DOI: https://doi.org/10.63712/bpsrj-v2i2p002

Bioequivalence Evaluation of Digoxin Tablets C.S.D 0.125 mg Under Fed Conditions in Healthy Adult Subjects

Bioequivalence Evaluation of Digoxin Tablets C.S.D 0.125 mg Under Fed Conditions in Healthy Adult Subjects

Dr. M. Narender, Dr. K. Ramulu, Clinical Research, Hyderabad.

ABSTRACT:

A randomized, double-blind, two-treatment, two-sequence, two-period crossover study was conducted to evaluate the bioequivalence of Digoxin Tablets C.S.D 0.125 mg manufactured by Chormo labs Ltd compared with the reference product ^{Pr}Toloxin® 0.125 mg. The study was performed in healthy adult volunteers under fed conditions. A single oral dose of two tablets (0.25 mg total dose) was administered in each study period with an appropriate washout interval between periods. Plasma concentrations of digoxin were determined using a validated LC–MS/MS method, and pharmacokinetic parameters were calculated using a non-compartmental approach. Statistical analysis was performed on logarithmically transformed pharmacokinetic parameters to assess bioequivalence. The 90% confidence interval for $AUC_{0\text{-}72h}$ was within the predefined acceptance range, whereas the interval for Cmax did not fully meet the regulatory bioequivalence criteria.

Both formulations were generally well tolerated, and no serious adverse events were reported. The findings indicate that although systemic exposure was comparable, the test product did not meet all criteria required for bioequivalence under fed conditions.

Keywords: Digoxin, Bioequivalence study, Pharmacokinetics, Randomized crossover study, LC-MS/MS analysis, Fed conditions.

INTRODUCTION:

Digoxin is a cardiac glycoside widely used in the management of cardiovascular disorders such as congestive heart failure and atrial fibrillation. It improves cardiac contractility and helps regulate heart rhythm, thereby reducing symptoms associated with impaired cardiac function. Due to its narrow therapeutic index, evaluation of pharmacokinetic properties and equivalence between generic and reference formulations is essential.

Bioequivalence studies are conducted to determine whether two pharmaceutical products demonstrate comparable bioavailability and similar pharmacokinetic characteristics. Such studies are particularly important for drugs like digoxin where small variations in plasma concentration may influence therapeutic response or safety. This study was designed to compare the pharmacokinetic profile of a test formulation of digoxin tablets with that of an established reference product in healthy adult subjects under fed conditions

DOI: https://doi.org/10.63712/bpsrj-v2i2p002

Bioequivalence Evaluation of Digoxin Tablets C.S.D 0.125 mg Under Fed Conditions in Healthy Adult Subjects

AIM AND OBJECTIVES

Aim

To evaluate the bioequivalence of Digoxin Tablets C.S.D 0.125 mg between the test formulation and the reference formulation following a single oral dose under fed conditions.

Objectives

Primary Objective:

To compare the pharmacokinetic parameters and bioavailability of the test formulation with the reference formulation after oral administration in healthy volunteers.

Secondary Objective:

To assess the safety and tolerability of both formulations during the study period.

MATERIALS AND METHODS

Study Design

This investigation was conducted as a Phase I, randomized, double-blind, balanced, two-treatment, two-sequence, two-period crossover bioequivalence study in healthy adult volunteers. A washout interval of 22 days was maintained between study periods

Study Population

Healthy male and female volunteers aged between 18 and 45 years with a body mass index within the acceptable range were included. All participants underwent screening procedures including medical history evaluation, laboratory investigations, electrocardiogram, and physical examination prior to enrolment.

Sample Size

Eighteen subjects were enrolled and completed both study periods, and their data were included in the pharmacokinetic and statistical analysis.

Drug Administration

Participants received either the test or reference formulation consisting of two tablets of digoxin (total dose 0.25 mg) administered orally with water after consumption of a high-fat, high-calorie meal. The alternate formulation was administered during the second study period according to the randomization schedule.

Blood Sample Collection

Blood samples were collected at predetermined intervals before dosing and up to 72 hours after administration in each study period to determine plasma digoxin concentrations.

Bioanalytical Method

Plasma samples were analyzed using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method to quantify digoxin levels.

Pharmacokinetic and Statistical Analysis

Pharmacokinetic parameters including maximum plasma concentration (Cmax), area under the concentration-time curve (AUC_{0-72h}), and other

DOI: https://doi.org/10.63712/bpsrj-v2i2p002

Bioequivalence Evaluation of Digoxin Tablets C.S.D 0.125 mg Under Fed Conditions in Healthy Adult Subjects

related parameters were calculated using a non-compartmental approach. Statistical analysis of log-transformed data was performed to determine the geometric mean ratios and 90% confidence intervals for bioequivalence assessment.

Safety Evaluation

Safety was monitored through clinical assessments, vital signs, electrocardiograms, and laboratory investigations throughout the study.

RESULTS

Pharmacokinetic Findings

Both formulations showed comparable plasma concentration–time profiles. The mean pharmacokinetic parameters indicated similar systemic exposure between the test and reference products. The geometric mean ratio for AUC_{0-72h} was within the acceptable regulatory limits, demonstrating comparable extent of absorption. However, the confidence interval for Cmax extended outside the predefined bioequivalence range.

Descriptive Statistics of Formulation Means for Digoxin

Parameters (Units)	Mean ± SD			
	N	Test Product-T	N	Reference Product-R
C_{max} (pg/mL)	18	871.841 ± 265.421	18	974.556 ± 334.200
AUC_{0-72} (hr*pg/mL)	18	13092.374 ± 2292.122	18	12913.091 ± 2376.241
AUC_T (hr*pg/mL)	[1]17	13099.256 ± 2450.601	18	12777.401 ± 2463.574
AUC_I (hr*pg/mL)	[1]17	19800.069 ± 4419.554	18	18659.110 ± 3538.933
[#]T_{max} (hr)	18	1.50 (0.750 - 3.000)	18	1.50 (0.500 - 4.000)
AUC_T/AUC_I*100	[1]17	66.961 ± 6.651	18	68.588 ± 4.675
K_{el} (1/hr)	[1]17	0.015 ± 0.003	18	0.015 ± 0.002
K_{el} Lower (hr)	[1]17	19.531 ± 11.844	18	22.444 ± 11.713
K_{el} Upper (hr)	[1]17	70.597 ± 5.834	18	70.696 ± 5.682
$t_{1/2}$ (hr)	[1]17	48.536 ± 11.039	18	45.806 ± 6.211
Rsq adjusted	18	0.938 ± 0.064	18	0.950 ± 0.046

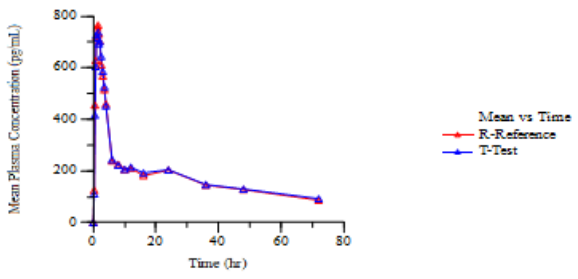
* Tmax is represented in median (min-max) value

Bioavailability Results for Digoxin

Parameters	Geometric Least Squares Means				90% CI
	N	Test Product	Reference Product	Ratio (T/R) %	
C_{max} (pg/mL)	18	837.338	922.017	90.82	75.6 - 109.1
AUC_{0-72} (hr* pg/mL)	18	12923.720	12693.787	101.81	95.3 - 108.8
AUC_I (hr* pg/mL)	17*	19439.005	18197.666	106.82	99.7 - 114.4

Mean plasma concentration vs time curve for Digoxin

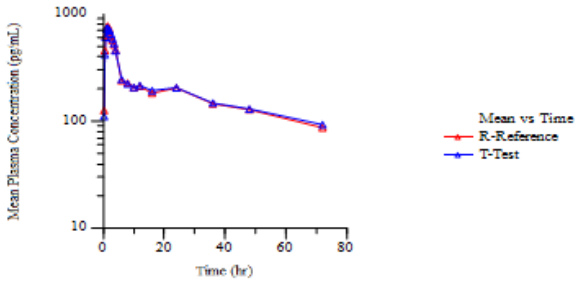
Linear Plot



DOI: https://doi.org/10.63712/bpsrj-v2i2p002

Bioequivalence Evaluation of Digoxin Tablets C.S.D 0.125 mg Under Fed Conditions in Healthy Adult Subjects

Semi Log Plot



Safety Outcomes

No deaths, serious adverse events, or clinically significant safety concerns were observed during the study. Both formulations were generally well tolerated by the participants.

DISCUSSION

Bioequivalence studies play a critical role in ensuring that generic formulations provide therapeutic outcomes similar to the reference products. In the present study, the overall pharmacokinetic profile of the test digoxin formulation showed similarity to the reference product in terms of systemic exposure. The AUC values met the regulatory criteria for bioequivalence, indicating comparable extent of drug absorption.

However, the peak plasma concentration parameter did not fully satisfy the acceptance criteria. Variability in Cmax could be influenced by factors such as inter-subject variability, food effects, and the narrow therapeutic index associated with digoxin. Despite this observation, both formulations demonstrated acceptable safety and tolerability during the clinical evaluation.

Further studies with a larger sample size or modified study design may be helpful to confirm these findings and evaluate the variability observed in peak concentration values

CONCLUSION

The study demonstrated that the test and reference digoxin formulations showed comparable systemic exposure under fed conditions. Although the AUC parameter met bioequivalence requirements, the Cmax parameter did not fall entirely within the specified acceptance range. Therefore, the test product could not be concluded to be bioequivalent to the reference formulation under the conditions of this study. Both products were found to be safe and well tolerated among the study participants.

REFERENCE:

1. International Council for Harmonisation (ICH). Guideline for Good Clinical Practice (E6 R3).
2. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.
3. Indian Council of Medical Research (ICMR). Ethical Guidelines for Biomedical Research on Human Subjects.
4. Standard bioequivalence guidelines for pharmacokinetic studies.

Source of Support: Nil. **Conflicts of Interest:** None