Comparison between 200 mg generic celecoxib hard capsules and Celebra®: bioequivalence study in healthy male and female subjects under fasting conditions after a single dose

Comparação entre celecoxibe genérico de 200 mg em cápsulas duras e Celebra®: estudo de bioequivalência em indivíduos saudáveis do sexo masculino e feminino, em jejum, após uma dose única

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ABSTRACT

BACKGROUND AND OBJECTIVES: The objective of this study was to assess the bioequivalence between two 200 mg celecoxib hard capsule formulations administered to healthy male and female participants under fasting conditions with the aim of providing an alternative pharmaceutical product to the reference drug, Celebra®.

METHODS: A randomized, open label, single dose, 2x2 crossover trial was conducted with 60 adult healthy subjects under fasting conditions comparing single doses of two celecoxib hard capsules formulation. Pharmacokinetic parameters were calculated following the determination of drugs concentrations in human plasma using a validated liquid chromatography with a tandem mass spectrometer detector method (LC-MS/MS).

RESULTS: Statistical analysis provided geometric mean of test/reference ratio, confidence intervals, intra-subject variation coefficient and power of the test to the pharmacokinetic parameters C_{max}, $AUC_{0-t,}$ and $AUC_{0-\infty}$. Confidence intervals for the geometric mean (90% CI) of the test/reference drugs for celecoxib were 98.26 to 122.75% for C_{max}, 100.27% to 110.78% for AUC_{0-t}, and 96.87% to 110.29% for $AUC_{0-\infty.}$ The power of the test found was 95.09% for C_{max}, 100.00% for AUC_{0-t}, and 99.99% for $AUC_{0-\infty.}$

CONCLUSION: The formulations met the Brazilian standards for interchangeability, as the confidence intervals for C_{max} and AUC_{0-t} ratios are within the range of 80% to 125%, thus meeting the requirements of the legislation during market registration. The researched product was approved by the regulatory authorities and became a commercially competitive option to the reference product for the Brazilian population.

Keywords: Analgesics, Arthritis, Bioequivalence, Celecoxib, COX-2, Osteoarthritis rheumatoid.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O objetivo deste estudo foi avaliar a bioequivalência entre duas formulações de cápsulas duras de celecoxibe de 200 mg administradas a participantes saudáveis do sexo masculino e feminino em condições de jejum com o objetivo de fornecer um produto farmacêutico alternativo ao fármaco de referência, Celebra®.

MÉTODOS: Estudo randomizado, aberto, de dose única e cruzado 2x2. Foi conduzido com 60 indivíduos adultos saudáveis em condições de jejum, comparando doses únicas de duas formulações de cápsulas duras de celecoxibe. Os parâmetros farmacocinéticos foram calculados após a determinação das concentrações dos fármacos no plasma humano usando uma cromatografia líquida validada com um método detector de espectrômetro de massa em tandem (LC-MS/MS).

RESULTADOS: A análise estatística forneceu a média geométrica da razão teste/referência, os intervalos de confiança, o coeficiente de variação intra-sujeito e o poder do teste para os parâmetros farmacocinéticos $C_{máx}$, AUC_{0-t} e $AUC_{0-\infty}$. Os intervalos de confiança para a média geométrica (IC 90%) dos fármacos teste/

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Conflict of interests: none – Sponsoring sources: Eurofarma Laboratórios.

HIGHLIGHTS

- Celecoxib is one of the few COX-2 inhibitors anti-inflamatory currently in use in Brazil.
- The study was conducted with a 2x2 crossover design with 60 healthy adult subjects, comparing generic Celecoxib 200 mg hard capsules with Celebra®.
- The study demonstrated that the generic test drug has a pharmacokinetic profile equivalent to that of the reference drug and meets the criteria for bioequivalence based on Cmax and AUC, thus concluding that the formulations are interchangeable.

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referência para o celecoxibe foram 98,26 a 122,75% para $C_{máx}$, 100,27% a 110,78% para AUC_{0-t} e 96,87% a 110,29% para $AUC_{0-\infty}$. O poder do teste encontrado foi de 95,09% para $C_{máx}$, 100,00% para AUC_{0-t} e 99,99% para $AUC_{0-\infty}$.
CONCLUSÃO: As formulações atenderam aos padrões brasileiros de intercambialidade, pois os intervalos de confiança para as razões $C_{máx}$ e AUC_{0-t} estão dentro da faixa de 80% a 125%, atendendo, assim, às exigências da legislação para o registro no mercado. O produto pesquisado foi aprovado pelas autoridades regulatórias e tornou-se uma opção comercialmente competitiva ao produto de referência para a população brasileira.
Descritores: Analgésicos, Artrite, Artrite reumatoide, Bioequivalência, Celecoxibe, COX-2, Osteoartrite reumatoide.

INTRODUCTION

Lower-cost generic drugs have been shown to enhance patients' adherence to essential prescribed drugs and positively impact their health outcomes. A generic drug is a pharmaceutical product that is bioequivalent to the innovator product in dosage form, strength, route of administration, intended use, quality, safety and performance characteristics.
Bioequivalence refers to the absence of a significant difference in the rate and extent of drug availability at the bloodstream following the administration of a test product compared to a reference product. Bioequivalence is generally established by crossover clinical studies involving healthy subjects, in which the bioavailability of the reference and test drugs are compared.
The assessment of bioequivalence between two drug products relies upon the fundamental assumption that if the rate and extent of absorption of the test product do not significantly differ from those of the reference drug after an administration of the same molar dose of the therapeutic component under the same experimental conditions, then the two drug products are equivalent.
This applies to both single and multiple dose regimens. Manufacturers are required to conduct studies to confirm that their product is bioequivalent to the original drug. This process involves verifying that the generic drug will release its active ingredient into the blood stream at a similar rate and in a similar amount as the original drug. Since the active ingredient in the generic drug has already been deemed safe and effective by testing the brand-name drug, bioequivalence studies ought to solely confirm that the generic version creates comparable drugs concentrations in the blood over the time.
According to the *Agência Nacional de Vigilância Sanitária's* (National Health Surveillance Agency - ANVISA) resolution RE No. 1170/20061, in effect during the period of the study, and the resolution reviewed by RDC 742/2022, the two formulations are equivalent and, therefore, interchangeable, when the intervals of confidence for the C_{max} and AUC_{0-t} ratios are between 80% and 125%[1,2].
Celecoxib is a non-steroidal anti-inflammatory (NSAID) drug with anti-inflammatory, analgesic and antipyretic properties that treat osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS), and relieves acute pain, primary dysmenorrhea and lumbago[3,4]. The anti-inflammatory and analgesic properties of celecoxib result from the inhibition of prostaglandin (PG) synthesis[3]. The drug is a selective inhibitor of COX-2, a NSAID subclass colloquially called "coxibs"[5]. Introduced in the United States market in December 1998, it quickly became one of the most frequently prescribed drugs to relieve pain and inflammation. It still remains the only approved COX-2 inhibitor for marketing in the USA[3,5].
In the early 2000s, concerns arose regarding the thrombotic cardiovascular risks linked to COX-2 selective NSAIDs. In 2005, the FDA concluded, after a meeting of the Advisory Committee, that this risk was present for both selective and non-selective COX-2 NSAIDs[6]. Nevertheless, after the publication of the "Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen" (PRECISION) study, the FDA approved a label supplement including study findings that demonstrated the comparable cardiovascular safety of lower-dose celecoxib to moderate-dose naproxen and ibuprofen[6,7]. In 2006, the Brazilian regulatory agency ANVISA published technical information regarding the potential cardiovascular risks associated with COX-2 inhibitors NSAIDs. Later, in 2008, ANVISA listed celecoxib and other coxibs as controlled substances under regulation SVS/MS 344/1998[8,9].
Regarding pharmacokinetics, celecoxib reaches its maximum plasma concentration (C_{max}) 2 to 4 hours after dose administration, and its elimination half-life is approximately 11 hours. Notably, fluconazole and lithium have been shown to cause significant interactions, while ketoconazole or methotrexate do not. Additionally, bioavailability of celecoxib can increase up to 100% with food intake[3,5,10-12].
To provide another generic option in the market, Eurofarma supported a bioequivalence study comparing the bioavailability of two celecoxib products in 200 mg hard capsules.

METHODS

The research was designed as a randomized 2x2 (2 sequences and 2 periods), crossover, comparative study of two drugs, both hard capsules: Celebra® and Celecoxib Eurofarma. Commercially available Celecoxib (Celebra® 200 mg from *Laboratórios Pfizer Ltda.*, Brazil) and generic 200 mg Celecoxib from Eurofarma, Brazil, were used in the trial. All eligible male and female healthy volunteers were orally administered a single dose of each drug in a fasting state, with the treatments given in alternating stages. Following the two planned periods, each drug was administered as a single dose with fresh water at approximately 7:00 AM, and subjects stayed at the clinical site from the previous night until 25 hours after dosing. There was a seven-day washout period between the administration of each of the two drugs.
The clinical and statistical stages of the study were conducted at UNIFAG – *Unidade Integrada de Farmacologia e Gastroenterologia / Universidade São Francisco (*Integrated Pharmacology and Gastroenterology Unit / University of São Francisco*),* in Bragança Paulista, and the analytical stage was conducted at Magabi Bioequivalence Center, in São Paulo, Brazil.

The research was carried out adhering to appropriate clinical, laboratory, and statistical practices, in accordance with Brazilian regulations governing the research on human subjects who all provided informed consent. Furthermore, this research was conducted following the Good Clinical Practice, Good Laboratory Practice, The Declaration of Helsinki, and the ANVISA bioequivalence guidelines.

Sixty eligible participants of both genders were enrolled, meeting the criteria of being between 18 and 50 years of age, non-smokers or former smokers who have abstained for over a year, weighing 50 kg or more, with a body mass index (BMI) ranging between 20 and 27 kg/m^2, and testing negatively for human immunodeficiency virus (HIV-1 and HIV-2) in serum tests. Further inclusion criteria were: hemoglobin, leukocyte and platelet counts values within the normal range; normal urinalysis and serum levels of creatinine, urea, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubins, fasting glucose, and cholesterol; and no evidence of infections with hepatitis B or hepatitis C viruses.

The primary exclusion criteria included: a previous allergic reaction to celecoxib or related drugs; any indication of organ dysfunction; a history of gastrointestinal, hepatic, renal, cardiovascular, pulmonary, neurological, psychiatric, or hematological illness, diabetes, or glaucoma; and a history of using psychotropic drugs or consuming over two units of alcohol daily (equivalent to one glass of beer or wine or a shot of spirits). Other exclusion criteria were: recent use of substances metabolized by hepatic microsomal cytochrome P-450 within 30 days prior to the study, participation in a clinical trial within the past 6 months, recent (less than three months) blood donation or absence of adequate venous access.

Study formulations

The 200 mg celecoxib hard capsule, which underwent testing, was manufactured by *Eurofarma Laboratórios S/A*. The reference drug used in the study was Celebra® (200 mg celecoxib hard capsule) which was marketed in Brazil by *Laboratórios Pfizer Ltda*.

Study subjects

Participants were selected based on predetermined criteria and provided with comprehensive information about the selection process. Upon voluntarily agreeing to participate in the study, each subject signed the approved Free and Informed Consent Term (FICT) from the Research Ethics Committee of the University of São Francisco, as well as the study protocol.

This was a confirmatory trial that aimed to reject the null hypotheses of inequivalence. The statistical power for a bioequivalence trial is the probability of correctly rejecting the null hypothesis when the alternative hypothesis of equivalence is true. This probability is derived based on fixed values of all input parameters, particularly the assumed values for log(T/R)-ratio and the coefficient of variability (CV). The study's sample size was determined by taking into account the coefficient of variation from a prior study done by the research center, as well as potential dropouts, in order to achieve a minimum statistical power of 80%.

Initially, based on the inclusion and exclusion criteria specified in the protocol, 60 healthy male and female volunteers were selected and randomized. However, due to reasons related to exclusion criteria and dropouts, the trial was completed by only 53 volunteers.

Study design

The monocentric bioavailability study was a randomized crossover (crossover 2x2) single-dose trial conducted with healthy adult male and female subjects under fasting conditions. The study compared the effects of two formulations of 200 mg celecoxib hard capsule: a test drug labeled T and a reference drug labeled R. The study followed a balanced design with two treatments and two sequences, RT and TR, was open-label, and each gender group (male and female) had fifty percent participation allocated to TR (reference-test) and RT (reference-test) sequences.

Subjects were randomly assigned to one of two treatment sequences (RT or TR) in a crossover design with a sufficient washout period to prevent any plasma drug concentration carryover from the previous intake.

Drug administration

The test and reference drugs were administered in the morning (around 7:00 am), after an eight-hour fast. The study was conducted under fasting conditions, as required by ANVISA[13], and in accordance with the usage guidelines in the package insert of the reference drug.

During each period of confinement, participants were administered a single oral dose of one 200 mg celecoxib capsule with 200 mL of room temperature water. The drug was taken in its complete form without any manipulation or addition.

Blood sampling

Participants' blood samples were collected at 21 time points: before treatment (-01h; baseline), and at 0h30, 1h30,2h00, 2h20, 2h40, 3h00, 3h20, 3h40, 4h00, 4h20, 4h40, 5h00, 5h30, 6h00, 8h00, 12h00, 24h00, 36h00, and 48h00 after treatment. The participants were kept in the clinical unit for 36 hours.

Biological samples processing

Immediately after collection, the blood samples underwent centrifugation at 3,000 rpm for 10 minutes. At least 2 mL of plasma were then separated and stored in an appropriately labeled container at -20ºC.

Celecoxib quantification in human plasma

Method validation

The bioanalytical method, which used SC-58125 as an internal standard, underwent full validation to quantify celecoxib in human plasma. SC-58125 is a celecoxib analogue with a fluoride-phenyl substitution for the methyl-phenyl ending. The heparinized plasma samples were prepared according to acceptance criteria for selectivity, calibration curve, precision, accuracy, residual effect, matrix effect, and stability tests in both the solution and biological matrix, the parameters of which are summarized in table 1. The procedure entailed extracting the sample via protein precipitation

Table 1. Summary of the bioanalytical method

Analyte	Celecoxib
Internal standard	SC-58125
Biological matrix	Human plasma
Anticoagulant	Heparin
Linearity	5.00 ng/mL to 1000.00 ng/mL
Curve equation	$y = a + bx\ [1/x^2]$
Lower limit of quantification (LLQ)	5.00 ng/mL
Low quality control (LQC)	15.00 ng/mL
Medium quality control (MQC)	400.00 ng/mL
High quality control (HQC)	800.00 ng/mL
Post-processing stability time	158 hours
Freeze/thaw cycles	3 cycles
Short-term stability time	16 hours
Long-term stability time	94 days

and liquid chromatography, which was then analyzed via mass spectrometry in multiple-reaction monitoring mode (MRM).
Samples were stored at 6°C in the sampler. The injection volume was 20 µL, and the analyte and internal standard had retention times of 1.50 ± 0.23 min and 1.40 ± 0.21 min, respectively. The total running time was 2.20 min.
The method displayed a linear relationship within the concentration range of 5.00 ng/mL to 1000.00 ng/mL, based on the equation $y = a + bx\ [1/x^2]$. Here, "y" indicates the response, "x" represents the analyte concentration, and "$1/x^2$" represents the chosen weight that yielded the lowest sum of relative errors obtained by comparing the curve equation values to the nominal values of the calibration standards, in line with regulatory requirements[14].
The method was established with a Lower Limit of Quantification of 5.0 ng/mL, and quality control samples validated at 15.00 ng/mL, 400.00 ng/mL, and 800.00 ng/mL were used.

Stability
Stability tests were performed on plasma samples at 15.00 ng/mL and 800.00 ng/mL concentrations, satisfying the acceptance criteria. The samples underwent short-term stability testing following 16 hours at room temperature prior to processing, post-processing stability testing 158 hours after extraction, 3 freeze and thaw cycles, and long-term testing for 94 days at -20ºC.
The study found that both the primary and work solution samples of both the analyte and the internal standard remained unchanged for at least 253 days, without any significant degradation (greater than or equal to 10% of their responses as compared to the responses of newly prepared solutions), even when stored on a counter for a minimum of 18 hours[14].

Standard solutions and reagents
The materials used consisted of ultrapure water obtained through a Millipore purification apparatus, HPLC grade methanol (Carlo Erba), HPLC grade acetonitrile (Carlo Erba), and analytical grade 88% formic acid (J.T. Baker).
Celecoxib reference standards from the United States Pharmacopeia (USP/EUA) were used as the analyte, while SC-58125 from Sigma-Aldrich (EUA) was used as the internal standard for preparing the primary solutions in methanol/water (75:25, v/v).

Compound quantification in biological samples
Compounds were extracted from plasma samples obtained from human subjects and quantified through liquid chromatography coupled with mass spectrometry (LC-MS/MS). The API 5500 QTrap spectrometer from Sciex/Applied Biosystems equipped with a positively charged electrospray ionization source (ESP+) was used to detect both analyte and internal standards via MRM, with m/z transitions of 328.1>362.0 and 385.1>365.0, respectively.

Software used
The Analyst software version 1.5.2 was used for the determination of sample concentrations during the analytical phase. Phoenix WinNonlinTM and Microsoft Excel were used for conducting the statistical analyses.

Pharmacokinetic parameters
A 90% confidence interval was computed for the distinction between the average values of the log-transformed information of the reference and test drugs for the AUC_{0-t} (area under the curve of concentration over time) and C_{max} (maximum concentration) parameters. To be considered statistically bioequivalent, these ranges must fall within the 80% to 125% limits, as outlined by regulations.

RESULTS

The study was completed with 53 healthy adult participants (25 females and 28 males) aged 18 to 50 with a body mass index (BMI) ranging from 18.5 to 29.9 kg/m². All participants met the inclusion and exclusion criteria specified in the protocol.

Pharmacokinetics and statistical analysis
Pharmacokinetic parameters, including C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, were determined using the Phoenix WinNonlinTM and Microsoft Excel software.
Pharmacokinetic parameters are presented in table 2. The pharmacokinetic curves are shown in figure 1 and represent the plasma concentration of the drugs over the time.
The average maximum concentration (C_{max}) of the reference drug Celebra® was 378.022 ng/mL, which was reached in 3.2 hours. The test drug Celecoxib had a C_{max} of 397.265 ng/mL, which was reached in 3.3 hours.

Tolerability and safety analysis
Forty-three adverse events were reported from confinement until the end of the trial period. Among these cases, 12 were possibly related to the study drug, 29 were unlikely to be related, and 29 were deemed unrelated to the study drug. Additionally, all adverse events observed were mild, and no serious adverse events were reported.

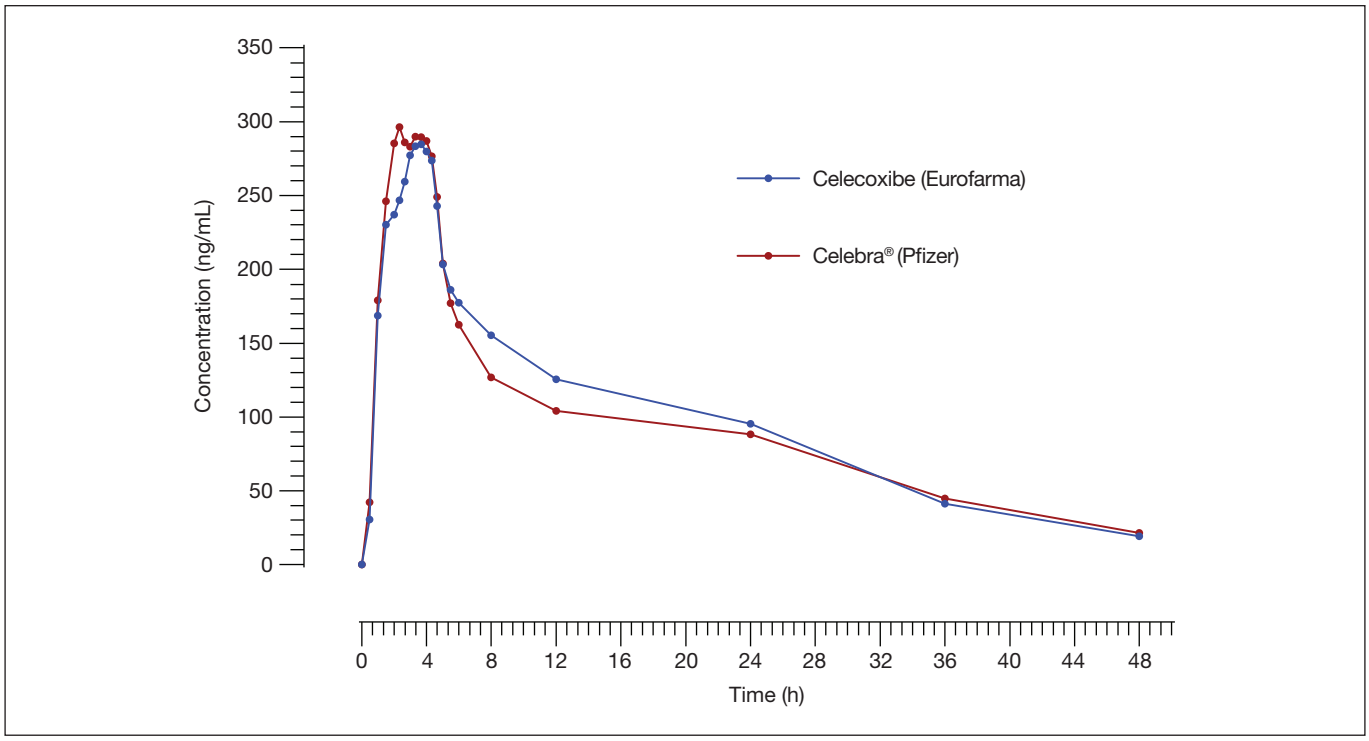

Figure 1. Plasma concentration of the drugs over the time.

Table 2. Pharmacokinetic parameters (n=53)

Parameters	Geometric Mean		CV % intra-subject	Ratio T/R (%)	CI (90%)	Power % (TOST)	p-value (sequence effect)
	Test	Reference					
C_{max} (ng/mL)	367.3137	334.4479	35.16	109.83	98.26 – 122.75	95.09	0.9981
ASC_{0-t} (ng.h.mL^{-1})	4448.6700	42209093	15.37	105.40	100.27 – 110.78	100.00	0.9751
$ASC_{0-\infty}$ (ng.h.mL^{-1})	4859.4909	4701.5008	19.77	103.36	96.87 – 110.29	99.99	0.7545

Eleven out of twelve adverse events that were possibly associated with the researched drug were minor changes in laboratory tests (hemogram), and one event of tonsillitis was also possibly linked to the drug. These adverse events were all anticipated in the Celebra® drug leaflet.

Furthermore, there were minor laboratory changes (urine and total protein), one viral gastrointestinal event, and one distress event that were deemed unrelated to the study drug.

DISCUSSION

According to researches, co-administration of celecoxib with food increases drug bioavailability[11,12]. Previous literature supports the Brazilian Agency's recommendation to conduct bioequivalence studies under fasting conditions, as was done in the present study, to avoid interference from food intake on plasma concentrations[13].

The planned, selected and included number of subjects were 60 healthy male and female participants, of whom 53 completed the study. This sample size is consistent with other published studies in this area[15].

The study was well-designed and executed, resulting in the acquisition of pharmacokinetic parameters C_{max}, ASC_{0-t} and $ASC_{0-\infty}$. The 90% confidence interval values for the ratio between the geometric means of the test and reference products are within the acceptable limit (80-125%), as prescribed by Brazilian legislation.

Both formulations were well tolerated throughout the study and no serious adverse events were reported, indicating an appropriate safety profile, as reported in previous studies[16,17]. Taking into account the concerns of regulatory agencies regarding the cardiovascular safety associated with celecoxib and the warnings included in the reference drug insert about cardiovascular effects, and considering that no adverse events related to cardiovascular effects were identified in the study, it can be concluded that the dosage administered was appropriate and did not pose any risks to the health and safety of the study subjects[4]. Therefore, the test drug serves as a safe alternative to the reference drug.

The seven-day washout period was adequate as no baseline collection sample of any of the subjects in the second period had a concentration above the LLQ. The concentration range selected for the calibration curve during the analytical phase

was deemed suitable since sample dilution was not necessary and only a small number of samples had concentrations below the LLQ.

The chosen analytical technique has been previously described in literature[18,19]. As previously reported, the study used LC-MS/MS as the analytical method for quantifying celecoxib levels in human plasma samples. To comply with Brazilian legislation, the quantification was conducted on the unchanged form of celecoxib[20].

Both the reference and the test drugs exhibited a maximum plasma concentration C_{max} of 378.022 ng/mL and 397.265 ng/mL, and a T_{max} of 3.2 and 3.3 hours, respectively, consistent with those found in the literature[19,21].

Studies have shown that incorporating generic drugs in the treatment of inflammation, pain, and arthritis can improve patient adherence. The importance of generic drugs in centralized healthcare systems, such as Brazil's National Health System (*Sistema Único de Saúde* - SUS), is maintained through government-led efforts to negotiate long-term supply agreements with pharmaceutical companies. This approach results in lower costs compared to branded products and promotes competition among various market players, including industry professionals and distributors.

The promotion of using generic drugs in clinical practice is a practical solution to diminish healthcare expenses without affecting treatment quality. This approach is especially advantageous, as bioequivalence trials have validated the interchangeable between the generic and reference drugs.

CONCLUSION

The adoption of an alternative drug option is crucial in offering an economical solution to patients and other stakeholders. The bioequivalence of various formulations has been established through absorption rate and extent and meets the Brazilian regulatory authority's criteria (90% CI within 80-125%).

The study demonstrated the bioequivalence between the 200mg hard capsule test formulation of celecoxib, manufactured by *Eurofarma Laboratórios S/A*, and the reference formulation Celebra®, marketed by Pfizer. Consequently, they can be deemed interchangeable.

AUTHORS' CONTRIBUTIONS

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Data Collection, Validation
Vinicius Rezende
Writing - Review and Editing
Carlos Sverdloff
Writing - Preparation of the original, Supervision
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