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Research paper

Pharmacokinetics of meloxicam administered as regular and fast dissolving formulations to the rat: Influence of gastrointestinal dysfunction on the relative bioavailability of two formulations

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ABSTRACT

It is believed that acute pain suppresses *nervus vagus*, thereby, influencing gastrointestinal secretion and motility, which are the two factors that are necessary for disintegration and dissolution of solid dosage forms. We studied the pharmacokinetics of meloxicam and the effect of vagal suppression on the oral bioavailability and bioequivalence using a marketed (Brand) and a fast dissolving (FD) formulation. In simulated gastric juice, FD was disintegrated in 30 s and released 30% of its meloxicam in 15 min and 60% in 2 h. Brand was disintegrated in 4.5 min with a dissolution rate of 5.6% in 30 min that stayed plateau for the 2 h experiment time. To suppress the vagus nerve, intraperitoneal injection of 20 mg/kg propantheline 1 and 2 h before meloxicam administration was used. Meloxicam (0.9 mg/kg) was administered to both control and vagally suppressed rats i.v. (n = 4–6/group) as well as orally in a paired random fashion as broken pieces of Brand or FD tablets (n = 7/ group). Serial (0–48 h) blood samples were collected for pharmacokinetic and bioavailability studies. Relative bioavailability was measured according to a method in use for bioequivalence assessments. Systemic pharmacokinetics of meloxicam was not affected by vagal suppression. Absolute bioavailability of meloxicam, based on 0–48 h measurement, was >0.68 regardless of the type of formulation and treatment. Vagal suppression, however, significantly reduced AUC_{0-24} ($\mu g\,h\,mL^{-1}$) for Brand (control, 58.8 ± 22.0 vs treated, 22.1 ± 9.7) but not for FD (control, 63.5 ± 17.9 vs treated, 64.6 ± 8.9) indicating a reduced absorption rate for the former. The peak time for Brand was also significantly delayed by over 20 h for Brand and not for FD. Relative bioavailability was confirmed between FD and Brand that were in control but not in the vagally suppressed rats, indicating a disease-dependent bioequivalence. The effect of vagal suppression on the drug absorption rate can be obviated if the disintegration and dissolution become independent of gastrointestinal motility and secretion.

1. Introduction

It is known that pain or its associated trauma impairs oral absorption of drugs [1–3] due, likely, to decreased gastric fluid secretion and motility [4–6]. These physiological changes have direct impact on disintegration and dissolution rate of oral formulations, hence, the rate of drug absorption. Since there appears to be a link between the plasma analgesic concentration and analgesia [7–8], a reduced rate of absorption [1–3] is expected to result in a delayed onset of action. Thus, a pain-associated delayed absorption is likely to be more pronounced for poorly soluble drugs.

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the enolic class that is more selective in inhibiting cyclooxygenase (COX)-2 than COX-1 [9]. It is a potent anti-inflammatory agent with favorable gastrointestinal safety profile [10–15]. Although used mainly as an antirheumatic, the drug is also an effective analgesic for various conditions [16–20]. Meloxicam possesses zwitterionic property with pK_a values of 1.09 and 4.18 and is practically insoluble under acidic conditions [21]. Under healthy conditions, oral doses of meloxicam administered to the rat [22–24], dog [22] and human [22,25–27] yielded peak plasma concentrations in 5–11 h. The peak time is expected to be much longer under pain condition [1,3]. It is, therefore, reasonable to investigate approaches that may facilitate oral absorption of meloxicam for treating acute pain. Numerous approaches have been taken to improve solubility and bioavailability of NSAIDs including meloxicam [28–30]. In addition, the effect of, in vitro improvement of meloxicam dissolution on the drug absorption has been studied in humans but under healthy conditions [29]. Indeed, there is no evidence of faster onset of analgesia following the administration of any product containing the same active ingredient regardless of the

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formulation, e.g., soft gelatin capsule, rapidly disintegrating tablets. Hence, the absorption profile of these formulations in patients with pain remains to be examined.

The reported delayed absorption during pain episodes is suggested to be due to a suppression of the *vagus nerve*. We have tested the absorption profile of ibuprofen in both humans who experienced pain of post-dental surgery [1,3] and whose rats *vagus nerve* was suppressed with propantheline [3]. In both species, significant delay in absorption was noticed following administration of regular-release ibuprofen formulations but not after a formulation as its disintegration and dissolution were less dependent on gastric motility and secretion [3]. In addition, the study [3] provided additional evidence that the rat is a suitable model to study the gastrointestinal absorption of drugs [31,32].

Physical–chemical properties of meloxicam are different from those of ibuprofen. Ibuprofen has limited solubility (in stomach 58 μg/mL, pH 1.2) while meloxicam, a zwitterionic drug, is practically insoluble in stomach [0.86 μg/mL, pH 1.0] [21,33]; under the alkaline condition of the intestine, ibuprofen forms a salt while meloxicam turns to an anionic form. It was, therefore, of interest to investigate meloxicam absorption pattern under vagal suppression.

In this study, we have attempted to test whether meloxicam absorption is also delayed by reduced gastric motility and secretion, and if a formulation with enhanced disintegration and dissolution is exempted from the erratic and incomplete absorption.

The relative bioavailability and bioequivalence of products is usually carried out in healthy volunteers with the assumption that the parity observed between two products of the same drug under healthy conditions can be extrapolated to the disease conditions. Herein, we report the result of our study on the effect of altered pathophysiology on the relative bioavailability of two meloxicam products.

2. Materials and methods

Meloxicam powder was purchased form Unichem Laboratories Limited (Mumbai, India) and Piroxicam was obtained from Sigma Chemical Co. (St. Louis, MO, USA). The fast dissolving tablets (FD) were provided by EquiTech Corporation (Edmonton, AB, Canada). Mobicox (Brand) marketed by Boehringer Ingelheim (Burlington, ON, Canada) was purchased from the in-patient pharmacy of University Hospital (Edmonton, AB, Canada) and used as the commercially available product (Brand). All other chemicals and solvents were of HPLC grade and purchased from Caledon Laboratories or Sigma Chemical Co.

2.1. Disintegration and dissolution

Disintegration tests were carried out on intact tablets in water at 37 ± 2 °C using the USP basket-rack assembly [34] and the Manesty Tablet Disintegration Test Unit (Manesty Machines LTD, Liverpool, England).

Dissolution tests were conducted on both formulations using United State Pharmacopeia (USP) Apparatus II (Erweka GmbH, Heusenstamn, Germany) [34]. Tablets were placed in 900 mL of USP simulated gastric fluid pH 1.2 (NaCl 2.0 g and HCl 7.0 mL per liter, without pepsin, and the pH was adjusted using 1.0 N NaOH), at 50 rpm and 37 ± 0.5 °C. Aliquots of the dissolution medium (3 mL) were withdrawn at 0, 5, 15, 30, 60, 90 and 120 min and replaced with equivalent volumes of preheated fresh medium. The collected samples were filtered (10 μm, full flow-type filters, VanKel, Cary, NC, USA) and the filtrate was assayed for meloxicam at 364 nm using a UV spectrophotometer (Milton Roy Spectronic 3000 Array, Cambridge, MA, USA).

The correlation between UV absorbance and meloxicam concentration in standard solutions for dissolution test was found to be linear within the examined range of 0.78–25 μg/mL with a correlation coefficient of 0.9999. The intra-day and inter-day variation of this assay were 5.6% and 8.8%, respectively.

2.2. Pharmacokinetics

The protocol for animal use was approved by the Health Science Animal Policies and welfare committee of The University of Alberta. All experiments were performed on adult male Sprague–Dawley rats (230–250 g).

One day prior to the administration of meloxicam formulations, rats were anesthetized using halothane. Silastic catheters (0.58 mm i.d.× 0.965 mm o.d. Clay Adams, Parsippany, NJ, USA) were implanted into the right jugular vein for intravenous dosing and blood sample collection. Animals were made to recover and were fasted overnight until 4 h post-meloxicam dose with water being available ad libitum.

Vagal suppression (treatment) was achieved by intraperitoneal injection of 20 mg/kg of propantheline solution (20 mg/mL in saline) 2 and 1 h prior to the meloxicam dosing. The treatment has been reported to be effective in delaying the absorption of ibuprofen (3).

Three formulations, all as single dose of 0.9 mg/kg meloxicam, were tested following the administration to both healthy and treated rats. The formulations consisted of 1) a solution of the drug in 5 mM NaOH for i.v. bolus injection (injected over 1 min and catheter was flushed with 0.5 ml saline afterward) (n = 4–6/group); 2) Brand (n = 7/group) and 3) FD (n = 7/ group) tablets. Both Brand and FD were gently broken into small pieces, which would be suitable for oral administration, followed by 0.5 mL tap water. Oral delivery was performed using a flexible plastic tube attached to a stainless steel gavage.

For the assessment of the relative bioavailability, we paired individual rats and randomly administered to each either Brand or FD.

Blood samples (∼0.2 mL) were drawn from the jugular vein at 0.0, 0.16, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 4.0, 6.0, 12.0, 24.0 and 48.0 h post-meloxicam dose and transferred to heparinated tube. The plasma was separated and kept at −20 °C until analysis. After each blood sampling, the catheter was flushed with 0.2 mL heparinated saline (50 U/mL).

All assessments were made based on serial samples collected from pre-dose to 48 h post-dose period except for FD treated group that due to technical problems 48 h samples were not either collected or analyzed. For the latter group, therefore, the slope of the terminal phase was not calculated.

2.3. Meloxicam assay

A reversed phase HPLC method [35] with some modifications in the mobile phase was used to determine the concentrations of meloxicam in plasma. Briefly, stock solutions were prepared by dissolving 100 μg/mL meloxicam or piroxicam (internal standard) in methanol. Aliquots of 100 μL of blank rat plasma were spiked with various concentrations of meloxicam stock solutions to make the final concentrations of 0.1–100 μg/mL. Fifty microliters of 10 μg/mL piroxicam solution, 200 μL of 0.6 M H_2SO_4, and 2 mL of chloroform were added to each tube. The tubes were vortex-mixed (3 min) and centrifuged for 5 min. The lower organic layer was removed and evaporated to dryness. The residue was dissolved in 150 μL of mobile phase and an aliquot of 100 μL was injected into HPLC. The minimum detectable concentration of meloxicam in plasma was 0.1 μg/mL with a coefficient of variation <5.9 and a relative standard deviation of <0.43%.

2.4. Data treatment and statistical analysis

WinNonlin version 4.1 (Pharsigth Corporation, CA, USA) was used to analyze the generated data. The non-compartmental approach was applied to calculate pharmacokinetic indices. The area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal rule from 0 to the last measured plasma concentration (C_{last}). The terminal elimination rate constant, β, was estimated using the linear least square regression of the log-linear phase of the concentration-time curve considering the last three experimental points. $AUC_{0-\infty}$ was calculated by adding C_{last}/β to AUC_{0-t}. The total body clearance, Cl_{TB}, was determined by dividing the i.v. dose by $AUC_{i.v.}$ The steady state volume of distribution, V_{dss}, was calculated from: V_{dss} = dose.MRT/ $AUC_{i.v.}$, where MRT = $AUMC_{i.v.}/AUC_{i.v.}$, is the mean residence time and $AUMC_{i.v.}$ is the area under the first moment curve after i.v. administration. The highest observed concentration and corresponding sampling time point were defined as the peak plasma concentration (C_{max}) and time-to-peak concentration (T_{max}), respectively. The above indices were determined for each individual animal and their mean was calculated. Bioavailability (F) was calculated from $AUC_{p.o}/AUC_{i.v.}$.

To investigate the pharmacokinetic pattern of meloxicam disposition, the data were subjected to compartmental analysis. Plasma concentrations were fit to one- and two-compartment models. First-order absorption and lag times were also evaluated in the fitting of oral data. Due to significant absorption noted at early sampling time points, lag times were fixed at zero in the models. Model discrimination was determined using Akaike's information criterion (AIC) and goodness of fit (r^2).

All the means are expressed with their standard deviation. Statistical significance between the means of groups was examined using the ANOVA followed by Duncan New Multiple Range test using SAS statistical program (PC version 6.12) and it was set at $p < 0.05$.

Analysis of data for the relative bioavailability was carried out according to the method recommended for bioequivalence assessment in the Canadian Guidance for Industry [36]. We compared AUC_{0-24} and C_{max} values using 90% confidence interval for ln-transformed data at 80–125% range. Comparisons were made between the products following administration to both control and vagally suppressed rats using paired animals.

3. Results

3.1. Disintegration and dissolution

The dissolution profiles of meloxicam from Brand and FD are depicted in Fig. 1. In the dissolution medium, FD disintegrated in 30 s, and 30% dissolved in 15 min and 60% in 2 h. Brand was disintegrated in 4.5 min and reached its maximum meloxicam release of 5.6% at 30 min.

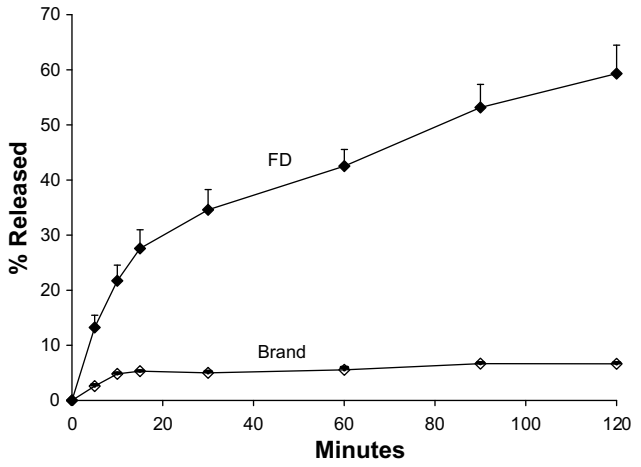

Fig. 1. Dissolution profiles of meloxicam from Brand and FD tablets in simulated gastric fluid at pH 1.2 and 37 °C (n = 3/group).

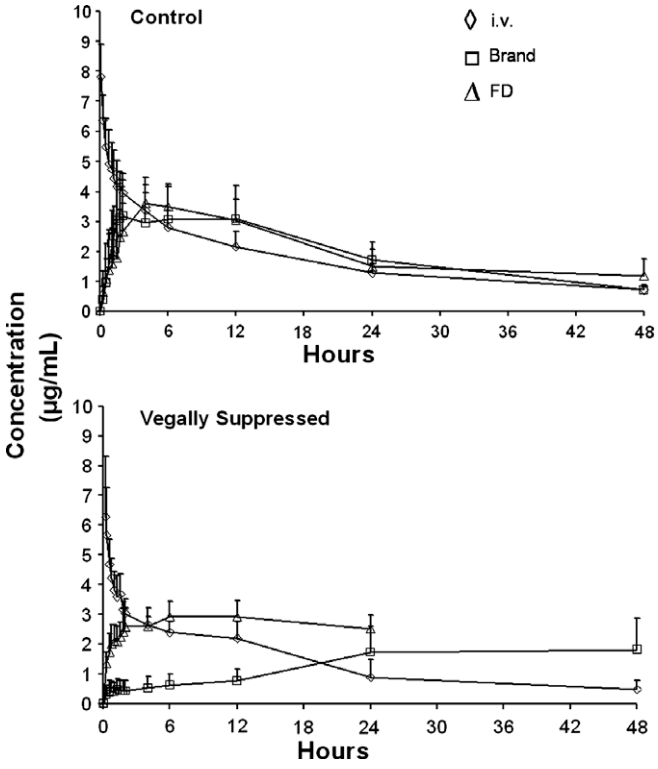

Fig. 2. Mean (±SD) plasma concentration–time profiles of meloxicam after administration of 0.9 mg/kg of an i.v. solution, oral Brand and oral FD to control (top) and vagally suppressed (bottom) rats. Data represent mean ± SD; n = 7/oral groups; n = 4/i.v. control; n = 4/i.v. treated.

3.2. Pharmacokinetics and absolute bioavailability study

3.2.1. Control rats

Following i.v. and p.o. doses to control rats (Fig. 2), meloxicam pharmacokinetics were best described by a two-compartment open model and a one-compartment open model with first order input, respectively. After i.v. administration, the rapid decline in plasma concentration was followed by a slow phase with a $t_{1/2}$ of 23.4 ± 2.3 h (Table 1).

Following oral doses of both Brand and FD to control rats, a rapid absorption phase was observed that brought the drug concentration to a mean of approximately 3.5 µg/mL in 2 h. Then the plasma concentration became rather flat for 12 h followed by a slow decline with a mean terminal t/12 value of 19 h (Fig. 2, Table 1). There was no significant difference between meloxicam AUC values following oral administration of Brand and FD.

Vagal suppression had no effect on the pharmacokinetics of meloxicam following i.v. doses.

Both Brand and FD exhibited complete bioavailability in control rats (Table 1).

3.2.2. Vagally suppressed rats

The propantheline treatment significantly reduced the rate of appearance of meloxicam in plasma from Brand so that the AUC_{0-24} of the formulation was only 43% of that from the i.v. dose (Table 1). T_{max} was significantly prolonged by vagal suppression for

Table 1
Pharmacokinetic indices of meloxicam after i.v. and oral administration of 0.9 mg/kg in control and vagally suppressed (treated) rats

	i.v.		Brand oral		FD oral	
	Control	Treated	Control	Treated	Control	Treated
C_{max}, μg/mL	nd	nd	3.35 + 1.23	1.78 ± 0.87*	3.80 ± 0.62	3.16 ± 0.42†
T_{max}, h	nd	nd	5.61 ± 4.89	30.9 ± 11.7*	5.14 ± 3.24	12.3 ± 8.8 †
AUC_{0-24}, μg h mL^{-1}	58.8 ± 10.5	51.0 ± 10.1	58.8 ± 22.0	22.1 ± 9.7*	63.5 ± 17.9	64.6 ± 8.9†
AUC_{0-48}, μg h mL^{-1}	83.3 ± 15.4	67.9 ± 19.8	86.3 ± 7.3	69.7 ± 32.3	113.6 ± 17.2	nd
$AUC_{0-\infty}$, μg h mL^{-1}	107.1 ± 18.7	81.0 ± .4	105.6 ± 7.0	nd	nd	nd
$t_{1/2}$, h	23.4 ± 2.3	17.7 ± 3.8	19.0 ± 6.4	nd	nd	nd
V_{dss}, L/kg	0.29 ± 0.07	0.30 ± 0.07	nd	nd	nd	nd
Cl_{TB}, L/h/kg	0.009 ± 0.002	0.012 ± 0.005	nd	nd	nd	nd
AUMC, h^2 μg/mL	3264 ± 626	1983 ± 1189	3030 ± 1005	nd	nd	nd
MRT, h	30.5 ± 2.9	22.3 ± 9.7	29.2 ± 8.9	nd	nd	nd
F_{24}			1.0	0.38	1.08	1.1
F_{48}			1.04	0.84	1.36	nd
F_{∞}			0.99	nd	nd	nd

Data represent mean ± SD; n = 7/oral groups; n = 4 /i.v. control; n = 4/i.v. treated; F, absolute bioavailability measured from 0 to 24 h (24), from 0 to 48 h (48) and from 0 to ∞ (∞); nd, not determined; *significantly different from Brand Control, †significantly different from Brand Treated ($p < 0.05$).

Table 2
Bioequivalence data based on paired animal design

		Controls		Vagally suppressed	
		Brand	FD	Brand	FD
C_{max}	Mean ± SD	3.70 ± 1.1	3.80 ± 0.6	1.78 ± 0.9	3.16 ± 0.4*
	ln-transformed	1.26 ± 0.29	1.32 ± 0.20	0.49 ± 0.42	1.14 ± 0.13*
	90%CI	91.4 – 124.0		144.2 – 254.2†	
AUC_{0-24}	Mean ± SD	63.1 ± 19.8	63.1 ± 16.4	22.1 ± 9.7	64.6 ± 8.9*
	ln-transformed	4.11 ± 0.30	4.08 ± 0.28	3.0 ± 0.52	4.2 ± 0.11*
	90%CI	89.6 – 114.7		250.0 – 398.8†	

N = 7/group; *significantly different from Brand; †outside 80–125 for ln-transformed means.

Brand (Control, 5.61 ± 4.89 vs treated, 30.9 ± 11.7 h). Meloxicam absorption from FD, however, was rapid and complete with comparable AUC_{0-24} to that of the i.v. dose and a mean T_{max} value that, although numerically longer, was not significantly prolonged as compared with that observed in control rats (Control, 5.14 ± 3.24 vs Treated, 12.3 ± 8.8.4 h) (Fig. 2, Table 1).

In the treated animals, AUC_{0-24} was significantly less and T_{max} significantly longer for Brand as compared with FD (Table 1).

3.2.3. Relative bioavailability

In control rats, Brand and FD were comparable in terms of C_{max} and AUC_{0-24} values (Table 2). In the vagally suppressed rats, on the other hand, the relative bioavailability was not confirmed between the two products based on both C_{max} and AUC_{0-24} (Table 2).

3. Discussion

Pharmacokinetics of meloxicam in the rat following i.v. doses is only known based on the measurement of labeled drug [22]. Our data, however, agree with the previously reported observations that the drug has a very low systemic clearance (Table 1) and is eliminated with a long $t_{1/2}$ (~23 h). Interestingly, in addition to the rat being an acknowledged model for drug absorption in general [3,31,32], meloxicam appears to be a rare drug that its pharmacokinetics in rats (Table 1) are remarkably similar to those reported for humans [22–27]; CL, 0.006-0.009 in humans vs 0.009 L/h/kg in rats; $t_{1/2}$, 17–23 in humans vs 19–23 h in rats; Vd, 0.14–0.35 in humans vs 0.27 L/kg in rats. Recently, Aguilar-Mariscal et al have reported a shorter $t_{1/2}$ (9 h) for meloxicam in the rat [23]. Their value, however, may be an underestimation as their estimation has been based on a sampling schedule that ended in 24 h.

The absorption pattern of meloxicam administered as pure powder to control rats is reported to indicate a rise in plasma that reaches its peak as late as 12 h [24]. Our data suggest a peak time of approximately 5 h following administration of both FD and Brand to control rats (Fig. 2, Table 1). The absorption phase appears to be prolonged, so that the early rise in concentration is followed by a flat pattern that continues for 12 h post-dose (Fig. 2). We do not have an unequivocal explanation for the flat absorption rate, although we noticed second peaks in the individual plasma-concentration-time curve following all administrations that are masked by data pooling. This may indicate, at least in part, a role for enterohepatic recirculation as has been suggested by 'Busch et al for humans [37].

When the gastrointestinal motility and fluid secretion are suppressed, meloxicam absorption from Brand becomes significantly slower as compared to that observed in the control rats Fig. 2. Indeed, the sharp rise in concentration detected in the control animals with Brand formulation is replaced by a slow rise in the treated rats that does not peak until 23 h post-dose. This demonstrates the significant role of the gastrointestinal motility and fluid that are both diminished in response to vagal suppression. In contrast to Brand, absorption of meloxicam from FD was not influenced by vagal suppression. This, we suggest, was due to the fact that upon exposure to the water given following oral administration, the solid dosage form is rapidly disintegrated and meloxicam released from FD and becomes available for absorption. This notion is supported by our dissolution data (Fig. 1). The composition of FD formulation is such that the released meloxicam remains in the dissolved form even if the drug is kept in the gastric fluid.

The rapid disintegration of the formulation and quick dissolution of meloxicam following oral administration of FD to vagally suppressed rats appear to render disintegration and dissolution processes independent of the physical motion provided by the gastrointestinal motility and the fluid in the tract. The difference between the absorption patterns of the two examined formulations supports the notion that the slow and erratic absorption of drugs

in vagally suppressed rats [3] (Fig. 2) and during acute pain experienced by humans [1,3] are, indeed, formulation-dependent; i.e., a direct result of depressed dissolution of the drug from tablets or disintegration of soft or hard shell capsules. This occurs under the above mentioned experimental or disease conditions and not in the normal healthy subjects; i.e., the observation made in healthy state may not reflect that made under disease conditions.

The rapid rise in concentration following oral administration to healthy rats may suggest that meloxicam absorption commences from stomach. Interestingly, when the dissolved meloxicam is available for absorption, e.g., following FD, a rapid rise in concentration is again observed despite the suppression of the *nervus vagus* (Fig. 2). The possibility of enhanced gastric emptying in response to the rapid disintegration cannot be equivocally ruled out as the major site of absorption for most drugs is the intestine. Delayed gastric emptying has been identified as a plausible explanation for therapeutic failure of oral analgesic therapy also during migraine attacks [4–6]. Indeed, concomitant administration of analgesics or triptans with the gastric emptying stimulant metoclopramide has been proposed [38]. Interestingly, triptans, the present drugs of choice in the treatment of migraine, also appear to prolong gastric emptying time [39] rendering their oral route of administration problematic.

The observed pronounced effect of gastrointestinal dysfunction on the absorption of drugs prompted us to examine the implication of the effect on the comparative bioavailability of meloxicam. We wanted to assess if the relative bioavailability of the two meloxicam products administered to our animal model of gastric dysfunction can be predicted from data generated under healthy conditions. We carried out an experiment in which instead of the cross-over design, that is usually used in bioequivalence studies, we paired rats receiving different formulations in a random fashion. The observation was interesting and important as despite equivalence of the bioavailability between Brand and FD in the healthy rats, we found significant differences in relative bioavailability between the two products in the vagally suppressed rats (Table 2). The observed condition-dependent results are potentially important as the experimentally induced gastrointestinal dysfunction in our rats mimics the condition of humans in pain [1–3]. This raises the possibility of pharmacokinetic equivalence in the healthy condition but inequivalence during the disease condition. In other words, the relative bioavailability parameters of the products estimated under healthy conditions did not predict the significant differences observed under the experimentally altered conditions. This possibility may exist in conditions when the disease influences the release properties of the formulations.

Gastrointestinal dysfunction alters absorption pattern of meloxicam that can be normalized if absorption is rendered independent of disintegration and dissolution. Our preliminary observation made in the rat suggests that if the site of absorption is affected by pathophysiological alterations, the bioequivalence observed under healthy conditions may not necessarily reflect that expected under disease conditions.

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