"COMPARATIVE BIOAVAILABILITY AND SAFETY OF SINGLE DOSE BACLOFEN TABLETS, 20 MG OF TEST AND REFERENCE FORMULATION IN HEALTHY ADULT HUMAN SUBJECTS UNDER FASTING CONDITION: AN OPEN LABEL, RANDOMIZED, BALANCED, 2-WAY CROSSOVER STUDY"

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Abstract

Objective: The objectives of this study were to compare and evaluate the oral bioavailability of Baclofen Tablets, USP 20 mg (Test Product) of Zydus Lifesciences limited, India with that of Baclofen Tablets, USP 20 mg (Reference Product) of Teva Pharmaceuticals USA, Inc. in healthy, adult, human subjects under fasting conditions and to monitor safety of the subjects.
Methods: This was a randomized, open-label, two-period, two-treatment, two-sequence, crossover, balanced, single dose study with a 7-day washout period. A total twenty-eight healthy adult male human subjects were enrolled and completed the study. All the subjects were dosed orally according to the randomization sequence, after 10 hours of fasting with 240 mL of water at ambient temperature. Serial blood samples were collected at predefined specific interval and was quantified by validated liquid chromatography-tandem mass spectrometry (LCMS/MS) method. The bioavailability was compared using pharmacokinetic parameters
Cmax, Tmax, AUC0-t, and AUC0-∞. Moreover, the 90% confidence interval (CI) for the ratio of logarithmic transformed Cmax, AUC0-t and AUC0-∞ was also used to determine bioequivalence.
Results: The results demonstrate that the pharmacokinetic profile of Baclofen of Test product is comparable to the Reference products. There were no serious adverse events or adverse events reported in the study.
Conclusions: Overall, Baclofen Tablets, USP 20 mg were well tolerated as a single (1 × 20 mg) oral dosage administered under Fasting condition in both test and reference formulation.

Introduction

Development of generic drugs is a very crucial for improving healthcare affordability, promoting competition, fostering innovation, and advancing public health initiatives on both local and global scales. The United States Food and Drug Administration (USFDA) has recently reauthorized Generic

Drug User Fee Amendments (GDUFA) III as, "Generic drug user fees make it possible for Food and Drug Administration (FDA) and industry to continue to ensure that their public has access to safe, effective and high-quality generic drugs". The implementation of the GDUFA encompasses a wide range of activities that fall within the scope of regulating the generic drug industry[1.] Ninety percent of the prescriptions distributed in the US are now comprised of FDA-approved generic medications. Over the past decade, the introduction of generic alternatives has led to a cost saving of approximately $1.67 trillion within the healthcare system [2.]

Baclofen was originally developed as an antiepileptic in 1962 by Swiss chemist Heinrich Keberle. Although it failed to effectively treat epilepsy, baclofen was found to reduce spasticity in selected patients. It was introduced in 1971 and ultimately approved by the US Food and Drug Administration (FDA) in 1977 for the treatment of spasticity related to multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity, reversible spasticity, spinal cord injuries, and other spinal cord pathologies[3, 4, 5]

Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although baclofen is an analogue of the putative inhibitory neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. In studies with animal, baclofen has been shown to have general central nervous system (CNS) depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression. Baclofen is rapidly and extensively absorbed and eliminated. Absorption may be dose-dependent, being reduced with increasing doses. Baclofen is excreted primarily by the kidney in unchanged form and there is relatively large intersubject variation in absorption and/or elimination[3]. Baclofen has a 70% to 85% bioavailability and is rapidly absorbed through the gastrointestinal tract following oral administration. Peak plasma concentrations are generally observed 2 to 3 hours after ingestion. The absorption is dose-dependent and increases with higher doses. Due to the short half-life of 2 to 6 hours, baclofen should be administrated frequently to achieve optimal effect. Seventy percent of baclofen is eliminated in an unchanged form by renal excretion and the remaining via feces. Thereby, baclofen is a useful agent in patients with impaired hepatic function or a high potential for cytochrome P450-mediated drug-drug interactions. Research has observed significant inter-individual variability in baclofen's absorption and elimination processes [6].

The objective of this study was to describe the pharmacokinetic profile and to compare the oral bioavailability between Baclofen Tablets, USP 20 mg of Zydus Lifesciences limited, India and Baclofen Tablets, USP 20 mg of Teva Pharmaceuticals USA, Inc. under fasting conditions in Indian healthy volunteers and supporting the use of Zydus Baclofen Tablets, USP 20 mg as a therapeutic alternative.

Materials and Methods

The study was conducted after obtaining approval from the institutional ethics committee and Central Drugs Standard Control Organisation of Government of India. This was an open-label, randomized, single-dose, two-treatment, two-sequence, two-period crossover oral bioequivalence study conducted in 28 healthy, adult human subjects under fasting condition. Male participants, between 18 and 45 years, were screened, and medical history and examination, electrocardiograph, haematology, biochemistry, serology, urine analysis, and chest X-ray were done within 14 days before start of the study. Participants having a history of major illnesses, habituated to tobacco or alcohol, and a history of hypersensitivity to baclofen were excluded from the study. After being given detailed information about the study, the participants were requested to sign an informed consent. Participants were randomized into two groups of 14 volunteers each, and each group received the two drug treatments at two different times, with a 7-day washout period.

In each period, a total of 17 venous blood samples (06 mL each, except pre-dose 12 mL) were collected in vacutainers containing K2EDTA at pre-dose and at 0.333, 0.667, 1.0, 1.333, 1.667, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hours post dose. After collection, the blood samples were placed in an ice bath until centrifugation and then placed in a refrigerated centrifuge within 45 minutes of blood sample collection, and then spun at 3000 revolutions per minute (RPM) at 4°C for 15 minutes. The plasma was separated, transferred to labelled polypropylene tubes in duplicates (primary aliquot contained approximately 0.5 mL plasma and secondary aliquot contained remaining plasma). The plasma was stored in the freezer at –20ºC ± 10ºC at clinical facility until shipment to bio-analytical facility to perform the analysis using LC-MS/MS. A method for determining Baclofen in human plasma has been validated using an API 4000 LC/MS/MS system and solid phase extraction method with detection in the range of 10.00 to 900.0 ng/mL. The method was validated for sensitivity, specificity, linearity, accuracy, and precision.

All Below Limit of Quantitation (BLQ) concentration values were set to zero before pharmacokinetic analysis. There were no missing sample during the study. The Pharmacokinetic parameters were determined by noncompartmental methods using WinNonlin® professional software (Phoenix version: 6.4 Pharsight Corporation, USA). The primary endpoints were AUCt, AUC∞ and Cmax for Baclofen. All other PK parameters were regarded as secondary or exploratory. Statistical analysis was performed on the pharmacokinetic parameter using SAS® statistical software (Version: 9.4, SAS Institute Inc., USA) to compare and evaluate the bioavailability of Test and Reference Formulation. Bioequivalence was determined by a statistical comparison of Cmax, AUCt and AUC∞ of the test to Reference formulation for Baclofen. The 90% confidence interval of the relative mean (geometric least square mean) of the tests to Reference formulation for Ln-transformed Pharmacokinetic parameters Cmax, AUCt and AUC∞ was to be within 80.00% to 125.00% for Baclofen to establish bioequivalence.

The vital signs that included, sitting blood pressure, pulse rate and body temperature were measured at the time of check-in, prior to dosing and prior to checkout in each period. Sitting/supine blood pressure and pulse rate were measured at 2, 6, 10 hours (± 40 minutes) post dose in each period. For well-being assessment, the subjects were advised to report any adverse event and were specifically asked by trained study personnel in a non-leading manner about any adverse event at the time of clinical examinations, during vital signs recording, at about 12.0 and 24.0 hours post dose of each study period. All dosed study subjects were assessed for clinical examination including vital sign (sitting blood pressure, pulse rate and body temperature) and laboratory tests at the end of the study. The safety assessments conducted in this study were standard, appropriate and adequate and all subjects' details were documented in the subjects' Case Report Forms.

Results

Study was conducted on Asian subjects and all subjects were selected based on the absence of any clinically significant findings on the medical history, medication history, family medical history, vital signs and well-being, comprehensive physical examination, ECG, chest X-ray recordings (within past six months), menstrual & postmenopausal status, breast examination, pelvic examination and clinical laboratory evaluations performed within 28 days of initial study dosing. The Investigator evaluated all the laboratory values individually. All were determined to be non-reactive, normal, negative or not clinically significant for those subjects enrolled in the study. A total twenty-eight subjects were enrolled and completed the study. Mean demographic data, including standard deviations are presented in Table 1 for all subjects dosed and completed.

Twenty-eight subjects were enrolled and completed the study [28 Male, mean (± SD) age 33 years (±7), mean weight 62.2 kg (± 9.1) kg, Height 165.7 cm (± 5.7) BMI 22.6 kg/m2 (± 2.9) respectively].

Table 1 Summary of Mean Demographic Data

Parameter	Dosed & Completed Subjects Male (N=28)
Age (years)	33 (± 7)
Weight (kg)	62.2 (± 9.1)
Height (cm)	165.7 (± 5.7)
BMI (kg/m²)	22.6 (± 2.9)

BMI body mass index, N number of subjects

A total 28 subjects were planned for the entire study. All 28 subjects completed and were included pharmacokinetic analysis and statistical analysis for bioequivalence evaluation. All values below the lower limit of quantification were considered as Zero in Pharmacokinetic and Statistical analysis. The observed intra-subject CV (%) was 11.701ng/mL, 12.443 ng/mL*hr and 10.369 ng/mL*hr for $C_{max,}$ $AUC_{t, and}$ AUC0-∞ respectively, this is in line with our hypothesis of having intra-subject CV (%) of ~12 in sample size selection.

The Pharmacokinetic summary and bioequivalence data for Baclofen has been given in below mentioned **Table 2** and **Table 3** respectively. The mean plasma concentration–time profiles of both test and Reference formulations of Baclofen has been illustrated in the **Figure 1** Linear plot and **Figure 2** Semi-logarithmic plot.

Table 2 Summary of Pharmacokinetic Data for Baclofen

Parameter	Test Product (N=28) Arithmetic mean ±SD (CV%)	Reference Product (N=28) Arithmetic mean ±SD (CV%)
Cmax (ng/mL)	366.936 ± 79.782 (21.743)	348.321 ± 62.085 (17.824)
AUCt (ng/mL)*(hr)	2355.021 ± 468.522 (19.895)	2306.461 ± 398.638 (17.284)
AUC∞ (ng/mL)*(hr)	2498.611 ± 468.389 (18.746)	2432.336 ± 418.670 (17.213)
Kel (1/hr)	0.123 ± 0.012 (9.470)	0.122 ± 0.010 (8.390)
Tmax (hr)^	1.667 (0.667 – 4.000)	1.667 (0.667 - 3.500)
$T_{1/2}$ (hr)	5.663 ± 0.516 (9.109)	5.729 ± 0.464 (8.099)

AUC t area under the plasma concentration-time curve from time zero to time t, AUC∞ area under the plasma concentration-time curve from time zero to infinity, Cmax maximum observed plasma concentration, CV% percentage coefficient of variation, Kel terminal elimination rate constant, N number of subjects, SD standard deviation, t½ elimination half-life, tmax time to reach the maximum plasma concentration following drug administration.

^Median (minimum, maximum)

Table 3 Bioequivalence results for Baclofen

Parameter	Geometric mean of Test (N= 28)	Geometric mean of Reference (N= 28)	Ratio (%)	90% CI
Cmax (ng/mL)	358.606	342.844	104.60	(99.18%;110.31%)
AUCt (ng/mL) *(hr)	2307.311	2273.864	101.47	(95.90%;107.37%)
AUC∞ (ng/mL) *(hr)	2456.136	2399.595	102.36	(97.64%;107.30%)

AUC t area under the plasma concentration-time curve from time zero to time t, AUC ∞ area under the plasma concentration-time curve from time zero to infinity, Cmax maximum observed plasma concentration, CI confidence interval, N number of subjects.

Figure. 1 Linear Plot

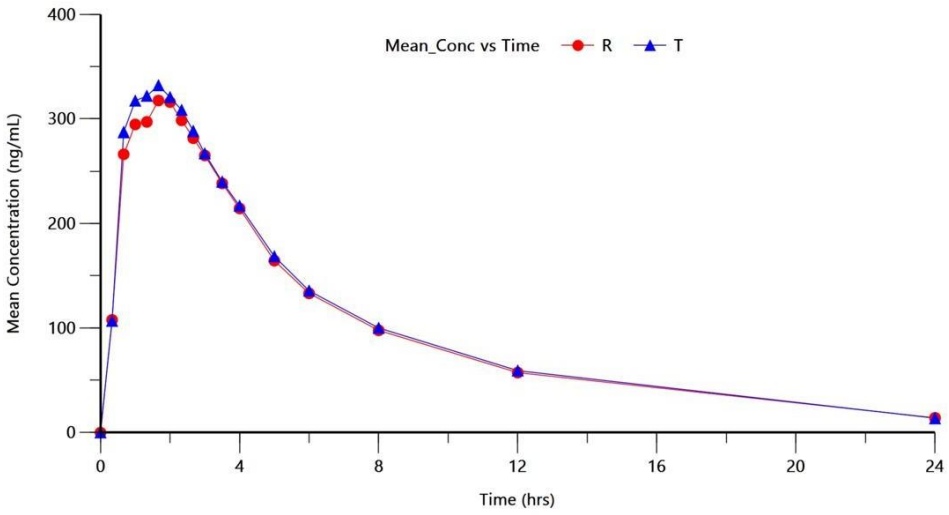
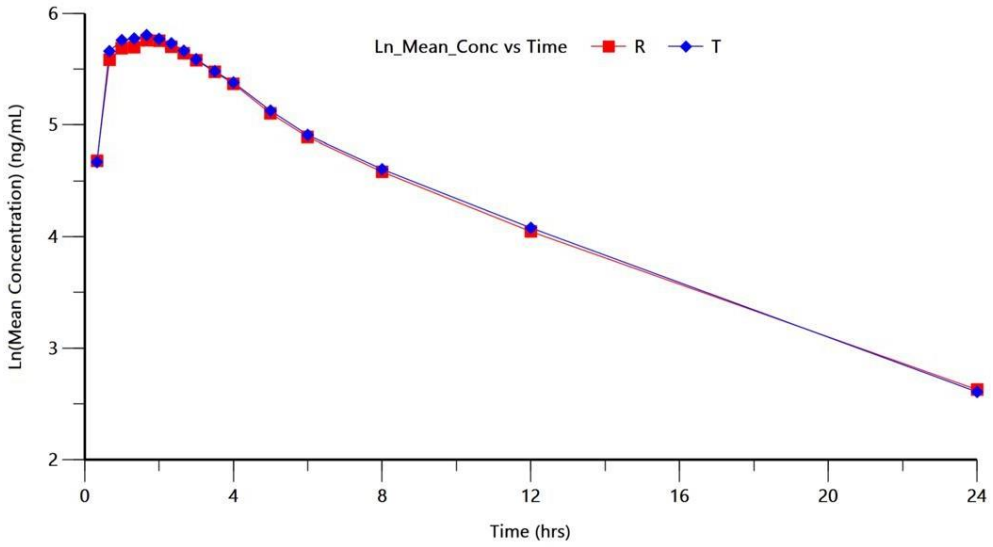


Figure. 2 Semi-logarithmic Plot



The study results shows that bioequivalence has been achieved as the 90% confidence interval of the relative mean (Geometric least square mean) of test to Reference formulation of Baclofen for Ln-transformed Cmax, AUCt and AUC∞ was within 80.00% to 125.00%.

Subject's safety and integrity of data was maintained and well managed throughout the conduct of the study. During the course of study safety parameters assessed were medical history, medication history & family medical history, vital signs as well as well-being, physical examination, Chest X-ray (within past six months), ECG examination and safety related clinical laboratory assessment (haematology,

biochemistry, urinalysis, immunological tests) at baseline. Laboratory parameters (haematology & blood chemistry) were reassessed at the end of the study. In this study, all the out-of-range laboratory parameters were evaluated as clinically insignificant during post study assessment. There was no serious adverse event or adverse event reported in the study.

Discussion

Baclofen is an effective therapeutic for the treatment of spasticity related to multiple sclerosis, spinal cord injuries, and other spinal cord pathologies. It has been increasingly used off-label for the management of several disorders, including musculoskeletal pain, gastroesophageal reflux disease (GERD) and alcohol use disorder[4]. This meta-analysis performed by evaluating the efficacy and safety of baclofen for the treatment of GERD. Nine studies were identified with a total of 283 GERD patients and healthy subjects. Comparative analysis provided high quality data supporting the ability of baclofen to promote a short-term decrease in the number of reflux episodes per patient, the average length of reflux episodes, and the incidence of transient lower esophageal sphincter relaxation. No serious adverse events or death events were reported, and there were no significant differences in the overall adverse events between baclofen and placebo[7].

Zydus Lifesciences Ltd is developed the generic formulation of Baclofen tablets which is cost-effective and therapeutically equivalent to the innovator product for US Market in compliance with cGMP. This study was conducted to evaluate the comparative oral bioavailability of Generic formulation Zydus Test product and Reference formulation of Teva Pharmaceuticals in fasted conditions in compliance with Independent Ethics Committee approved Protocol, ICH GCP and applicable regulatory guidance. The results show that all the 90% CIs of the geometric mean ratios of Baclofen pharmacokinetic parameters (Cmax, AUCt, and AUC0-∞) were found to be within the pre-established interval (80%-125%). These findings prove there is no significant differences between the rate (Cmax) and degree of absorption (AUCt and AUC0-∞) of the test and reference formulations. Furthermore, no differences were observed in the elimination kinetics of Baclofen between the test and reference products: the values of t1/2 and the terminal elimination rate constant (Kel) were similar between the groups. No significant formulation, period, or sequence effects were observed in the ANOVA test for the pharmacokinetic parameters Cmax, AUCt and AUC0-∞.

The results obtained in this study are comparable to the pharmacokinetic profiles obtained from the study Saol 1001-01 of Lyvispah® (baclofen granules) (NDA 215422) In this study, single dose of 20mg evaluated by comparative bioavailability study of Baclofen Granules and Baclofen Oral Tablets under fasted condition [8].

Conclusion

Based on the results of the study, it is concluded that, the Test product of Baclofen Tablets, USP 20 mg of Zydus Lifesciences limited, India is bioequivalent with the Reference formulation of Baclofen Tablets, USP 20 mg of Teva Pharmaceuticals USA, Inc under fasting conditions. There were no serious adverse events or adverse events reported in the study. Overall, Baclofen Tablets, USP 20 mg, were well tolerated as a single (1 × 20 mg) oral dosage administered under fasting conditions in both test and reference formulation.

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