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Comparative Bioequivalence Evaluation of Two Formulations of Metaxalone 800 mg Tablets Under Fed Conditions in Healthy Adult Volunteers A Randomized, Open-Label, Three-Way Crossover Study

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ABSTRACT:

Background: Metaxalone is a centrally acting skeletal muscle relaxant widely used for the management of musculoskeletal pain and discomfort. Demonstration of bioequivalence between generic and innovator formulations is essential for ensuring therapeutic interchangeability.

Objective: To compare the pharmacokinetic characteristics and bioequivalence of two test formulations of Metaxalone 800 mg tablets manufactured by RA Chem Pharma Ltd. with the reference product, Skelaxin® 800 mg tablets, under fed conditions in healthy adult volunteers.

Methods: An open-label, randomized, single-dose, three-treatment, three-period, three-sequence crossover bioequivalence study was conducted in healthy adult male volunteers under fed conditions. Eighteen subjects were enrolled, and fifteen completed all study periods and were included in the pharmacokinetic analysis. Following administration of a standardized high-fat meal, subjects received a single oral dose of either Test Formulation 1 (T1), Test Formulation 2 (T2), or the Reference formulation (R). Plasma concentrations of metaxalone were quantified using a validated LC-MS/MS method. Pharmacokinetic parameters including Cmax, AUC0-t, AUC0-inf, Tmax, Kel, and t½ were calculated. Statistical analysis was performed on logarithmically transformed Cmax, AUC0-t, and AUC0-inf values.

Results: The geometric mean ratios for T1 versus R were 99.07% for Cmax, 102.89% for AUC0-t, and 87.14% for AUC0-inf. For T2 versus R, the ratios were 104.72%, 104.09%, and 120.46%, respectively. The corresponding 90% confidence intervals exceeded the regulatory acceptance range of 80.00–125.00%. One mild adverse event (indigestion) was reported, and no serious safety concerns were observed.

Conclusion: Neither test formulation met the regulatory bioequivalence criteria under fed conditions. The two generic formulations of Metaxalone 800 mg tablets were not bioequivalent to the reference product, Skelaxin® 800 mg tablets.

Keywords: Metaxalone, Bioequivalence, Pharmacokinetics, Generic Drug, Fed Study, Crossover Design, LC-MS/MS, Skelaxin.

INTRODUCTION:

Metaxalone is a skeletal muscle relaxant indicated for the relief of discomfort associated with acute musculoskeletal disorders. It acts centrally and is

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frequently prescribed as an adjunct to rest and physical therapy. Because the therapeutic efficacy of oral formulations depends on the rate and extent of drug absorption, bioequivalence studies are required before approval of generic products.

Bioequivalence studies evaluate whether two pharmaceutical products exhibit comparable bioavailability when administered under similar experimental conditions. Regulatory agencies such as the CDSCO, USFDA, and EMA generally require the 90% confidence intervals for the ratios of logarithmically transformed Cmax and AUC parameters to fall within the acceptance range of 80.00%–125.00%.

The present investigation was designed to compare two generic formulations of Metaxalone 800 mg tablets with the innovator product Skelaxin® under fed conditions in healthy adult volunteers. The study followed accepted bioequivalence guidelines and Good Clinical Practice principles

AIM AND OBJECTIVES

Aim:

To evaluate the oral bioequivalence of two formulations of Metaxalone 800 mg tablets relative to the reference formulation Skelaxin® 800 mg tablets under fed conditions.

Objectives

Primary Objective

To compare Cmax, AUC0-t, and AUC0-inf between test and reference formulations.

Secondary Objectives

To determine Tmax, elimination rate constant (Kel), and elimination half-life (t½).

To assess the safety and tolerability of Metaxalone 800 mg tablets in healthy volunteers.

To establish whether the formulations satisfy regulatory bioequivalence requirements.

MATERIALS AND METHODS

Study Design

A randomized, open-label, three-treatment, three-period, three-sequence, single-dose crossover study was conducted under fed conditions.

Study Population

Eighteen healthy adult male volunteers aged 18–45 years were enrolled. Subjects had a BMI between 18.5 and 24.9 kg/m² and body weight ≥45 kg. Fifteen participants completed all study periods and were included in the final pharmacokinetic and statistical analyses.

Fed Conditions

Subjects fasted overnight for approximately 10 hours and consumed a standardized high-fat, high-calorie breakfast (~1000 kcal). Drug administration occurred 30 minutes after initiation of the meal.

Blood Sampling

Twenty-five blood samples were collected during each period at predose and up to 72 hours post-dose. Plasma samples were processed and stored under controlled conditions until analysis

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Bioanalytical Method

Metaxalone plasma concentrations were quantified using a validated LC-MS/MS method with a quantification range of 53.503–10025.590 ng/mL.

Pharmacokinetic Analysis

The following pharmacokinetic parameters were determined:

Cmax, Tmax, AUC0-t, AUC0-inf, Kel and t½

Statistical Analysis

Log-transformed pharmacokinetic parameters (Cmax, AUC0-t, and AUC0-inf) were analyzed using ANOVA. Bioequivalence was concluded if the 90% confidence intervals fell within 80.00%–125.00%

RESULTS

Subject Disposition

A total of 18 subjects were enrolled, while 15 subjects completed all study periods and were included in the final statistical analysis. Three participants withdrew before completion.

Pharmacokinetic Results

Test Formulation 1 vs Reference

Geometric Mean		
Parameter	Ratio (%)	90% CI
Cmax	99.07	71.50–137.26
AUC0-t	102.89	80.55–131.42
AUC0-inf	87.14	54.47–139.41

Test Formulation 2 vs Reference

Geometric Mean		
Parameter	Ratio (%)	90% CI
Cmax	104.72	75.58–145.09
AUC0-t	104.09	81.50–132.96
AUC0-inf	120.46	75.00–193.48

Intra-Subject Variability

Parameter	ISCV (%)
Cmax	56.2
AUC0-t	40.9
AUC0-inf	73.9

Safety Results

Only one mild adverse event (indigestion) was reported during the study. No serious adverse events occurred, and the investigational products were generally well tolerated.

DISCUSSION

The present study evaluated the bioequivalence of two generic formulations of Metaxalone 800 mg tablets under fed conditions. The crossover design minimized inter-subject variability and allowed direct comparison among the three treatments.

Although the point estimates for Cmax and AUC parameters were generally close to 100%, the associated confidence intervals were considerably wider than the regulatory acceptance limits. High intra-subject variability, particularly for AUC0-inf (73.9%), likely contributed to the inability to demonstrate bioequivalence.

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The observed variability may be attributed to differences in formulation characteristics, food effects on drug absorption, and inherent pharmacokinetic variability among participants. Similar challenges have been reported for highly variable drugs where larger sample sizes or alternative study designs may be required.

Safety findings were favorable, with only one mild adverse event reported. Therefore, lack of bioequivalence was not related to safety concerns but rather to pharmacokinetic variability and formulation performance.

CONCLUSION

This randomized, open-label, three-way crossover study compared two generic formulations of Metaxalone 800 mg tablets with the reference product under fed conditions. Statistical analysis demonstrated that the 90% confidence intervals for Cmax, AUC0-t, and AUC0-inf were outside the regulatory bioequivalence range of 80.00%–125.00%.

Therefore, both test formulations failed to meet bioequivalence criteria and cannot be considered bioequivalent to Skelaxin® 800 mg tablets under fed conditions. The study confirmed acceptable safety and tolerability of all formulations

REFERENCE:

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2. International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice.
3. US Food and Drug Administration. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products.

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