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Safety, Tolerability And Bioequivalence Assessment Of Misoprostol 200 µg Tablet

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Abstract : *Misoprostol is a drug widely used in both pregnant and non pregnant women. It has cervical ripening and uterotonic properties. It is a Prostaglandin E_1 derivative.Micro Labs is a generic drug company who had developed a Misoprostol 200 µg tablet formulation. The formulated tablets were tested in healthy adult human volunteers under fasting and fed conditions for bioequivalence as per United States (US) guideline for conduct of bioequivalence studies. The Reference product considered for bioequivalence was Cytotec® of Pfizer. The formulation developed by MicroLabs was safe and well tolerated without major Adverse Events and was found to be bioequivalent to the reference drug formulation.*

Keywords: *Misoprostol, bioequivalence, Tablet, safe*

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I. INTRODUCTION

Bioequivalence studies are very important for the development of a pharmaceutical preparation in the pharmaceutical industry. Their rationale is the monitoring of pharmacokinetic and pharmacodynamic parameters after the administration of tested drugs. The target of such study is to evaluate the therapeutic compatibility of tested drugs (pharmaceutical equivalents or pharmaceutical alternatives). The importance of bioequivalence studies is increasing due to the large growth of the production and consumption of generic products. Generic products represent approximately 50 % of the whole consumption in many European countries and USA.

The comparison of the original and the generic product via bioequivalence study is suggested as sufficient for the registration of generic products.[1]

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. In determining bioequivalence between two drugs such as a reference drug (Brand) and potential to be test drug (marketed generic drug), pharmacokinetic studies are conducted.

For a pharmacokinetic comparison, the plasma concentration data are used to assess key pharmacokinetic parameters such as area under the curve (AUC), peak concentration (Cmax), time to peak concentration (Tmax), and absorption lag time (tlag). Testing should be conducted at several different doses, especially when the drug displays non-linear pharmacokinetics.

If 90% Confidence interval for the ratio of the geometric least square means of natural log transformed Cmax, AUC_{0-t} and AUC_{0-inf} of Test and Reference drugs are within 80.00% to125.00%, then bioequivalence will be established.[2]

Misoprostol is a synthethic analogue of PGE which has been successfully used for cervical ripening. [5]
Because of its uterotonic properties, it has been widely used in both pregnant and non pregnant women. [4]

Misoprostol is used in obstretics and gynaecology for various indications like medication abortion, medical management of miscarriage, induction of labour, cervical ripening before surgical procedures, and the treatment of postpartum hemorrhage. [3]

Micro Labs Ltd. had developed a generic version of Misoprostol 200 µg tablets. It had been tested in healthy human volunteers in fasting and fed condition. The bioavailability, safety and tolerability were assessed along with Cytotec® of Pfizer. Approval had been taken to conduct the studies from Chennai Ethics Committee, Chennai, India and DCGI (Drug Controller General of India).
The bioequivalence studies were conducted as per US guideline for conduct of bioequivalence studies. [6]

II. MATERIALS AND METHODS

An open-label, balanced, randomized, single-dose, two-treatment, three-period, three-sequence, crossover, partial-replicate, reference-scaled, oral bioequivalence study of Misoprostol Tablets 200 mcg of Micro Labs Limited, India and Cytotec® misoprostol tablets 200 mcg of G. D. Searle LLC, Division of Pfizer Inc, NY, NY 10017, in healthy, adult, human subjects under fasting and fed conditions.

The studies were conducted at Micro Therapeutic Research Labs Private Limited, No.6, KamarajarSalai, Selaiyur, East Tambaram, Chennai – 600 059, Tamil Nadu, India.

Volunteers selected were healthy young adults within 18-45 years age, BMI within the range of 18.50 kg/m^2 to 24.99 $kg/m^2$and having no history of smoking or drug abuse. Informed consent was obtained from each volunteer before screening.

Dosing: In each period, a single oral dose of one capsule of either Test formulation (Test T) or Reference formulation (Reference R), both containing 200 µg of Misoprostol, was administered with about 240 mL drinking water at ambient temperature in fasting condition (at least 10.00 hours before dosing) and fed condition (30 minutes after start of a high calorie and high fat breakfast) as per randomisation schedule in the morning.

PK Blood Draw Time Points (both Fasting and Fed studies):pre-dose (within 75 minutes prior to dosing) and at 00.07, 00.13, 00.20, 00.27, 00.33, 00.42, 00.50, 00.67, 00.83, 01.00, 01.25, 01.50, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00 and 08.00 hour post-dose.

Vital signs like Blood Pressure (B.P.), pulse rate, temperature and respiratory rate were measured at regular intervals. Subjects were asked about their well-being status from time to time.

There were thirty six (36) healthy, adult, eligible human subjects enrolled in the fasting study and forty two (42)subjects enrolled for the fed study. Out of 36 enrolled subjects, thirty four (34) subjects completed the fasting study. For the fed study, out of 42 (forty two) subjects, and thirty four (34) subjects completed the fed study.

Statistical Evaluation:

For Misoprostol acid, the Ln transformed pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ has been subjected to analysis of Variance (ANOVA). Sequence has been included as main effect in the ANOVA model when analysis was done using scaled average bioequivalence procedure using General Linear Model (PROC GLM) of SAS® software. Sequence, Treatment and Period are included as fixed effects and subject (Sequence) as a random effect in the ANOVA model, when the analysis was done using average bioequivalence procedure using Mixed Effect ANOVA Model (PROC MIXED) of SAS® software. In this case, Sequence effect has been tested using subject (Sequence) as error term.

An F-test was performed to determine the statistical significance of the effects involved in the ANOVA models at a significance level of 5 % (alpha =0.05). Ratio analysis, Intra-Subject Variability, Power and Within-subject standard deviation of the reference product were also determined.

A 90% Confidence Intervals for the ratio of the Test and Reference product averages (Geometric Least Squares Means) has been calculated for Misoprostol acid individual pharmacokinetic parameters having within-subject standard deviation of the reference product (SWR) < 0.294, by two one-sided tests procedure at 5% level of significance that compares the average (Least Squares Means) values of pharmacokinetic parameters determined using PROC MIXED model of SAS ® version 9.2 software.

95 % Confidence bound:

The 95% upper confidence bound for $(\mu T-\mu R)^2 - \theta * S^2WR$ to the Test and Reference product average (Geometric Least Squares Means) has been determined for Misoprostol acid individual pharmacokinetic parameters having within-subject standard deviation of the reference product (SWR) ≥ 0.294.

Criteria for Evaluation:

For Case 1 (Within-subject standard deviation of the reference formulation (SWR) is < 0.294 for Cmax and/or AUC0-t and/or AUC0-∞:

Using the two one-sided tests for bioequivalence, The test product will be considered bioequivalent to the reference product, if 90% confidence interval for ratio of the geometric least square means of C_{max} and/or AUC_{0-t} and/or $AUC_{0-\infty}$ of the test and referenceformulations is between the ranges of 80.00% to 125.00% for Misoprostol acid based on Ln- transformed data

For Case 2 (Within-subject standard deviation of the reference formulation (SWR) is ≥ 0.294 for C_{max} and/or AUC_{0-t} and/or $AUC_{0-\infty}$:

The test product will be considered bioequivalent to the reference product if the following two conditions are met for C_{max} and/or AUC_{0-t} and/or $AUC_{0-\infty}$ using Ln-transformed data of Misoprostol acid.

- The 95% upper confidence bound for $(\mu T-\mu R)^2 – (\theta S^2WR)$ determined must be ≤ 0.

- The point estimate (test/reference geometric least square mean ratio) must fall within 80.00% to 125.00%.

III. RESULTS

The bioequivalence assessment between the formulation manufactured by Micro Labs and Cytotec® misoprostol tablets of Pfizer is presented below in fasting and fed conditions:

Table 1: Fasting Summary of Pharmacokinetic Profile of Test product (T), Misoprostol Acid, (N=34)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max}(pg/mL)	1331.9531±722.9772	54.2795	1069.4324	457.4602	4323.3377
AUC_{0-t} (pg.hr/mL)	741.0279±345.3316	46.6017	641.1761	369.1175	2277.9870
$AUC_{0-\infty}$ (pg.hr/mL)	764.9567±349.4888	45.6874	669.2773	389.1934	2308.8330
t_{max}(hr)	0.27±0.09	33.11	0.27	0.13	0.50
$t_{1/2}$ (hr)	0.6614±0.3196	48.3166	0.5638	0.2903	1.8260
K_{el}(1/hr)	1.2434±0.4743	38.1433	1.2296	0.3796	2.3878
AUC_{0-t}/ $AUC_{0-\infty}$	0.97±0.02	1.62	0.97	0.92	0.99

Table 2: FastingSummary of Pharmacokinetic Profile of Reference product (R1), Misoprostol Acid, (N=34)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
Cmax (pg/mL)	1361.0483±511.1233	37.5537	1298.4706	445.3685	2784.5183
AUC_{0-t} (pg.hr/mL)	724.5390±297.0088	40.9928	674.8590	317.8834	1936.7446
$AUC_{0-\infty}$ (pg.hr/mL)	751.6156±302.7781	40.2836	695.6718	338.6708	1977.8890
t_{max} (hr)	0.26±0.10	38.33	0.27	0.13	0.50
$t_{1/2}$ (hr)	0.7530±0.4240	56.3146	0.5895	0.2872	1.8223
K_{el} (1/hr)	1.1888±0.5485	46.1344	1.1783	0.3804	2.4136
AUC_{0-t}/ $AUC_{0-\infty}$	0.96±0.02	2.17	0.97	0.87	0.99

Table 3: Fasting Summary of Pharmacokinetic Profile of Reference product (R2), Misoprostol Acid, (N=34)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (pg/mL)	1636.7901±769.2701	46.9987	1427.8753	471.4495	4388.2248
AUC_{0-t} (pg.hr/mL)	791.2815±378.4317	47.8252	737.4441	293.2097	2370.4315
$AUC_{0-\infty}$ (pg.hr/mL)	818.6927±383.8666	46.8878	760.8133	305.0414	2418.1150
t_{max}(hr)	0.23±0.09	38.78	0.20	0.07	0.50
$t_{1/2}$ (hr)	0.6781±0.3621	53.4018	0.5818	0.2643	2.1119
K_{el} (1/hr)	1.2517±0.5282	42.1969	1.1922	0.3282	2.6221
AUC_{0-t}/ $AUC_{0-\infty}$	0.96±0.03	2.66	0.97	0.83	0.99

Table 4: Geometric mean of Pharmacokinetic Profile of Test product (T), Reference Product (R1) and Reference product (R2) of Misoprostol Acid (N=34) under fasting condition

Pharmacokinetic Parameter	Geometric Mean		
	Test Product (T)	Reference Product (R1)	Reference Product (R2)
C_{max}(pg/mL)	1202.4347	1275.2239	1487.4800
AUC_{0-t} (pg.hr/mL)	688.2291	677.7141	725.9699
$AUC_{0-\infty}$ (pg.hr/mL)	712.1528	704.4471	753.3232
t_{max} (hr)	0.26	0.24	0.22
$t_{1/2}$ (hr)	0.6032	0.6568	0.6082
K_{el}(1/hr)	1.1491	1.0553	1.1397
AUC_{0-t}/ $AUC_{0-\infty}$	0.97	0.96	0.96

R1 = Reference replicate 1; R2 = Reference replicate 2

Table 5: Statistical Results of Test product (T) versus Reference product (R) for, Misoprostol Acid, (N=34) under fasting condition

Pharmacokinetic Parameter	**Geometric Least Square Mean**		**Within-Subject SD (Swr)**	**ISCV%**	**T/R Ratio %**	**Power %**	**90% Confidence Interval**
	Test Product (T)	**Reference Product (R)**					
C_{max} (pg/mL)	1205.466	1378.531	0.235	23.80%	87.45%	96.2%	78.56%-97.34%
AUC_{0-t} (pg.hr/mL)	689.121	701.306	0.157	15.81%	98.26%	100.0%	94.23%-102.47%
$AUC_{0-\infty}$ (pg.hr/mL)	713.088	728.469	0.153	15.42%	97.89%	100.0%	93.69%-102.27%

Table 6: Fed Summary of Pharmacokinetic Profile of Test product (T), Misoprostol Acid, (N=38)

Pharmacokinetic Parameter	**Arithmetic Mean ± Standard Deviation**	**Coefficient of Variation**	**Median**	**Minimum**	**Maximum**
C_{max} (pg/mL)	369.4412±147.0092	39.7923	326.3015	107.2544	825.8299
AUC_{0-t} (pg.hr/mL)	683.8684±251.7472	36.8122	653.2487	235.1855	1356.8584
$AUC_{0-\infty}$ (pg.hr/mL)	740.6424±239.5703	32.3463	702.5726	296.6554	1389.8004
t_{max} (hr)	0.88±1.28	146.50	0.25	0.08	5.00
$t_{1/2}$ (hr)	1.2806±0.5923	46.2495	1.1057	0.5013	2.9540
K_{el} (1/hr)	0.6468±0.2689	41.5738	0.6269	0.2346	1.3826
AUC_{0-t}/ $AUC_{0-\infty}$	0.90±0.07	8.24	0.92	0.68	0.98

Table 7: Fed Summary of Pharmacokinetic Profile of Reference product (R1), Misoprostol Acid, (N=38)

Pharmacokinetic Parameter	**Arithmetic Mean ± Standard Deviation**	**Coefficient of Variation**	**Median**	**Minimum**	**Maximum**
C_{max}(pg/mL)	398.6520±240.6977	60.3779	300.3220	101.6987	977.4242
AUC_{0-t} (pg.hr/mL)	644.0810±201.8702	31.3424	679.4531	319.2136	1212.9857
$AUC_{0-\infty}$ (pg.hr/mL)	719.3244±186.0642	25.8665	729.9992	384.5902	1251.4628
t_{max} (hr)	1.051±1.42	136.05	0.21	0.08	5.00
$t_{1/2}$ (hr)	1.4865±0.9960	67.0050	1.1782	0.4906	4.8009
K_{el} (1/hr)	0.6245±0.2919	46.7482	0.5884	0.1444	1.4128
AUC_{0-t}/ $AUC_{0-\infty}$	0.88±0.10	11.67	0.92	0.60	0.98

Table 8: Fed Summary of Pharmacokinetic Profile of Reference product (R2), Misoprostol Acid, (N=38)

Pharmacokinetic Parameter	**Arithmetic Mean ± Standard Deviation**	**Coefficient of Variation**	**Median**	**Minimum**	**Maximum**
C_{max} (pg/mL)	324.6290±164.3186	50.6174	296.2803	87.1623	786.0727
AUC_{0-t} (pg.hr/mL)	667.3840±209.5565	31.3997	645.1302	247.0450	1160.8017
$AUC_{0-\infty}$ (pg.hr/mL)	740.6318±202.7898	27.3806	704.4200	307.4062	1202.7275
t_{max} (hr)	1.28±1.40	109.32	0.25	0.08	4.00
$t_{1/2}$ (hr)	1.4320±0.9169	64.0312	1.0575	0.6889	4.0905
K_{el} (1/hr)	0.6217±0.2478	39.8548	0.6555	0.1695	1.0062
AUC_{0-t}/ $AUC_{0-\infty}$	0.91±0.07	7.42	0.93	0.68	0.98

Table 9: Geometric mean of Pharmacokinetic Profile of Test product (T), Reference Product (R1) and Reference product (R2) of Misoprostol Acid (N=34) under fed condition

Pharmacokinetic Parameter	**Geometric Mean**		
	Test Product (T)	**Reference Product (R1)**	**Reference Product (R2)**
C_{max} (pg/mL)	340.2673	336.1897	286.9403
AUC_{0-t} (pg.hr/mL)	637.6770	612.8425	633.1337
$AUC_{0-\infty}$ (pg.hr/mL)	702.5312	696.6039	712.7654
t_{max} (hr)	0.37	0.41	0.56
$t_{1/2}$ (hr)	1.1677	1.2616	1.2384
K_{el} (1/hr)	0.5936	0.5494	0.5597
AUC_{0-t}/ $AUC_{0-\infty}$	0.90	0.88	0.91

R1 = Reference replicate 1; R2 = Reference replicate 2

Table 10: Statistical Results of Test Product (T) versus Reference product ® for, Misoprostol Acid (N=38)

Pharmacokinetic Parameter	**Point Estimate (%)**	**Within-Subject Variability (S^2wr)**	**Within-Subject SD (Swr)**	**95% Upper Confidence Bound**
C_{max}(pg/mL)	109.00%	0.117	0.3431	-0.0350

Table 11: Statistical Results of Test product (T) versus Reference product (R) for, Misoprostol Acid, (N=38) under fed condition

Pharmacokinetic Parameter	**Geometric Least Square Mean**		**Within-Subject SD (Swr)**	**ISCV%**	**T/R Ratio %**	**Power %**	**90% Confidence Interval**
	Test Product (T)	**Reference Product (R)**					
AUC_{0-t} (pg.hr/mL)	637.8116	623.3279	0.1024	10.27%	102.32%	100.0%	98.14%-106.69%
$AUC_{0-\infty}$ (pg.hr/mL)	713.8915	704.3821	0.1266	12.71%	101.35%	100.0%	97.75%-105.08%

Figure 1: Mean plot of Test and Reference formulation under fasting condition:

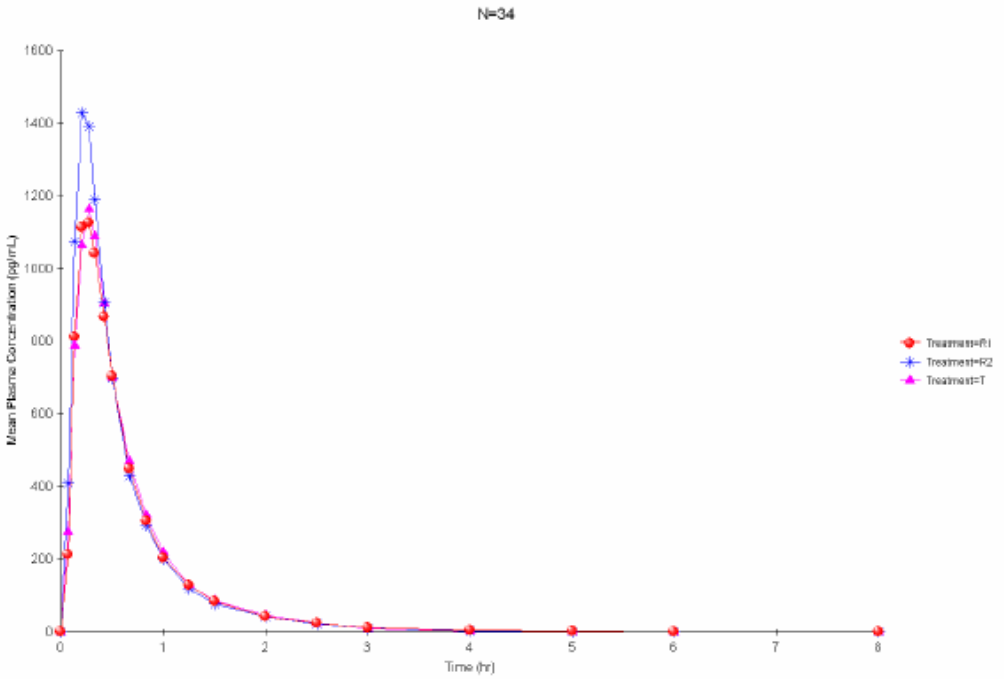


Figure 2: Semi-Logarithmic plot of Test and Reference formulation under fasting condition:

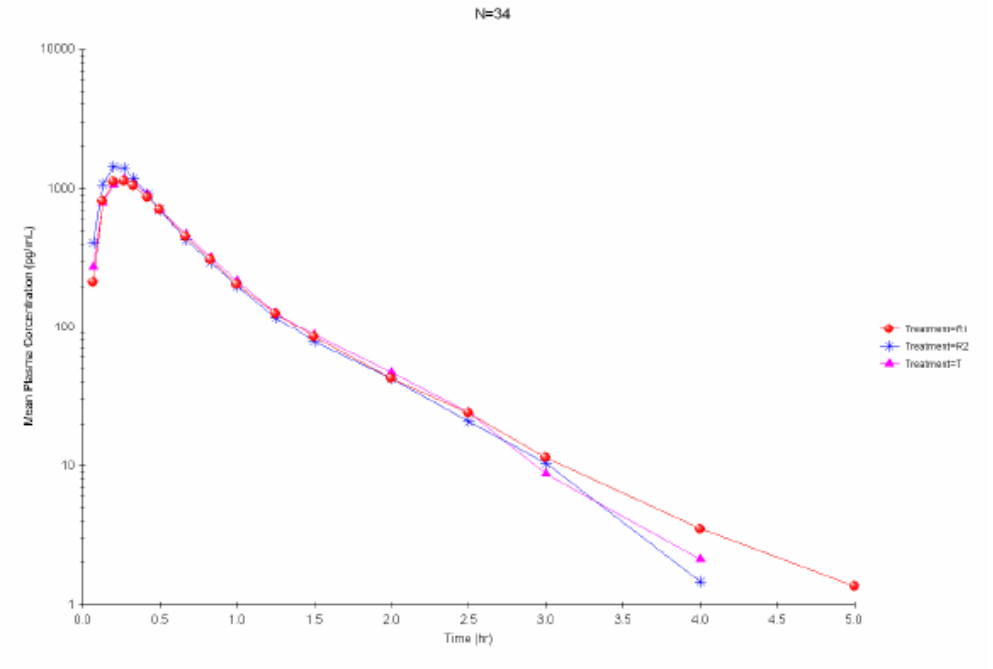


Figure 3: Mean plot of Test and Reference formulation under fed condition:

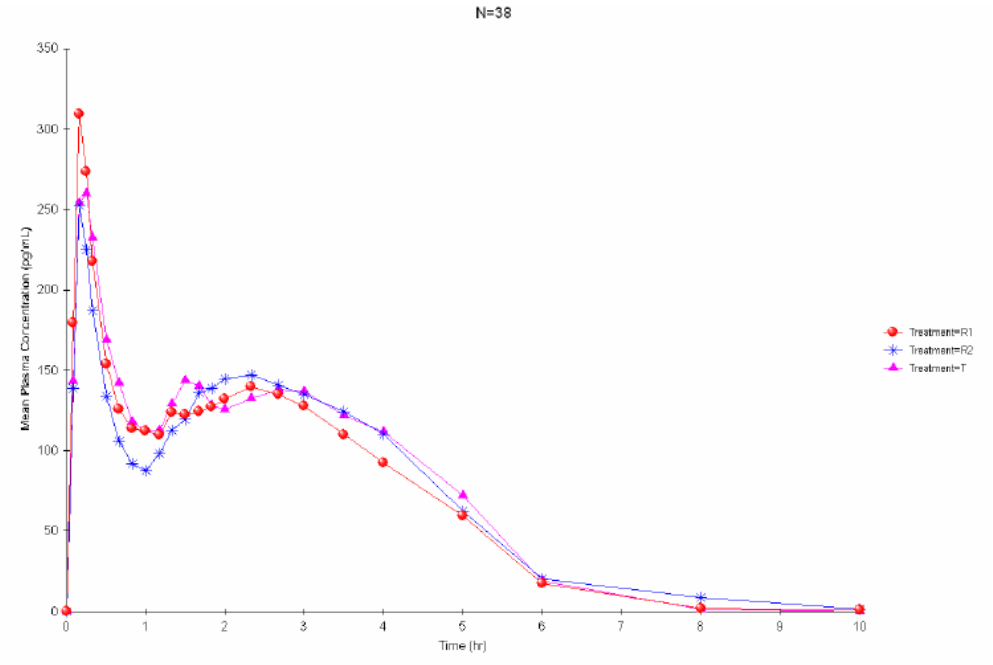
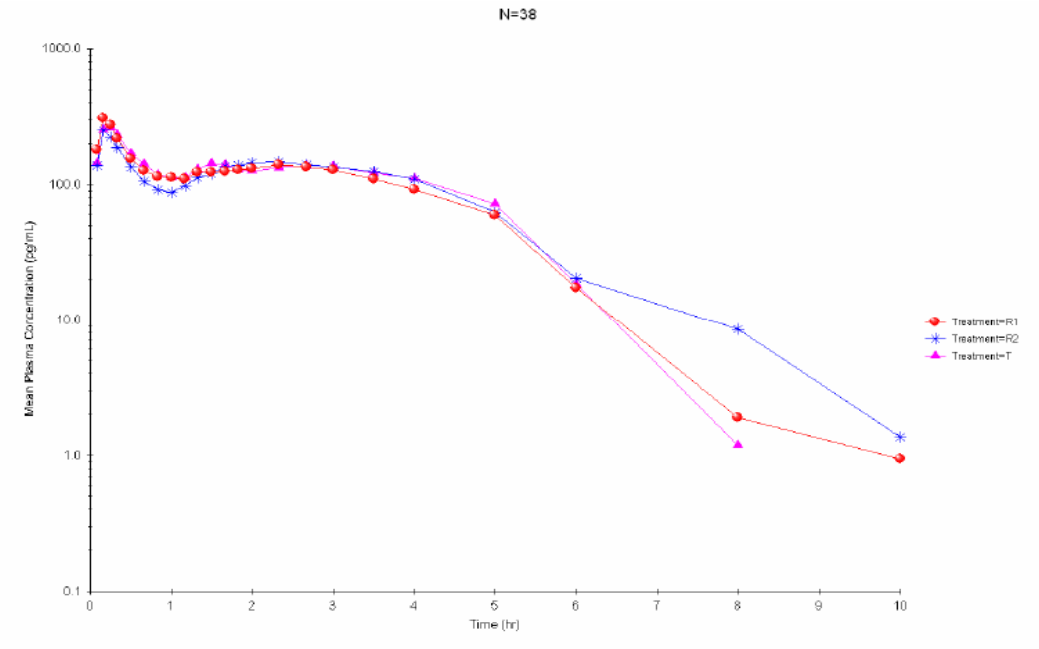


Figure 4: Semi-Logarithmic plot of Test and Reference formulation under fed condition:



The safety assessment in the fasting and fed conditions is presented below:

Fasting study:

There were no adverse events reported due to the drug during the study.

Fed study

There was one adverse event of mildspasmodic pain due to administration of Test formulation. It was possibly related to the drug.

IV. CONCLUSION

Bioequivalence:

Based on the statistical results obtained, Misoprostol Tablets 200 mcg of Micro Labs Limited, India and Cytotec® misoprostol tablets 200 mcg of G. D. Searle LLC, Division of Pfizer Inc, NY, NY 10017 are found to be bioequivalent in healthy, adult, human subjects under fasting and fed conditions.

Safety and tolerance:

From the assessment of safety presented above, it may be concluded that Misoprostol was safe and well tolerated when administered in healthy adult human volunteers under fasting and fed conditions. No major Adverse Events were observed due to the drug administration.

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