DOI: https://doi.org/10.63712/bpsrj-v2i3p005

Single-Dose Oral Bioavailability and Pharmacokinetic Characterization of S-Etodolac 200 mg Modified-Release Film Tablets in Healthy Male Volunteers Under Fasting Conditions

Dr. Bhanu Prakash Reddy

ABSTRACT:

Background: Etodolac is a non-steroidal anti-inflammatory drug (NSAID) characterized by a racemic mixture, with the S-enantiomer primarily responsible for therapeutic activity. Modified-release (MR) formulations are designed to prolong drug release, offering the advantage of reduced dosing frequency. Objective: This study aimed to characterize the oral bioavailability and pharmacokinetic (PK) profile of a newly developed S-Etodolac 200 mg MR film tablet. Methods: An open-label, single-dose, single-period study was conducted involving 24 healthy adult male subjects under fasting conditions. Following an overnight fast, each subject received a single 200 mg dose of the test formulation. A total of 23 blood samples were collected over a 48-hour period. Plasma concentrations of S-Etodolac were quantified, and PK parameters were derived using non-compartmental analysis. Safety and tolerability were also assessed. Results: All 24 enrolled subjects completed the study. The drug exhibited a delayed absorption profile consistent with an MR formulation, achieving a median peak plasma concentration (Tmax) at 5.5 hours. The mean peak concentration (Cmax) was 1992.07 ± 503.94 ng/mL. The mean area under the curve from time zero to the last measurable concentration (AUC0-t) and extrapolated to infinity (AUC0-inf) were 37415.07 ± 12775.43 ng·hr/mL and 39521.14 ± 13914.82 ng·hr/mL, respectively. The mean elimination half-life (t1/2) was 8.44 ± 1.91 hours. The formulation was well-tolerated, with no adverse events reported during the study. Conclusion: The S-Etodolac 200 mg MR film tablet demonstrates a prolonged absorption and elimination profile suitable for modified-release drug delivery. The formulation is safe and well-tolerated in healthy male subjects under fasting conditions

Keywords: S-Etodolac, Modified-Release, Bioavailability, Pharmacokinetics, Healthy Volunteers, NSAID.

INTRODUCTION:

Etodolac belongs to the pyranocarboxylic acid class of non-steroidal anti-inflammatory drugs (NSAIDs). Chemically, it exists as a racemic mixture comprising [+] S and [-] R-enantiomers, with the S-enantiomer exerting the primary pharmacological effect. The compound is highly protein-bound (>99%) and demonstrates variable solubility, being insoluble in water but soluble in alcohols and certain organic solvents.

Conventional immediate-release formulations of etodolac typically reach peak plasma concentrations within 1 to 2 hours and possess a terminal half-life of approximately 6 to 7 hours.

DOI: https://doi.org/10.63712/bpsrj-v2i3p005

Single-Dose Oral Bioavailability and Pharmacokinetic Characterization of S-Etodolac 200 mg Modified-Release Film Tablets in Healthy Male Volunteers Under Fasting Conditions

To improve patient compliance and maintain stable therapeutic plasma levels, modified-release (MR) formulations have been developed. MR formulations of etodolac generally delay peak concentrations to around 6 hours post-administration and extend the terminal elimination half-life to approximately 8.4 hours. While etodolac is generally well-tolerated, common adverse reactions can include gastrointestinal disturbances, headaches, and rash. The present study was conducted to evaluate the oral bioavailability and pharmacokinetic characteristics of a generic S-Etodolac 200 mg MR film tablet developed by Neutec Ilac San. Tic. A.S, Turkey, in a healthy human population.

AIM AND OBJECTIVES

The primary objective of this study was to investigate and characterize the single-dose oral bioavailability of S-Etodolac 200 mg MR Film Tablets in normal, healthy, adult male subjects under fasting conditions. A secondary objective was to evaluate the safety and tolerability of the formulation following a single oral dose.

MATERIALS AND METHODS

Study Design and Setting

This was an open-label, single-dose, single-period, fasting bioavailability study conducted.

Study Population

Twenty-four (24) healthy adult male subjects between the ages of 18 and 45 years were enrolled. Eligible subjects were required to have a body mass index (BMI) between 18.5 and 24.9 kg/m² and a body weight of at least 45 kg. Subjects were determined to be healthy based on normal medical and surgical histories, physical examinations, 12-lead electrocardiograms (ECGs), chest X-rays, and standard laboratory evaluations (hematology, biochemistry, urinalysis, and serology for HIV, HBsAg, HCV, and VDRL).

Key exclusion criteria included a history of hypersensitivity to NSAIDs, significant systemic diseases, substance abuse, smoking, or the use of any prescribed or over-the-counter medications within two weeks prior to the study. All participants provided written informed consent prior to any study-related procedures.

Investigational Product

The test product was S-Etodolac 200 mg MR Film Tablets (Batch No: 00387; Manufactured by: Neutec Ilac San. Tic. A.S, Turkey; Expiry Date: 01/2014).

Dosing and Sample Collection

Following an overnight fast of at least 10 hours, subjects received a single oral dose of 200 mg (1 × 200 mg tablet) with 240 ± 5 mL of water in a standing position. Subjects were instructed to swallow the tablet whole without chewing.

A total of twenty-three blood samples (5 mL each) were collected via an indwelling venous cannula into K2EDTA tubes. Samples were drawn at pre-dose, and at 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 10.0, 11.0, 12.0, 16.0, 20.0, 24.0, 36.0, and 48.0 hours post-

DOI: https://doi.org/10.63712/bpsrj-v2i3p005

dose. Samples at 36 and 48 hours were collected on an ambulatory basis. Plasma was harvested by centrifugation and stored until analysis.

Bioanalytical Method and Pharmacokinetic Analysis

Plasma concentrations of S-Etodolac were quantified using a validated Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) method. Pharmacokinetic parameters were calculated using non-compartmental analysis via WinNonlin Professional Software (Version 5.3, Pharsight Corporation, USA).

Primary parameters included peak plasma concentration (Cmax), area under the plasma concentration-time curve from zero to the last measurable time point (AUC0-t), and AUC extrapolated to infinity (AUC0-inf). Secondary parameters included time to reach Cmax (Tmax), elimination half-life (t1/2), elimination rate constant (Kel), mean residence time (MRTlast), and the ratio of AUC0-t to AUC0-inf.

Safety Assessment

Safety was evaluated through continuous monitoring of adverse events (AEs), vital signs (blood pressure, pulse rate, respiratory rate, and temperature) at predefined intervals, physical examinations, and clinical laboratory tests pre- and post-study.

RESULTS

Subject Disposition

All twenty-four (24) enrolled subjects completed the clinical portion of the study and were included in the pharmacokinetic and safety analyses. No subjects were discontinued or dropped out.

Pharmacokinetic Parameters

The mean plasma concentration-time profile confirmed a modified-release absorption pattern. The pharmacokinetic parameters for S-Etodolac are summarized in Table 1.

Table 1: Pharmacokinetic Parameters of S-Etodolac 200 mg MR Tablets (N=24)

PK Parameter	Mean ± SD
Cmax (ng/mL)	1992.07 ± 503.94
Tmax (hr)*	5.50
AUC0-t (ng·hr/mL)	37415.07 ± 12775.43
AUC0-inf (ng·hr/mL)	39521.14 ± 13914.82
t1/2 (hr)	8.44 ± 1.91
Kel (1/hr)	0.087 ± 0.022
MRTlast (hr)	16.34 ± 3.40
AUC0-t / AUC0-inf	0.948 ± 0.026

Safety and Tolerability

The single-dose administration of S-Etodolac 200 mg MR film tablets was well-tolerated. There were no adverse events, serious adverse events, or clinically significant abnormalities reported during the study period. Post-study laboratory evaluations showed some out-of-range values, but these were deemed clinically insignificant by the investigator.

DOI: https://doi.org/10.63712/bpsrj-v2i3p005

DISCUSSION

The pharmacokinetic profile of the S-Etodolac 200 mg MR film tablet observed in this study aligns with the expected characteristics of a modified-release NSAID formulation. In contrast to immediate-release etodolac, which typically achieves peak concentrations within 1 to 2 hours, the test formulation demonstrated a notably delayed median Tmax of 5.5 hours. This delayed absorption confirms the in vivo modified-release properties of the tablet matrix.

The mean elimination half-life (t1/2) of approximately 8.4 hours is consistent with previously reported data for extended-release etodolac formulations and supports a twice-daily dosing regimen. Furthermore, the ratio of AUC0-t to AUC0-inf was approximately 0.95, indicating that the 48-hour blood sampling schedule was sufficiently robust to capture greater than 90% of the total drug exposure, thereby validating the accuracy of the pharmacokinetic analysis.

The observed inter-subject variability, as denoted by the coefficient of variation for Cmax (~25%) and AUC parameters (~34%), falls within an acceptable range for oral NSAID formulations. From a safety perspective, the absence of adverse events following a single 200 mg dose under fasting conditions indicates an favorable acute tolerability profile for this generic MR formulation.

CONCLUSION

The S-Etodolac 200 mg MR film tablet successfully demonstrated a prolonged absorption and elimination profile suitable for modified-release drug delivery. The formulation is safe and well-tolerated in healthy adult male subjects under fasting conditions, providing a viable pharmacokinetic profile for further clinical development and therapeutic application.

REFERENCE:

1. European Medicines Agency. Guideline on the Investigation of Bioequivalence. London: 20 August 2010.
2. International Conference on Harmonisation. ICH Harmonized Tripartite Guideline for Good Clinical Practice (E6). 1996.
3. Indian Council of Medical Research. Ethical Guidelines for Biomedical Research on Human Participants. New Delhi: 2006.
4. Ministry of Health, Turkey. Guideline for Good Clinical Practices. 2009.
5. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Seoul: 2008.

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