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Research Article

Single-Dose, Randomized, Open-Label, Two-Way, Crossover Bioequivalence Studies of Two Formulations of 500 mg Delayed-Release Valproate Semisodium Tablets in Healthy Mexican Population under Fasted and Fed Conditions

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ABSTRACT

Therapeutic adherence has a key role in the clinical improvement of a disease; the adherence pattern of Immediate-Release formulation of Valproic Acid is relatively lower due to several gastrointestinal adverse events. Therefore, these studies evaluated the bioequivalence of a new 500 mg Delayed-Release Valproate Acid Tablets in Mexican population. The test formulation (Vupelsat®) was manufactured by Ultra Laboratorios S.A. de C.V. (Jalisco, Mexico) with batch number: DE-LPP-20016-A and expiration date March 2022 the reference formulation (Epival®) was manufactured by Abbott Laboratories de México, S.A. de C.V. (Mexico) with batch number: 08222MC and expiration date August 2021. The studies designs were: Single-center, single-dose, open-label, two-way, crossover with a 7-day wash-out period before the next dosing. Study A was evaluated at a fasted state (at least 10 hours before dosing) and study B was evaluated at a fed state (30 minutes before dosing). The study populations (per study) were 18 healthy male and female adult (aged 18-55 years) Mexican volunteers. Blood samples were collected before and 72.00 h after dosing were evaluated by UPLC-MS/MS. The bioequivalence of the 500-mg Delayed-Release Valproate semisodium Tablets was assessed by Non-Compartmental Pharmacokinetic analysis and under local law regulation. Tolerability and safety were evaluated throughout the research. The 90% CI (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) for Valproic Acid on fed conditions were 93.8279% to 103.2660%, 88.7329% to 99.7994%, and 87.7015% to 99.1945%; whereas, on fasted conditions were 99.3441% to 105.9729%, 95.8381% to 101.5227%, and 95.4785% to 101.6214%, respectively. Despite fasted or fed condition, concentration vs. time curves were similar for the test and reference products with a difference for the pharmacokinetic parameters of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ less than 20%, results that suggested a similar behavior *in vivo*. Five and three adverse events were reported in study A and B, respectively; both formulations, dosing on fed or fasted state, were considered well-tolerated and safe for human use.

Keywords: Bioequivalence; Valproate semi-sodium tablets; Epilepsy; Liquid chromatography

INTRODUCTION

Epilepsy is a chronic brain disorder characterized by recurrent episodic seizures attacks and other psychiatric and somatic consequences that require a life-treatment [1]. Therapeutic adherence especially for chronic illnesses with long-term therapy, including epilepsy, is lower than 50% [2]. Lack of adherence can be a result of incorrect dosage, forgetfulness, or discontinued medication associated with drug-related adverse events; these factors can lead to a decrease in patient health improvement [3]. It has been demonstrated that ineffective epilepsy drug therapy, increases the incidence of seizure episodes, and reduces life patients´ quality [4].

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Valproic Acid is a traditional antiepileptic drug, and its antiepileptic mechanism is related to decreased neuronal excitability caused by a variety of comprehensive factors. It mainly acts on the Gamma-AminoButyric Acid (GABA) metabolic pathway; by inhibition of GABA transaminase and succinate semialdehyde dehydrogenase, reduces glutamate and aspartic acid levels in the brain, and acts on different ion channels to increase action potential amplitude and threshold [5].

It was first approved for the treatment of epilepsy in France in 1967 [6,7]. Subsequent clinical studies reported its efficacy in indications other than epilepsy, including manic episodes in bipolar disorder and migraine prophylaxis [8]. However, clinical experience demonstrated the poor gastrointestinal tolerability of the drug, leading to the development of several pharmacological entities derived from it, including valproate semisodium, which has been used for the treatment of bipolar disorder, obtaining better results of efficacy and safety compared to treatment with Valproic Acid or sodium valproate [9,10].

After oral dosage, Valproate Semisodium dissociates to Valproic Acid in the digestive system, obtaining a bioavailability in the range of 90% to 100% [11]. After a dosage of a single dose of a 500 mg Delayed-Release tablet of divalproex (containing sodium valproate and valproic acid) in fasted conditions, the time to reach maximum plasma concentration (t_{max}) and the maximum plasma concentration (C_{max}) of Valproic Acid were 3.67 (1.16) hours and 55.40 (7.74) µg/mL, respectively. While, after food intake, the t_{max} and C_{max} were 6.07 (2.62) hours and 41.48 (7.40) µg/mL, respectively [12]. Valproic Acid is widely distributed in all organs and tissues, crosses the blood-brain barrier, poorly crosses the placental barrier, and is even detectable (in low concentrations) in breast milk [13-16]. His protein binding is high and variable; 90.00%-92.50%, a fact probably attributed to the variable affinity that it presents in several albumin sites [12]. The apparent volume of distribution is 11 L/1.73 m^2 [12]. It is metabolized into glucuronide conjugates (30%-50%) of the parent drug or its metabolites. Another large part is metabolized through mitochondrial β-oxidation (40%). The rest of the metabolism (15%-20%) goes through oxidation, hydroxylation, and dehydrogenation processes, resulting in the formation of hydroxyl, ketone, carboxyl, and lactone metabolites [12]. The main cytochrome involved in the metabolism of Valproic Acid is CYP2C9 [17]. The other important contributing pathway is mitochondrial β-oxidation, about 40%. Other oxidative pathways constitute an additional 15%-20% [18]. Finally, approximately 3% is excreted unchanged in the urine [12]. The $t_{1/2}$, expressed as mean (standard deviation) is 15.36 (3.17) hours and 15.08 (2.91) hours after dosing under fasted and fed conditions, respectively [12].

The Immediate-Release Valproic Acid formulation has been associated with several gastrointestinal adverse events; effects related to a lower therapeutic adherence pattern [19]. Therefore, several modified release formulations, including the Delayed-Release Valproate Semisodium, have been developed, and have shown better safety, and therapeutic profile compared with Valproic Acid immediate release tablet [20,21].

MATERIALS AND METHODS

Research subjects and methods ethics considerations

Bioequivalence evaluation was performed by two clinical trials (Study A: Fasted state and Study B: Fed state). Before study start-up, research protocols and informed consent forms, following local law, were reviewed, and approved by the independent ethics committee Unidad Clinica de Bioequivalencia S. de R.L. de C.V. (Jalisco, Mexico) and by the Mexico Ministry of Health; Federal Commission for Prevention Against Health Risks (COFEPRIS). The clinical trials were conducted under the current version of the World Medical Association's Code of Ethics for research involving humans (Declaration of Helsinki), Good Clinical Practice Guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and applicable local regulatory requirements.

Study design

They were a single-center, single-dose, randomized, open-label, two-way, crossover trial, with a 7-day wash-out period before next dosing (Figure 1). Study A was evaluated at a fasted state (at least 10 hours) whereas study B was evaluated at a fed state (30 minutes before dosing). The trials population was healthy male and female adult (aged 18-55 years) Mexican volunteers.

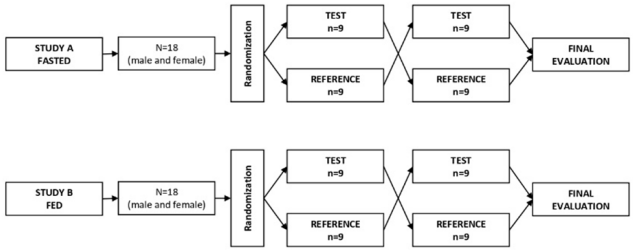

Figure 1: Study design for 500-mg delayed-release valproate semisodium tablet bioequivalence evaluation.

The trials were conducted at the Unidad Clínica de Bioequivalencia S. de R.L. de C.V. (Jalisco, Mexico). Volunteers were submitted for a 39-hour confinement period, admitted to the investigational site from around 5:00 PM on day 0 until around 8:00 AM on day 2, for drug dosing, safety and tolerability assessment, and pharmacokinetic blood sampling. Randomized subjects received a 500-mg Delayed-Release Valproate Semidosium tablet of the test (Vupelsat®) or reference (Epival®) formulation with 250 mL of water on fasted (trial A) or fed (trial B) state. During the confinement period, subjects received a 2300-kcal standardized diet and were restricted from water for at least 4 hours after dosing, breakfast of trial B was an approximately 800-kcal high-fat and high-calorie meal and was given 30 minutes prior dosing. Blood sampling and determination of vital signs at time intervals were made. After finalizing the scheduled activities subjects were discharged from the unit and returned at 36.00-hours, 48.00-hours and 72.00-hours post-dosing for pharmacokinetic blood sampling. Adverse Events information; duration, severity, causality, and outcomes were recorded by the Principal Investigator or site staff members. All subjects were medically monitored closely throughout the whole study.

Study population

All subjects provided writing informed consent form before the conduction of any protocol-related procedures or assessments. 18-55 years old healthy male or female volunteers were enrolled. A Body Mass Index (BMI) in the interval 18-27 kg/m^2 was required. Clinically health status was determined at screening visit with

the collection of the clinical record, physical examination, 12-lead ECG (electrocardiogram), complete blood cell count, blood chemistry, blood pregnancy test, urinalysis and urinary drug abuse test. Additionally, on day 0, urine pregnancy test, urinary drug abuse test, and breath alcohol test were made. Key exclusion criteria included: History or evidence of drug or alcohol abuse, clinically significant abnormalities in medical history or laboratory tests, history of significant gastrointestinal surgery or disease, 14-day prior consumption of prescription or over-the-counter drugs and grapefruit or caffeine/xanthine consumption within 10 hours before the dosing and drug allergy.

Sample size

According to the formula proposed by Liu and Chow, it was estimated that a total sample size of 18 subjects per study, would allow for a difference between the pharmacokinetic parameters of interest of at least ± 20% (considering, for the log transform data, standard bioequivalence limits of 0.80-1.25) to be detected with 90% power at a significance level of 5% [22]. Intrasubject % CV for valproic acid was obtained for a bioequivalence study performed in Mexican population by CINASI, S. de R.L. de C.V. (unpublished data) with a maximum intrasubject % CV for Valproic Acid of 12.27% for $AUC_{0\text{-}t}$ derived from the residual variability obtained in the analysis of variance (ANOVA) after log-transformation. A total sample size of 18 subjects per study (A or B) was randomized.

Bioanalytical assessments

Blood samples of 10 mL each were collected into heparinized tubes before and 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 y 72.00 h after oral administration. A total of 18 blood samples were withdrawn from each volunteer at each period. The plasma samples were prepared by centrifugation the blood samples at 3500 rpm for 5 minutes at 4°C. The plasma was transferred into cryovials and stored at -70 °C until analysis.

Pharmacokinetic parameters were determined from analyzed plasma by Ultra Performance Liquid Chromatography coupled Tandem Mass Spectrometry (UPLC-MS/MS).

Sample preparation

Valproic Acid plasma levels were quantified by using an Ultra Performance Liquid Chromatography coupled Tandem Mass Spectrometry (UPLC-MS/MS) method developed and validated by CINASI, S. de R.L. de C.V. (Jalisco, Mexico). For the bioanalytical analysis 200 µL plasma samples were transferred to microtubes, and then added 10 µL of ibuprofen as Internal Standard (IS) to 20 µg/mL final concentration. Protein precipitation was made using 800 µL of methanol at 5°C. These components were mixed for 5 minutes and centrifuged at 15000 rpm for 5 minutes at 5°C. The supernatant was separated and 5 µL were injected into the chromatographic system.

Chromatographic conditions

Liquid chromatography was performed on a triple quadrupole mass spectrometry system Acquity TQD (Waters Corporation) with an Agilent Zorbax Eclipse XDB C18 column (Agilent Technologies, Inc.) 4.6 × 150 mm, 5.0 µm. The mobile phase consisted of 0.2% acetic acid in water and acetonitrile (35:65 v/v). The flow rate was 0.8 mL/min. The overall run time was 6.0 min. The column temperature was 35°C. Detection was through negative Electrospray Ionization (ESI) with the Selected Ion Recording (SIR) monitoring the ions 143.10 m/z and 205.15 m/z for Valproic Acid and IS, respectively.

Method validation

The method was validated according to Mexican normativity and U.S. Food and Drug Administration (FDA) guidelines for bioanalytical method validation. Seven spiked calibration samples were used to constructing the calibration curves into the range 0.20 µg/mL to 100.00 µg/mL. The linearity was evaluated with 9 curves on 3 days in a row. The intra-day precision and accuracy were evaluated by analyzing 3 levels quality control samples (0.5 µg/mL, 30 µg/mL, and 85 µg/mL) and lower limit of quantification (0.2 µg/mL) with five replicates for each concentration. The inter-day precision and accuracy were evaluated by analyzing quality controls and lower limit of quantification over 3 days. Quality control samples were included during analysis volunteer samples to verify performance. The validation of the chromatographic analytical method included other parameters like selectivity, matrix effect, stability (stock solution, freeze-thaw cycles, autosampler, processed sample, short and long-term stability), and robustness.

Tolerability and safety assessments

Tolerability was assessed by adverse events monitoring (prevalence and severity of adverse events), physical examination (before dosing and before discharge), and vital sign measurements (before dosing and at 1.00, 3.00, 6.00, 12.00, 24.00, 36.00, 48.00, and 72.00 h after dosing).

Pharmacokinetic and statistical analysis

To elucidate any potentially relevant difference in the subject's demographic data, and to support the use of data from the further analysis, descriptive statistics of demographic data were made. Per-protocol population (subjects with evaluable pharmacokinetic data) was included in the pharmacokinetic analysis.

The mean, standard deviation, coefficient of variation, and range for C_{max}; the time when C_{max} is reached (t_{max}); the time taken for a drug to appear in systemic circulation following extravascular administration (t_{lag}); the area under the curve (AUC) until the last measurable concentration ($AUC_{0\text{-}t}$) and extrapolated to infinity ($AUC_{0\text{-}\infty}$); plasma elimination half-life ($t_{½}$); mean residence time from zero to last sampling time ($MRT_{0\text{-}t}$), and extrapolated to infinity ($MRT_{0\text{-}\infty}$) were calculated from plasma concentrations of Valproic Acid using the non-compartmental method.

C_{max} and $AUC_{0\text{-}t}$ were considered as the primary variables to assess the bioequivalence between the test and reference formulations. ANOVA test for a standard 2 × 2 crossover design was utilized to evaluate fixed effects such as period, sequence and formulation. The 90% Confidence Intervals (CI) for the ratio of the geometric means (test/reference) of C_{max} and $AUC_{0\text{-}t}$ were calculated using log-transformed data. Bioequivalence was concluded when the 90% CI where within the range of 80% to 125% and if the probability of exceeding these limits was <0.05 (obtained by the two one-sided test described by Schuirmann test).

Pharmacokinetic parameters were calculated using Phoenix WinNonlin version 8.2 software (Certara L.P., NJ. USA). Statistical analysis of the mean values for the pharmacokinetic parameters was

conducted using Statgraphics Centurion version 18.1.12 software (StatPoint, Inc., Herndon, Virginia).

Intention to treat population (subjects who received at least 1 dose of the study drug) were included in the tolerability and safety assessments, evaluation was made descriptively and consider all adverse events observed.

RESULTS

Baseline demographic characteristics

A total of 36 subjects were included (18 research subjects per study). Study A was finalized without dropouts and two dropouts were reported in the study B. Demographic data: age, sex, height, BMI, and weight, are shown in Table 1. Study A population consisted of male and female subjects with a mean (SD) age of 30.22(9.55) years, a height of 169(10) cm, a weight of 67.54(9.92) kg, and a BMI of 23.73(2.54) kg/m^2. Finally, the study B population consisted of male and female subjects with a mean (SD) age of 31.61(9.94) years, a height of 168(9) cm, a weight of 65.77(10.04) kg, and a BMI of 23.30(2.18) kg/m^2. Demographic characteristics were similar throughout both studies.

Table 1: Demographic characteristics of study research subjects.

Characteristic	Study A (n=18)	Study B (n=16)
Age (years), mean (SD)	30.22 (9.55)	31.61 (9.94)
Sex #, (%)	-	-
Female	8 (44.44)	6 (33.33)
Male	10 (55.55)	12 (66.67)
Height, m, mean (SD)	1.69 (0.10)	1.68 (0.9)
Weight, kg, mean (SD)	67.54 (9.92)	65.77 (10.04)
BMI, kg/m^2, mean (SD)	23.73 (2.54)	23.30 (2.18)

Pharmacokinetics of valproic acid

In Figures 2 and 3, the mean plasma concentration-time curves for fasted state and fed state, respectively, of the 2 formulations are shown. Pharmacokinetic parameters for both formulations, in both conditions (C_{max}, t_{max}, t_{lag}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$, MRT_{0-t} and $MRT_{0-\infty}$) can be obtained in Table 2.

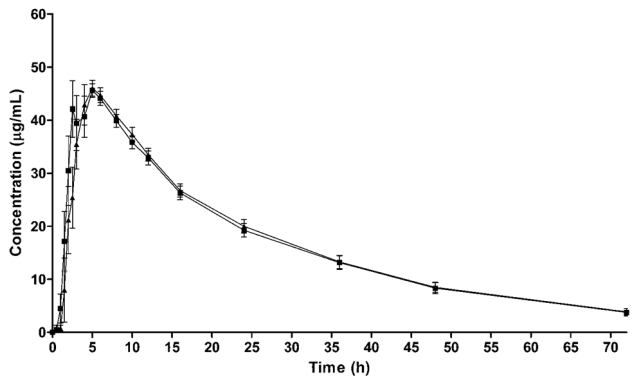

Figure 2: Mean (SD) plasma concentration-time profiles of valproica from 18 healthy volunteers after single oral administration of 500-mg delayed-release formulation in fasted state. Test (square) and reference (triangle). **Note:** (▲) Reference, (■) Test.

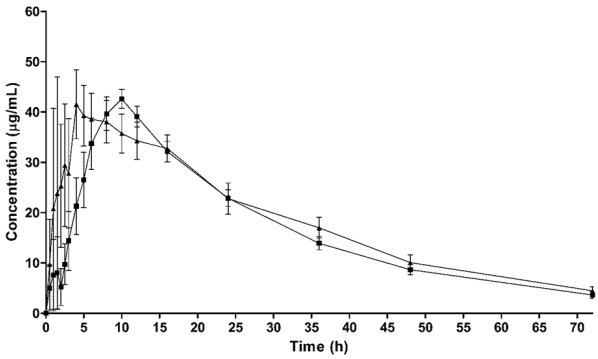

Figure 3: Mean (SD) plasma concentration-time profiles of valproic acid from 16 healthy volunteers after single oral administration of 500-mg delayed-release formulation in fed state. Test (square) and reference (triangle). **Note:** (▲) Reference, (■) Test.

Table 2: Pharmacokinetic profiles of valproic acid after a single dose of 500-mg delayed-release formulation at fasted and fed state. Data are given as mean (SD).

Parameter	Test		Reference	
	Fasted	Fed	Fasted	Fed
C_{max} (µg/mL)	50.683 (6.668)	49.548 (6.690)	49.390 (6.640)	50.165 (5.092)
t_{max} (h)	3.639 (1.270)	6.688 (1.991)	4.556 (1.338)	10.156 (7.856)
t_{lag} (h)	2.171 (0.997)	4.080 (2.343)	2.666 (0.923)	3.694 (6.958)
AUC_{0-t} (µgh/mL)	1166.715 (327.546)	1182.224 (265.319)	1177.389 (305.092)	1262.356 (303.659)
$AUC_{0-\infty}$ (µgh/mL)	1293.363 (466.296)	1291.103 (358.720)	1303.711 (428.462)	1392.995 (405.666)
$t_{½}$ (h)	18.987 (5.861)	17.553 (4.919)	19.016 (5.366)	17.535 (5.084)
MRT_{0-t} (h)	22.323 (2.890)	23.743 (3.546)	22.632 (2.898)	25.351 (5.866)
$MRT_{0-\infty}$ (h)	28.766 (8.183)	29.256 (7.894)	29.107 (7.778)	31.263 (9.676)

Using log-transformed data, no significant formulation, period or sequence effects were detected in the ANOVA test of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (data not provided). The results of the bioequivalence analysis are summarized in Table 3.

Table 3: Geometric mean ratios (90% CI) of pharmacokinetic parameters of valproic acid after a single dose of 500-mg delayed-release formulation at fasted and fed state.

Parameter	(%) Geometric mean ratio (90% CI)	Schuirmann test		(%) Intra-subject CV
		Prob 80	Prob125	
Fasted state				
C_{max} (µg/mL)	102.60 (99.344-105.973)	<0.001	<0.001	5.554
AUC_{0-t} (µgh/mL)	98.64 (95.838-101.523)	<0.001	<0.001	4.954
$AUC_{0-\infty}$ (µgh/mL)	98.50 (95.479-101.621)	<0.001	<0.001	5.361

Fed state				
C_{max} (µg/mL)	98.43 (93.828-103.266)	<0.001	<0.001	7.707
AUC_{0-t} (µgh/mL)	94.10 (88.733-99.799)	<0.001	<0.001	9.458
$AUC_{0-\infty}$ (µgh/mL)	93.27 (87.702-99.195)	<0.001	<0.001	9.912

The 90% CI of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for Valproic Acid on fed conditions were 93.8279% to 103.2660%, 88.7329% to 99.7994% and 87.7015% to 99.1945%, respectively; whereas on fasted conditions, were 99.3441% to 105.9729%, 95.8381% to 101.5227%, and 95.4785% to 101.6214%, respectively. All 90% CI of the geometric mean ratios of the parameters fell within the bioequivalence acceptance limits 80%-125%. All probabilities values were <0.05, power values were >80%, suggesting that the sample size was sufficient for both studies.

Finally, despite fasted or fed condition, concentration vs. time curves were similar for the test and reference products with a difference for the pharmacokinetic parameters of C_{max} and AUC_{0-t} less than 20%, results that suggested a similar behavior *in vivo*.

Tolerability and safety

Five and three adverse events were reported in study A and B, respectively; headache (16.66%), retroorbital pain (5.55%), and dyspnoea (5.55%) in study A, whereas in study B; dizziness (5.55%), nausea (5.55%), and vomit (5.55%). Except for retroorbital pain, which was considered not related to Valproate semisodium dosing, all observed events have been previously described after dosing and were considered as probably related. The AEs were mild (1 AEs) and moderate (07 AEs) severity and no Serious Adverse Events (SAEs) were observed. According to AEs characteristics, the 500-mg Delayed-Release Valproate Acid tablet (reference and test formulation) dosing on fed or fasted state was considered well-tolerated and safe for human use.

DISCUSSION

The studies were conducted to evaluate the bioequivalence of 500-mg Delayed-Release Valproate semisodium Tablets at fed and fasted state. For both studies, all of the 90% CI of the geometric mean ratios of the pharmacokinetic parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) were found to be within the bioequivalence range (80-125%). These results met the Mexican regulatory requirements (COFEPRIS) to ensure bioequivalence. No significant formulation, period or sequence effects were detected in the ANOVA test of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Additionally, it was observed that at fed state (study B) the reference formulation is released in a more accelerated way (compared to the fasted condition) obtaining a concentration vs. time curve similar with an immediate release form and a shorter t_{lag}, results that correlate with the phenomenon described as "dose-dumping effect" a pharmacokinetic event reported in Delayed-Release Valproate Acid Tablets formulations [23,24]. This effect was not observed with the test formulation, suggesting its higher pharmaceutical integrity.

Despite the "dose-dumping effect" both formulations were bioequivalent and did not significantly impact the therapeutic and safety profile of Valproic Acid. Minimum Therapeutic Concentration of Valproic Acid defined at ≥ 45 µg/mL, was achieved for both formulations in both conditions (fed or fasted). Whereas Minimum Toxic Concentration of Valproic Acid, defined at ≥ 125 µg/mL, was not obtained by any formulation in any condition (fed or fasted) [25,26].

CONCLUSION

In these single-doses, randomized, open-label, two-way, crossover, fed, and fasted bioequivalence studies, the test formulation of 500-mg Delayed-Release Valproate semisodium Tablets met the bioequivalence regulatory requirements (based on the rate and extent of absorption). Despite the reference formulation has a dose-dumping effect on the fed condition, both formulations were well tolerated.

Derived from the declaration of bioequivalence, it is also declared that the pharmaceutical products are interchangeable and therapeutic equivalents with the same safety and clinical efficacy, so it is certain that the introduction of the formulation made by Ultra Laboratories prescribed as generic drug product in Mexican population, will provide an *in vivo* performance that will be within of the therapeutic interval and consequently it will be a more accessible and effective pharmacological treatment for diseases treated with Valproate semisodium.

LIMITATIONS

Bioavailability clinical trials are controlled scenarios with a specific population (healthy subjects, age, and BMI range) and with a systematic dosing process, facts that prevent the proper evaluation of the pharmacokinetic behavior in the target population, which on anticonvulsant drugs is vital for adequate therapeutic monitoring.

Additional studies to compare the truly therapeutic efficacy in the Mexican population of the test product compared to reference formulation are required.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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