The Pharma Innovation Journal 2022; SP-11(5): 349-354

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2022; SP-11(5): 349-354

www.thepharmajournal.com
Received: 09-03-2022
Accepted: 19-04-2022

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Pharmacokinetic evaluation of single oral dose of meloxicam with or without co-administration of andrographolide or bromelain in rats

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Abstract
The study was designed to evaluate pharmacokinetics of single oral dose of meloxicam with or without co-administration of andrographolide or bromelain in Wistar rats. The pharmacokinetic parameters of meloxicam in Group I (meloxicam @ 5 mg.kg^{-1}, *p.o.*), II (meloxicam + andrographolide @ 60 mg.kg^{-1}, *p.o*) and III (meloxicam + bromelain @ 50 mg.kg^{-1}, *p.o*) revealed no significant change in observed T_{max} of 4 h in all groups (n=8 per group). The pharmacokinetic parameters were analyzed with High Performance Liquid Chromatography and calculated by using PK Solver®, version 2.0. The time *vs* concentration of meloxicam data was found best fit in to noncompartmental model. The C_{max} of meloxicam was decreased in Groups II, III compared to Group I. The area under curve of meloxicam was decreased in Groups II and III compared to Group I. The half-life of meloxicam was decreased in Group II, while it had increased in Group III compared with Group I. In conclusion, andrographolide had no influence on the pharmacokinetics of meloxicam, while bromelain was found to interfere to result in increased half-life of meloxicam, following co-administration with single oral dose of meloxicam.

Keywords: Meloxicam, andrographolide, bromelain, interactions, HPLC, pharmacokinetic, noncompartmental model

1. Introduction
Meloxicam (MLX) is a commonly used non-steroidal anti-inflammatory drug (NSAID) in veterinary medicine, belonging to enolic acid oxicams group. It is a preferential inhibitor of cyclooxygenase-2 (COX-2), with potent analgesic and anti-inflammatory activity after oral administration in animals, with the lower dose showing selective COX-2 inhibition and at higher doses inhibiting both COX-1 and COX2 with fewer ulcerogenic properties than nonselective NSAID. Gastrointestinal (GI) adverse effects, most commonly associated with MLX therapy included abdominal pain, diarrhea, constipation, flatulence, dyspepsia, nausea and vomiting. The clinical benefits were related to inhibition of COX-2 enzyme whereas adverse effects were related to inhibition of COX-1 enzyme [1]. MLX is considered as standard NSAID which metabolized by the cytochrome P450 (CYP) subgroup of isoenzymes, possibly CYP2C9/2C8 and partly by CYP3A4 [2-3].
Andrographis paniculata popularly known as "Kalmegh", is an annual herb mainly distributed in the tropical Asian countries and been enormously used in traditional medical systems such as Ayurveda, Siddha, Unani and Chinese herbal system of medicine [4]. Andrographolide isolated from the aerial parts and roots, is the chief diterpenoid lactone and active constituent with the medicinal properties such as anti-inflammatory, antimicrobial, anti-atherosclerotic, anti-platelet aggregatory, antidiabetic, antihypertensive, anticancer, immune modulatory, hepatoprotective and bio enhancing actions [5]. The anti-inflammatory activity of AGL is believed to achieved through COX-2 inhibition, tumor necrosis factor alpha (TNF-α) and interleukin-12 (IL-12), IL-8 regression and suppression of nitric-oxide synthase (NOS) [6]. Several studies have reported that AGL could modulate expression of several CYP450 isoenzymes like CYP2C9, CYP3A4, CYP2C6/11, CYP1A1/2 and CYP3A1/2 and thus the herb preparations containing AGL would possibly result to herb drug interactions (HDIs) in combination therapy [7].
Bromelain (BRM) is the crude, aqueous extract, belonging to a group of protein digesting enzyme is obtained from the immature fruit or stem of pineapple plant: *Ananas comosus.* Although present in all parts of the pineapple plant, stems are the most common source

because they are readily available after the fruit is harvested [8]. BRM has exhibited many medicinal properties such as antiplatelet aggregation, fibrinolysis, antioxidant, anti-inflammatory activity, antihypertensive, anti oedematous, modulation of cell adhesion, cytokine induction, potentiation of antibiotics, digestive aid and debridement. The anti-inflammatory activity of BRM was thought to be due to the specific inhibitory activity of COX-2 enzyme, inhibition of prostaglandin (PG), decrease substance P, reduce the migration of leucocytes and slows the accumulation of kinin, another by product of inflammation. The most common adverse effects observed in overdose of BRM were nausea, vomiting, diarrhea, mild to severe sorts of allergies, hives, skin rashes, itching, breathing problems and heavy bleeding [9].

Natural products have been frequently administered concurrently with therapeutic drugs for the remedy of predominent ailments, and the HDIs could increase their potential [10].

The pharmacokinetics of MLX has been studied in several mammalian species, including rats, horses, cows, goats, sheep, pigs, dogs, donkeys, chickens, humans, and some exotic and wild species [11]. The same CYP enzyme isoforms being involved in the biotransformation of AGL and MLX might influence the possible interactions between two drugs on co-administration. Despite, its widespread use, there are fewer documented NSAIDs-Natural products interactions. The concomitant administration of active plant ingredients or herbal medicines may result in potential HDI that produces synergistic or additive or antagonistic effects [4].

2. Materials and Methods

2.1 Chemicals

Meloxicam, Andrographolide and Bromelain (Sigma - Aldrich, USA), Acetic acid glacial (Merck), Acetonitrile HPLC grade (Hi-media, India), Methanol HPLC grade (Hi-media, India), 70% Perchloric acid (Hi-media, India), Carboxymethylcellulose (SD fine-chem limited, India), Aqueous methyl cellulose (SD fine-chem limited, India), Normal saline and Water HPLC grade (Hi-media, India) were procured commercially and used in the study. Millipore water was employed for preparing the solutions required for various laboratory procedures.

2.2 Instrumentation

The High Performance Liquid Chromatography (HPLC) system (Shimadzu Corporation, Kyoto, Japan) consisted of LC-20AD quaternary gradient pump, a rheodyne manual injector with 20 µL loop, a SPD-20 AV UV-Vis detector. The analytical column was a 5µ C_{18} (RP-C_{18}) column (4.6 mm × 250 mm, 5 µm particle size). The mobile phase comprised of 50 parts of solution 'A' acetonitrile and 50 parts of solution 'B' 1% glacial acetic acid in the ratio of 50:50 (v/v). The mobile phase liquid was filtered through membrane filter (0.22 µm diameter) and later degassed with the help of ultrasonic cleaner (SONICA®, Soltec Soluzion Technologiche, and Italy). The flow rate was kept at 1.0 ml.min^{-1} with run time of 10 min each sample. Chromatography was performed at 40ºC with detection at 355 nm using PDA detector [12]. The room temperature was maintained at 23 ºC during the assay. A calibration curve was prepared using peak heights obtained for each concentrations of meloxicam in plasma standards. The retention time for meloxicam in this study was 7.259 minutes.

2.3 Experimental animals

Male Wistar albino rats (n= 24) of 5-6 weeks of age and weighing 160-170g were procured from the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) approved private firm. Animals were housed in Small Animal Facility, Veterinary College, Shivamogga in polypropylene cages under controlled temperature of 25 ± 3°C and relative humidity of 55 ± 5% and 12 h light/dark cycle and standard managemental practices. Animals were fed with the standard rodent chow procured commercially and provided free access to water (reverse osmosed) *ad libitum*. After one week of acclimatization, twenty-four male rats were randomly divided into 3 groups (n=8 per group). Animals were fasted overnight (water was not withheld) and weighed before dosing. MLX suspension (1% W/V; in carboxymethylcellulose) was administered through oral gavage as single dose @ 5mg.kg^{-1} in Group I, II and III, while after the administration of MLX, AGL @ 60 mg.kg^{-1} (in 0.5% W/V aqueous methyl cellulose) and BRM @ 50 mg.kg^{-1} (in normal saline) were co-administered orally in Group II and III respectively with the doses of MLX, AGL and BRM being selected as per the previous studies [13, 4, 14].

2.4 Collection of blood samples

Blood samples had been collected from saphenous or tail vein under mild anesthesia at different time intervals from the time of administration of the drugs *viz:* 0.5, 0.75, 1, 2, 4, 6, 8, 12 and 24 h. Multiple number of rats had been used for serial collection of blood in alternating time points**.** The blood samples were centrifuged @ 5500 rpm and the resultant plasma was stored at -20^0 C until quantitative analysis of MLX using HPLC was done as per the approved method [12].

2.5 Extraction of plasma samples

To 0.1 ml of plasma in 2 ml eppendorf tubes, 0.55 ml of a 0.1 M sodium dihydrogen phosphate buffer (pH 3.3) was added. Proteins have been precipitated by the addition of 50 µl of 70% perchloric acid, and tubes have been agitated in a vortex mixer for minimal of one min. To this solution, 50 µl of acetonitrile was added, and the tubes were agitated again for one min. Further, the resultant solution was centrifuged at 4500 rpm for ten minutes. After centrifugation, the clear supernatant have been separated and filtered through a 0.1 µm nylon membrane syringe filter. 20 µl of the resultant plasma sample solution was used for loading into HPLC system for the pharmacokinetic studies of MLX [13]. Various pharmacokinetic parameters have been calculated from time *vs* plasma concentration of meloxicam by applying noncompartmental model using software PK solution (Version 2.0).

2.6 Standardization and partial validation of assay

A stock solution of 100 µg.ml^{-1} of meloxicam was prepared. Five milligrams of pure MLX was dissolved in 50ml of methanol. Dilutions of the MLX stock standard were prepared in methanol to produce 0.1, 0.25, 1, 5, 10, 15, 25, 50 and 100 μg.ml^{-1} working stock solutions. Standards were aliquoted into 2 ml vials to prevent evaporation and cross contamination. All solutions were protected from light in bottles wrapped in parafilm and stored at -20ºC.

The calibration curve was constructed in the range of 0.1 to 100 µg.ml^{-1} of MLX in methanol. The standard curve was constructed by plotting the concentration of drug (X-axis) against peak area (Y-axis). The standard curve was linear in

the range of 0.1 to 100 µg.ml^{-1} with R^2 value 1. A representative chromatogram and calibration curve of MLX was depicted in Fig. 1 and Fig. 2 respectively. The limit of detection (LOD) and limit of quantification (LOQ) were determined to be 1 and 3 ng.ml^{-1} respectively. The precision and accuracy of the assay were assessed using samples at concentration 1, 10 and 25 µg.ml^{-1}. At all concentration studied, the co-efficient of variation was less than 8.0%. The percent recovery of MLX in rat plasma was 96.93%.

2.7 Statistical analysis
The MLX plasma concentration and pharmacokinetic data had been subjected to statistical analysis by applying two samples t-test assuming unequal variances.

3. Results and Discussion
The present study was taken up with the aim of studying the effects of AGL or BRM on the pharmacokinetics of meloxicam in rats. The plasma concentration of meloxicam observed at different time intervals in Group I (MLX), Group II (MLX + AGL) and Group III (MLX + BRM) treated rats. MLX was absorbed rapidly following oral administration with a mean plasma concentration 1.150 ± 0.027 µg.ml^{-1}, 1.072 ± 0.03 µg.ml^{-1} and 0.996 ± 0.029 µg.ml^{-1} at 30 min in Group I (MLX), Group II (MLX + AGL) and Group III (MLX + BRM) treated animals respectively. The peak plasma MLX concentration (C_{max}) 6.370 ± 0.161 µg.ml^{-1}, 5.317 ± 0.107 µg.ml^{-1} and 5.288 ± 0.151 µg.ml^{-1} was achieved (T_{max}) at 4 h in Group I (MLX), Group II (MLX + AGL) and Group III (MLX + BRM) treated animals respectively. The pharmacokinetic parameters of rats belonging to three groups were calculated. The comparative mean pharmacokinetic variables are represented in Table 1.

Table 1: Mean ± S.E.M values of pharmacokinetic parameters of meloxicam in different groups of experimental rats

Parameters	Unit	Group I (MLX)	Group II (MLX + AGL)	Group III (MLX + BRM)
$t_{1/2}$	h	11.87 ± 0.666	10.66 ± 0.898	14.71 ± 0.862
AUC_{0-t}	µg.h^{-1}.ml^{-1}	70.81 ± 1.061	51.51 ± 1.109	59.09 ± 2.318
$AUC_{0-\infty}$	µg.h^{-1}.ml^{-1}	96.22 ± 4.859	66.83 ± 2.495	95.62 ± 10.746
MRT	h	17.48 ± 1.158	15.79 ± 0.686	24.26 ± 3.500
C_{max}	µg.ml^{-1}	6.37 ± 0.161	5.31 ± 0.107	5.28 ± 0.151
T_{max}	h	4.00 ± 0.000	4.00 ± 0.000	4.00 ± 0.000

In the current study, an attempt was made to study the possible interference of AGL or BRM co-administration on the pharmacokinetics of MLX by estimating its concentration in rats. The pharmacokinetic analysis of MLX with or without co-administration of AGL or BRM in the present study revealed that the time *vs* concentration of MLX data was found best fit in to noncompartmental model of pharmacokinetics. As AGL has been suggested to inhibit the activity of CYP3A4 and CYP2C9 [15] and MLX was specifically metabolized by CYP3A4 and CYP2C9 in liver, it was speculated that AGL might increase the plasma concentration of MLX by inhibiting CYP3A4 or CYP2C9 mediated metabolism. However, in the present study, it was observed that the pharmacokinetic parameters *viz:* C_{max} and AUC values of MLX were decreased following co-administration with AGL or BRM. One of the reasons which could be attributed for the findings in the study, was that MLX undergoes extensive metabolism, primarily by cytochrome P450 isoenzyme CYP2C9 and to a minor extent by CYP3A4 as per the reports of [3]. The findings in the present study are variable from the pharmacokinetic study of [4], who reported a considerable increase in the C_{max}, T_{max}, mean residence time (MRT) and $t_{½}$ of MLX on co-administration with AGL. The findings of present study are in accordance with [16], who reported that C_{max} and Vd were significantly decreased following co-administration of AGL with MLX after single intramuscular administration in rats. In another study conducted by [17], it was observed that licorice, though being a CYP2C9 and CYP3A4 inhibitor, did not significantly alter the important pharmacokinetic parameters like $t_{1/2}\beta$ and CL of MLX. [18] also had reported significant decrease in C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of 6-methoxy-2-naphthylacetic acid (6-MNA) after co-administration with pure AGL and standardized APE. [19] Observed that the co-administration of AGL with Naproxen (NP) significantly ($p<0.05$) decreased the C_{max}, T_{max}, AUC_{0-t}, $t_{1/2}$, MRT_{0-t} and CL and increased the $AUC_{0-\infty}$, $MRT_{0-\infty}$ and Vd of NP. The C_{max}, AUC and $t_{1/2}$ were significantly decreased and Vd and CL of Etoricoxib (ETO) was increased after co-administration with pure AGL and APE [20]. In the present study, was observed that neither AGL nor BRM had any effect on T_{max} of MLX. Additionally, the $t_{1/2}$ of MLX was decreased on co-administration with AGL, while with co-administration of BRM the $t_{1/2}$ of MLX was slightly increased. This finding of reduced half-life of MLX with AGL co-administered group was in contrast to the pharmacokinetic study of [4] who reported a considerable increase in the C_{max}, the time taken to reach C_{max} (T_{max}), mean residence time (MRT) and $t_{½}$ of MLX upon co-administration with AGL. [21] reported that the C_{max} of MLX was non significantly higher in MLX and licorice pretreated group than that of the value obtained in the MLX alone group. There were no significant differences in $t_{1/2}$, AUC_{0-t}, MRT, Vdss and Cl_B of MLX alone and MLX in licorice pretreated group. The results obtained suggested that there has been no pharmacokinetic interaction between licorice and MLX in birds when licorice was given 60 min prior to the administration of MLX as single dose. The findings of the present study are in accordance with [22] who reported that the pineapple juice, which also contain bromelain, reduced the CL and AUC of celecoxib by 45% without altering the $t_{1/2}$. The difference in the pharmacokinetic parameters of the present study may be attributed to the findings of [23] who observed that CYP1A2 catalyzed meloxicam bio activation, and it is the methyl group of drugs which would possibly effect enzyme affinity for the drugs, thus might alter isozymes which catalyzed the metabolic pathways. Another factor which could be the reason for AGL not having any effect on the AUC and C_{max} of MLX in the present study, might be due to the poor oral bioavailability of AGL because of its rapid biotransformation and efflux by P-glycoprotein. Absolute bioavailability of *A. paniculata* was 2.67%. In the duodenum and jejunum, *A. paniculata* was rapidly metabolized to a sulfonate, recognized as 14-deoxy-12-sulfo- andrographolide. *A. paniculata* was also rapidly

metabolized through liver S9 fraction and in clean perfusates collected from duodenum and jejunum [24]. The factor that the commercially available bromelain is that of stem origin and might differ in the composition of proteases from that of fruit BRM, also need to be considered, became in the present study commercial BRM was used for MLX pharmacokinetic interactions and safety studies. Though there have been reports that BRM increasing the absorption of amoxicillin and tetracycline, chemotherapy drugs *viz*., 5-fluorouracil and vincristine and ACE inhibitors *viz.*, captopril and lisinopril [9, 25]. In the present study it was observed that BRM increased the half-life of MLX, with no effect on the bioavailability as suggested by AUC values. The reason that could be attributed was due to its proteolytic action, and that BRM was absorbed directly when administered orally and had better bioavailability [26]. Further, BRM strongly inhibited CYP2C9 activity and thereby would have inhibited the CYP2C9 mediated drug metabolism in accordance with [27].

However, in order to evaluate the mechanisms involved in interactions associated with variable pharmacokinetic parameters of MLX, further studies may be warranted with prior administration of AGL or BRM hours before administration of MLX at different time intervals.

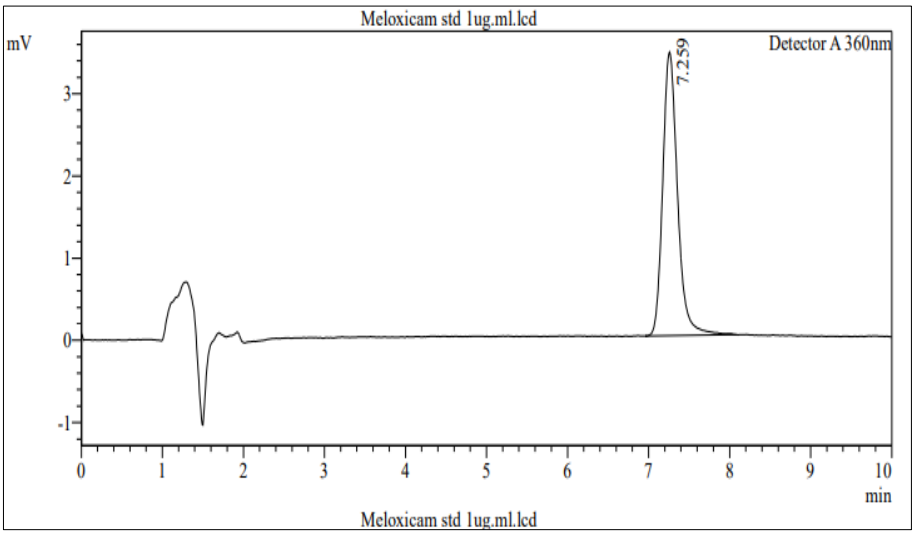

Fig 1: A representative chromatogram of meloxicam

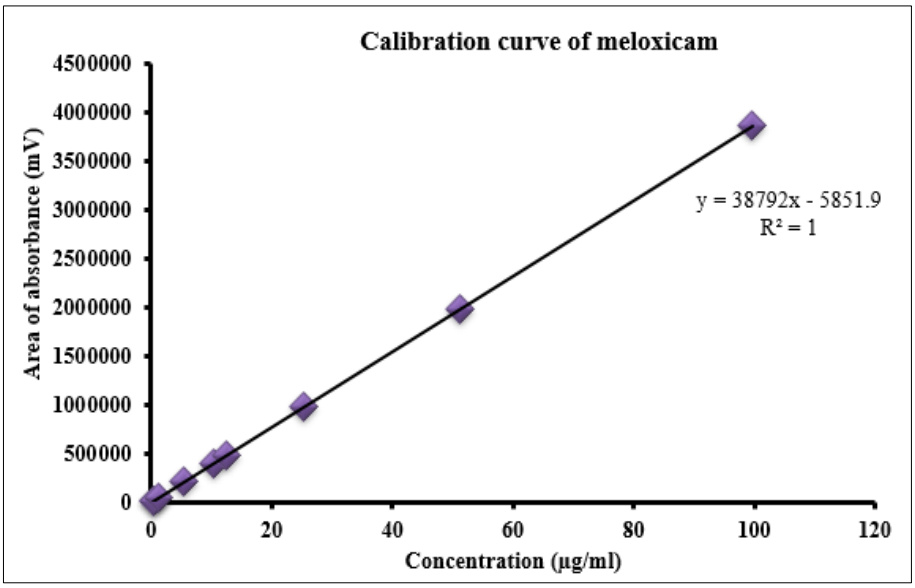

Fig 2: The calibration curve of meloxicam assessed by HPLC

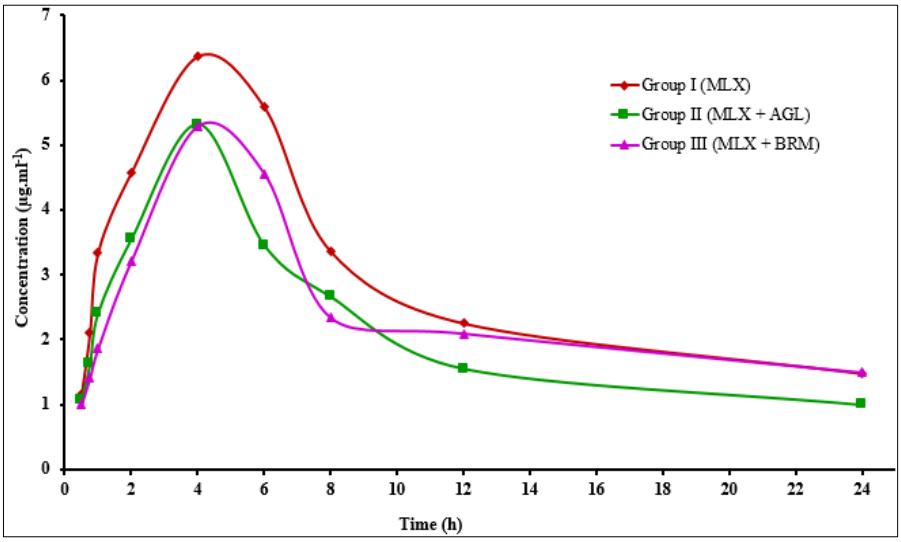

Fig 3: Mean ± S.E.M plasma concentration-time profile of meloxicam in experimental rats of Group I (MLX), Group II (MLX + AGL) and Group III (MLX + BRM)

4. Conclusion

In the present study, it was concluded that AGL after co-administration with single dose of MLX, had no major influence on the oral pharmacokinetics of MLX, while BRM had increased the half-life of MLX on co-administration. AGL was found to be relatively safer to be used with MLX, though the extent of enzyme inhibition and effect on the bioavailability may require further studies. Thus, further studies may be warranted to elucidate the mechanism on influence of andrographolide or bromelain on pharmacokinetics of meloxicam, by taking in to consideration of the factors *viz*: route of administration, vehicle used for oral administration, formulation, dose and administering of AGL or BRM at different intervals of time before administering meloxicam.

5. Acknowledgment

The study was part of the research work carried out by the first author during her M.V.Sc. programme. The National Talent Scholarship grant provided by Indian Council of Agricultural Research (ICAR) to the first author and post graduate student grants sanctioned. by Karnataka Veterinary Animal and Fisheries Sciences University (KVAFSU), Bidar is hereby acknowledged.

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