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RESEARCH ARTICLE

The Relative Bioavailability Study of Two Cefdinir Formulations in Healthy Males Under Fasting Conditions

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SUMMARY

A new oral formulation of cefdinir, Cefdinir 600 mg tablets has been developed and, in this study, its relative bioavailability has been compared with another oral solid dosage form, Cefdinir 300 mg Capsules, which is already on the market. An open-label, randomized, two-period, cross-over relative bioavailability study has been conducted with healthy males under fasting conditions in compliance with Good Clinical Practice (GCP) principles. A single dose of the novel tablet formulation of 600 mg cefdinir has been compared to two doses of Cefdinir 300 mg Capsules (two capsules at once) regarding pharmacokinetic properties. The comparison study was performed as a single-center clinical study, and blood samples of the participants were withdrawn at specified time points, before and after dosing. The plasma concentrations and pharmacokinetic properties of two cefdinir formulations were assessed from the collected samples by using a validated LC-MS/MS analytical method. The relative bioavailability of the new formulation has been shown, and both products were introduced as safe.

Keywords: *Bioavailability, cefdinir, cephalosporin, GCP*

İki Sefdinir Formülasyonunun Sağlıklı Erkeklerde Açlık Koşulları Altında Bağıl Biyoyararlanım Çalışması

ÖZ

600 mg sefdinir içeren yeni bir oral tablet formülasyonu geliştirilmiş ve bu çalışmada bu formülasyonun bağıl biyoyararlanımı halihazırda piyasada bulunan başka bir oral katı dozaj formu olan Sefdinir 300 mg kapsül ile karşılaştırılmıştır. Sağlıklı erkeklerde, açlık koşulları altında açık etiketli, randomize, iki periyotlu, çapraz geçişli bir bağıl biyoyararlanım çalışması İyi Klinik Uygulamaları (İKU) ilkelerine uygun olarak yürütülmüştür. Tek doz uygulanan 600 mg Sefdinir Tablet formülasyonunun farmakokinetik özellikleri, iki doz (tek seferde iki kapsül) olarak uygulanan Sefdinir 300 mg Kapsül ile karşılaştırılmıştır. Bu karşılaştırma çalışması, tek merkezli bir klinik çalışma olarak gerçekleştirilmiştir ve katılımcıların kan örnekleri, dozlamadan önce ve sonra belirtilen zaman noktalarında alınmıştır. Sefdinir formülasyonlarının plazma konsantrasyonları ve farmakokinetik özellikleri, valide edilmiş bir LC-MS/MS analitik yöntemi ile toplanan örnekler kullanılarak değerlendirilmiştir. Çalışmada yeni formülasyonun bağıl biyoyararlanımı gösterilmiş ve her iki ürünün de güvenli olduğu bildirilmiştir.

Anahtar Kelimeler: *Biyoyararlanım, sefdinir, sefalosporin, İKU*

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INTRODUCTION

Cefdinir is a semi-synthetic cephalosporin that exhibits its antimicrobial effects against a broad spectrum of bacteria, both gram-negative and gram-positive (Cabri, 2006). It is used for the treatment of mild to moderate infections caused by various conditions in pediatric, adolescent, and adult patients (Richer, 1995, Cefdinir Capsules USP 300 mg Label, 2020), and its capsule formulation is generally prescribed as either 300 mg twice a day or 600 mg once a day via oral administration (Perry, 2004). However, cefdinir exerts low oral bioavailability and dose-disproportionality. Previous studies showed that in adults, while a single oral dose of 300 mg capsule showed 21% bioavailability, the bioavailability of a single oral dose of 600 mg capsule was 16% (Perry, 2004). For the 300 mg single dose capsule, some pharmacokinetic properties are as follows: the time to reach the peak concentration (t_{max}) is 2 – 4 hours, the maximum plasma concentration (C_{max}) is 1.60 µg/mL, the volume of distribution is 0.35 L/kg, and the terminal half-life ($t_{½}$) is 1.7 ± 0.6 hours. It is eliminated principally via renal excretion without significant metabolization (Cefdinir Capsules USP 300 mg Label, 2020).

To improve drug compliance of patients who needs to take 600 mg of cefdinir at once, a novel 600 mg tablet formulation has been developed by Elixir İlaç Araştırma ve Geliştirme AŞ for İ.E. Ulagay İlaç Sanayii Türk A.Ş. (Istanbul, Turkey). Together with this, to assess the impact on the bioavailability of the new formulation, a pharmacokinetics study on healthy males has been designed in accordance with the regulations of the International Council on Harmonization (ICH), European Medicines Agency (EMA), and Food and Drug Administration (FDA).

Therefore, the aim of this study is to evaluate the pharmacokinetic properties and bioavailability of the single oral dose of novel Cefdinir 600 mg Tablets (Test Drug) formulation compared to Cefdinir 300 mg Capsules (Reference Drug), which was administered as two capsules in healthy males under fasting conditions.

MATERIALS AND METHODS

In Vitro Characterization of the Test and Reference Drugs

The test drug product was developed by Elixir İlaç Araştırma ve Geliştirme AŞ (Ankara, Turkey), with a formulation comprising cefdinir, microcrystalline cellulose, calcium carboxymethyl cellulose, polyoxyl 40 stearate, colloidal silicon dioxide, magnesium stearate and Opadry® Y-1-7000 White as the film-coating. Dissolution profiles of the test and reference drugs were studied in physiological media.

Clinical Study

Twenty-four healthy adult males aged 18 – 55 years with a body mass index of 18.5 – 30 kg/m^2 were enrolled in this study. The participants voluntarily involved in the clinical study have read, understood, and signed the written informed consent form of their free will.

The volunteers who have atopic constitution or asthma and/or known allergy to cefdinir and, or other cephalosporin group antibiotics and, or penicillin or any excipients of the study products were excluded from the study. The volunteers who have the following conditions were also excluded from the study: (*i*) who have any history or presence of clinical relevance to cardiovascular, neurological, musculoskeletal, hematological, hepatic, gastrointestinal, renal, pulmonary, endocrinological, metabolism disorders; (*ii*) who have a history of malabsorption or other conditions that might affect the pharmacokinetics of study drugs; (*iii*) who donated blood more than 400 mL within the last two months before the first administration or were included in another clinical trial; (*iv*) who took depot injectable solutions within six months and, or enzyme-inducing, organotoxic or long half-life drugs within four weeks before the start of the study.

The volunteers who have been consuming beverages or food containing methylxanthines over a certain amount, taking any grapefruit, or grapefruit juice for seven days before drug administration, during the

study, or during the washout periods, who had a history of drug or alcohol abuse and, or had a positive alcohol breath test result were excluded, as well. The eligible volunteers who gave their written informed consents and understood that they could withdraw from the study anytime without specifying any reason were enrolled.

This study was designed as an open-label, randomized, single oral dose, cross-over, two-period study, under fasting conditions. It was conducted at FARMAGEN Good Clinical Practice Center (Gaziantep, Turkey), enrolling 24 healthy adult males. Erciyes University Ethical Committee of Bioequivalence/Bioavailability Studies (2019/78; 19.06.2019) and the Turkish Medicines and Medical Devices Agency (28.06.2019) reviewed and approved this study in compliance with the Declaration of Helsinki and Good Clinical Principles (GCP) (The Ministry of Health of Turkey, 2015).

The duration of the clinical study period was approximately four weeks, including pre-study screening (Day -14 to -1), a wash-out period (7 days), and a final examination (2 – 8 days after the last blood sampling). The individuals who voluntarily attended the study were screened for their eligibility with the standard clinical and biochemical examinations of blood and urine samples. The standard clinical screening included brief anamnestic and demographic data, physical analysis, body temperature determination, weight, and height, standard electrocardiogram (12 lead), blood pressure (BP), and pulse rate (PR) measurements. All laboratory tests were carried out in a certified local laboratory. The volunteers were checked for the presence of Hepatitis B surface antigen (HBsAg), hepatitis C virus antibodies (HCV-Ab) and human immunodeficiency virus antibody (HIV-Ab) in serum to avoid possible infections. They were requested to provide urine samples for drug screening for amphetamines, cannabinoids, benzodiazepines, cocaine, opioids, and barbiturates. Their alcohol breath tests were also applied on entry visits and hospitalization days in both periods of the study.

Twenty-four volunteers were hospitalized and randomized on the day before the dosing day at the GCP clinic. An evening meal was provided on hospitalization days (total caloric value of approximately 1200 kcal) in each period.

After staying ten h fasted, they received their study drugs and were not allowed to drink water from one h before until one h after the administration of study products, except while dosing. On medication days, a standard lunch (total caloric value is approximately 1200 kcal) was provided four h after dosing, and a standard dinner (total caloric value is approximately 1200 kcal) was provided ten h after dosing in each period. Immediately after pre-dose sampling, one tablet of the test drug (600 mg cefdinir) or two capsules of the reference drug (2 x 300 mg cefdinir) was administered to the volunteers with 240 mL water. Blood samplings were done just before dosing and following 16-time points after administration: at 0.33, 0.66, 1.00, 1.33, 1.66, 2.00, 2.33, 2.66, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 14.00 h and the samples were collected into polypropylene tubes using K_2EDTA as an anti-coagulating agent. After sampling, the samples were immediately refrigerated at approximately +4 °C not more than 30 min. Following the centrifugation (3.000 rpm, 4 – 6°C, 10 min), the separated plasma from each sample was transferred into two 3 mL transparent, polypropylene tubes, transferred to a deep freezer, and stored at -70 °C until the clinical study ended. Later, they were transported to the bioanalytical center for the analysis.

Following the washout period, in Period II, the volunteers took the other product they did not take in Period I. The same procedures were applied in each period.

Bioanalytical Study

The bioanalytical studies have been run using a validated chromatographic in-house method at Novagenix Bioanalytical R&D Center (Ankara, Turkey). To be in compliance with GCP rules and avoid bias, the analytical studies were done analytically blinded.

The analytical reference standard of cefdinir was

supplied by Covalent Laboratories Private Limited (India) and the internal standard (IS), cefaclor, was supplied from Alsachim (France). Solvents: methanol, acetonitrile, dichloromethane, and formic acid were supplied from Merck (Darmstadt, Germany). Ultrapure (Type 1) water was supplied from Millipore MilliQ water purification system; K_2EDTA blank human plasma was supplied from Gaziantep University Farmagen GCP Centre (Turkey).

A Shimadzu Liquid Chromatograph Mass Spectrometer LCMS-8040 was used as the high-performance liquid chromatography with mass spectrometry (LC-MS/MS) system. Atlantis dC18, 3 µm (4.6 × 75 mm) column was chosen with a mobile phase consisting of 0.2% formic acid and acetonitrile/methanol (1:1) (80/20, *v*/*v*) with a column oven temperature maintained at 30 °C. The flow rate was 0.9 mL/min. Electrospray ionization was performed in MRM mode to detect *m*/*z* 396.00 > 126.05 (cefdinir) and *m*/*z* 368.00 > 118.05 (cefaclor) ions, simultaneously. The total run time for the method was 5.5 min.

Stock standard solutions of cefdinir were prepared at a concentration of 1 mg/mL. Working solutions were prepared in the concentration range of 0.4 – 180 µg/mL. The working IS was prepared at a concentration of 1 mg/mL. Stock solutions of cefdinir and IS were stored at -70 °C. Calibration standards were prepared by spiking the appropriate amounts of standard solutions into the blank plasma to obtain final concentration levels between 20 – 9,000 ng/mL. The quality control samples were prepared similarly, at concentrations between 20 – 6,750 ng/mL. The lower limit of quantification (LLOQ) was 20 ng/mL. Calibration standards and quality control (QC) samples were stored at -70 °C freezer until analyses.

Protein precipitation followed by liquid-liquid extraction was selected to extract cefdinir, and the sample preparation has done according to the bioanalytical center sample preparation standard operation procedures.

The method was validated for selectivity, specificity, carry-over, linearity, precision and accuracy, recovery, dilution integrity, the influence of hemolyzed and hyperlipidemic plasma, drug-drug interaction, matrix effect, and stabilities, and the validation was performed with K_2EDTA human plasma according to EMA Guideline on Bioanalytical Method Validation (EMA, 2011).

The analytical curves were constructed from a plasma sample processed without IS (blank), a plasma sample processed with IS (zero), and eight concentrations of cefdinir, including the LLOQ, ranging from 20 to 9,000 ng/mL. The concentrations were calculated using peak area ratios and the linearity of the calibration curve was determined using least squares regression analysis. The acceptance criteria for each calculated standard concentration were not more than 15% deviation from the nominal value, except for the LLOQ, which was set at 20%. The within-batch precision and accuracy were evaluated by analyzing QC samples at four different concentration levels between 20 – 6,750 ng/mL. The matrix effects of cefdinir were evaluated by comparing the peak areas of post-extraction blank plasma that were spiked at certain concentrations of QC samples with the areas obtained by the direct injection of the corresponding standard solutions.

An in-house LC-MS/MS was developed and validated to quantify cefdinir in plasma. The plasma samples were maintained at -70 °C during the assay.

Pharmacokinetic and Statistical Analyses

1. To assess relative bioavailability, 24 volunteers were included in the study. The C_{max} and area under the curve from time 0 to the last sampling time ($AUC_{0\text{-}tlast}$) were considered the primary target variables; the area under the curve from time 0 to the infinite time ($AUC_{0\text{-}\infty}$), t_{max} and $t_{½}$ are secondary target variables. The terminal rate constant (λ_z) and mean residence time (*MRT*) were determined, as well. Relative bioavailability (*F*) was calculated using $AUC_{0\text{-tlast}}$ values of the test and reference products. Since this study was designed as a relative bioavailability study, demonstration of the acceptance intervals was not applicable.

C_{max} and t_{max} for cefdinir were obtained directly by plasma concentration-time curves. $AUC_{0\text{-}tlast}$ was calculated using the trapezoidal rule. $AUC_{0\text{-}\infty}$ was calculated by summing $AUC_{0\text{-}tlast}$ and extrapolated area (residual area). The latter was determined by dividing the last measured concentration by λ_z, which was estimated by regression of the terminal log-linear plasma concentration-time points.

C_{max} and $AUC_{0\text{-}tlast}$ were tested for statistically significant differences by means of the analysis of variance (ANOVA) test procedure after logarithmic transformation (ln). The effects of ANOVA were treatment, period, sequence, and volunteer within the sequence and tested at 5% level of significance. 90% confidence interval for the ratio of mean values of C_{max} and $AUC_{0\text{-}tlast}$ which are indicatives of the rate and extent of absorption, respectively, were calculated using ln-transformed.

All statistical analyses were done using Phoenix WinNonlin (Version 8.1, Certara L.P.).

RESULTS AND DISCUSSION

In Vitro Characterization of the Test and Reference Drugs

In vitro dissolution data and similarity factors are given in Table 1 – 6. All tests were conducted with 900 mL media volume with a temperature set at 37 ± 0.5 °C using a paddle apparatus with 50 rpm agitation.

Table 1. *In vitro* dissolution data of the Reference Product (2 x 300 mg capsules) in 0.1 N HCl medium (%) (n = 12).

No.	Time Point (min)							
	0	5	10	15	20	30	45	60
1	0	62.2	82.9	84.9	86.8	89.3	90.7	91.3
2	0	40.6	64.1	76.3	80.0	84.5	87.9	89.2
3	0	59.1	82.9	84.6	85.6	87.0	88.6	89.7
4	0	56.8	78.9	81.2	84.9	87.7	90.1	91.8
5	0	49.6	76.9	79.9	84.3	86.8	90.6	93.2
6	0	46.9	72.6	75.7	78.5	81.8	86.6	89.3
7	0	54.6	87.4	82.1	83.8	87.3	90.6	92.2
8	0	48.9	85.5	86.5	88.1	89.7	91.0	91.8
9	0	53.2	84.5	85.9	86.8	88.2	88.7	90.9
10	0	54.0	80.8	83.2	84.4	86.5	88.8	90.4
11	0	42.4	76.0	79.7	82.8	87.4	89.4	90.7
12	0	51.0	77.3	80.0	82.1	85.6	88.0	89.5
Average	0	51.6	79.1	81.7	84.0	86.8	89.3	90.8
Standard Deviation	-	6.4	6.4	3.5	2.8	2.1	1.4	1.3
Relative Standard Deviation	-	12.4	8.1	4.3	3.4	2.5	1.5	1.4

Table 2. *In vitro* dissolution data of the Test Product (600 mg film-coated tablets) in 0.1 N HCl medium (%) (n = 12).

No.	Time Point (min)							
	0	5	10	15	20	30	45	60
1	0	55.6	75.7	81.6	84.5	87.2	88.2	88.9
2	0	47.6	69.5	76.8	80.6	85.2	87.3	88.1
3	0	43.5	70.9	78.5	82.4	85.4	86.6	87.3
4	0	47.0	75.1	81.4	83.6	86.4	88.4	88.5
5	0	46.5	68.2	75.1	79.5	82.9	85.0	85.4
6	0	52.1	78.5	84.3	86.9	89.2	89.8	89.8
7	0	65.1	81.4	86.0	87.2	88.8	89.0	90.1
8	0	42.3	68.5	81.9	84.4	87.3	88.3	88.4
9	0	61.8	82.0	86.2	88.1	89.7	90.1	90.2
10	0	54.2	78.6	83.0	85.1	86.7	87.5	87.6
11	0	48.0	70.1	76.2	79.3	83.4	85.1	85.9
12	0	43.5	70.1	76.8	79.9	83.8	85.9	86.3
Average	0	50.6	74.1	80.7	83.5	86.3	87.6	88.1
Standard Deviation	-	7.3	5.1	3.9	3.1	2.3	1.7	1.6
Relative Standard Deviation	-	14.5	6.9	4.8	3.7	2.6	1.9	1.8

The similarity factor between the test and reference products was found to be 79.3 in the 0.1 N HCl medium.

Table 3. *In vitro* dissolution data of the Reference Product (2 x 300 mg capsules) in pH 4.5 acetate buffer medium (%) (n = 12).

No.	Time Point (min)							
	0	5	10	15	20	30	45	60
1	0	44.8	83.3	87.1	88.6	89.7	91.4	92.0
2	0	42.9	85.1	89.3	90.8	92.5	94.1	95.0
3	0	35.2	86.2	89.0	90.3	91.1	91.8	92.4
4	0	39.6	83.0	84.4	85.8	87.2	89.0	90.0
5	0	34.4	78.9	86.5	88.6	90.1	91.3	92.4
6	0	42.8	85.0	89.0	90.3	92.0	93.7	94.6
7	0	52.8	82.6	84.6	85.3	87.6	89.0	90.0
8	0	39.5	85.2	88.2	89.1	88.9	92.0	93.6
9	0	43.8	75.7	79.6	81.9	84.6	87.2	88.7
10	0	43.3	74.8	83.1	85.7	88.4	90.0	91.0
11	0	54.9	87.6	89.2	90.2	91.2	91.8	92.8
12	0	55.2	88.1	89.8	90.8	91.8	92.4	93.4
Average	0	44.1	82.9	86.6	88.1	89.6	91.1	92.2
Standard Deviation	-	7.0	4.4	3.1	2.8	2.4	2.0	1.9
Relative Standard Deviation	-	15.9	5.3	3.6	3.2	2.6	2.2	2.1

Table 4. *In vitro* dissolution data of the Test Product (600 mg film-coated tablets) in pH 4.5 acetate buffer medium (%) (n = 12).

No.	Time Point (min)							
	0	5	10	15	20	30	45	60
1	0	33.8	73.6	81.3	85.4	89.9	91.3	91.8
2	0	39.2	77.0	84.8	88.4	90.4	91.2	92.1
3	0	43.6	79.2	88.4	91.1	92.7	93.7	93.9
4	0	45.8	76.0	84.7	88.6	91.6	93.1	93.6
5	0	38.4	73.9	81.7	85.3	89.0	90.7	91.9
6	0	34.0	77.0	85.1	88.2	90.3	91.2	91.9
7	0	52.0	81.4	88.0	88.5	92.2	92.8	92.0
8	0	40.6	79.2	85.0	88.0	89.8	90.6	91.0
9	0	49.9	80.2	86.9	89.2	91.5	92.6	93.5
10	0	49.3	89.4	91.8	93.2	93.0	93.5	93.8
11	0	34.5	83.4	89.3	91.5	92.5	93.1	93.5
12	0	51.9	82.4	87.4	90.1	92.0	92.7	93.0
Average	0	42.8	79.4	86.2	89.0	91.3	92.2	92.7
Standard Deviation	-	6.9	4.5	3.0	2.3	1.3	1.1	1.0
Relative Standard Deviation	-	16.2	5.6	3.5	2.6	1.4	1.2	1.1

Since both the test and reference products were dissolved more than 85%, the similarity factor was not calculated in pH 4.5 acetate buffer medium.

Table 5. *In vitro* dissolution data of the Reference Product (2 x 300 mg capsules) in pH 6.8 phosphate buffer medium (%) (n = 12).

No.	Time Point (min)							
	0	5	10	15	20	30	45	60
1	0	56.1	87.3	93.3	94.2	94.9	96.9	96.9
2	0	36.4	79.5	90.4	91.7	93.7	96.0	97.1
3	0	46.3	84.3	93.4	94.0	94.3	95.6	96.8
4	0	38.6	72.2	83.2	85.0	88.7	92.1	94.2
5	0	44.9	81.3	90.2	89.8	95.3	97.5	98.8
6	0	43.9	78.6	87.2	89.5	92.2	93.9	95.3
7	0	62.6	88.2	90.3	91.8	93.2	94.9	95.0
8	0	54.9	87.4	90.0	91.3	93.2	95.2	96.8
9	0	57.8	91.0	93.1	93.8	95.1	97.0	97.6
10	0	51.2	87.1	91.0	92.9	95.0	97.0	97.3
11	0	55.3	86.5	88.9	90.5	93.1	95.4	96.6
12	0	67.6	91.5	92.6	93.1	94.2	95.9	96.1
Average	0	51.3	84.6	90.3	91.5	93.6	95.6	96.5
Standard Deviation	-	9.5	5.7	2.9	2.6	1.8	1.5	1.2
Relative Standard Deviation	-	18.5	6.7	3.2	2.8	1.9	1.6	1.3

Table 6. *In vitro* dissolution data of the Test Product (600 mg film-coated tablets) in pH 6.8 phosphate buffer medium (%) (n = 12).

No.	Time Point (min)							
	0	5	10	15	20	30	45	60
1	0	52.3	86.2	90.2	92.1	94.0	94.8	95.0
2	0	58.8	84.2	89.6	91.3	93.5	94.2	95.0
3	0	50.0	82.7	88.6	91.5	93.7	94.5	95.3
4	0	47.5	82.1	86.0	88.3	89.8	90.8	91.3
5	0	50.6	83.5	88.6	90.3	92.1	93.0	93.3
6	0	51.4	80.8	86.5	88.6	91.0	91.6	92.2
7	0	49.9	84.9	91.0	92.8	94.6	95.3	95.9
8	0	54.5	88.8	91.5	92.9	93.6	94.1	94.3
9	0	49.9	85.0	90.9	93.2	94.6	95.4	95.6
10	0	42.4	86.2	90.6	92.2	93.1	93.9	94.3
11	0	47.3	79.8	84.8	87.1	90.0	93.5	92.2
12	0	45.5	79.0	85.5	87.7	90.4	91.7	92.1
Average	0	50.0	83.6	88.6	90.7	92.5	93.6	93.9
Standard Deviation	-	4.2	2.9	2.4	2.2	1.8	1.5	1.6
Relative Standard Deviation	-	8.4	3.4	2.7	2.4	2.0	1.6	1.7

Since both the test and reference products were dissolved more than 85%, the similarity factor was not calculated in pH 6.8 phosphate buffer medium.

Based on the *in vitro* dissolution tests that are conducted in three different media, the test and reference drug products' release profiles were found to be similar.

Clinical Study

To enroll in this study, 46 volunteers were screened; 24 of them were included and randomized into two groups and completed the clinical study. All the volunteers were Caucasian. The mean ± SD age of volunteers is 24.17 ± 6.48 years, and the mean ± SD body mass index (BMI) was 25.01 ± 2.34. The demographic data of volunteers are presented in Table 7. There was no protocol deviation throughout the clinical period.

Table 7. Demographic data of the volunteers.

n = 24	Age	Weight (kg)	Height (cm)	BMI
Mean	24.17	78.88	177.38	25.01
SD	6.48	9.89	5.64	2.34
Minimum	19	62	165	20.6
Maximum	50	98	186	29.7

To estimate the pharmacokinetic parameters, the actual time of sampling was used. The wash-out duration was sufficient since no pre-dose concentration of cefdinir was detected in t_0 samples of the second period. As primary variables, the mean ± SD of C_{max} were found to be 3,098.30 ± 1,102.72 ng/mL and 3,461.70 ± 1,013.93 ng/mL, and the mean ± SD of $AUC_{0\text{-tlast}}$ were found to be 14,287.11 ± 5,146.29 h.ng/mL and 15,244.83 ± 4,406.45 h.ng/mL for test and reference products, respectively (Table 8).

Table 8. The arithmetic means ± SD of pharmacokinetic parameters of a single oral dose of 600 mg cefdinir in test drug and the reference drug in healthy adult male volunteers under fasting conditions (Arithmetic Mean ± SD) (n = 24).

Parameters (Units)	Test (T)	Reference (R)
C_{max} (ng/mL)	3098.30 ± 1102.72	3461.70 ± 1013.93
$AUC_{0\text{-tlast}}$ (ng.h/mL)	14287.11 ± 5146.29	15244.83 ± 4406.45
$AUC_{0\text{-}\infty}$ (ng.h/mL)	14458.54 ± 5218.76	15397.98 ± 4457.30
t_{max} (h)*	3.10 ± 0.79	3.04 ± 0.66
$t_{½}$ (h)	1.75 ± 0.13	1.74 ± 0.15
λ_z (1/h)	0.40 ± 0.03	0.40 ± 0.03
MRT (h)	4.71 ± 0.68	4.48 ± 0.52

* t_{max} values are presented as median with range (minimum – maximum) in parentheses.

In Table 8, the pharmacokinetic parameters of the study drugs; in Table 3, the geometric least-square means, ratios and 90% Confidence Intervals (CI)s are shown. The 90% CIs for the geometric mean ratios of C_{max} and $AUC_{0\text{-tlast}}$ have been found as 80.67 – 96.37% and 86.23 – 98.17%, respectively (Table 9).

Table 9. Geometric Least Square Means, Ratio and 90% Confidence Intervals of the test drug and the reference drug in healthy adult male volunteers under fasting conditions.

Parameter	Difference	DiffSE	TESTLSM	REFLSM	Ratio%	90% CI	ISCV%	Power%
ln(C_{max})	-0.1259	0.0518	7.9793	8.1052	0.8817	0.8067 – 0.9637	18.09	56.92
ln($AUC_{0\text{-tlast}}$)	-0.0833	0.0377	9.5093	9.5926	0.9201	0.8623 – 0.9817	13.13	97.40
ln($AUC_{0\text{-}\infty}$)	-0.0814	0.0378	9.5211	9.6025	0.9218	0.8639 – 0.9836	13.14	97.66
t_{max} (h)	0.0563	0.1802	3.0958	3.0396	1.0185	0.9167 – 1.1203		
$t_{½}$ (h)	0.0054	0.0199	1.7453	1.7399	1.0031	0.9835 – 1.0227		
λz (1/h)	-0.0016	0.0045	0.3994	0.4009	0.9961	0.9770 – 1.0151		
MRT (h)	0.2264	0.1140	4.7062	4.4798	1.0505	1.0068 – 1.0942		

The average plasma concentration-time curves and the average ln plasma concentration-time curves of study drugs are displayed in Figures 1 and 2, respectively.

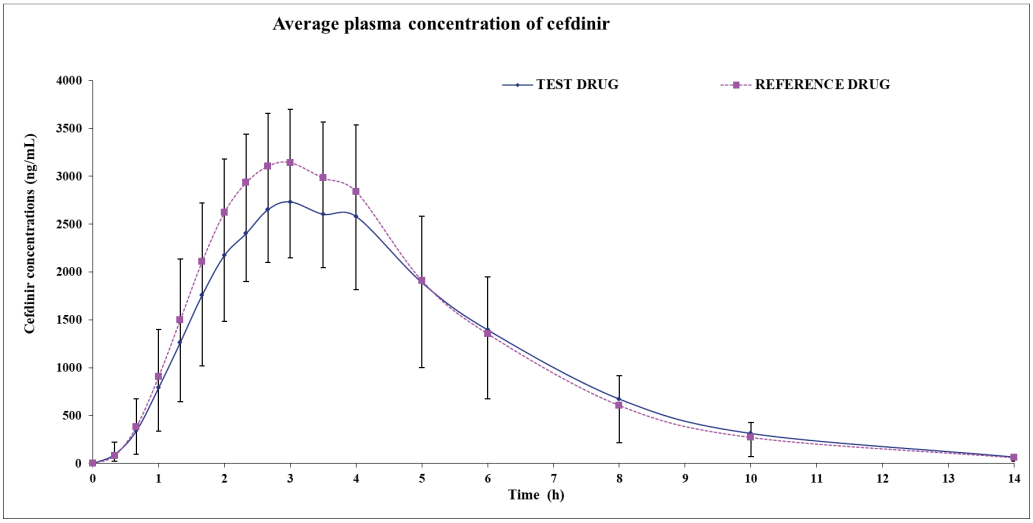

Figure 1. Mean plasma concentration-time curves of cefdinir after a single dose of the test drug and the reference drug of oral cefdinir in healthy adult male volunteers (n = 24) under fasting conditions.

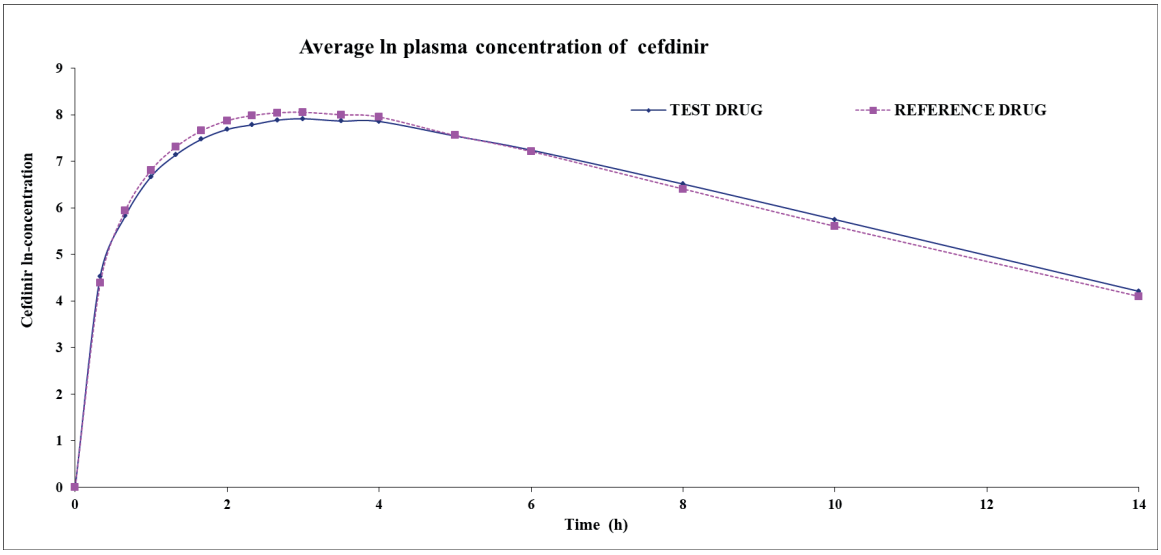

Figure 2. Average ln plasma concentration curves of cefdinir after a single dose of the test drug and the reference drug of oral cefdinir in healthy adult male volunteers (n = 24) under fasting conditions.

As the secondary variables, the median of t_{max} for study drugs was found to be three h and ranged from 2.0 to 5.0 h for the test, and from 2.0 to 4.0 h, for the reference drug. In addition, the mean ± SD of $t_{1/2}$ for the test and reference products were found similar: 1.75 ± 0.13 h and 1.74 ± 0.14 h, respectively (Table 8).

Three adverse events occurred during the study, and one of them was defined as "probable" and the other two were assessed as "possible" drug-related adverse events that occurred in all two periods. Two of those three have fully recovered. One volunteer received concomitant medication (paracetamol, an analgesic agent known to have no interaction with cefdinir as stated in the study protocol) due to a headache. The overall tolerability of the products was considered as good. There were no serious adverse events or adverse reactions reported throughout the study.

There are no pharmacokinetic studies in the literature with 600 mg cefdinir doses, yet, we have identified some recent studies conducted with various doses and formulations of cefdinir (Table 10) (Abdel, 2011, Zhang, 2011, Chen, 2012).

Table 10. Recent pharmacokinetic studies conducted with various doses of cefdinir.

Author	Dose	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (μg.h/mL)
Abdel	125 mg/5 mL	T*: 2.49 ± 1.15	T: 2.81 ± 0.55	T: 4.92 ± 1.58	T: 15.09 ± 5.00
		R*: 2.41 ± 1.04	R: 3.02 ± 0.85	R: 5.07 ± 1.66	R: 14.74 ± 5.68
Chen	100 mg	T: 0.95 ± 0.24	T: 2.68 ± 0.77	T: 1.99 ± 0.71	T: 4.34 ± 0.94
		R: 0.88 ± 0.16	R: 3.68 ± 0.99	R: 1.78 ± 0.42	R: 4.21 ± 0.74
Zhang	200 mg	T: 1.52 ± 0.48	T: 3.08 ± 0.73	T: 2.04 ± 0.53	T: 7.12 ± 1.85
		R: 1.42 ± 0.39	R: 3.22 ± 0.81	R: 1.87 ± 0.29	R: 6.86 ± 1.60

*T: Test Drug, R: Reference Drug

Cefdinir is a preferred antibiotic in mild and moderate infections due to its extensive spectrum against bacteria, despite its low oral bioavailability. Together with this, the non-linear pharmacokinetics of cefdinir gives rise to the risk of limiting the adequacy of treatment. Therefore, a 600 mg tablet formulation of cefdinir was developed, which is aimed to improve compliance of patients in need of 600 mg/day taken

as a single dose, and a relative bioavailability study has been designed and conducted over the current regulations. In this single-dose study, the subjects received either one tablet of 600 mg cefdinir or two capsules of 300 mg cefdinir in a randomized order, and plasma cefdinir concentrations of study drugs were evaluated relatively.

CONCLUSIONS

The overall objective of this study is to assess the oral relative bioavailability of two formulations of cefdinir on 24 healthy volunteers. Concluding the results, the *F* value was found as 93.52%. Moreover, both study drugs were well-tolerated and considered to be safe.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

FY: Writing, Design, Review; AA: Experimenting, Interpretation, Review; ÖA: Design, Interpretation, Review; SK: Design, Interpretation, Review; AP: Design, Interpretation, Review; MÖK: Design, Interpretation, Review; OS: Statistics, Design, Interpretation, Review; SPA: Writing, Review.

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