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EFFECT OF FOOD ON PHARMACOKINETICS OF MELOXICAM

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ABSTRACT

The primary objective of the study was to investigate the effect of food on the pharmacokinetics of MELOXICAM. Cmax, Tmax and AUC of MELOXICAM were defined as the main parameters for the assessment of bioavailability and bioequivalence of MELOXICAM administered in fasting and fed conditions. The 90% CI for the fed/fasting MELOXICAM did not contained within the acceptance interval (80, 125) and, therefore, it can be concluded that the rate of systemic exposure to MELOXICAM does not fit the claim of bioequivalence between administration in fasting and fed conditions. This study has demonstrated that all the pharmacokinetic parameters of both the treatments were statistically different from each other. In the fed condition the values of Cmax and AUC were decreased while Tmax increases than that of fasting which demonstrated that the extent of systemic exposure to MELOXICAM was affected by the delay in absorption of MELOXICAM in the presence of food. None of the study volunteers reported any serious adverse effects throughout the study. The only two AEs reported were mild and not related to the study medication. The AEs reported were, according to the study medical expert, related to the sampling procedure and were self limiting and did not require any treatment. There was no change in the vital signs of the volunteers throughout the study period. The presented data are of major importance in identifying the optimal dosing regimen for future clinical trials with oral MELOXICAM. In our study, only one type of food (a standardized continental breakfast) was evaluated; further studies are needed to assess the effects of foods with different compositions and contents on the bioavailability of MELOXICAM.

Keywords: Food effect bioavailability, HPLC, Bioequivalence studies.

INTRODUCTION

With increasing generic substitution, food– drug interaction studies have gained considerable importance. [1-8] Food–drug interaction studies focus on the effect of food on the release and absorption of a drug. In view of dramatic and clinically relevant food effects observed with certain Theophylline sustained release formulations, bioequivalence between a Test and a Reference formulation under only one nutritional condition, e.g. fasting, is by no means sufficient to allow generic substitution.[9-12] The reported food effects, with AUC increases of 100 % and decreases of 50 % for certain formulations, are far beyond the usually accepted 25 % increase and 20 % decrease in bioequivalence studies between formulations.[13] The CPMP (2001) guidance on bioequivalence also addresses this issue with particular emphasis on controlled release formulations. The FDA (2002) guidance recommends a study comparing the bioavailability under fasting and fed conditions for all orally administered modified release drug products. Modified release formulations include two essentially different types of release modifications, so-called 'prolonged release' formulations and 'delayed release' formulations.

Understanding the possible clinical implications of taking medicines with or without a meal is important for achieving quality use of medicines. Although the effect of food is not clinically important for many drugs, there are food–drug interactions which may have adverse consequences. Often these interactions can be avoided by advising the patient to take their medicines at the same time with respect to meals. [14-25]

SUBJECT AND METHOD

Twenty (20) male volunteers were screened out of that Eighteen (18) were considered eligible as per protocol. Out of eighteen subjects sixteen subjects successfully completed both the studies i. e. fasting and fed, as two subjects were dropped out during the study. Samples from all the male subjects who completed both the periods of the study were analyzed. The blood samples were used for pharmacokinetic analysis of MELOXICAM.

The subjects were examined within 15 days prior to their first administration of study medication and assessed for their eligibility to participate. No clinically relevant abnormalities in physical examinations and blood and urine analysis were reported in subjects who were included in the study. Results from hematological and clinical biochemistry laboratory data indicating that one or more values were outside the "normal range" did not necessarily lead to exclusion of a subject from the study. At the discretion of the principal investigator, certain laboratories values outside the "normal range" could be repeated two times. If the value returned to within the "normal range" for the particular laboratory test, or if the study physician considered the repeated laboratory value to be at an acceptable level in relation to the "normal range", the subject was considered eligible, with respect to hematological and clinical chemistry criteria, to participate in

the study.

The post-study safety evaluation included obtaining hematological and clinical biochemistry laboratory data. Post-study laboratory data with values outside the "normal range" were not necessarily repeated to establish if and when those variables returned to within the "normal range". The variables were reviewed against the clinical background, other relevant information and their relevance to the administered study drug, before a decision was taken to repeat the values in question. The results of the pre- and post-study laboratory data are included in the CRF where the study physician's assessments on the relevance of all variables outside the "normal range" are documented.

Vital signs and physical examinations showed no marked changes throughout the study. All the other subjects who participated in the study were declared healthy at the post-study examination, except those subjects who failed to follow-up for further post study laboratory examination. Pathological findings observed during the post-study laboratory tests were documented in the CRF. Laboratory tests found to be marginally outside the normal range were considered not to be of clinical relevance. All subjects enrolled in the study underwent safety assessments until the completion of the study. To the principal investigator's knowledge, all subjects refrained from using any prescription and over the counter medications, for two and one weeks respectively, before the first administration of study medication and for the duration of the study, with the exception of the study medication taken on clinic days. No moderate or serious adverse events (AEs) were reported to the investigators. Potential recall bias of AEs in this study was not likely because only one dose of each formulation was administered during each treatment; subjects were under medical surveillance in the clinical unit.

This study was carried out as per the ICH (Step 5), 'Guidance for Good Clinical Practices (GCP)'150 and the principles of Declaration of Helsinki (Scotland, October 2000).151 The MGM Institute of Biosciences and Technology, Independent Ethics Committee (IEC) has reviewed and approved the protocol and the Informed Consent Form (ICF) for this study.

This was a randomized, open label, 2-way crossover study in 18 healthy, male subjects. The screening consent & study consent were taken respectively before drug application. Thereafter, subject's medical records were documented and physical examination was conducted. Inclusion eligibility was also based on successful completion of a clinical health evaluation, which consisted of a personal interview; a complete physical examination (BP, pulse, weight, temperature, and respiratory rate); laboratory testing that included a complete blood cell count and urine analysis. Testing was performed by Shrikrushna Pathology Laboratory, Samarth nagar, Aurangabad, (MS) INDIA 431005. Subjects were excluded if laboratory values were significantly above or below the reference range and/or if all tests had not been performed. In addition, the laboratory data were reviewed by the investigators of the clinical unit prior to the enrollment of the

subjects. Subjects were compensated for their participation.

The subjects were hospitalized for 12 h before and until 48 h after dosing. After an overnight fast of at least 12 h, each volunteer received single oral doses (150 mg MELOXICAM) of either under fasting conditions or immediately after a high fat breakfast. Wash-out periods of at least 1 week between the treatments were maintained. A standardized meal was served to all subjects 4 h after dosing followed by standardized meals 7 and 11 h after dosing. Conditions were chosen in accordance with international requirements for food interaction studies.

Blood samples (1x 3 mL) will be collected by the intravenous route using heparinized disposable syringes at the following times: Pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, and 24.0 hours post-dose after drug administration. The blood samples will be collected in vacutainers containing EDTA as anticoagulant and immediately centrifuged at 3000 rpm for 15 min and divided in two aliquots immediately after receiving the blood samples from all the subjects. The separated plasma samples will be stored at or below -20^{o}C until analyzed. A validated HPLC method will be employed for the estimation of MELOXICAM in human plasma.

Vital signs, ECG and laboratory parameters were repeatedly determined during the hospitalization phase. Subjective well being was monitored by asking for adverse events in a non leading manner and by documentation of spontaneously reported adverse events. These were classified according to their severity and potential relationship to the study drug. Any concomitant medication taken during the course of the study was documented.

The following Pharmacokinetic parameters of MELOXICAM were calculated:

Cmax: Maximum measured plasma concentration over the entire sampling period, directly obtained from the experimental data of plasma concentration versus time curves, without interpolation.

Tmax: Time of maximum measured plasma concentration (Cmax). If maximum value occurs at more than one point, Tmax is defined as the first point with this value in each period.

AUC_{0-t}: Area under plasma concentration versus time curve from time of dosing to time of the last quantifiable concentration, as calculated by the linear trapezoidal method.

Individual plasma concentration VS time curves were constructed; Cmax and Tmax were directly obtained from these curves. AUC from time 0 (baseline) to 24 hour (AUC^{0-24}) was calculated using the trapezoidal rule. Extrapolation of AUC from baseline to infinity ($AUC^{0-\infty}$) was calculated as follows: $AUC_{0-\infty}$ = AUC0–24 + (C24/ke) where C24 was defined as concentration at 24 hours.

Geometric means of the pharmacokinetic parameters Cmax and AUC0-t were used to calculate the

formulation ratios. These values were expressed as point estimates. 90% confidence interval for the ratio of study formulations was calculated for the log transformed pharmacokinetic parameters [Cmax, and AUC_{0-t}] using ANOVA output from the analysis of log-transformed data. 90% confidence interval then formed the basis for concluding the equivalence of study formulation. If the point estimate of geometric mean ratio and confidence intervals for the entire log transformed pharmacokinetic parameters [Cmax and AUC_{0-t}] are entirely included in the range of 80-125%, then the treatments was claimed to be bio-equivalent. [26-42]

ANALYTICAL METHOD [43-49]

HPLC Method development for pure meloxicam:

Today the development of a method of analysis is usually based on prior art or existing literature, using the same or quite similar instrumentation. It is rare today that an HPLC – based method is developed that does not in some way relate or compare to existing, literature-based approaches. The development of any new or improved method usually tailors existing approaches and instrumentation to the current analyte, as well as to the final needs or requirements of the method. Method development usually requires selecting the method requirements and deciding on what type of instrumentation to utilize and why. The extraction reported to detect MELOXICAM was liquid-liquid extraction.

They were reported for the determination of MELOXICAM and its related substances in biological fluids like plasma, blood, and urine only but, very few methods have been reported for its determination in bulk and solid (tablet) dosage forms by reversed phase high-performance liquid chromatographic (RP-HPLC) method. However, these methods presented some disadvantages such as being of low sensitivity, time consuming, and costly. This study was designed to develop a simple and reliable method to quantitate MELOXICAM in a relatively short time with high linearity. Therefore, this study involves the development of simple and rapid isocratic RP-HPLC method which can be employed for the routine analysis of MELOXICAM. The established method was validated with respect to specificity, linearity, precision, accuracy, and ruggedness.

Reagents:

Water	:	Milli-Q / HPLC Grade
Ortho phosphoric acid (88%)	:	GR Grade
Trimethyl amine	:	GR Grade
Acetonitrile	:	HPLC Grade
Methanol	:	HPLC Grade

The linearity of the response of drug was verified from 1 g/ml to 10 g/ml concentrations. The

calibration graphs were obtained by plotting the response versus the concentration.

Preparation of Mobile Phase:

The separation was carried out under isocratic elution with mobile phase was a mixture (75 volumes) of 1.4 mL of ortho-phosphoric acid in 1000 mL of water and adjust the pH 3.0 by using triethyl amine and acetonitrile (25 volumes), was filtered through 0.4 µm nylon membrane filter before use.

Chromatographic Conditions:

Column	:	C8 column (250 mm × 4.6 mm), 5-µm particle size SS column
Flow	:	1.0 ml/min
Wavelength	:	220 nm
Injection volume	:	20µl

Standard Preparation:

A standard stock solution of 50 mg of MELOXICAM in mobile phase was prepared in a volumetric flask. From this stock solution, about 10 mL was diluted to 100 mL with mobile phase.

HPLC METHOD DEVELOPMENT FOR MELOXICAM TABLET DOSAGE FORM

Preparation of sample solution for MELOXICAM in tablet dosage form:

Twenty tablets were weighed and crushed to a fine powder. The powder equivalent of 50 mg of MELOXICAM was taken in a 100-mL volumetric flask containing mobile phase and kept sonication for 10 min and made up to mark with mobile phase. The resultant mixture was filtered through 0.45 µm nylon filter. The desired concentration for the drug was obtained by accurate dilution, and the analysis was followed up as in the general analytical procedure.

Evaluation of system suitability:

- The column efficiency determined for the MELOXICAM peak from the standard preparation should not be less than 5000 theoretical plates and tailing factor for the same peak should not be more than 2.0.
- The percentage relative standard deviation for five replicate injections of standard preparations should not be more than 2.0.

Sr. No.	Name	RT	Area	% Area	USP Platecount	USP Tailing Factor
1	MELOXICAM	4.217	4437618	100	12144	1.44

Table 1: Peak Results for MELOXICAM WS

Weight of samples (g)	Injection Volume (µL)	Mean Area	RSD (%)
304.4	20	4429594	0.03
305.6	20	4462525	0.59
308.2	20	4568540	0.23
299.1	20	4319730	0.11
305.6	20	4395803	0.04
300.1	20	4322305	0.01

Table 2: Intraday precision characteristics of MELOXICAM

Weight of samples (g)	Injection Volume (µL)	Mean Area	RSD (%)
304.1	20	4446587	0.40
303.7	20	4453466	0.19
307.9	20	4548451	0.00
300.3	20	4333103	0.14
302.7	20	4397236	0.14
304.1	20	4332490	0.40

Table 3: Interday precision characteristics of MELOXICAM

Labeled amount (mg)	Amount added (mg)	Amount recovered (mg)	% Recovery
150.0	40.40	40.38	99.95
150.0	50.90	51.30	100.79
150.0	60.10	59.68	99.29

Table 4: Recovery studies of MELOXICAM

Specificity	Weight of sample (g)	Time (h)	RT of MELOXICAM	RT of degraded Product
Acid stress (0.5 N)	0.305	0	4.300	4.308
		8	4.301	4.310
Base stress (5 N NaOH)	0.305	0	4.325	4.317
		8	4.322	4.314
Peroxide stress (3 % H2O2)	0.305	0	4.233	4.217
		8	4.244	4.221

Table 5: Recovery studies of MELOXICAM

Assay calculation for MELOXICAM Tablet formulations:

% Assay

$$\frac{AT1}{AS} X \frac{W}{100} X \frac{5}{50} X \frac{5}{50} X \frac{100}{W1} X \frac{50}{5} X \frac{P}{PC}$$

Where,

AT1 : Average area counts of MELOXICAM peak in sample preparation.

AS : Average area counts of MELOXICAM peak in standard preparation.

W : Weight of MELOXICAM working standard, in mg.

P : Potency of MELOXICAM working standard, on as is basis.

LC : Label claim of MELOXICAM in mg / gm

W1 : Weight of sample in gm

Factor	Level	Retention Time
Flow Rate (mL/min):		
0.9	-1	4.675
1.0	0	3.833
1.1	+1	3.825
pH of mobile phase:		
2.9	-1	3.667
3.0	0	3.675
3.1	+1	4.808
Percentage acetonitrile in the mobile phase:		
22.5	-1	3.800
25.0	0	3.792
27.5	+1	5.233

Table 6: Robustness characteristics of MELOXICAM

Sr. No.	Percentage assay value for Precision
1	99.43
2	99.64
3	99.60
4	99.08
5	99.20
6	100.12
Mean	99.50
RSD	0.36

Table 7: Determination of Precision for HPLC system validation

Sample No.	Assay of MELOXICAM as % of labeled amount	
	Analyst-I (Intra-day precision)	Analyst-II (Inter-day precision)
1	99.43	99.73
2	99.62	99.20
3	99.50	99.88
4	99.18	99.57
5	99.22	100.00
6	100.10	99.23
Mean	99.50	99.60
RSD	0.38	0.27

Table 8: Determination of Precision for HPLC method validation

Formulation	Level	%Recovery	%RSD*
MELOXICAM Tablet formulation	50%	99.20	0.2834
	100%	99.90	0.3050
	150%	99.60	0.3491

Table 9: Recovery Studies for HPLC method validation

* RSD of six observations

Formulation	Amount		% label claim	%RSD*
	Labeled	Found		
MELOXICAM Tablet formulation	150 mg	147.9 mg	98.60	0.2223

Table 10: Analysis of Formulation for HPLC method validation

* RSD of six observations

Statistic	Cmax (ng/mL)	Tmax (h)	AUC (0-t) (ng*h/mL)	AUC (0-inf) (ng*h/mL)	Kel (1/h)	t1/2 (h)	T lag (h)
Mean	201.28	2.21	1823.87	2333.79	0.08	6.95	0.31
GeoMean	188.22	2.06	1595.73	1903.17	0.07	5.87	0.31
Median	180.76	2.30	1493.85	1638.87	0.08	5.31	0.19
Minimum	83.58	1.15	707.66	777.13	0.02	3.02	0.00
Maximum	375.59	4.59	3976.97	6792.34	0.13	19.88	0.77
S.D.	100.40	1.17	1287.33	2201.47	0.04	6.46	0.26
Range	381.48	4.50	4270.93	7858.09	0.15	22.04	1.00
%CV	38.2	40.5	54.0	72.2	43.0	71.1	64.4
N	18	18	18	18	18	18	18

Table 11: Summary Table of Descriptive Statistics of Pharmacokinetic Variables of Fed study.

Statistic	Cmax (ng/Ml)	Tmax (h)	AUC (0-t) (ng*h/mL)	AUC (0-inf) (ng*h/mL)	Kel (1/h)	t1/2 (h)	T lag (h)
Mean	89.26	3.51	1312.55	1572.23	0.07	5.43	0.48
GeoMean	76.20	4.66	1079.07	1412.74	0.06	6.29	0.49
Median	77.62	4.59	1246.55	1444.09	0.06	5.98	0.38
Minimum	40.29	1.55	459.60	548.77	0.02	3.09	0.00
Maximum	147.10	9.19	2540.90	4365.39	0.13	21.08	1.15
S.D.	40.32	2.48	778.96	1405.16	0.04	5.08	0.34
Range	139.53	9.98	2718.96	4985.92	0.15	23.51	1.50
%CV	37.8	37.6	48.8	63.5	40.8	55.9	53.4
N	19	19	19	19	19	19	19

Table 12: Summary Table of Descriptive Statistics of Pharmacokinetic Variables of fasting study

Method precision was evaluated by carrying out the independent assays of MELOXICAM. The sample of known concentration was injected thrice for every formulation. The relative standard deviation was then calculated.

Accuracy or recovery test was studied by adding known amount of drug in the blood samples. The recovery was performed at about 50%, 100% and 150% of MELOXICAM. The method used in determining the

accuracy of the samples was adopted to prepare the samples for the recovery studies. The solutions were analyzed and the percentage recoveries were calculated.

Parameter	Fed		fasting		F (treatment)	Infe-rence	P
	Mean	CV%	Mean	CV%			
Cmax (ng/mL)	118.611	37.8	252.945	38.2	81.926	S	1.37e-017
Tmax (h)	6.59	37.6	2.889	40.5	-	S	-
AUC(0-t) (ng*h/mL)	2546.240	48.8	2782.655	54.0	5.0362	S	0.0045
AUC(0-inf.) (ng*h/mL)	2851.89	63.5	2948.791	72.2	N/A	N/A	N/A
t1/2 (h)	5.089	55.9	5.080	71.1	N/A	N/A	N/A

Table 13: Summary Table (ANOVA) of the Main Study Results for fed and fasting studies.

Parameter (Log transformed)	Geo-Mean ratio (fed /fasting)	90% Confidence limit (0.8-1.25)		Conclusion (fed vs fasting)
		Lower	Upper	
Cmax	0.526	0.4819	0.5736	Not equivalent
AUC(0-t)	0.883	0.7950	0.9551	Not Equivalent

Table 14: Summary Table of the Comparative Bioavailability Data for fed and fasting conditions

VALIDATION OF HPLC METHOD FOR MELOXICAM TABLET FORMULATION

Preparation of sample solution for MELOXICAM in tablet dosage form:

Twenty tablets were weighed and crushed to a fine powder. The powder equivalent of 50 mg of MELOXICAM was taken in a 100-mL volumetric flask containing mobile phase and kept sonication for 10 min and made up to mark with mobile phase. The resultant mixture was filtered through 0.45 µm nylon filter. The desired concentration for the drug was obtained by accurate dilution, and the analysis was followed up as in the general analytical procedure.

PK Parameters	Fed	Fasting
Cmax (ng/mL)Mean±SD	116.611+40.32	272.945+100.40
AUC(0-t) (ng*h/mL) Geomean±SD	1379.668+778.96	2274.615+1287.33
AUC(0-inf) (ng*h/mL)Geomean±SD	1795.558+1405.16	2516.244+2201.47
Tmax(h)Median±SD	6.00+2.48	3.00+1.17
Kel(1/h)Mean±SD	0.091+0.03	0.102+0.04
t1/2Mean±SD	5.089+5.08	5.080+6.46
T lag (h)Mean±SD	0.632+0.34	0.403+0.26

Table 15: Summary of comparative pharmacokinetic data of feds and fasting studies

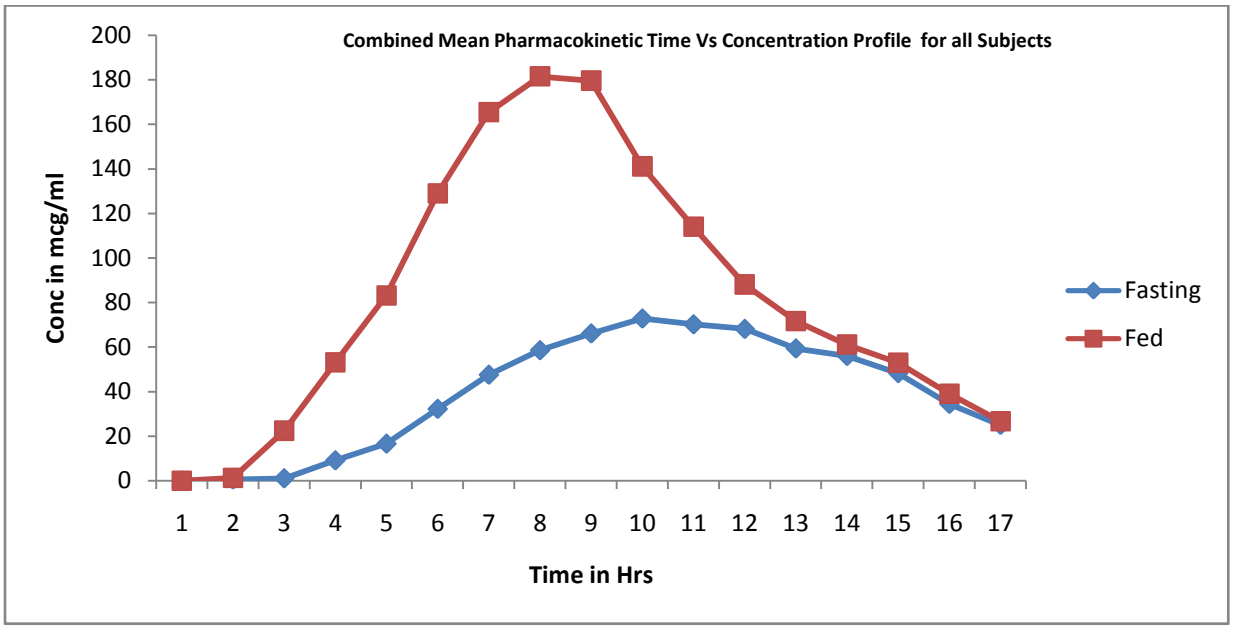

Figure 1: Combined Pharmacokinetic Time Vs Concentration Profile in fasting and fed conditions for all subjects

Sample Injection Procedure:

Six injections of each of the MELOXICAM sample were injected into the chromatographic system. The chromatograms were recorded and the peak area counts were measured for the MELOXICAM peak.

Specificity / Purity plots:

The MELOXICAM samples prepared as per the above mentioned methodology were foremost

analyzed for the purity of the samples and the purity peaks were obtained.

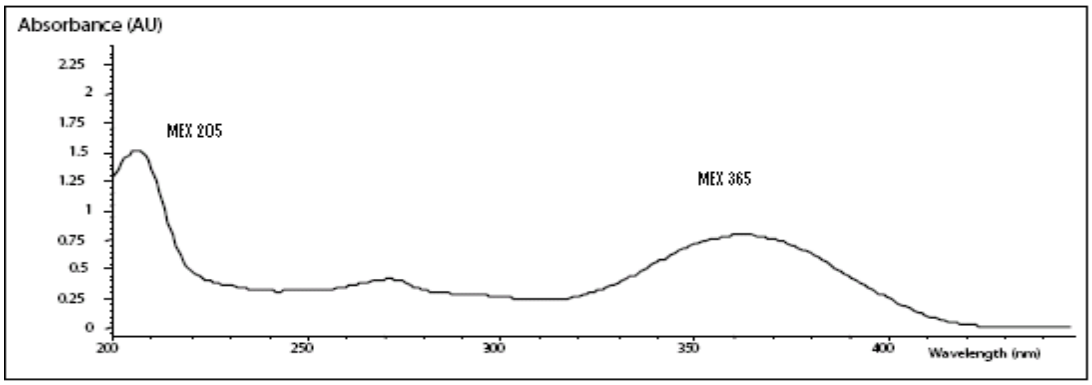

Figure 2: Spectrum Index Plot of MELOXICAM by HPLC

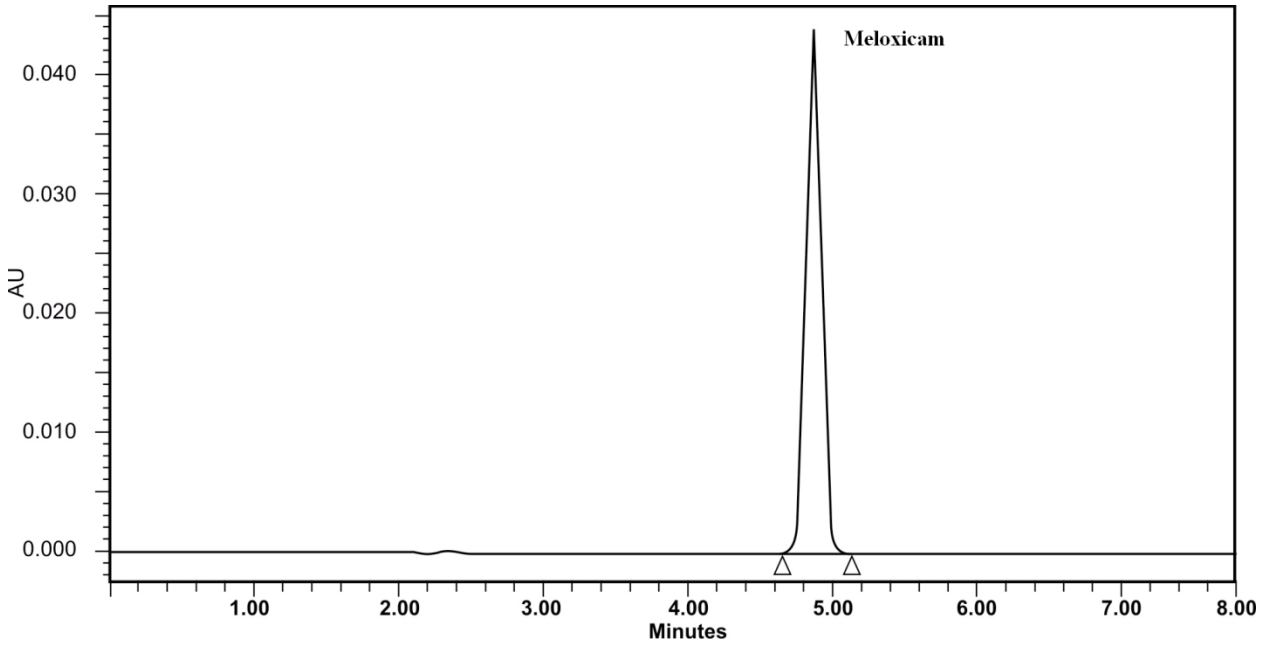

Figure 3: Chromatogram of MELOXICAM

System Precision:

Six replicates of the standard solution were injected into the HPLC system and the area of the peak and RSD was calculated.

Method Precision:

Assay of method precision (intraday precision) was evaluated by carrying out six independent assays for both formulations of MELOXICAM. The intermediate precision (inter-day precision) of the method was also evaluated using two different analysts, systems and different days in the same laboratory.

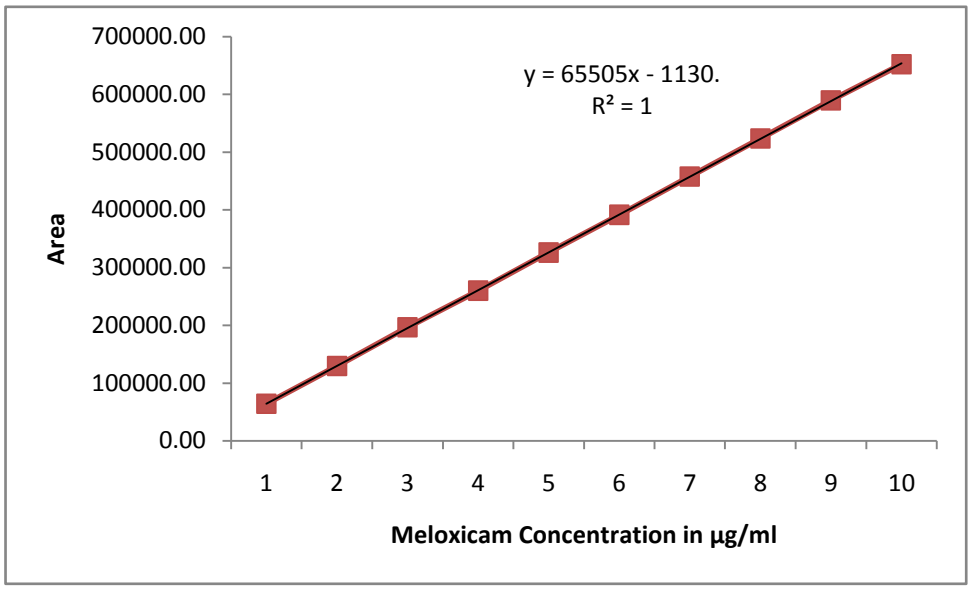

Figure 4: Linearity graph of MELOXICAM at 205 nm by HPLC

Accuracy (Recovery test):

Accuracy of the developed method was studied by recovery experiments. The same solutions were analyzed for percentage recovery studies at three levels (50%, 100% and 150%) for each formulation. The assay results were expressed as percentage of label claim of amount of MELOXICAM found in the tablet formulations.

These solutions were analyzed for its percentage drug contents with respect to label claim, by a single analyst six times a single day and by another analyst once a day for six days, to calculate the percentage precision of the method.

RESULTS

This study has demonstrated that all the pharmacokinetic parameters of both the treatments were statistically different from each other. In the fed condition the values of Cmax and AUC were decreased while Tmax increases than that of fasting which demonstrated that the extent of systemic exposure to MELOXICAM was affected by the delay in absorption of MELOXICAM in the presence of food. None of the study volunteers

reported any serious adverse effects throughout the study. The only two AEs reported were mild and not related to the study medication. The AEs reported were, according to the study medical expert, related to the sampling procedure and were self limiting and did not require any treatment. There was no change in the vital signs of the volunteers throughout the study period. The presented data are of major importance in identifying the optimal dosing regimen for future clinical trials with oral MELOXICAM. In our study, only one type of food (a standardized continental breakfast) was evaluated; further studies are needed to assess the effects of foods with different compositions and contents on the bioavailability of MELOXICAM.

CONCLUSION

This study has demonstrated that all the pharmacokinetic parameters of both the treatments were statistically different from each other. In the fed condition the values of Cmax, AUC and Tmax increases than that of fasting which demonstrated that the extent of systemic exposure to MELOXICAM was affected in the presence of food.

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