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Research paper

Improved absorption of meloxicam via salt formation with ethanolamines

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Abstract

The present study aimed to investigate the effect of ethanolamine salt formation on the dissolution as well as in vivo pharmacokinetics of meloxicam. Three meloxicam-ethanolamine salts were prepared and their in vitro dissolution profiles were examined at pH 1.2 and 6.8. The pharmacokinetic profiles of meloxicam following an oral administration of meloxicam or its ethanolamine salts were also evaluated in rats. The dissolution rates of meloxicam and its ethanolamine salts were similarly slow at pH 1.2, however, at pH 6.8, ethanolamine salt formation significantly enhanced the dissolution rate of meloxicam. Meloxicam diethanolamine salt exhibited the highest dissolution rate at pH 6.8. The faster dissolution of meloxicam via ethanolamine salt formation at pH 6.8 appeared to be correlated well with more rapid absorption of meloxicam in rats. T_{max} of meloxicam was significantly ($p < 0.05$) shortened following an oral administration of ethanolamine salts. Furthermore, ethanolamine salts exhibited a trend toward the increase in AUC_{0-4} (initial exposure), while the overall exposure (AUC_{0-24}) was similar between meloxicam and its salts. In conclusion, the ethanolamine salts of meloxicam, particularly diethanolamine salt of meloxicam, facilitated the rapid absorption of meloxicam while maintaining the prolonged exposure and may be used for the earlier onset of action for meloxicam.

Keywords: Meloxicam; Ethanolamine salts; Pharmacokinetics; Dissolution rate; Rats

1. Introduction

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) to preferentially inhibit the cyclooxygenase-2 (COX-2) over COX-1 [1]. It is highly effective against various arthritic conditions and inflammations [2], but confers superior gastrointestinal tolerability with a good overall safety profile [3]. While meloxicam is known to be almost completely absorbed after oral administration, the rate of absorption is relatively slow [4–7]. Previous pharmacokinetic studies have shown that meloxicam has prolonged absorption with T_{max} of longer than 5-h, indicating the slow absorption of meloxicam after an oral administration [4–7]. In comparison, intramuscular injection of meloxicam reached the maximum plasma concentration (C_{max}) within 1.5 h of administration and 90% of the C_{max} within 30–50 min over the dose range of 5–30 mg in humans [8,9]. Therefore, meloxicam may initially be administered intramuscularly to shorten the onset of action, since rapid pain relief is required in case of acute and painful exacerbations of rheumatoid arthritis and sciatica. However, due to the potential local tissue irritation and necrosis, intramuscular administration of meloxicam was not recommended for the chronic use and should be switched to oral formulation as soon as the rapid onset of action is achieved [9]. Therefore, it should be more desirable to develop an oral formulation of meloxicam with faster onset of action while maintaining the prolonged exposure.

Meloxicam is a practically water-insoluble drug at physiological pH and has a zwitterionic property with two pK_a values ($pK_{a_1} = 1.09, pK_{a_2} = 4.18$) (Fig. 1) [10].

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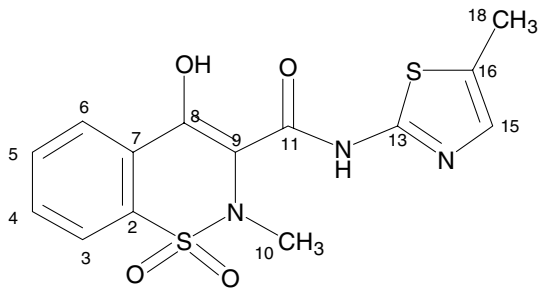

Fig. 1. Structure of meloxicam (enol) with atomic numbering.

A zwitterionic drug possesses a large intramolecular multipole moment due to its multiplicity of oppositely charged groups. Consequently, most of these drugs show low solubility in polar and nonpolar media [11,12]. Meloxicam can be classified as a Class II compound having a low solubility and high permeability according to the Biopharmaceutics Classification System [13]. The pharmacokinetic profiles of Class II drugs can be altered by increasing their aqueous solubility. Therefore, several attempts have been made to improve the solubility of meloxicam by using co-solvents [14–16] as well as by using techniques other than the use of co-solvents [17,18]. Although those attempts appeared to be successful to increase the solubility as well as in-vitro dissolution rate of meloxicam, there should be further clarification on the in vivo performance of those formulations to evaluate the in vivo relevance of in vitro findings.

The salt formation of zwitterionic drugs may sometimes improve the physical and chemical properties, resulting in higher solubility and enhanced biological membrane permeability. Therefore, the present study aimed to prepare meloxicam-ethanolamine salts with improved physicochemical properties and investigate the effect of salt formations on the pharmacokinetics of meloxicam.

2. Materials and methods

2.1. Materials

Meloxicam and piroxicam were kind gifts from Hana Pharm. Co. (Seoul, South Korea). The monoethanolamine, diethanolamine, and triethanolamine were purchased from Sigma Chemical Co. (St. Louis, MO). All other chemicals were of reagent grade and all solvents were HPLC grade.

2.2. Preparation of meloxicam ethanolamine salts

The meloxicam ethanolamine salts were prepared using the method reported by Ki and Choi [19]. Briefly, meloxicam was dispersed in organic solvents (ethanol, acetone, methylene chloride or methanol) and an equi-molar amount of monoethanolamine, diethanolamine, or triethanolamine was added. The solutions were stirred for 24 h and the precipitated salt was collected by filtration. After washed with *n*-hexane several times, light yellow solid residues were dried in a vacuum for 3 h. The sum of the weight of meloxicam and ethanolamine added was equal to the weight of the precipitate. The salt formation was confirmed by DSC and FTIR as described by Ki and Choi [19].

2.3. Dissolution

The release rates of meloxicam and its ethanolamine salts were measured using a dissolution tester (DST-810, LABFINE, Inc., Korea). Meloxicam and its ethanolamine salts were filled into gelatin capsule (50 mg as meloxicam). Each capsule was placed in 900 mL of a dissolution medium and stirred at 50 rpm at 37 °C. The pH values of the dissolution medium tested were 1.2 (84 mM HCl buffer) and 6.8 (50 mM phosphate buffer). An aliquot of the release medium (5 mL) was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the dissolution medium. The collected samples were filtered through a 0.45 μm nylon syringe filter after discarding first 3 mL and analyzed by HPLC.

2.4. Animal studies

All animal studies were performed in accordance with the Principles for Biomedical Research Involving Animals developed by the Council for International Organizations of Medical Sciences as well as institutional guidelines. Male Sprague–Dawley rats weighing 280–300 g were obtained from Samtako Bio Co., Ltd. (Osan, Korea) and had free access to normal standard chow diet (Jae II Chow, Korea) and tap water. Animals were kept in these facilities for at least one week before the experiment and fasted overnight prior to the experiments but were allowed water ad libitum. At the experiment, rats were divided into four groups, comprising 5 rats per each group. Groups 1–4 were administered meloxicam, meloxicam monoethanolamine salt (MX-MEA), meloxicam diethanolamine salt (MX-DEA), and meloxicam triethanolamine salt (MX-TEA), respectively. A dose equivalent to 10 mg/kg of meloxicam was administered orally to each of the animals. The oral suspensions were prepared with 5% PEG/95% methylcellulose and dosing volume was 1 mL for each animal. Blood samples were collected from the right femoral artery at 0, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 h following the administration of each drug and then centrifuged at 3000 rpm for 10 min to obtain the plasma for the HPLC assay. All samples were stored at −70 °C until analyzed.

2.5. HPLC assay

The plasma samples were analyzed by using a high-performance liquid chromatography (HPLC) system (Shimadzu Scientific Instruments, MD) comprising a UV detector (SPD-10A), a pump (LC-10AD), and an automatic injector (SIL-10A). Fifty microliters of piroxicam (20 μg/mL) was used as an internal standard (IS) and was added to 50 μL

of the plasma sample. The sample was then acidified by adding 50 μL of 0.1 N hydrochloride and extracted with 6 mL of diethyl ether for 4 min at 1800 rpm using a mini-shaker (MS 1, IKA, Germany). The tubes were centrifuged at 4000 rpm for 15 min. After the organic layer was pooled in the capped test tube, it was removed by rotary evaporator. The residue was dissolved in 500 μL of mobile phase by vortex-mixing for 2 min and then, 20 μL of the solution was injected into the HPLC system. UV detector was set at 360 nm. An ODS column (Gemini C18, 4.6 × 150 mm, 5 μ, Phenomenex, CA) was eluted with a mixture of a 50 mM phosphate buffer (pH 3.2) and acetonitrile (60:40, v/v) at a flow rate of 1 mL/min at 30 °C. The calibration curve from the standard samples was linear over the concentration range of 10–140 μg/mL. The coefficient of variation for the standard curve ranged from 2.3% to 4.9%, and the squared correlation coefficient (r^2) was over 0.99. For the assay of in vitro dissolution samples, an ODS column (Gemini C18, 4.6 × 150 mm, 5 μ, Phenomenex, USA) was eluted with a mixture of a phosphate buffer and CH_3OH (65:35, v/v) at a flow rate of 1 mL/min at 30 °C and UV detector was set at 320 nm.

2.6. Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was performed using Kinetica-4.3 (InnaPhase Corp., Philadelphia, PA, USA). The area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal method. Maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}) were read directly from the plasma concentration–time data. The terminal elimination rate constant (λz) was estimated from the slope of the terminal phase of the log plasma concentration–time points fitted by the method of least-squares, and then the terminal elimination half-life ($T_{1/2}$) was calculated as $0.693/\lambda z$.

2.7. Statistical analysis

All the means are presented with their standard deviation. The pharmacokinetic parameters were compared with a one-way ANOVA, followed by a posteriori testing with the use of the Dunnett correction. A P value < 0.05 was considered statistically significant.

3. Results and discussion

The effect of salt formation on the pharmacokinetics of meloxicam was evaluated in rats and the results were summarized in Table 1 and Fig. 2. As appeared to be comparable to the previous reports [6,7], relatively high and persistent systemic exposure of meloxicam followed by a slow decrease was observed in rats after an oral administration of meloxicam (Fig. 2). In addition, meloxicam exhibited the slow absorption with a T_{max} of 8.5 h in rats. However, T_{max} of meloxicam was significantly ($p < 0.05$) shortened following an oral administration of ethanolamine salts (MX-MEA, MX-DEA and MX-TEA), whereas the overall exposure (AUC_{0-24}) of meloxicam was similar between freebase and ethanolamine salts. Furthermore, all of three ethanolamine salts exhibited a trend toward the increase in AUC_{0-4} (the exposure during the first 4 h post-dose), implying the faster absorption of meloxicam with the ethanolamine salts. These results are somewhat different from our previous results with piroxicam (PX) ethanolamine salts [20]. Overall, the salt formation of PX resulted in the enhanced oral exposure of PX without changing T_{max}, while the salt formation of MX resulted mainly in shorter T_{max} and higher initial drug exposure (AUC_{0-4}).

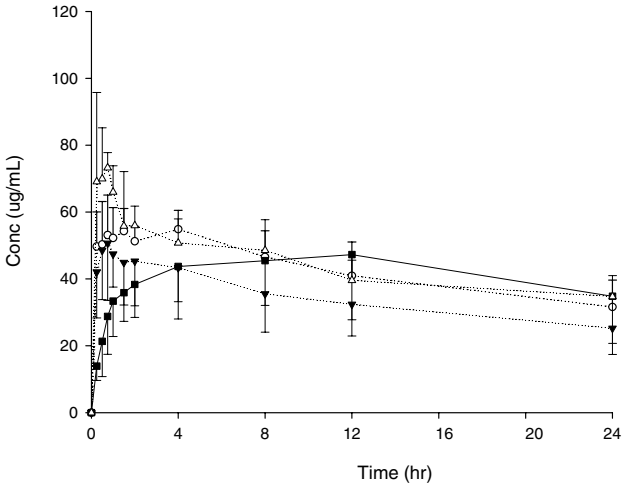

Fig. 2. Pharmacokinetic profiles of meloxicam following a single PO administration of meloxicam or its ethanolamine salts to rats: (■) MX, (▼) MX-MEA, (△) MX-DEA, and (○) MX-TEA. The data are expressed as means ± SD ($n = 4$–5).

Table 1
Pharmacokinetic parameters of meloxicam following a single PO administration (10 mg/kg) of meloxicam or its ethanolamine salts to rats (means ± SD, $n = 4$–5)

Parameters	MX	MX-MEA	MX-DEA	MX-TEA
T_{max} (h)	8.5 ± 4.4	0.8 ± 0.1*	0.5 ± 0.2*	2.2 ± 1.1*
C_{max} (μg mL^{-1})	54.6 ± 13.2	56.2 ± 13.1	82.4 ± 15.3	67.4 ± 9.68
AUC_{0-4} (μg h mL^{-1})	138 ± 29.4	176 ± 43.8	226 ± 28.0*	204 ± 27.1*
AUC_{0-24} (μg h mL^{-1})	994 ± 309	914 ± 75.7	1046 ± 116	1017 ± 130
$T_{1/2}$ (h)	n.d.	22 ± 3.2	27 ± 4.5	20 ± 2.7

n.d., not determined.
* $p < 0.05$, significant difference compared to the control (given with meloxicam).

This difference may be explained by the dissolution characteristics of PX and MX as described below.

In order to determine the relationship between the dissolution rate and the oral absorption, the dissolution profiles of meloxicam as well as its ethanolamine salts were evaluated at pH 1.2 and 6.8. As illustrated in Fig. 3, the dissolution rates of meloxicam and its ethanolamine salts were similarly very slow at pH 1.2 resulting in less than 10% dissolution in 12 h and thus, it may not be meaningful to compare the dissolution rates at pH 1.2. Based on the small volume of gastric fluids and short residence time in the stomach, meloxicam and its ethanolamine salts should be dissolved and absorbed mainly in the intestine. Therefore, the dissolution profiles were also examined at pH 6.8. On the contrary to those at pH 1.2, ethanolamine salt formation significantly enhanced the dissolution rate of meloxicam at pH 6.8 (Fig. 3). Meloxicam diethanolamine salt (MX-DEA) exhibited the highest dissolution rate at pH 6.8 followed by the monoethanolamine salt (MX-MEA) and triethanolamine salt (MX-TEA). Accordingly, the faster dissolution of meloxicam via ethanolamine salt formation at pH 6.8 appeared to be correlated well with more rapid absorption (shorter T_{max}) of meloxicam in rats. The dissolution profiles of MX and its salts were quite different from those of PX and its salts [20]. The dissolution rate of PX was faster than MX, especially during the initial phase, which may partly account for shorter T_{max} of PX than MX (2.2 h vs 8.5 h). While the initial dissolution rates of PX and PX salts were similarly fast and thus resulted in the similar T_{max} in rats [20], the large difference in the initial dissolution rates between MX and MX salts may lead to the significant difference in T_{max} between MX and MX salts.

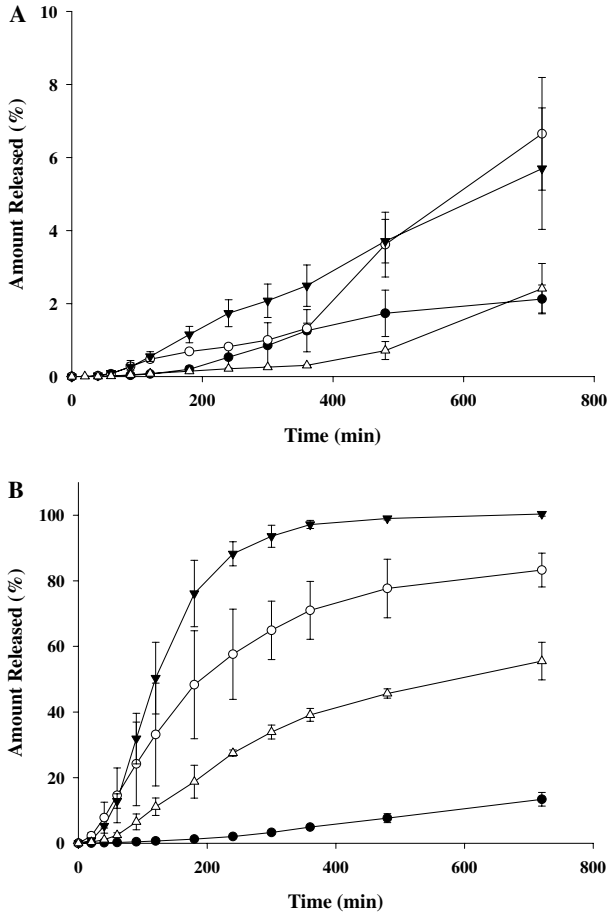

Fig. 3. Dissolution profiles of meloxicam and its ethanolamine salts at pH 1.2 (A) and pH 6.8 (B): (●) MX, (○) MX-MEA, (▼) MX-DEA, (△) MX-TEA. The data are expressed as means ± SD ($n = 3$).

Ghorab et al. [16] have attempted to utilize the cyclodextrin complex formation for the rapid onset of action after an oral administration of meloxicam. In their studies, the complexation of meloxicam with β-cyclodextrin enhanced the dissolution rate of meloxicam up to 30%. Consequently, the presence of β-cyclodextrin significantly increased the systemic exposure of meloxicam and shortened the T_{max} from 5.6 to 2.8 h in humans. In comparison to the use of co-solvents, diethanolamine salt formation in the present study exhibited more profound effect on the dissolution of meloxicam with over four-fold increase in the dissolution rate and shortened the T_{max} from 8.5 up to 0.5 h in rats. These results suggest that diethanolamine salt formation could be useful as an alternative to the intramuscular injections of meloxicam for the earlier onset of action.

In conclusion, the ethanolamine salts of meloxicam, particularly diethanolamine salt of meloxicam (MX-DEA), exhibited faster absorption of meloxicam while maintaining the prolonged exposure and may be used for the earlier onset of action for meloxicam.

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