetylsalicylic acid and have been shown to reduce, at least partially, these GI toxicity [7,8]. Regarding the anti-platelet effects, some studies suggest the enteric-coated formulations may be less bioavailable and might decrease the anti-thrombotic activity, mainly at low doses [9-11]. However, an enteric-coated, low-dose (81 mg acetylsalicylic acid) study reported that the anti-platelet effects are not adversely affected by enteric coating [12].

After oral administration, acetylsalicylic acid is well absorbed in the gastrointestinal tract and quickly hydrolyzed to form salicylic acid, the primarily responsible for the pharmacological effect of acetylsalicylic acid. Further, salicylic acid is metabolized to salicyluric acid, gentisic acid and other conjugates or the compound can be directly excreted [13,14]. The maximum plasma concentration ($C_{max}$) was 170 ng/mL reached in 3.25 ($t_{max}$) for acetylsalicylic acid and 3780 ng/mL with $t_{max}$ of 4.75 h for salicylic acid. Their elimination half-life (t1/2) was 0.65 and 2.04 h for acetylsalicylic acid and salicylic acid, respectively, after a single oral dose administration of an enteric-coated pellets 100 mg acetylsalicylic acid in healthy volunteers [2].

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This study aims to compare the bioavailability of two acetylsalicylic acid formulations (Ecasil-81®, 81 mg coated tablet) in fasting healthy volunteers after a single oral dose administration. Considering that acetylsalicylic acid is rapidly converted to salicylic acid and it is the primarily responsible for the pharmacological effect of the parent drug, the acetylsalicylic acid formulations bioavailability was investigated through the salicylic acid measurement in plasma using high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS).

## Materials and Methods

### Clinical protocol

Sixteen healthy volunteers of both sexes (8 female and 8 male) aged between 18 and 55 years old and not obese (Table 1) were included in this study. They had liver, kidney and cardiac function within normal limits previously accessed by clinical evaluation (medical history, physical examination and ECG) and the laboratory tests (haemoglobin, haematocrit, total and differential white cell counts, blood glucose, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, albumin, total protein, triglyceride, total cholesterol, uric acid, routine urinalysis and proto-parasitological). All subjects were negative for HIV, HCV, HBsAg and Anti-HBc. All female subjects were negative for the beta human chorionic gonadotropin test. One volunteer dropped out of the study for personal reasons. The study was approved by the local Research Ethics Committee (protocol GDN 014/15) and the subjects signed the informed consent. The study was performed according to the 2008 revised Declaration of Helsinki for biomedical research involving human subject.

This study was performed with a monocentric, open label, randomized, two-way crossover pharmacokinetic study, with seven days washout period between the treatments. The healthy volunteers were hospitalized and received a single oral 81 mg dose of a test (new formulation) or standard reference formulation of acetylsalicylic acid (Ecasil-81® Biolab Sanus Farmacêutica, Brazil) with 200 mL of water after an overnight fast (approximately 8 h). Blood samples (7 mL) were collected via a venous catheter into heparinized tubes at times zero, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24 and 36 h after drug administration.

The plasma samples for chromatographic analysis were obtained by centrifugation (2000 g × 10 min) of the blood samples. Plasma samples were stored at -70°C until the time analysis.

The safety assessment was based on recording adverse events throughout the study duration. The subject's systolic and diastolic pressures, heart rate and temperature were determined prior and at approximately 4, 8, 12 and 24 h after drug administration. The clinical evaluation and the laboratory tests were also performed at the end of the study.

### Analytical assays

**Chemicals and reagents:** Salicylic acid was purchased from the United States Pharmacopeia (Rockville, MD, USA), and salicylic acid-d4 was purchased from Toronto Research Chemicals (North York, Canada). Acetonitrile and methanol (HPLC grade) were purchased from J.T. Baker (Phillipsburg, NJ, USA); ammonium acetate, acetic acid, ethanol and dichloromethane (analysis grade) from J.T. Baker (Ecatepec, Mexico). The water was obtained from the purification system Synergy UV® (Millipore, Molsheim, France).

### Calibration standards and quality controls

Stock solutions of salicylic acid and salicylic acid-d4 (IS: Internal Standard) were prepared in methanol/water (50/50, v/v). Calibration curves for salicylic acid were prepared by adding salicylic acid to blank plasma to yield final concentrations of 50, 100, 200, 500, 1000, 1800, 2800 and 4000 ng/mL. The calibration curves were performed in duplicate for each day's assays. The Quality Control (QC) samples were prepared in blank plasma at low, middle 1, middle 2 and high concentrations of 80, 160, 1600, and 3200 ng/mL, respectively. The dilution QC was prepared in blank plasma at 6400 ng/mL.

### Sample preparation

Aliquots of 100 µL of plasma were added to glass tubes and spiked with 50 µL of IS solution (salicylic acid-d4 5000 ng/mL). The tubes were vortexed for 5 s and 10 µL of formic acid 88% were added. The samples were vortexed for 5 s again. Three mL of ether/dichloromethane (60/40, v/v) were added and the samples were vortexed for 50 s. The samples were frozen at -80°C and the organic phase transferred to another tube in which the organic solvents were evaporated under N2 flow at 45°C. The dry residues were dissolved in 200 µL of methanol/water (50/50, v/v)+20 nM ammonium acetate, vortexed for 10 s and transferred to microvials for analysis.

### Liquid chromatography

An aliquot (15 µL) of each plasma extracted was injected into a 150 × 4.6 mm Inertsil ODS-3 column. The temperature of column was maintained constant at 60°C. The mobile phase used was methanol/water (50/50, v/v)+20 nM ammonium acetate at a flow rate of 900 µL/min. The temperature of the auto-sampler was maintained at 25°C.

### Mass spectrometry

A Quattro Micro mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray interface operating in negative ion mode was configured for Multiple Reaction Monitoring (MRM) to monitor the transitions 137.00>93.00 and 141.30>97.20 for salicylic acid and salicylic acid-d4, respectively. The ion-spray capillary voltage was set at -2.8 kV. The voltage of the cone was kept at -35 V for salicylic acid and -25 V for salicylic acid-d4. The collision energy was -20 eV for salicylic acid and salicylic acid-d4. The data acquisition and quantification were performed using MassLynx version 4.0 software (Micromass, Manchester, UK).

### Method validation

The method validation was carried out according to the United States Food and Drug Administration (FDA) bioanalytical method validation guidance [15] and the Brazilian National Sanitary Surveillance Agency (ANVISA) [16]. To evaluate the specificity of the method, eight different blank plasma lots (4 normal, 2 hemolyzed and 2 lipemic plasmas) were tested for its interferences using the proposed extraction procedure and the chromatographic or spectroscopic conditions and compared with those obtained in the samples processed from the Lower Limit

| Variable | Healthy volunteers |
|---|---|
| Age (years) | 31.0 (18.0-51.0) |
| Weight (kg) | 71.0 (51.0-86.0) |
| High (m) | 1.68 (1.55-1.75) |
| Body mass index (kg/m²) | 25.28 (21.23-28.73) |
| Gender (Male/Female) | 8/7 |

**Table 1:** Demographic data of the healthy volunteers (n=15).

of Quantification (LLOQ). The calibration curves were prepared by assaying standard plasma samples at eight concentrations of salicylic acid (50-4000 ng/mL) in triplicate and the linearity of each calibration curve was determined by plotting the peak area ratio (y) of salicylic acid/internal standard vs. nominal concentration of analyte. The calibration curve was constructed by weighted (1/x) least squares linear regression. The accuracy and precision of assay were evaluated by intra- and inter-assay studies. Seven aliquots of each QC plasma samples (80, 160, 1600, 3200 and 6400 ng/mL) were run in three validation batches on three different days. Inter and intra-day precisions were determined as coefficient of variation, CV (%)=(SD/M) × 100 and the accuracy as the percentage relative error, RE (%)=[(E-T)/T] × 100, where M is the mean, SD is the standard deviation of M, E is the experimentally determined concentration and T is the theoretical concentration. The matrix effect experiments were performed using the ratio between salicylic acid (80 and 3200 ng/mL) and IS injected directly into the mobile phase and standard solutions added to blank plasma extracts (4 normal, 2 hemolyzed and 2 lipemic plasmas). Each sample was obtained by a matrix factor normalized by IS (MFN) according to the following formula: MFN=(response of the analyte in matrix/internal standard response matrix)/(response of the analyte in solution/response of the internal standard solution). Stability QC plasma samples (80 and 3200 ng/mL) were subjected to short-term (6 h 24 min) room temperature, three freezes-thaw (-20-25°C) cycles and 44 h 40 min autosampler (25°C) stability tests in triplicate. The stability results were compared with the nominal value.

### Pharmacokinetic and statistical analysis

Pharmacokinetic analysis was performed using the WinNonlin software, version 5.0 (Pharsight Corp, Mountain View, CA, USA). The pharmacokinetic parameters were calculated based on the plasma concentrations obtained experimentally using a non-compartmental model.

Statistical analysis was performed based on a multivariate model for values of area under curve of plasma concentration (AUC) and $C_{max}$ using Graph Pad Prism Version 3.02 software. The design was evaluated using an appropriate model (Mixed Models Procedure), having the treatment as fixed effect and the subjects as a random effect. The comparative bioavailability mean evaluation was performed by the geometric mean of the confidence interval, using two-tailed tests. The established criteria for all the parameters were 90% confidence interval within the range of 80-125%.

## Results and Discussion

The healthy volunteers included in the study (n=15) well tolerated the clinical protocol and reported no clinically significant adverse effects. Only eight subjects reported headache, which was considered probably not related to the administration of acetylsalicylic acid. The clinical evaluation, the monitoring of vital signs and laboratory tests presented no clinically relevant alterations after acetylsalicylic acid administration.

The method for analysis of salicylic acid was developed using the HPLC-MS/MS system and a liquid-liquid extraction. The salicylic acid was separated on a Inertsil ODS-3 column, with a mobile phase consisting of methanol/water (50/50, v/v)+20 nM ammonium acetate. The retention time of salicylic acid and IS was 2.36 ± 0.3 and 2.32 ± 0.3, respectively, and the total run time was 3.7 min. The spectrum for compounds showed base peak ions ([M+H]-) at mass-to-charge ratio (m/z) of 137.30 for salicylic acid and 141.36 for salicylic acid-d4 (Figure 1A and 1C). The product ion scan showed that m/z 93.18 and 97.06 were the most abundant product ions for salicylic acid (Figure 1B) and salicylic acid-d4 (Figure 1D). Figure 2 exhibits the chromatograms of blank human plasma (Figure 2A), human plasma spiked with 1000 ng/mL salicylic acid and 5000 ng/mL salicylic acid-d4 (Figure 2B),

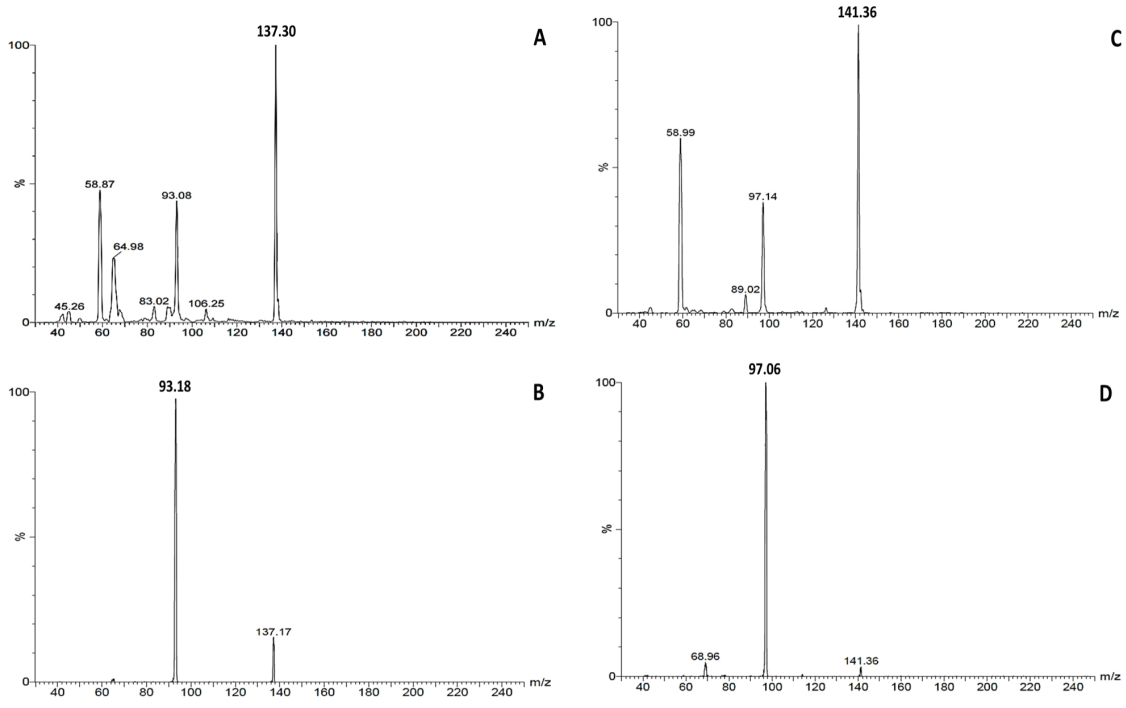


**Figure 1:** (A) Mass spectrum of the protonated molecular ion of salicylic acid-m/z=137.30; (B) Ion product of salicylic acid-m/z=93.18; (C) Protonated molecular ion of salicylic acid-d4-m/z=141.36; and (D) The ion product of salicylic acid-d4-m/z=97.06.

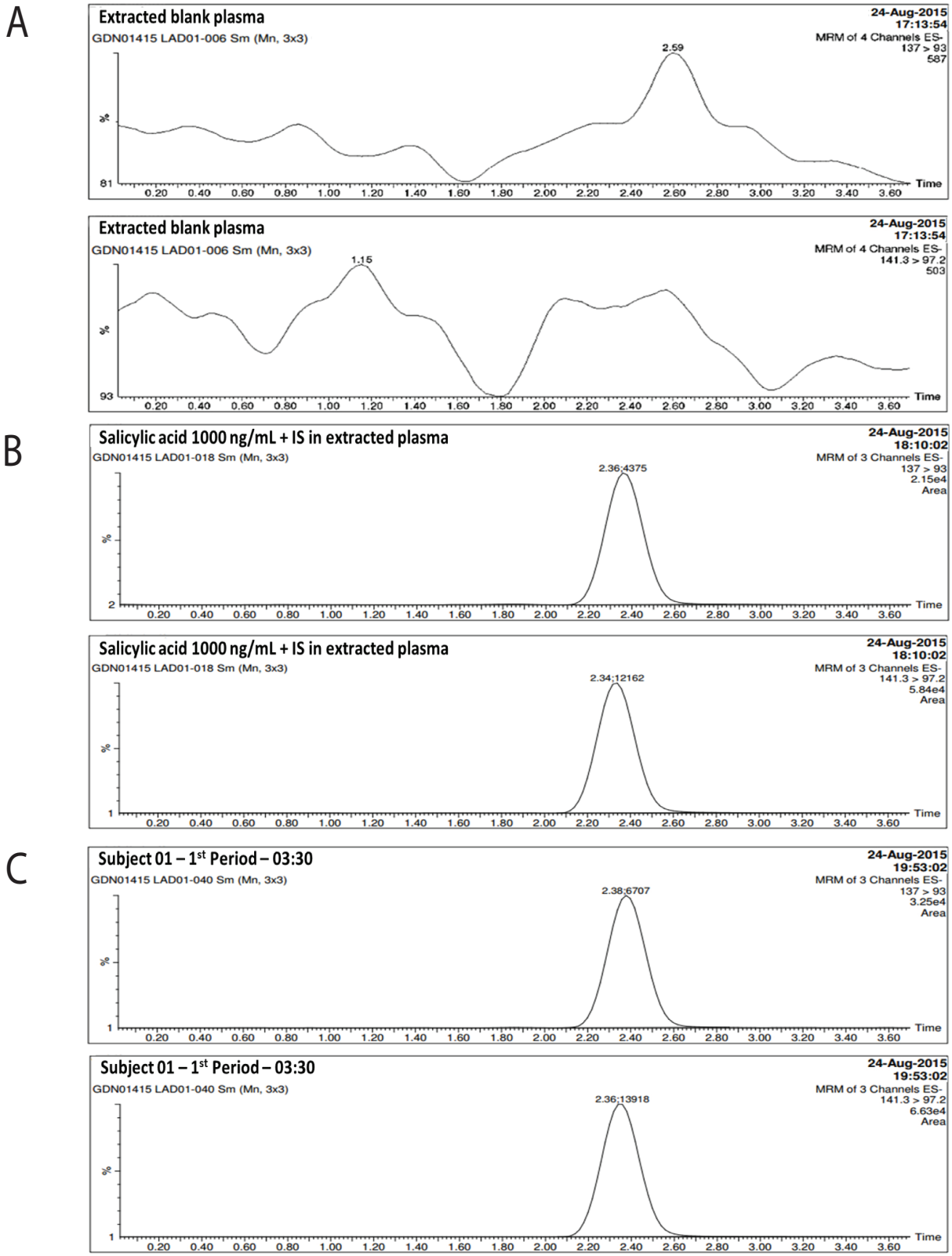


**Figure 2:** Chromatograms obtained in the analysis of salicylic acid in plasma. (A) Blank human plasma; (B) Blank plasma spiked with salicylic acid (1000 ng/mL) and salicylic acid-d4 (5000 ng/mL); and (C) Plasma of a healthy volunteer obtained 3.30 h after oral dose administration test formulation of 81 mg salicylic acid.

and plasma obtained from a healthy volunteer at 3.5 h after the test drug administration (Figure 2C). The retention times for salicylic acid-d4 and salicylic acid-d4 were 3.36 ± 0.3 min and 3.32 ± 0.3 min, respectively (Figure 2). No endogenous peaks were observed in this area of the chromatogram of blank plasma. Thus, for all eight different blank plasma samples, the retention time regions were free from endogenous interfering peaks. The calibration curves were linear for concentrations of 50-4000 ng/mL and the representative regression equation for the calibration curves was y=0.000331944x+0.00295049 (r =0.999504). The within- and between-run precision and accuracy for the LLOQ and QCs are summarized in Table 2. The percentage relative error accuracy and the CV obtained in precision studies were lower than 15%, insuring the reproducibility and repeatability of the results. The data presented in Table 3 indicate no significant matrix effect on ionisation of salicylic acid and IS in human plasma (four normal, two lipemic, and two hemolysates plasmas). The stability studies did not reveal any significant degradation under the conditions of the experiment in the short-term stability at room temperature (4 h), freeze-thaw test (three cycles) and post processing stability test (24 h), as shown by CV and accuracy lower than 15% (Table 4).

The salicylic acid plasma concentration versus time curves constructed from analysis of serial plasma samples collected from the healthy volunteers (n=15) after oral administration of 81 mg test or reference formulation of acetylsalicylic acid are shown in Figure 3 and the pharmacokinetic parameters of salicylic acid are shown in Table 5. After oral administration of acetylsalicylic acid, the metabolite salicylic acid reached a $C_{max}$ of 5433 and 5719 ng/mL in 3.66 and 4.02 h ($t_{max}$) for the test and for the reference formulation, respectively. The $AUC_{0-\infty}$ values were 23800 and 21527 ng.h/mL and the $t_{1/2}$ was 3.17 and 2.65 h for the test and for the reference formulation, respectively. Bae et al. [2] reported values of 3780 ng/mL for $C_{max}$, 4.45 h for $t_{max}$, 18200 ng.h/mL for $AUC_{0-\infty}$ and 2.04 for $t_{1/2}$ after a single oral dose administration of an enteric-coated pellets 100 mg acetylsalicylic acid in healthy volunteers.

The 90% confidence interval (CI 90 %) of the ratios of geometric means of $C_{max}$ and $AUC_{0\text{-}last}$ were completed contained in the interval 80-125% (Table 6), established by FDA [17] and ANVISA [18] indicating that the new acetylsalicylic acid formulation (test) has a bioavailability equivalent to the reference formulation for the rate and the extent of absorption.

## Conclusion

Considering that the 90% confidence interval of the geometric mean ratios of $C_{max}$ and $AUC_{0\text{-}last}$ were within the range 80-125%, it was concluded that the new formulation (Ecasil-81® coated tablet, 81 mg acetylsalicylic acid, Biolab Sanus Farmacêutica Ltda.) is bioequivalent to the reference formulation (Ecasil-81® coated tablet, 81 mg acetylsalicylic acid, Biolab Sanus Pharmaceuticals Ltd.) for the rate and the extent of absorption. In addition, both formulations were well tolerated by the subjects included in this study.

| Parameter | Salicylic acid (ng/mL) | | | | | |
|---|---|---|---|---|---|---|
| | LLOQ (50) | QC (80) | QC (160) | QC (1600) | QC (3200) | QC (6400-1:2) |
| **Intra-batch** | | | | | | |
| Mean (n=7) | 51.9 | 80.1 | 160.0 | 1620.0 | 3240.0 | 3300.0 |
| Precision (CV %) | 5.8 | 4.1 | 1.0 | 1.0 | 1.5 | 1.3 |
| Accuracy (%) | 103.8 | 100.1 | 101.1 | 101.4 | 101.2 | 103.1 |
| **Inter-batch** | | | | | | |
| Mean (n=21) | 52.2 | 84.7 | 168.5 | 1599.9 | 3179.6 | 3210.5 |
| Precision (CV %) | 7.5 | 5.9 | 4.7 | 2.2 | 3.5 | 4.9 |
| Accuracy (%) | 104.4 | 105.9 | 105.3 | 100.0 | 100.1 | 100.3 |

CV%=[(SD/M) × 100]; Accuracy%=[(E−T)/T] × 100; CV: Coefficient of Variation; M: Mean; SD: Standard Deviation of M; E: Experimentally Determined Concentration; T: Theoretical Concentration; LLOQ: Lower Limit of Quantification; QC: Quality Control

**Table 2:** Precision and accuracy data from salicylic acid validation in human plasma.

| Salicylic acid | FMN | CV (%) |
|---|---|---|
| 80 ng/mL | 0.027 | 2.6 |
| 3200 ng/mL | 1.017 | 1.0 |

FMN: Matrix factor normalized by internal standard [(response of the analyte in matrix/internal standard response matrix)/(response of the analyte in solution/response of the internal standard solution)]. CV: Coefficient of Variation [(standard deviation FMN/mean FMN) × 100]

**Table 3:** Matrix effect for salicylic acid and Internal Standard (IS) in eight different lots of human plasma: 4 normal, 2 lipemic and 2 hemolysate plasmas.

| Stability | Mean (ng/mL) | CV (%) | Accuracy (%) |
|---|---|---|---|
| **Short term (4 h)** | | | |
| 80 ng/mL | 76.2 | 5.0 | 95.3 |
| 3200 ng/mL | 3050 | 1.9 | 95.3 |
| **Freeze/thaw (3 cycles)** | | | |
| 80 ng/mL | 78.1 | 2.1 | 97.6 |
| 3200 ng/mL | 3050 | 1.0 | 95.3 |
| **Post-processing (24 h)** | | | |
| 80 ng/mL | 77.1 | 4.1 | 96.4 |
| 3200 ng/mL | 3070 | 0.1 | 95.9 |

CV %: Coefficient of Variation [(SD/mean) × 100]; Accuracy %=[(E−T)/T] × 100; E: Experimentally Determined Concentration; T: Theoretical Concentration

**Table 4:** Study of the stability method of analysis of salicylic acid in human plasma.

| Parameter | Salicylic acid - Test drug | | | | Salicylic acid - Reference drug | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Minimum | Maximum | Mean | SD | Minimum | Maximum |
| $AUC_{0\text{-last}}$ (ng.h/mL) | 21682 | 4203 | 13489 | 13539 | 21150 | 14758 | 14758 | 20447 |
| $AUC_{0\text{-}\infty}$ (ng.h/mL) | 23800 | 9298 | 13853 | 40352 | 21527 | 4926 | 14953 | 20445 |
| $AUC_{\%\ extrap}$ (%) | 4.75 | 12.71 | 0.31 | 50.33 | 1.79 | 1.17 | 0.55 | 4.12 |
| $C_{max}$ (ng/mL) | 5433 | 1235 | 3330 | 3950 | 5719 | 1359 | 3530 | 4910 |
| $C_{last}$ (ng/mL) | 181 | 344 | 53 | 1366 | 101 | 57 | 51 | 207 |
| $t_{max}$ (h) | 3.66 | 1.58 | 1.75 | 6.25 | 4.02 | 1.73 | 1.00 | 7.00 |
| $t_{1/2}$ (h) | 3.17 | 3.00 | 1.04 | 12.36 | 2.65 | 1.18 | 1.59 | 4.07 |
| Kel ($h^{-1}$) | 0.31 | 0.14 | 0.05 | 0.61 | 0.30 | 0.09 | 0.12 | 0.31 |

$C_{max}$, maximum plasma concentration; $t_{max}$, time to reach $C_{max}$; AUC, area under the plasma concentration versus time curve; $t_{½}$, elimination half-life; Kel, elimination rate constant.

**Table 5:** Pharmacokinetics of salicylic acid in healthy volunteers (n=15) after a single oral dose administration of a test or reference formulation of 81 mg coated tablet acetylsalicylic acid.

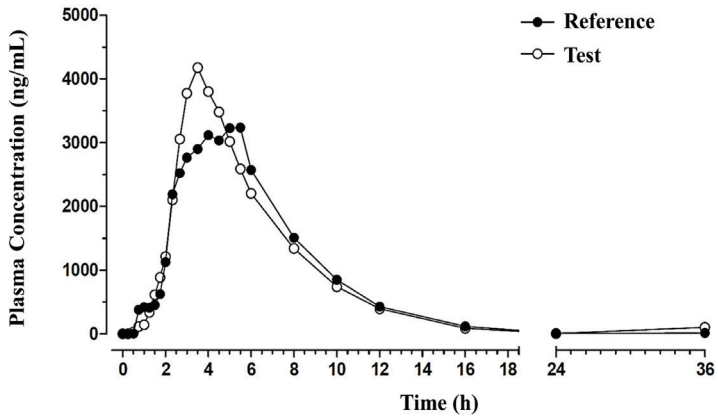


**Figure 3:** Plasma concentration versus time curves of salicylic acid in healthy volunteers (n=15) after oral administration of 81 mg dose of a test or reference formulation of acetylsalicylic acid. The data are expressed as mean.

| Parameter | Ratio (%) | 90% CI | Power | Intra subject CV (%) |
|---|---|---|---|---|
| $C_{max}$ | 95.05 | 82.02-110.15 | 0.8105 | 23.05 |
| $AU_{C0\text{-las}}t$ | 102.91 | 92.30-114.76 | 0.9570 | 16.92 |

CI (90%): Confidence Interval; CV%: Coefficient of Variation [(SD/mean) × 100]; $C_{max}$: Maximum Plasma Concentration; $AUC_{0\text{-last}}$: Area under the Plasma Concentration versus Time Curve Until the Last Concentration Observed

**Table 6:** Geometric mean ratios of $C_{max}$ and $AUC_{0\text{-last}}$, the respective 90% confidence intervals, power and intra subject coefficient of variation of a test and a reference formulation of 81 mg coated tablet acetylsalicylic acid.

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