

Bioequivalence Study of Norfloxacin Tablets (Oranor® and Noroxin®) in Healthy Male Volunteers. A Single Dose, Randomized, Open-label, 2 x 2 Cross-over, in Fasting Conditions Study

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Abstract

Background: Norfloxacin is a fluoroquinolone antibacterial agent suitable for oral administration. This study evaluates if the fasting bioavailability of two solid formulations of 400 mg of norfloxacin is equivalent for obtaining marketing approval from the Mexican regulatory agency.

Objective: Establish and compare the comparable bioavailability of 400 mg norfloxacin coated tablets (Oranor®) and 400 mg norfloxacin tablets (Noroxin®) after administration of an oral dose, in fasting conditions, in healthy male subjects.

Subjects and methods: This was a 2 x 2 cross-over, randomized, single-dose, open-label study which included 26 healthy male subjects under fasting conditions. In each of the two study periods (separated by a washout of 7 days) a single dose of test or reference drug was administered. Blood samples were taken up to 24 h post dose, the plasma was separated and the concentrations of norfloxacin were determined by a high performance liquid chromatography with fluorescence detection. Schürmann's unilateral double t- test and confidence interval of 90% to norfloxacin concludes that the bioavailability of C_{max} and AUC results between the two treatments are equivalent.

Results: All 26 subjects were included in the analysis mean \pm SD age: 31 \pm 7.51 years, height: 168 \pm 6.95 cm, weight: 69.58 \pm 8.53 kg and body mass index: 24.37 \pm 2.02 kg/m². All were Hispanic (Mexicans). The mean AUC_{0-t}, AUC_{0- ∞} , C_{max} , t_{max} and $t_{1/2}$ were 6228.18 ng/h/mL, 6658.62 ng/h/mL, 1436.19 ng/mL, 1.38 h and 6.51 h, respectively, for the test drug and 6706.32 ng/h/mL, 7161.03 ng/h/ml, 1470.14 ng/mL, 1.40 h and 6.55 h respectively, for the reference product.

Conclusions: This single dose study in a small population of fasting, healthy subjects found no statistically significant differences in bioavailability (C_{max} and AUC) between the test and reference products, meeting the National Ministry of Health regulatory requirements in México for assuming equivalence. Both formulations were well tolerated.

Keywords: Comparative bioavailability; Healthy subjects; Norfloxacin; High performance liquid chromatography

Introduction

Norfloxacin is a broad-spectrum synthetic antibacterial agent for oral administration; it belongs to the fluoroquinolones group. The chemical name of norfloxacin is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoleicarboxylic acid and its chemical formula is C₁₆H₁₈FN₃O₃ [1-3].

Norfloxacin exerts broad-spectrum bactericidal effects via inhibition of the essential bacterial enzyme DNA gyrase. It has demonstrated significant activity against gram-positive and gram-negative bacteria, including *Pseudomonas* [4-6].

Norfloxacin is indicated in urinary tract infections, prostatitis, gonorrhea (cervicitis or urethritis) and some enteric infections [4].

In fasting state about 30-40% of an oral dose of norfloxacin is absorbed from the gastrointestinal tract. The ferrous sulphate and antacids containing aluminum and magnesium compounds may reduce absorption of any fluoroquinolone [7,8]. Absorption is rapid following a single a dose of 200, 400 and 800 mg. At these doses, mean

peak plasma concentrations of 0.8, 1.5 and 2.4 μ g/mL, respectively, are obtained approximately 1 hour after ingestion. The presence of food may decrease absorption of norfloxacin. Plasma half-life is 3-4 hours and is increased in renal impairment. Although doses of norfloxacin between 200 and 800 mg result in linear increases in the peak serum level and area under the plasma concentration-time curve, dosages greater than 800 mg produce nonlinear increases in these parameters. Similarly, with higher doses, the T_{max} is slightly delayed.

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The liver appears to be the primary site of norfloxacin metabolism. Six metabolites of norfloxacin, which contain modifications of the piperazinyl ring and are excreted unconjugated in the urine have been identified [9].

Norfloxacin is eliminated through metabolism, biliary excretion and renal excretion. About 30% of one dose is excreted unchanged in urine within 24 hours [10-12].

In Mexico, the cost of innovator products tend to be higher compared to generic products; it is, therefore, important for patients to have this resource which allows them to treat their condition with an equally safe and effective product as the brand.

The reference product (Noroxin®) is the product established by the Mexican authority. This reference product is a commercially available formulation of 400 mg tablets. Mexican regulation provides that the reference product for pharmacokinetic comparisons shall be the first product registered with that active principle in the country. The Ministry of Health publishes and regularly updates this list.

Subjects and Methods

Subjects

Forty-four healthy male subjects between 21 and 55 years of age were recruited for the study. Subjects were identified from Asociación Mexicana para la Investigación Clínica A.C. (AMIC) volunteer database and contacted to determine whether they were interested in participating. All subjects provided written informed consent before any study activity or procedure. The informed consent form was previously reviewed and authorized by an independent Institutional Review Board (Ethics Committee and Research Committee of the Pachuca General Hospital) and also by the National Ministry of Health. Subject eligibility was evaluated through complete clinical evaluation, clinical laboratory tests (complete blood count, blood chemistry, urinalysis, HBV serology and HIV ELISA), chest X-ray and 12-lead electrocardiography. Blood samples for clinical laboratory test were analyzed at Quest Diagnostics Inc. (Van Nuys, California, Inc) a laboratory with Clinical Laboratory Improvement Amendments certifications and College of American Pathologists accreditation. Subjects with clinically significant abnormalities were excluded from the trial.

Inclusion criteria included male gender, aged between 22 and 55 years, of healthy status, a body mass index between 18.00 at 27.50 kg/m², with normal results in diagnostics test and time availability for the study activities. Exclusion criteria included history of hypersensitivity, reactions to norfloxacin or related compounds, hepatics failure, renal failure, history of cardiovascular disease, history of seizures, history of anemia of any kind, exposure of cytochrome enzyme inducitors or inhibitors in the previous 30 days, exposure to toxic substances in the previous 30 days, hospitalization or serious illness in the previous 60 days, participation in clinical trials within the last 60 days, blood donation or hemorrhage in the last 60 days and drug or alcohol abuse in previous 6 months. Subjects were asked to avoid smoking or taking medications for at least 14 days before the study, and to avoid xanthines-containing foods and alcoholic beverages for at least 48 hours before initiation of the trial.

Twenty-six healthy male subjects were randomized to study sequences. As drug absorption results from numerous intricate processes, all susceptible to show sex difference. Drugs are mostly

absorbed in the proximal intestine (norfloxacin), and thus their disposition is sensitive to gastric emptying time and small intestine motility. There are reports showing that gastric motility is partially controlled by sex hormones. The gastric emptying time is usually shorter in women than in men and does vary during pregnancy and the cycle menstrual. Women were not included in the study to reduce the intersubject plasma concentration variability [13,14]. Mexican regulation does not require strictly participation of female subjects or fed studies for this type of research.

Methods

This study was conducted in accordance with the principles established in the Declaration of Helsinki and its reviews, the Good Clinical Practice and national regulatory requirements [15-18].

Study design was an open-label, randomized, controlled, 2 x 2 cross-over, clinical trial conducted in March 2008; with 2 treatments, 2 study periods and 2 treatment sequences, 7-day wash-out period in between doses. On the first day, subjects were randomized to one of the treatment sequences (Sequence 1: Treatment B followed by treatment A, or Sequence 2: Treatment A followed by treatment B). All subjects were randomly assigned to a sequence group for the 2 treatments according to a randomization table [19]. A number was sequentially assigned to all subjects who met the eligibility criteria. Each group consisted of 13 subjects. Randomization was carried out by a trained study pharmacist, under authorization of the principal investigator, after all subjects were admitted to the clinical facilities and their eligibility was confirmed. Every subject received one dose of the corresponding investigational product (according to the sequence assigned) on each study period.

Treatment A (test product) was: norfloxacin 400 mg coated tablets for oral administration, batch: 704053, expiration date: APRIL 2010, manufactured by Aplicaciones Farmacéuticas S. A. de C. V. (Oranor®).

Treatment B (reference product) was norfloxacin 400 mg tablets for oral administration, batch: B000360, expiration date: JULY 2009, manufactured by Merck Sharp & Dohme, Mexico. (Noroxin®).

During study periods, subjects remained in the clinical facilities for at least 12 hours before the dose and 24 hours after it. During these inpatient periods, subjects remained under standardized conditions regarding physical activity, environmental conditions and diet.

For logistical reasons, subjects were divided into seven groups (six groups of four subjects each, and one group of two subjects); activities on each group were performed simultaneously, such as diet, doses, and blood sampling. Activities from one group to another were separated by five minutes.

To control the effects of food on drug bioavailability, diet was standardized, and meals were planned by a nutritionist and similar in schedule, quantity and ingredients for all study subjects during the internment period. The first day of each study period (Day-1) a dinner (~ 1064 kcal) was served 12 hours before dose administration. The second day of each period (day 0) a breakfast (~ 903 Kcal), lunch (~1064 Kcal) and dinner (~1041Kcal) were served at 4, 8 and 12 hours, respectively, after dose administration; and was the same every day during dosing schedule and blood sampling. On the last day of each period (Day 1) a free breakfast was served after the last blood sample was obtained. Diet was free from xanthines, irritants and grapefruit.

Water consumption was not allowed from 10 hours prior to the dose administration until 2 hours after it. Investigational product doses were administered PO with 250 mL of water.

During inpatient periods, vital signs were measured at admission, in the hour previous to the dose administration, 3.5, 7.0 and 11.0 hours after the dose, and before discharge. Vital signs measurements were performed by qualified nurses, using calibrated instruments and results were analyzed by the study investigator. On admission and discharge of each study period, clinical evaluations were performed on all subjects to confirm their health status and eligibility for study. Before the wash-out period, subjects were provided with written instructions for reporting adverse events, concomitant medication, alcohol and tobacco abstention, amongst others. Before admission to the second study period, the investigators questioned the study subjects about compliance with these instructions.

A study monitor from the sponsor supervised that the study was conducted according to the study protocol, the Good Clinical Practice and the Mexican national regulation.

Safety evaluation of investigational products

Once subjects were randomized in the trial, the medical staff provided the study subjects with detailed instructions about adverse events, they were instructed to report immediately any sign or symptom regardless of its relationship with the investigational product. Every report was considered an adverse event, and was registered and reported accordingly. Relationship of each adverse event with the investigational drug was established using Naranjo's algorithm [20] by the principal investigator. Subjects enrolled in the study received economic compensation for the time spent in the study; the amount was determined by the site and was based on study complexity, procedures performed, number of visits required, and length of in-unit stay, and was previously reviewed and approved by the Ethics and Research Committees. The subjects enrolled in the study were not eligible for participation in any other clinical trials at this site for 60 days after study termination.

Blood sampling for pharmacokinetic study

Each sample consisted of 6 mL of venous blood drawn through IV catheter or venipuncture, and collected in heparin sodium tubes (Vacutainer - BD, 1 Becton Drive, Franklin Lakes, NJ). Approximately 0.4 mL of blood was discarded before each sample, and catheters were flushed with 0.08 mL of 1000 IU/mL heparin solution after each sample. The blood samples were obtained for the pharmacokinetic characterization at these moments: 0 (pre-dose), and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours after the study drug dose. Blood samples were kept refrigerated (2-8°C) for a maximum of one hour before they were centrifuged. Centrifugation was performed for 15 minutes at 3000 ± 200 rpm, at 2 - 8°C. The plasma obtained from each sample was transferred to 2 cryotubes (two complete series to be safely transported separately to the analytical facilities), which were immediately stored at $-40 \pm 5^\circ\text{C}$ until analysis.

Tolerability

Drug tolerability was clinically assessed by medical personnel who questioned subjects about symptoms of possible adverse events and through evaluation of spontaneous reports from subjects throughout the study period.

Analytical method

The analytical method used for the quantification of norfloxacin in plasma included High Performance Liquid Chromatography with fluorescence detection (HPLC). The method was validated in selectivity, precision, accuracy, recovery and stability its concentration range was of 25 to 10,000 ng/mL with a limit of detection 12.5 ng/mL. This method was validated according to guidelines established in the national regulation (NOM-177-SSA1-1998). Analysis was performed at CAFET - Centro A. F. de Estudios Tecnológicos, S. A., in Mexico D. F., Mexico, which is an analytical laboratory approved by the Ministry of Health as a unit of research and development and validation of biological methods for drugs. Plasma samples were analyzed in CAFET.

Methods for results evaluation

Evaluation of results was performed through pharmacokinetic analysis, which calculated the following pharmacokinetic parameters: C_{\max} , t_{\max} , AUC_{0-t} , $AUC_{0-\infty}$, K_e and $t_{1/2}$. Bioavailability parameters (C_{\max} , AUC_{0-t} , $AUC_{0-\infty}$) were dose normalized (mg/kg) for statistical analyzed.

Pharmacokinetic variables

Statistical analysis and data processing were executed on WinNonlin® Professional Version 5.0.1., Microsoft® Office Excel® 2007, SAS® version 9.1 (September 2008) and Stat Graphics Plus version 5.0 [21,25].

Pharmacokinetic parameters were calculated by a non-compartmental method. Plasmatic concentrations versus time were averaged by administered dose and for each sampling time. For each parameter the following was calculated: Average, geometric average, standard deviation, variation quotient, minimum, maximum and number of determinations.

Statistical analyses

Analysis of variance (ANOVA) was performed to assess the effects of unbalanced sequences, variability in the number of subjects, and extreme inter- and intrasubject variability.

Power analysis indicated that this sample of 26 subjects had adequate size to detect statistically significant differences between the trial and reference products in pharmacokinetic parameters converted to natural logarithms of C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$. Schüirmann's unilateral double t test ($p \leq 0.05$), confidence intervals at 90% (80 - 125%) were used, with a power than 80%. Null hypotheses indicating bioinequivalence ($P > 0.05$) were rejected.

Results

Forty-four subjects signed the informed consent form, 18 were not eligible due to clinically significant abnormalities in diagnostic tests. Twenty-six were enrolled and randomized. All 26 subjects were compliant regarding inclusion and exclusion criteria, and satisfactorily completed the study.

All subjects were healthy Hispanic (all Mexicans), of male gender, with mean \pm SD (standard deviation) age of 31 ± 7.5 years (range: 29, minimum: 22, and maximum: 51), height 168.96 ± 6.95 cm (range: 27, minimum: 159.00 and maximum: 186.00), weight 69.58 ± 8.53 kg (range: 37, minimum: 52.00 and maximum: 89.00) and mean body mass index (BMI) of 24.37 ± 2.02 kg/m² (range: 8.11kg/m² minimum:19.49 and maximum 27.51).

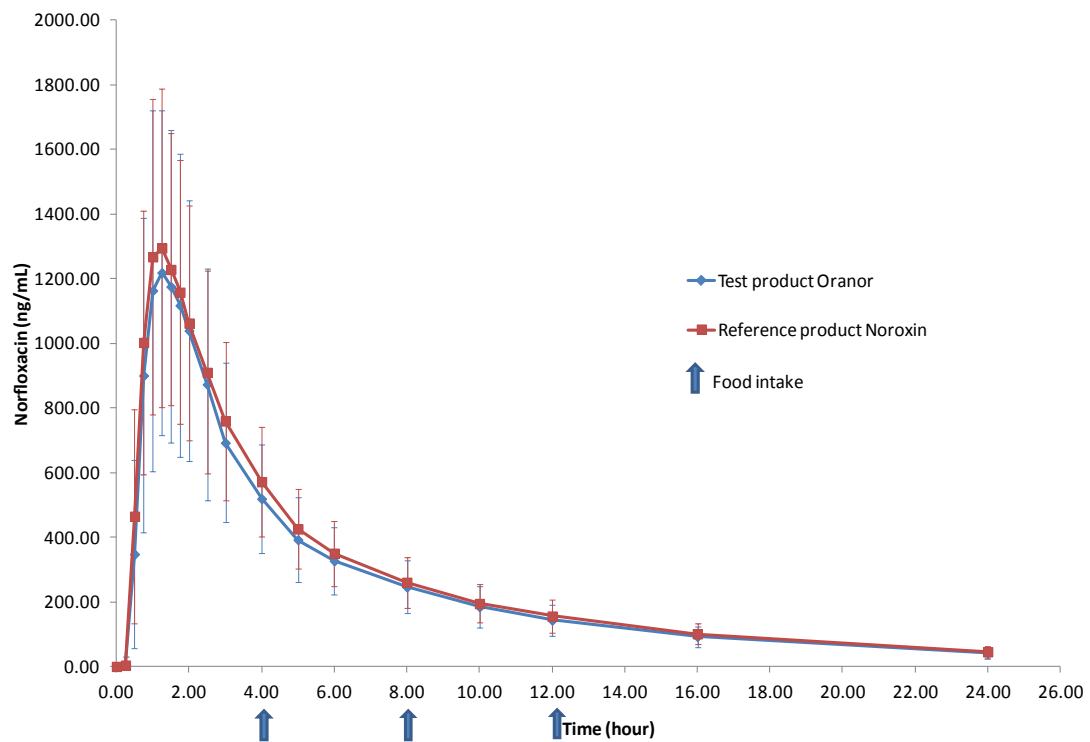


Figure 1: Mean (SD) plasma norfloxacin concentration over time for the test drug (trademark: Oranor®, Productos Científicos S.A de C.V., México City, Mexico) (n=26) and reference drug (trademark: Noroxin® Merck Sharp & Dohme Mexico.) (n=26). Arithmetic scale.

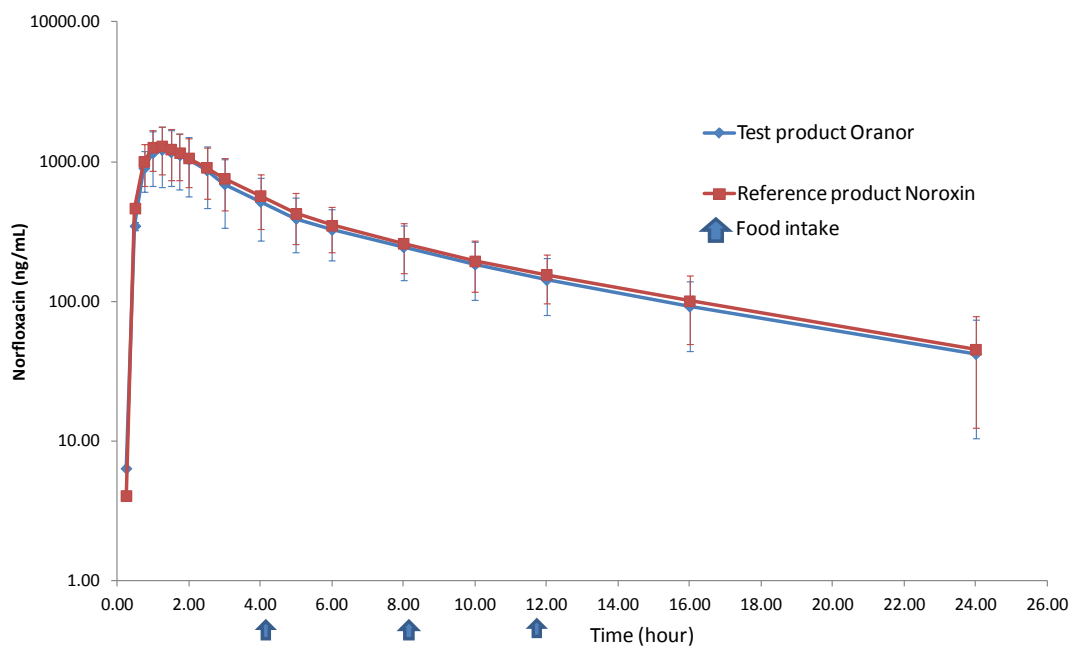


Figure 2: Mean (SD) plasma norfloxacin concentration over time for the test drug (trademark: Oranor®, Productos Científicos S.A de C.V., México City, Mexico) (n=26) and reference drug (trademark: Noroxin® Merck Sharp & Dohme Mexico.) (n=26). (Semilogarithmic scale).

Mean plasma concentrations in arithmetic and semilogarithmic scales are shown in Figures 1 and 2. The mean \pm SD of the C_{max} was 1436 ± 521.03 and 1470 ± 477.38 ng/mL with Oranor® and Noroxin®, respectively. This was achieved 1.5 hours after the administration of the dose (t_{max}). Elimination half-life for both products was approximately 6.51 hours.

Comparative bioavailability of norfloxacin 400 mg

Schüirmann's unilateral double t- test and confidence interval of 90% to norfloxacin C_{max} and AUC parameters concludes that the bioavailability results between the two treatments are equivalent in the pharmacokinetic parameters of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$. Also, the power (P) obtained was greater than 0.8 and intrasubject variability (CV%) of $\ln C_{max}$ was 25.10%, 20.93% for AUC_{0-t} , and 20.21% $AUC_{0-\infty}$. In, indicating that size sample of 26 subjects allowed an adequate description. Three adverse events not related to the investigational product were detected during the study. No serious or unexpected adverse events were detected.

Comparative bioavailability of investigational products

The results of pharmacokinetics analysis showed that there were no statistically significant differences between the pharmacokinetic parameters (C_{max} , AUC and t_{max}) of both products ($p \leq 0.05$, Schüirmman's t test, IC90% 80-125% and $P > 0.8$).

Schüirmann's unilateral double t-test and confidence intervals at

Pharmacokinetic Parameters	Test Oranor® coated Tablets 400 mg (ng/mL) n=26	Reference Noroxin® Tablets 400 mg (ng/mL) n=26
C_{max} (ng/mL)	1436.19 \pm 521.03 36.28 1310.30 310.66-2506.87	1470.14 \pm 477.38 32.47 1397.13 680.01-2625.92
AUC_{0-24h} (h*ng/mL)	6228.18 \pm 2041.06 32.77 5806.15 1666.65-9835.10	6706.32 \pm 1853.85 27.64 6454.54 3963.68-9957.76
$AUC_{0-\infty}$ (h*ng/mL)	6658.62 \pm 2139.56 32.13 6237.02 1905.93-10608.83	7161.03 \pm 1959.37 27.36 6898.09 4237.23-10435.53
t_{max} (h)	1.38 \pm 0.49 35.47 1.30 0.50-2.50	1.40 \pm 0.66 46.73 1.28 0.50-3.00
Ke (1/h)	0.1077 \pm 0.0115 10.65 0.1071 0.0848-0.1266	0.1073 \pm 0.0136 12.67 0.1065 0.0806-0.1490
$t_{1/2}$ (h)	6.51 \pm 0.73 11.26 6.47 5.48-8.17	6.55 \pm 0.80 12.18 6.51 4.65-8.60
AUC Extrapolated (%)	6.87 \pm 2.64 38.47 6.46 3.39-14.69	6.42 \pm 1.68 26.24 6.21 4.07-11.13

CV (%)
Geometric mean
Minimum and maximum

Table 1: Pharmacokinetic properties of the test and reference preparations Arithmetic mean \pm SD.

Pharmacokinetic parameters	Test product Oranor® coated tablet 400 mg n= 26	Reference product Noroxin® Tablets 400 mg n= 26	t-student test p value
C_{max} dn (ng/mL/mg/kg)	0.0533 \pm 0.0218 40.79	0.0541 \pm 0.0197 36.33	p= 0.8947
AUC_{0-t} dn (ng*h/mL/mg/kg)	0.2301 \pm 0.0866 37.65	0.2477 \pm 0.0859 34.68	p= 0.4659
$AUC_{0-\infty}$ dn (ng+h/mL/mg/kg)	0.2457 \pm 0.0905 36.84	0.2643 \pm 0.0903 34.17	p= 0.4613

dn: dose normalized mg/kg

Promedio \pm SD

C. V. (%)

Table 2: Norfloxacin pharmacokinetic dose normalized parameters (mg/kg).

Oranor® coated tablet 400 mg (A) vs Noroxin® tablets 400 mg (B)	C_{max}	AUC_{0-24ht}	$AUC_{0-\infty}$	Criteria equivalence
Schüirmann's two one-sided t-test	0.0044	0.0030	0.0026	≤ 0.05
p<80% p>125%	0.0007	0.0000	0.0000	
CI 90% for the ratio of the parameters	87.06-108.32	85.55-100.19	85.75-100.22	80%-120%
Power	0.9277	0.9966	0.9970	> 0.80

Table 3: Schüirmann's two one-sided t-test, 90% Confidence Interval (CI 90%) and Power of Norfloxacin pharmacokinetic parameters (non transformed) n = 26.

90% concludes that the fasting bioavailability of both oral forms of norfloxacin is equivalent on C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$.

Discussion

Norfloxacin was well tolerated by the subjects; unexpected incidents that could have influenced the outcome of the study did not occur. Both formulations were absorbed from the gastrointestinal tract and norfloxacin was measurable at the second sampling time (0.50 h) in all volunteers only in six subjects (three for period) norfloxacin was measurable in the first sampling time (0.25h). The mean concentration – time profile for the two formulations is shown by the Figure 2 and the parameter pharmacokinetics in the Table 1.

When a test drug meets the requirements to prove it can be interchangeable with the reference drug, they may be considered bioequivalent; questions arise as to which is the advantage of interchangeable generic drug and the most important is cost. The advantage of interchangeable generic drugs over brand-name drugs is the cost in general terms is up to 50% less; this is of great importance to the physician and the patient since it is often associated with treatment compliance especially in developing countries.

On the other hand, the pharmaceutical forms of investigational products used in the study were different: coated tablets (Oranor®) and tablets (Noroxin®). The definition used in National Regulation (NOM-177-SSA1-1998) for pharmaceutical equivalent is: medicines containing

Oranor® sugar coated tablet 400 mg(A) vs Noroxin® tablets 400 mg (B)	C _{max}	lnAUC _{0-t}	lnAUC _{0-∞}	Criteria equivalence
Schüirmann's two one-sided t-test p<80% p>125%	0.0146 0.0002	0.0261 0.0000	0.0186 0.0000	≤ 0.05
CI 90%	83.40-105.46	81.54-99.24	82.23-99.43	80%-125%
Power	0.9320	0.9801	0.9851	> 0.80

Table 4: Schüirmann's two one-sided t-test, 90% Confidence Interval (CI 90%) and Power of Norfloxacin normalized pharmacokinetic parameters n = 26.

Subject No.	Adverse event	Duration	Intensity	Relation to preparation
07	Neck pain	1 d 13 h	Mild	**Unrelated
13	Gastroenteritis	3 d	Moderate	*Unrelated
20	Lumbar pain	4 d 5 h	Mild	**Unrelated

*Test Oranor® manufactured by Productos Científicos S.A. de C.V.

**Reference: Noroxin® manufactured by Merck Sharp & Dohme Mexico.

Table 5: Adverse events after administration of the reference or trial preparations of norfloxacin.

the same amount of active substance in the same pharmaceutical form, which comply with the prescriptions of the Mexican Pharmacopoeia. Taking the above into account, the two products are not pharmaceutical equivalents, but pharmaceutical alternatives. According to the results of statistical tests both products are bioequivalent, since no statistical difference in the speed and amount of product absorbed was observed; on different sampling times used in the study that covered over 80% AUC was discovered. This becomes important when researchers are uncertain about whether it is possible to conduct a bioequivalence study with two products that are not pharmaceutical equivalents in the literature but there are no reports on differences in pharmacokinetic behavior between the two pharmaceutical forms (coated tablet versus a tablet).

In the literature there are very few of bioequivalence or bioavailability studies with norfloxacin is noteworthy that one was conducted using as biological samples urine (about 30% of a dose is excreted unchanged in urine within 24 h [12]). For bioequivalence studies in Mexico the National Regulation (NOM-177-SSA1-1998) stipulates that the drug must be excreted by the kidneys in an intact form at least 50% [16].

Nada et al. [12] conducted a comparative bioavailability study of norfloxacin in 12 Middle-East healthy male volunteers. They report a lower C_{max} (964 ± 362 ng/mL) and a similar AUC_{0-∞} (6888 ± 1954 h*ng/mL) for the reference product, compared with the values that we are reporting for Mexican healthy male volunteers.

The few studies found were for research the inhibition of norfloxacin absorption by antacids [7] and sucralfate [8] because the absorption of norfloxacin is affected for these products.

Conclusions

This single dose study in a small population of fasting, healthy subjects found that the test and reference products met the regulatory criteria for bioequivalence. No differences were found between

pharmacokinetics and comparative bioavailability of the coated tablets and 400 mg tablets of norfloxacin.

There were no treatment-related adverse events during the study.

Acknowledgements

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The sponsor did not participate in study design; collection, analysis, and interpretation of data; or writing of the study report.

None of the authors have significant financial interest in the test product (including: equity interests [e.g. stocks, stock options or other ownership interests]; or intellectual property rights [e.g. patents, copyrights and royalties from such rights]).

Authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

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