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Safety, Tolerability and Bioequivalence Assessment of a Dispersible Tablet Formulation of Pyrazinamide

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ABSTRACT

Pyrazinamide is a widely used drug for the treatment of tuberculosis. A 150 mg Dispersible Tablet (DT) formulation of the drug was prepared by Micro Labs, a generic drug company. The formulation was developed for easy administration into paediatric patients. It was tested for bioequivalence in healthy adult human volunteers in fasting condition. A total of 36 subjects were enrolled in the study and all the 36 subjects completed both the two periods of the study without showing major adverse events. The pharmacokinetic parameters determined for bioequivalence were C_{max} and AUC_{0-t} . The two parameters were within the limit of bioequivalence criteria. The 150 mg DT formulation developed by Micro Labs was found to be bioequivalent to 500 mg immediate release tablet formulation of Riemser Pharma. Both the formulations were safe and well tolerated among the tested human subjects. No major adverse events were observed.

Keywords: Pyrazinamide, dispersible, bioequivalence, safe.

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INTRODUCTION

Pyrazinamide is an anti-tuberculosis drug synthesized in the 1950s. [1] It is crucial for tuberculosis (TB) treatment, as it has a unique ability to eradicate persister bacilli. [2] Controlled release drug delivery systems provide uniform concentration of drug to the absorption site and thus allow the maintenance of plasma concentration within the therapeutic range which minimizes not only the side effects but also the frequency of administration. [3]

Orodispersible tablets are being preferred as advanced dosage form in most instances over conventional immediate release dosage form for various categories of drugs. Now-a-days, orodispersible drug delivery systems are extensively used to improve bioavailability and patient compliance. Over the past three decades, have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance, improved solubility and stability profiles. [4] The drug

Pyrazinamide is available as a dispersible tablet formulation. [5]

Bioavailability is used to describe the fraction of an administered dose of medication that reaches the systemic circulation, one of the principal properties of the drug. By definition, when the drug is administered intravenously, its bioavailability is 100%.

Bioequivalence studies compare both the rate and extent of absorption of various multisource drug formulations with the innovator (reference) product, on the basis that if two formulations exhibit similar drug concentration time profile in the blood/plasma, they should exhibit similar therapeutic effects. Once bioequivalence has been established via bioavailability testing in a statistically significant manner subsequent batches of the same product are deemed bio-equivalent based on *in-vitro* measures such as drug dissolution. [6]

Bioequivalence studies are very important for the development of a pharmaceutical preparation in the pharmaceutical industry. The aim of this type of studies is to evaluate the therapeutic compatibility of tested drugs (pharmaceutical equivalents or pharmaceutical alternatives). The importance of bioequivalence studies is increasing also due to the large growth of the production and consumption of generic products. The registration of generic products does not demand complicated and expensive clinical study contrary to original product. The comparison of the original and the generic product via bioequivalence study is suggested as sufficient. [7] Bioequivalence is a term in pharmacokinetics used to assess the expected *in vivo* biological equivalence of two proprietary preparations of a drug. If two drugs are bioequivalent it means that they would be expected to be, for all intents and purposes, the same. If 90% Confidence interval for the ratio of the geometric least square means of natural log transformed C_{max} , AUC_{0-t} and AUC_{0-inf} of Test and Reference drugs are within 80.00% to 125.00%, then bioequivalence will be established. [8]

Micro Labs had developed a 150 mg dispersible tablet formulation as an equivalent to 500 mg immediate release formulation of Riemser Pharma. The formulation was developed for ease of administration into pediatric patients. The same was tested in healthy human volunteers in fasting condition with an objective to compare the rate and extent of absorption of the two formulations and monitor the safety and tolerability of subjects. Prior to start of study, informed consent had been taken from all the subjects and permission obtained from Anveshhan Independent Ethics Committee.

MATERIALS AND METHODS

An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two period, crossover, oral bioequivalence study was conducted of Pyrazinamide dispersible tablets 150 mg at a dose of 450 mg (03 tablets of 150 mg) of Micro Labs Limited, India and PYRAFAT® 500 mg tablets of RIEMSER Pharma

GmbH-An der Wiek 7-17493 Greifswald-Insel Riems in healthy, adult, human subjects under fasting condition. The study was conducted at Veeda Clinical Research Pvt. Ltd, Shivalik Plaza, Near I.I.M., Ambawadi Ahmedabad - 380 015, India. The study has been conducted according to the Declaration of Helsinki (Brazil, October 2013).

A total of 36 healthy, adult, male human subjects were enrolled in the study and all (36) subjects completed both period of the study as per protocol. All the samples collected from 36 subjects were analyzed for Pyrazinamide Plasma concentrations.

Healthy, willing, male, volunteers of age between 18 and 45 years (both inclusive) were selected on the basis of laboratory evaluations, medical history, clinical examination (including physical examination and systemic examination), Chest X-ray (PA view) and ECG recordings during screening. Urine screen for drugs of abuse and alcohol breath test were performed on admission day of each study period.

Micro Labs product administration (T)

After overnight fasting at least 10 hours, in each period according to randomization, 03 tablets of test product were dispersed in 50 ml of water at ambient temperature and then this whole solution was administered to the subjects in a sitting posture followed by thorough mouth check using torch and disposable spatula.

Riemser Pharma product administration

After overnight fasting at least 10 hours, in each period according to randomization, one tablet was administered orally at schedule dosing time in sitting posture with 240 mL water at ambient temperature; this activity was followed by mouth check of the subjects by torch and disposable spatula to assess compliance to dosing. Subjects were instructed not to chew, crushed or divided the tablet but to consume as a whole.

For safety assessment, blood pressure, oral body temperature, radial pulse rate and respiratory rate for subjects were measures at regular intervals. Subjects were also enquired about their well being status at all times.

For Pyrazinamide, to establish bioequivalence based on dose normalize and statistical results of 90% confidence intervals for the geometric least square mean ratio for the pharmacokinetic parameters C_{max} and AUC_{0-t} , conclusions were drawn whether test formulation is bioequivalent to reference formulation under fasting condition. Acceptance range for bioequivalence is 80.00% - 125.00% for 90% confidence intervals of the geometric least square means ratio for C_{max} and AUC_{0-t} . Employing the estimated concentration time profiles of **Pyrazinamide following variables were calculated**

As reference product is innovator product with dose of 1 tablet of 500 mg. to compare test product with dose of 3 tablets of 150 mg = 450 mg, dose normalization was applied. For dose normalization ln of 1.1111 i.e 0.105359 were used. Using this 90% confidence intervals and

point estimate were calculated. The results with and without dose normalization were reported.

Primary variables

C_{max} and AUC_{0-t}

Secondary variable

$AUC_{0-\infty}$, T_{max} , $t_{1/2}$, K_{el} , $AUC_{\%} \text{Extrap}_{obs}$.

For Pyrazinamide, the statistical tests like ANOVA, least square means for test and reference formulations, difference between test and reference formulations, intra subject variability were calculated for ln-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$. Geometric least square means of test and reference formulations, its ratio and 90% confidence interval for geometric least square mean ratio and two one-sided tests for 90% confidence interval limits were calculated for pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$.

RESULTS

The statistical results for pharmacokinetic parameters of Pyrazinamide for 36 subjects without dose normalization are summarized below:

Parameters (Units)	Test Product (T)	Reference Product (R)	(T/R) %	Intra subject %CV	90% Confidence Interval
C_{max} ($\mu\text{g/mL}$)	12.839	13.925	92.20	6.56	89.83% - 94.64%
AUC_{0-t} ($\text{hr} \cdot \mu\text{g/mL}$)	142.057	161.053	88.21	9.01	85.10% - 91.42%

The statistical results for pharmacokinetic parameters of Pyrazinamide for 36 subjects with dose normalization are summarized below:

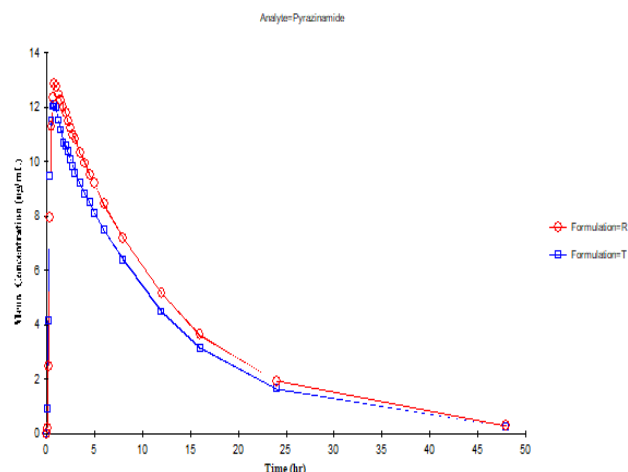
Parameters (Units)	Dose Normalization (T/R) (%)	Dose Normalization 90% CI
C_{max} ($\mu\text{g/mL}$)	102.45	99.81% - 105.15%
AUC_{0-t} ($\text{hr} \cdot \mu\text{g/mL}$)	98.01	94.56% - 101.58%

The measured pharmacokinetic parameters of Pyrazinamide are summarized below:

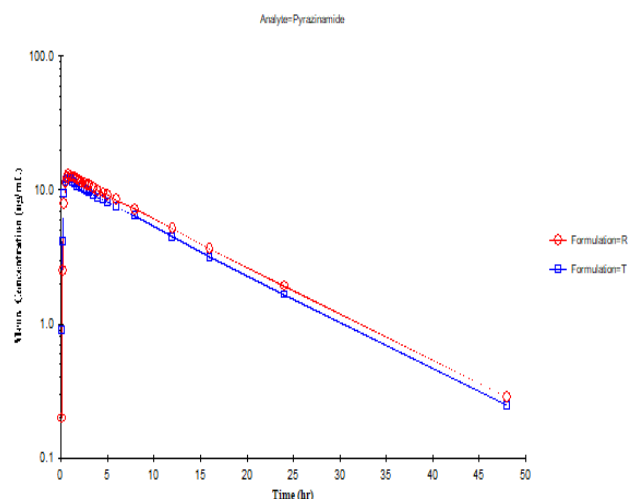
Parameters (Units)	Arithmetic Mean $\pm$ SD (%CV) (N = 36)	
	Reference Product (R)	Test Product (T)
C_{max} ($\mu\text{g/mL}$)	14.048 $\pm$ 1.8812 (13.39%)	12.944 $\pm$ 1.6933 (13.08%)
# T_{max} (hr)	0.830 (0.33 - 2.00)	0.830 (0.33 - 1.75)
AUC_{0-t} ($\text{hr} \cdot \mu\text{g/mL}$)	163.080 $\pm$ 25.2223 (15.47%)	144.563 $\pm$ 26.7263 (18.49%)
$AUC_{0-\infty}$ ($\text{hr} \cdot \mu\text{g/mL}$)	170.866 $\pm$ 25.0755 (14.68%)	151.503 $\pm$ 26.7082 (17.63%)
$t_{1/2}$ (hr)	8.704 $\pm$ 1.6386 (18.83%)	8.541 $\pm$ 1.9649 (23.01%)
K_{el} (1/hr)	0.0836 $\pm$ 0.02420 (28.95%)	0.0872 $\pm$ 0.02947 (33.79%)
$AUC_{\%} \text{Extrap}_{obs}$ (%)	4.622 $\pm$ 3.4425 (74.49%)	4.687 $\pm$ 3.4900 (74.46%)

For T_{max} median (min - max)

The figure of mean linear plasma concentrations versus time curve is presented below:



The figure of semi-logarithmic mean linear plasma concentrations versus time curve is presented below:



Four subjects reported adverse events after administration of test product and three subjects reported adverse events after administration of reference product. The Adverse events noted were itching and boils. Hence, they were mild in nature.

DISCUSSION

From the above table, it can be seen that dose normalized 90% confidence interval for geometric least square mean ratio of (T/R) is within the acceptance range of 80.00% to 125.00% for all primary pharmacokinetic parameters C_{max} and AUC_{0-t} required for concluding bioequivalence between the test and reference formulations.

The test product (T) (Pyrazinamide dispersible tablets 150 mg at a dose of 450 mg (03 tablets of 150 mg) of Micro Labs Limited, India) when compared with the reference product (R) (PYRAFAT® 500 mg tablets of RIEMSER Pharma GmbH-An der Wiek 7-17493 Greifswald-Insel Riems) meets the bioequivalence criteria in terms of rate and extent of absorption after administration of single dose as set in the regulatory guidelines for bioequivalence studies.

The test and reference products were well tolerated by the subjects. No serious adverse event occurred during the conduct of the study. Hence, the dispersible tablet formulation of Pyrazinamide manufactured by Micro Labs is therapeutically equivalent to the immediate release formulation of Riemser Pharma. It was also safe without any major adverse effects.

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