

Comparative bioavailability and pharmacokinetic study of Cefadroxil capsules in male healthy volunteers of Pakistan

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Abstract: The current study was aimed to judge bioequivalence between two formulations of cefadroxil capsules as guided by FDA guidelines. Another objective was to conduct pharmacokinetic evaluation in Pakistani population. A single-dose, randomized, cross-over pharmacokinetic study was conducted during the month of May'2013 to August'2013. Washout period was one week. Fourteen healthy male adult volunteers were enrolled in the study, however twelve completed the study. Cefadroxil plasma concentration was analyzed by using validated HPLC method. Protein precipitation was achieved by the addition of 6% tri chloro acetic acid in 1:1 ratio and detection was done at 260 nm. Retention time was 7.792 min and correlation coefficient (R^2) was 0.9953 showing linearity of the method. Blood sampling was carried out at different time intervals after administration of either test (TEST 500 mg) or reference (REF[®] 500mg) formulation. Pharmacokinetic parameters ($AUC_{0 \rightarrow \infty}$, $AUC_{0 \rightarrow t}$, C_{max} , T_{max} , $t_{1/2}$ and k_{el}) were calculated using Kinetica[®] PK/PD software. The geometric mean ratios and 90% confidence interval (CI) of these pharmacokinetic parameters for cefadroxil (test and reference) formulations were 0.986 (90.83-106.98%) for $AUC_{0 \rightarrow t}$; 0.967 (89.13-104.92%) for $AUC_{0 \rightarrow \infty}$ and 0.999 (91.06-109.69%) for C_{max} . The differences between T_{max} of both formulations were not found to be statistically significant (p-value was more than 0.05). The 90% CI of the test/reference AUC and C_{max} ratio of cefadroxil were within the FDA recommended range for bioequivalence. Maximum plasma concentration C_{max} was 12.5 µg/ml for test and 12.47 µg/ml for reference formulations. Average time to reach C_{max} for test and reference formulation was 1.54 and 1.5 hrs. The two formulations of cefadroxil studied during the above study were verified bioequivalent. Maximum plasma concentration of cefadroxil was lower than those mentioned in some previous studies, while T_{max} and half-life were near to values reported in literature

Keywords: FDA; cefadroxil; pharmacokinetic study; comparative bioavailability.

INTRODUCTION

Cefadroxil is semi synthetic, bactericidal antibiotics prescribed for skin, soft tissues, up per respiratory and urinary tract infections especially in children. Adult usual dose is 500-1000 mg/day in single or divided doses (Shetty *et al.*, 1999). It is well tolerated and readily absorbed after oral administration. It is mainly excreted as intact molecule in urine. Protein binding is 20% and half-life is 1.5 to 2 hrs. Its activity is similar to cephalixin, whereas its half life is 1.1 hrs after 500mg oral dose as compared to 0.7 hrs after similar dose of cephalixin (Welling *et al.*, 1985). In contrast with other cephalosporins like cephalixin, cefadroxil produces considerable higher concentration in physiological fluids and tissues like lung, skin, sputum, pleura after oral administration. The drug concentration attained is high enough to defeat bacterial growth (Bernhardt 1980; Nightingale 1986; Tanrisever and Santella 1986; Akimoto *et al.*, 1994).

FDA defines bioequivalence as “the absence of any significant change in rate and extent of absorption of any active pharmaceutical ingredient from its pharmaceutical products at similar molar dose administered under identical conditions”. The basic aim of bioequivalence study is that if two products of same active pharmaceutical ingredient are revealed to be bioequivalent at similar molar dose and dosage form, but different formulation ingredients; they are therapeutically equivalent regarding efficacy and safety; such products can be used substitutable (Meredith 1996). FDA guidance for industry endorses the requirement of bioequivalence studies whenever they apply for the approval of a new dosage form of established active pharmaceutical ingredient (FDA 2003). So, manufacturers have to submit applications to the regulatory authorities to prove the safety and efficacy of their product in contrast with innovator's brand. They have to document proof of similar rate and extent of absorption which should be within recommended limits (FDA 2003) and (EMA-CHMP 2010). To prove bioequivalency, the plasma drug concentration verses time curve and different Pharmacokinetic parameters including C_{max} , T_{max} and

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AUC of test formulation should be 80-125% that of reference formulation.

In Pakistan, there are more than 400 registered pharmaceutical companies, out of these 370 are local companies contributing the market share of 46.7% (Drug Control Organization 2005). The pharmaceutical products marketed by local and multinational companies registered in local index of pharmaceuticals have large variation in the cost. In developing countries like Pakistan, health related expenses have to be beard by the patient himself. In this scenario, use of generics should be encouraged instead of brands (Karim *et al.*, 1996; Simoens and De Coster 2006; Jamshed *et al.*, 2009). As 77% of medical expenditure in Pakistan is out of pocket, the introduction and use of generic medicines should be encouraged to solve the issues of access and affordability being a cost containment approach used worldwide (WHO 2004). The substitution should be supported by bioequivalence studies conducted in local population.

Approximately ten brands of cefadroxil are available in Karachi mostly produced by local companies. However, literature does not contain any published report about their pharmacokinetic and bioequivalence study conducted on Pakistani population. Physician and clinical pharmacist are prescribing such products according to the pharmacokinetic data available from developed countries. It is also observed that some significant variations in pharmacokinetic are found in different products of same active pharmaceutical ingredient as these products are manufactured by different pharmaceutical companies. Therefore, the present study was planned to investigate comparative bioavailability of a local formulation of cefadroxil (TEST capsule 500mg) with its reference brand (REF[®] capsule 500mg). Bioequivalence study was performed using randomized, two treatment, two period, cross over design as guided by FDA-CDER 2003 (FDA 2003). Pharmacokinetic variation in local population was also investigated.

MATERIALS AND METHODS

Formulations

The reference (REF[®] 500mg) and test formulation (TEST 500 mg) were selected from available brands of cefadroxil in Karachi. The reference formulation was the innovator's brand of multinational origin, while the formulation with lowest price was selected as test. These formulations were purchased from local market. Information written on labels was noted including price, manufacturing date, expiry date and batch number.

Chemical assay and dissolution profile comparison

These formulations were assayed by assay method as given in official monograph of cefadroxil (USP, 31). RP-HPLC method was adopted with UV detection at 230 nm. Mobile phase comprised of buffer pH 5.0 and acetonitrile

in the ratio of 960:40 and flow rate was 2 ml/min. Results were calculated as percent drug content of manufacturers claim. Dissolution profile of the test product (n=12) was compared with that of reference (n=12) in four different dissolution media (HCl pH 1.2, buffer pH 4.5, buffer pH 6.8 and distilled water). Dissolution apparatus (Pharma test DT70, Germany) and spectrophotometer (Spekol 2000 series, Analytikjena) were used. Similarity (f_2) and dissimilarity (f_1) factor was calculated using DDSolver[®] excel based Add in program by Zhang (Zhang *et al.*, 2010).

Study subjects

Fourteen participants were enrolled in the clinical part of the study. Their selection was based on inclusion/exclusion criteria. The clinical examinations like medical history, height, weight, body temperature, body-mass index, heart rate, systolic and diastolic blood pressure were completed. They were communicated about the side effects that may be encountered after administration. Such side effects are nausea, vomiting diarrhea, abdominal discomfort and hardly ever allergic reactions including skin rash or urticaria. During the study period, volunteers were not permitted to ingest alcohol or cold drinks and foods having caffeine from 48 hrs earlier to administration of products till the termination of clinical part of study. The volunteers were instructed to refrain from taking medicines during 4 weeks before and during the study.

Criteria for inclusion and exclusion of volunteers

As the study was conducted on healthy subjects, so that inclusion and exclusion criteria was just for healthy volunteers as follows:

Inclusion criteria

Volunteers were Pakistani, male, age ranges from 18 to 38 years. Body weight can deviate from average body weight by 10%. They should be healthy deprived of sign/symptoms of any clinical condition and medical history of chronic diseases like diabetes, hypertension. They should not be allergic to beta lactam antibiotics including penicillins and cephalosporins.

Exclusion criteria

The volunteers who failed in their physical examination and did not fit in the inclusion criteria were not enrolled in the study. Smokers and volunteers who are taking any type of medication were not included. Those who participated in clinical trial three months before the study and intended to hospitalize within three months after the study were also excluded.

Study protocol

A single-dose, randomized, cross-over pharmacokinetic study was executed on adult male volunteers proved healthy. Volunteers were randomly divided in two groups and each group received the one drug treatments at one

time. Table 1 displays the details of two periods of the study. The capsules were administered with water (240 ml) in the morning of the study day after overnight fasting. Breakfast was served at 4 hrs and lunch at 8 hrs after administration. A non-blind approach was adopted. Both volunteer and researchers were aware of the formulations under test. Blood samples (5ml) were withdrawn using an indwelling cannula inserted on the forearm, into Vacutainer™ tubes (containing EDTA) at time intervals of 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 10 hrs after drug administration. The blood samples were centrifuged at 6000 rpm for 5 min; plasma samples were stored in cryo vials and kept frozen at -20°C until analyzed. Volunteers were inquired about the incidence of any side effects/adverse event through the treatments periods. Radial pulse and blood pressure were examined as vital signs before study and through the study period.

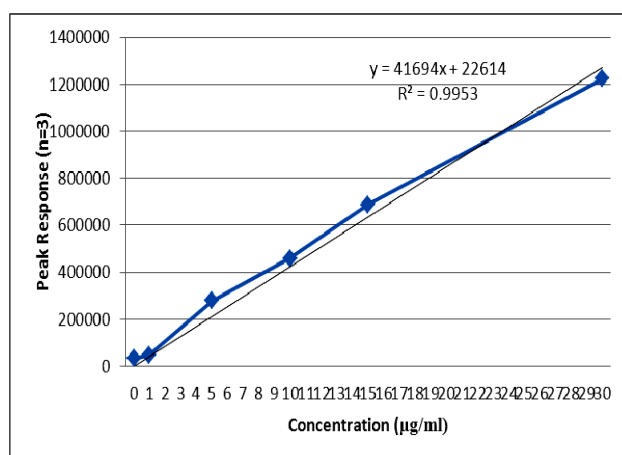


Fig. 1: Calibration curve of the HPLC method for plasma

Ethical issues

The study protocol was submitted and got approval from Ethical & Scientific Review Committee, Karachi Medical and Dental College, Abbasi Shaheed Hospital, Karachi. Participation of the subjects in the study was voluntarily and anonymous. They were briefed about the rationale, length and risks of the study. They were also informed about the opportunity of withdrawal whenever they want. Participants were asked to read carefully and signed the informed consent approved by above-mentioned ethical committee before their enrolment in the study. Helsinki declaration and good clinical practices were followed (ICH 1996; WMA 2000).

HPLC analysis of plasma samples

Validated high performance liquid chromatographic method was used for plasma sample analysis (Rahim et al., 2014). Shimadzu HPLC (20A) with LC solution software was used with Waters Spherisorb ODS2, C18 (5µm, 150mm×4.5 mm) column. Protein extraction was achieved by using 6% trichloroacetic acid in the ratio of 1:1. Sodium dihydrogen phosphate buffer pH 4.0 and methanol (96:4) was used as mobile phase. 1.5 ml/min

was flow rate and 100µl was injection volume. UV detection was recorded at 260 nm. Method specificity was achieved as the blank plasma presented no peak near the retention time of cefadroxil. Linearity was found over the range of 0.5-30µg/ml ($R^2=0.9953$). LOD and LLOQ were 0.03 and 0.06µg/ml, respectively. The precision was in the acceptable range of COV% i.e. 0.35-4.01%, 1.88-7.9% for inter-day and intra-day precision, respectively. Calibration curve is mentioned in fig. 1.

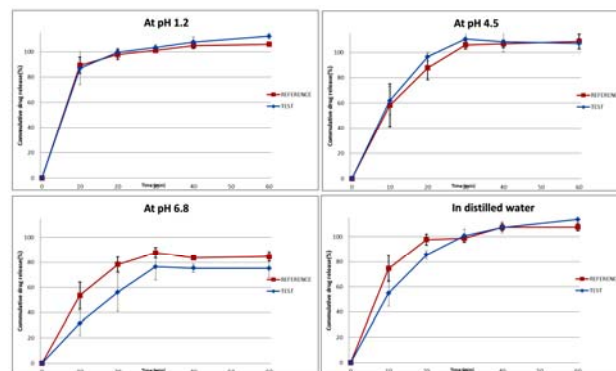


Fig. 1: Dissolution profile comparison of test and reference formulations.

Calculation of pharmacokinetic parameters

The plasma concentration of cefadroxil verses time curve was plotted. The values of C_{max} , T_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were estimated from Kinetica® PK/PD software as guided in FDA documents, approved for two period, two treatment, cross-over bioequivalence studies. In addition, other parameters including k_a , absorption half-life, k_{el} , terminal half-life and total clearance were also determined from the above-mentioned software.

STATISTICAL ANALYSIS

The pharmacokinetic parameters after logarithmic transformation (multiplicative model) were subjected to an analysis of variance (ANOVA) with the factors sequence; subject nested within sequence; period and drug formulation using a general linear model procedure. For evaluation of bioequivalence 90% confidence intervals for the formulations geometric mean ratio in the parameters AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were determined using the log-transformed data. If the calculated 90% confidence intervals were within 0.80 to 1.25, bioequivalence was proved.

RESULTS

The percent cefadroxil content in test and reference formulation were 101.75% and 98.9%, respectively. Results of dissolution profile study are given in fig. 2 and table 2. Similarity (f_2) and dissimilarity (f_1) was within the recommended range i.e. f_2 should be 50-100% and $f_1 = 1-15$. A total of fourteen male healthy Pakistani volunteers

comply with the selection criteria were enrolled. Twelve volunteers were completed the study. Their ages were in between 18 and 38 years, with average body weight and body mass index of 74.33kg and 24.31kg/m² (table 3). Blood samples of them were collected after the administration of test and reference formulations and analyzed through validated HPLC method (Rahim *et al.*, 2014). Detection was done at 260nm and mean retention time was 7.792min. Inter-day and intra-day analysis showed adequate precision.

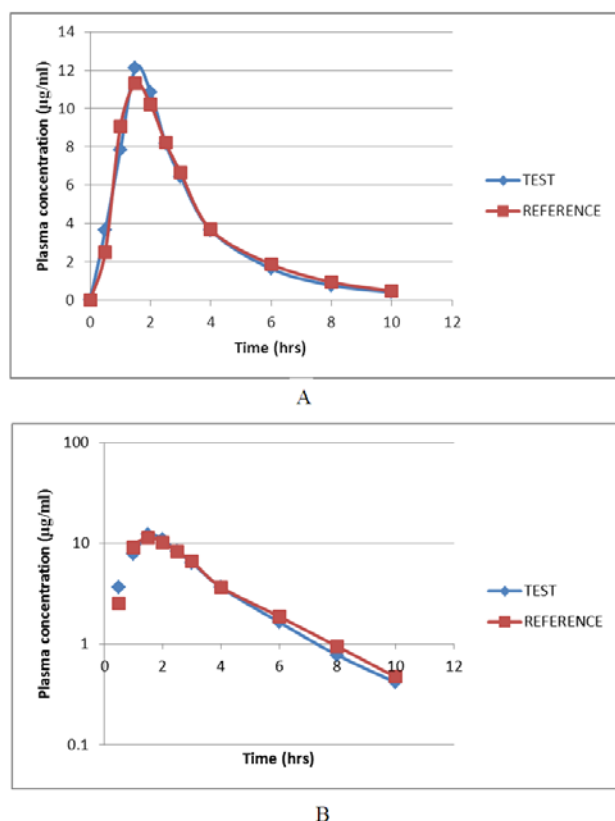


Fig. 3: Linear and (B) semi-log plot of mean cefadroxil plasma concentration versus time in human volunteers.

Pharmacokinetic evaluation of both cefadroxil formulations was done by Kinetica[®] PK/PD software. The linear and semi log plot of mean plasma concentrations versus time of volunteers (n=12) for the two formulations are mentioned in fig. 3. Pharmacokinetic parameters are depicted in table 4. The 90% CI of pharmacokinetic parameters (AUC_{0-t} , $AUC_{0-\infty}$ and C_{max}) for cefadroxil test and reference formulation were 90.83-106.98%, 89.13-104.92% and 91.06-109.69%, respectively. The differences between the drug products under test for T_{max} and $t_{1/2}$ values were not found to be statistically significant ($P>0.05$) using Anova and two one sided t test (table 5).

DISCUSSION

The present study was conducted with two drop out due to non-compliance of volunteer. The cross-over design as

recommended by FDA for a bioequivalence study was adopted since it can eradicate inter-subject variations. The carry-over effect may hinder in a cross-over design study. It was excluded by providing washout period (one week) large enough to eliminate drug from the body. A total of twelve male healthy Pakistani volunteers were participated till the end of the study. Blood samples of subjects were withdrawn after the administration of both formulations. A validated high performance liquid chromatographic method was adopted. The concentration at first sampling point i.e. 0.5 hr after dosing was above the limit of quantification of the bioanalytical method adopted (i.e. 0.06µg/ml) (Rahim *et al.*, 2014). The plasma drug concentration verses time plots of test as well as reference formulation were comparable (fig. 3). Pharmacokinetic parameters as mean $\pm$ SD are depicted in table 4 including C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$ and k_{el} as estimated by Kinetica[®] PK/PD. ANOVA was applied on the log transformed data of such pharmacokinetic parameters to prove the assumption that period/carry over effect on these parameters was statistically insignificant. For the bioequivalence of two drugs, the 90% confidence interval should be fall in the range given by FDA i.e. 0.8-1.25. We did not found any significant effect of sequence, subject, period and drug formulation for all PK parameters. The 90% confidence interval for geometric mean ratios of test and reference formulations of AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were observed as 90.83-106.98%, 89.13-104.92% and 91.06-109.69%, respectively. All these 90% confidence intervals were found within the FDA recommended range for bioequivalence i.e. 80%-125% (table 5). In vitro dissolution profile comparison already revealed that the two products were similar in releasing drug from two products under test and can produce similar rate and extent of absorption in vivo (table 2).

The two formulations of cefadroxil investigated during the study were proved to be bioequivalent. The test formulation is a generic product, which can substitute the reference formulation of innovator's brand to reduce the cost of treatment in the patient interest. Analogous studies of comparative bioavailability of cefadroxil oral dosage forms (tablets, capsules, suspensions) have been executed formerly in different populations (Oliveira *et al.*, 2000; Otoom *et al.*, 2004; Kano *et al.*, 2008; Mansour 2012). But, such studies outwardly did not assess the same formulation that was tried in the current study. The product under test had its particular formulation unlike from those studied in previous studies. Therefore, the findings of this bioequivalence study were categorically distinctive only to the tested formulation used in the study and cannot be in-discriminated to other cefadroxil generics.

Table 1: Study design for comparative bioavailability study of two formulations of cefadroxil.

Study Period	Group	Treatment
Period one	1	One capsule (500 mg dose) of cefadroxil test formulation*
	2	One capsule (500 mg dose) of cefadroxil reference formulation [®]
One week washout period		
Period two	1	One capsule (500 mg dose) of cefadroxil reference formulation [®]
	2	One capsule (500 mg dose) of cefadroxil test formulation*

*Test = TEST 500 mg capsule (manufactured by local company of Pakistan), Batch number 12647, manufacturing date 6/2012, expiration 5/2014.

[®]Reference = REF[®] 500 mg capsule (manufactured by multinational company), Batch number 2G552, manufacturing date 7/2012, expiration 7/2015.

Table 2: Dissolution profile comparison of cefadroxil test and reference products (n=12 units)

Dissolution media	Similarity factor (f_2)	Dissimilarity factor (f_1)
HCl pH 1.2	73.49	3.14
Buffer pH 4.5	67.19	4.33
Buffer pH 6.8	50.24	14.04
Distilled water	51.14	8.29

Recommended ranges of $f_2 = 50-100$ and $f_1 = 1-15$.

Table 3: Demographics of the volunteers participated in the study.

Parameters	Mean	SD	Range
Age (years)	21	5.48	18-38
Body weight (Kg)	74.33	7.27	60-80
Body height (Inches)	68.08	2.84	62-73
BMI* (Kg/m ²)	24.31	1.66	19.8-27

*body mass index

Table 4: Pharmacokinetic parameters of cefadroxil (test and reference) formulations determined by Kinetica[®] from plasma-drug concentration data.

Pharmacokinetic parameters	Test (TEST)	Reference (REF [®])
AUC _{0-t} (µg/ml).hr	35.28±2.24	36.31±7.31
AUC _{0-∞} (µg/ml).hr	36.08±2.59	37.85±7.74
C _{max} (µg/ml)	12.5±1.72	12.47±1.314
T _{max} (hr)	1.54±0.144	1.5±0.001
t _{1/2β} (hr)	1.72±0.3	1.99±0.538
k _{el} (1/hr)	0.82±0.41	0.7±0.22
t _{1/2ka} (hr)	0.32±0.11	0.232±0.133
k _a (1/hr)	2.6±1.51	4.2±2.8
Clearance (L/hr)	14.6±2.04	14.86±3.06
MRT (mean residence time) (hr)	1.47±0.7	1.64±0.61

Values in table 4 represent mean ±SD.

Table 5: Results of statistical analysis of log transformed data of pharmacokinetic parameters of cefadroxil test and reference formulations.

Pharmacokinetic parameters	Geometric mean ratio (test/reference)	90% CI
AUC _{0-t}	0.9858	90.83-106.98
AUC _{0-∞}	0.967	89.13-104.92
C _{max}	0.999	91.06-109.69

During the study, different pharmacokinetic parameters were studied in local Pakistani population, as regional variation may cause amendments in drug absorption, distribution, metabolism and excretion (Zhou *et al.*, 1989; Shoaib *et al.*, 2008). The plasma concentration data was the best fitted in two compartmental model, demonstrating linear pharmacokinetics, whereas elimination was carried out from the central compartment. Such type of information was also documented by other investigators (Marino *et al.*, 1982; Shen *et al.*, 2007). Previously some researchers also suggested that cefadroxil monohydrate followed one compartmental model after oral administration (Pfeffer *et al.*, 1977; Lode *et al.*, 1979). Maximum plasma concentrations achieved were 12.5 µg/ml for test and 12.47 µg/ml for reference. These values were slightly lower than the values of C_{max} reported by other researches (Kano *et al.*, 2008; Mansour 2012). Kano *et al.* in 2008 reported C_{max} as 16.04 µg/ml for test and 16.01 µg/ml for reference formulation (Kano *et al.*, 2008). The mean time for the attainment of C_{max} as reported in the present study was 1.5 hr and 1.54 hr for reference and test formulations. The values of T_{max} observed were in close agreement of previous results reports by (Prenna and Ripa 1980) and shorter than another report (Otoom *et al.*, 2004). The $t_{1/2}$ (mean±SD) of cefadroxil was 1.72±0.3 hr and 1.99±0.538 hr for test and reference formulations. These values were near to the reports of (Barbhaya 1996) and (Oliveira *et al.*, 2000), whereas higher than the $t_{1/2}$ reported by Prenna and Ripa (Prenna and Ripa 1980) and Otoom, *et al.* (Otoom *et al.*, 2004). Otoom *et al.*, in 2004 reported the $t_{1/2}$ as 1.4 hrs for reference and 1.36 hrs for test (Otoom *et al.*, 2004), while Olivera *et al.* in 2000 documented 1.8 hr for test and 1.9 hr for reference formulation analyzed (Oliveira *et al.*, 2000). All though most of the pharmacokinetic parameters of cefadroxil were similar to published data from other parts of the world, however some variations were observed that might be due to inter-subject and inter-racial variability.

CONCLUSION

In the current single-dose, two period, cross-over study in healthy fasted volunteers, the two formulations of cefadroxil capsules i.e. REF[®] 500mg and TEST 500mg were verified bioequivalent and can substitute each other. Maximum plasma concentration of cefadroxil observed in Pakistani population was lower than reported in some previous studies, while T_{max} and half-life were near to values reported in literature

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REFERENCES

- Akimoto Y, Komiya M, Kaneko K and Fujll A (1994). Cefadroxil concentrations in human serum, gingiva, and mandibular bone following a single oral administration. *J. Oral Maxillofac. Surg.*, **52**(4): 397-400.
- Barbhaya RH (1996). A pharmacokinetic comparison of cefadroxil and cephalixin after administration of 250, 500 and 1000mg solution doses. *Biopharm. Drug Dispos.*, **17**(4): 319-330.
- Bernhardt L (1980). Tissue and fluid concentrations of cefadroxil monohydrate. *J. Int. Med. Res.*, **8**(Suppl 1): 58.
- Drug Control Organization (2005). Ministry of Health, Government of Pakistan. Available from: <http://www.dcomoh.gov.pk/> [Accessed December 2013].
- EMA-CHMP (2010). Note for Guidance on the Investigation of Bioavailability and Bioequivalence. The European Agency for the Evaluation of Medicinal Products (EMA), The European Agency for the Evaluation of Medicinal Products (EMA), Committee for Proprietary Medicinal Products (CPMP). pp.1-15.
- FDA (2003). Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General Considerations. U S. Department of Health Services, Food and Drug Administration and CDER. pp.1-17.
- ICH (1996). ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1). Geneva, Switzerland International Conference on Harmonisation. pp.1-33.
- Jamshed S, Babar Z, Ibrahim M and Hassali M (2009). Generic medicines as a way to improve access and affordability: A proposed framework for Pakistan. *J. Clin. Diagn. Res.*, **3**(3): 1596-1600.
- Kano EK, Porta V, Koono EE, Schramm SG and Serra CH (2008). Bioequivalence study of two oral formulations of cefadroxil in healthy volunteers: *Arzneimittelforschung*, **58**(1): 42-47.
- Karim SA, Pillai G, Ziqubu-Page T, Cassimjee M and Morar M (1996). Potential savings from generic prescribing and generic substitution in South Africa. *Health Policy Plan*, **11**(2): 198-202.
- Lode H, Stahlmann R and Koeppel P (1979). Comparative pharmacokinetics of cephalixin, cefaclor, cefadroxil, and CGP 9000. *Antimicrob. Agents Chemother.*, **16**(1): 1-6.
- Mansour NO (2012). Pharmacokinetics and bioequivalence evaluation of 2 cefadroxil suspensions in healthy egyptian male volunteers. *Clin. Pharmacol. Drug Dev.*, **1**(3): 110-113.
- Marino E, Dominguez-Gil A and Muriel C (1982). Influence of dosage form and administration route on the pharmacokinetic parameters of cefadroxil. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **20**(2): 73.

- Meredith P (1996). Generic Drugs. *Drug Saf.*, **15**(4): 233-242.
- Nightingale C (1986). Penetration and concentration of cefadroxil in sputum, lung and pleural fluid. *Drugs*, **32**(3): 17-20.
- Oliveira C, Salmon J, Sucupira M, Ilha J and De Nucci G (2000). Comparative bioavailability of two cefadroxil formulations in healthy human volunteers after a single dose administration. *Biopharm. Drug Dispos.*, **21**(6): 243-247.
- Otoom S, Hasan M and Najib N (2004). Comparative bioavailability of two cefadroxil products using serum and urine data in healthy human volunteers. *Clin. Exp. Pharmacol. Physiol.*, **31**(7): 433-437.
- Pfeffer M, Jackson A, Ximenes J and De Menezes JP (1977). Comparative human oral clinical pharmacology of cefadroxil, cephalixin, and cephradine. *Antimicrob. Agents Chemother.*, **11**(2): 331-338.
- Prenna M and Ripa S (1980). Serum levels and urinary excretion in humans of BL-S 578 (cefadroxil), a new semisynthetic cephalosporin. *Chemotherapy*, **26**(2): 98-102.
- Rahim N, Naqvi BS, Alam M, Iqbal E and Bibi R (2014). Validated high performance liquid chromatography method for analysis of cefadroxil monohydrate in human plasma. *Trop. J. Pharm. Res.*, **13** (6): 975-979.
- Shen H, Ocheltree SM, Hu Y, Keep RF and Smith DE (2007). Impact of genetic knockout of PEPT2 on cefadroxil pharmacokinetics renal tubular reabsorption and brain penetration in mice. *Drug Metab. Dispos.*, **35**(7): 1209-1216.
- Shetty N, Shulmant R and Scott G (1999). An audit of first generation cephalosporin usage. *J. Hosp. Infect.*, **41**(3): 229-232.
- Shoaib MH, Shaikh D, Yousuf RI, Naqvi BS and Hashmi K (2008). Pharmacokinetic study of cephradine in Pakistani healthy male volunteers. *Pak. J. Pharm. Sci.*, **21**(4): 400-406.
- Simoens S and De Coster S (2006). Potential savings from increased substitution of generic for originator medicines in Europe. *Journal of Generic Medicines*, **4**(1): 43-45.
- Tanrisever B and Santella PJ (1986). Cefadroxil. *Drugs*, **32**(3): 1-16.
- USP (2008). United States Pharmacopeia 31. Roukville: The United States Pharmacopeial Convention. 2: 1163-1165.
- Welling PG, Selen A, Pearson JG, Kwok F, Rogge MC, Ifan A, Marrero D, Craig WA and Johnson CA (1985). A pharmacokinetic comparison of cephalixin and cefadroxil using HPLC assay procedures. *Biopharm. Drug Dispos.*, **6**(2): 147-157.
- World Health Organization (2004). The world medicines situation. Geneva: World Health Organization, WHO. pp.61-74.
- WMA (2000). Declaration of Helsinki Recommendations Guiding Physicians in Biomedical Research Involving Human Patients. Amended by the 52nd WMA General Assembly, Edinburgh, Scotland, World Medical Association. pp.1-5.
- Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C and Xie S (2010). DDSolver: An add-in program for modeling and comparison of drug dissolution profiles. *AAPS. J.*, **12**(3): 263-271.
- Zhou HH, RP Koshakji RP, Silberstein DJ, Wilkinson GR and Wood AJJ (1989). Racial differences in drug response. *N. Engl. J. Med.*, **320**(9): 565-570.