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RESEARCH ARTICLE

Influence of ion-pairing and chemical enhancers on the transdermal delivery of meloxicam

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Abstract

Purpose: To investigate the influence of ion pairing and chemical enhancers on the transdermal delivery of meloxicam. *Method*: We examined the increased permeation of meloxicam produced by ion pair formation with six organic bases, diethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, and *N*-(2′-hydroxyethanol)-piperidine, and four normal permeation enhancers, oleic acid, menthol, azone, and *N*-methyl-2-pyrrolidone. The cumulative permeation was markedly increased in the presence of either a counter ion or chemical enhancers. In particular, we proved the formation of a meloxicam/amine ion-pair in solution by ^{13}C-NMR (nuclear magnetic resonance). *Results and conclusion*: The cumulative permeation was markedly increased in the presence of either a counter ion or chemical enhancers. These results suggest that the degree of enhancement possibly depends on the structure and hydrophilicity of the counter ions.

Key words: *^{13}C-NMR; enhancers; ion pairs; meloxicam; transdermal*

Introduction

Meloxicam, 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1, 1-dioxide (Figure 1), is a potent nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid class of oxicam derivatives that produces preferential inhibition of cyclooxygenase-2 and inhibits prostaglandin synthesis. However, its oral administration is accompanied by common adverse effects that affect the gastrointestinal tract and even reduce the life expectancy of patients with rheumatoid arthritis[1]. To avoid irritation of the gastrointestinal tract, one promising method is to administer the drug via the skin[2], and this is an attractive option because the daily dose of meloxicam ranges from 7.5 to 20 mg and the elimination half-life period ($T_{1/2}$) of meloxicam in plasma is approximately 20 hours[3]. Previous pharmacokinetic studies have shown that meloxicam has prolonged absorption with T_{max} more than 5 hours and C_{max} within 3.5 μg/mL[4], which is very suitable for transdermal drug delivery system.

Meloxicam is a practically water-insoluble drug at physiological pH and has a zwitterionic property with two pK_a values (pK_{a1} = 1.09, pK_{a2} = 4.18)[5]. Most of these drugs show low solubility in polar and non-polar media[6].

Owing to their poor solubility, the permeation of these drugs is also no good. Therefore, several studies have been carried out to enhance the transdermal delivery of meloxicam. One of these involved the formation of a lipophilic ion-pair by adding oppositely charged species[8]. Ki and Choi[9] confirmed the formation of three meloxicam/ethanolamine salts using differential scanning calorimetry (DSC), which facilitated the penetration of meloxicam. Chang et al.[10] used meloxicam sodium salt to screen an optimal transdermal formulation. Another primary approach to overcome skin resistance to drug penetration is the selection of suitable penetration enhancers, substances that facilitate penetration by reversibly altering the structure of the skin. Jantharaprapap and Stagni[1] investigated the penetration-enhancing effect of oleic acid and menthol on meloxicam, while Sawada and Kawakami[11] studied several terpenes and surfactants with regard to their ability to promote the penetration of meloxicam. In addition, Yuan et al.[1,12] used a microemulsion system to enhance the penetration of meloxicam by altering the

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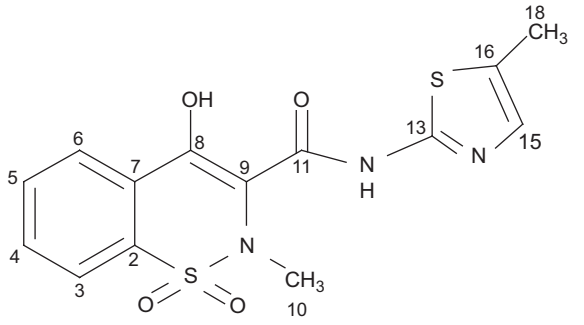

Figure 1. The structure of meloxicam (enoyl) with atomic numbering.

distribution properties of the drug. However, there is still no published systemic evaluation either of the effects of ion-pair formation or chemical enhancers.

In this study, we examined the permeation increase in meloxicam by ion-pair formation with six organic bases, diethylamine (DETA), triethylamine (TETA), ethanolamine (EA), diethanolamine (DEA), triethanolamine (TEA), and *N*-(2′-hydroxyethanol)-piperidine (HEPP), and four normal permeation enhancers, oleic acid (OA), menthol (ME), Azone (AZ), and *N*-methyl-2-pyrrolidone (NMP). In particular, we confirmed the formation of a meloxicam/amine ion-pair in solution using ^{13}C-NMR. Considering their different mechanisms of action, we also investigated the combination of organic amine and permeation enhancers.

Materials and methods

Equipments and materials

Meloxicam was a gift from the Taiyang Pharmaceutical Co. Ltd. (Berjing, China); isopropyl myristate (IPM), NMP, and ME were supplied by China National Medicines Co. Ltd. (Shanghai, China); DETA, TETA, EA, DEA, TEA, and HEPP were purchased from the Yuwang Pharmaceutical Co. Ltd. (Shandong, China); propylene glycol (PG), ethanol (EtOH), OA, and AZ were obtained from the Bodi Drug Manufacturing Co. Ltd. (Tianjin, China). Methanol was of high-performance liquid chromatography (HPLC) grade and was obtained from the Yuwang Pharmaceutical Co. Ltd. (Shandong, China). All other chemicals were of the highest reagent grade available.

Skin sample preparation

Male Wistar rats weighing 180–220 g (6–8 weeks old) used in all experiments were supplied by the Experimental Animal Center of Shenyang Pharmaceutical University (Shenyang, China). The experiments were performed in accordance with the guidelines for animal use published by the Life Science Research Center of Shenyang Pharmaceutical University. The rats were anesthetized with urethane (20%, w/w, i.p.) and the abdomen was carefully shaved with a razor after removal of hair by electric clippers (model 900; TGC, Osaka, Japan), in order to eliminate all tiny roots of hair. About 5 cm^2 (circle of 2.5 cm diameter) of skin on the left- and right-hand sides of the abdomen was excised, and the skin membrane was checked with a magnifier to ensure that no obvious defects were present[13].

Permeation experiments

Permeation experiments were conducted at 32°C in two-chamber diffusion cells (with an effective diffusion area of 0.95 cm^2 and a receiver volume of 2.5 mL)[14]. After the removal of hair and subcutaneous fat, the rat abdominal skin membrane was mounted on a two-chamber diffusion cell with the epidermal side facing the donor cell. The donor cell was filled with a 2.5 mL suspension of meloxicam, which ensured that the solubility of meloxicam in donor phase was sufficient to allow permeation. As meloxicam has a low solubility in water, the receptor cell was filled with 2.5 mL of 40% PEG 400 PBS to increase the drug solubility and maintain sink conditions during the experiments. At predetermined time intervals, 2.0 mL of receptor solution was sampled for analysis and replaced with the same volume of fresh solution to maintain sink conditions. The drug concentration was determined by reversed-phase HPLC with reference to a calibration curve.

Preparation of meloxicam complex with amines

Equimolar amounts of meloxicam and the amines were dissolved in chloroform by gentle stirring. The solvents were then removed using a rotatory evaporator, and the meloxicam combined with EA, DEA, and TEA was precipitated. No precipitation was obtained in the solvents with added DETA, TETA, and HEPP.

DSC and NMR spectroscopy

Thermal analysis was carried out using a DSC-60 instrument (Shimadzu Corporation, Kyoto, Japan). The samples were weighed into a nonhermetically sealed aluminum pan and then heated from 30°C to 300°C at a heating rate of 10°C/min. The instrument was calibrated using indium. All the DSC measurements were made in a nitrogen atmosphere and the flow rate was 100 mL/min.

To verify the formation of the meloxicam/DETA, TETA, and HEPP ion-pairs, we reconstituted the liquid meloxicam/DETA, TETA, and HEPP complex in $CDCl_3$ and recorded the ^{13}C-NMR spectra. ^{13}C-NMR spectra were recorded at 300 Mz using a Bruker Advance 300 spectrometer (Karlsruhe, Germany). Samples were

dissolved in $CDCl_3$ and chemical shifts for carbon resonance were reported in ppm relative to TMS.

HPLC assays

Meloxicam was determined by using an HPLC system equipped with an L-2420 variable-wavelength ultraviolet absorbance detector and an L-2130 pump (Hitachi High-Technologies Corporation, Tokyo, Japan). Samples were introduced by means of a 25-µL Hamilton syringe (Hamilton Company, Reno, NV, USA) into a Rheodyne Model 7725 loop injector equipped with a 20-µL loop. The reversed-phase stainless steel column (20 cm × 4.6 mm) was packed with Diamonsil C18 (5-µm particle size; Dikma Technologies, Beijing, China). The mobile phase consisted of methanol and PBS buffer (75:25, v/v), and the pH was adjusted to 5.2. The mobile phase was filtered by passing it through a 0.45-µm pore size membrane filter. The flow rate for meloxicam was 1.0 mL/min, propylparaben was used as the internal standard, and the detector wavelength was set at 270 nm. With this eluting solvent system, the drug and the internal standard were well separated from interfering skin constituents. The retention time for meloxicam and internal standard was 5.7 and 7.9 minutes, respectively.

Analysis

The amount of each drug permeating through the skin during a sampling interval was calculated on the basis of the measured receptor-phase concentration and volume. The cumulative amount of drug permeating per unit area versus time was plotted. The flux was calculated from the slope of the linear portion of the plot, using the following equation:

$$J(\text{flux}) = \frac{dQ}{Adt} \quad (1)$$

The χ-intercept of the linear portion of the plot was the lagtime. The permeability coefficient was obtained by dividing the flux by the initial drug concentration in the donor phase. The penetration-enhancing effect of the adjuvant was calculated in terms of the enhancement ratio (E_R), using the following equation:

$$E_R = \frac{Q_{8,\text{with enhances}}}{Q_{8,\text{control}}} \quad (2)$$

Statistical analysis was carried out using analysis of variance (ANOVA) with the help of the SPSS program. The level of significance was taken as $P < 0.05$.

Results and discussion

Influence of the vehicle solution

To find out the optimum vehicle, vehicles with different PG ratios were investigated. The final amount of meloxicam permeating from pure IPM and 5%, 10%, 20% PG/IPM was 8.73, 7.55, 10.99, and 9.13 mcg/cm^2/h, respectively. As shown in Figure 2, the most suitable ratio was obtained for IPM with 10% PG. There was a significant difference between 10% PG and the others ($P < 0.05$). The resultant increase in the flux of meloxicam can be attributed in part to the increased solubility of meloxicam in the donor phase, in addition to the greater membrane fluidity and pore formation associated directly with the increasing PG content[15].

DSC and ^{13}C-NMR spectroscopy

The DSC curves are shown in Figure 3. The melting points and the enthalpy of meloxicam and its EA/DEA/TEA complexes are summarized in Table 1. The DSC curve of meloxicam shows a sharp endothermic peak at 264.87°C, which is about 10°C higher than the results of Ki and Choi[9], and this is probably because of the difference in the crystal form, while the melting points of three complexes were similar to theirs. The melting points of the meloxicam-EA/DEA/TEA complexes were markedly reduced compared with pure meloxicam, which agrees well with the finding that complexes of zwitterions have lower melting points than the parent compounds due to a reduced crystalline lattice energy[6]. The altered melting point and

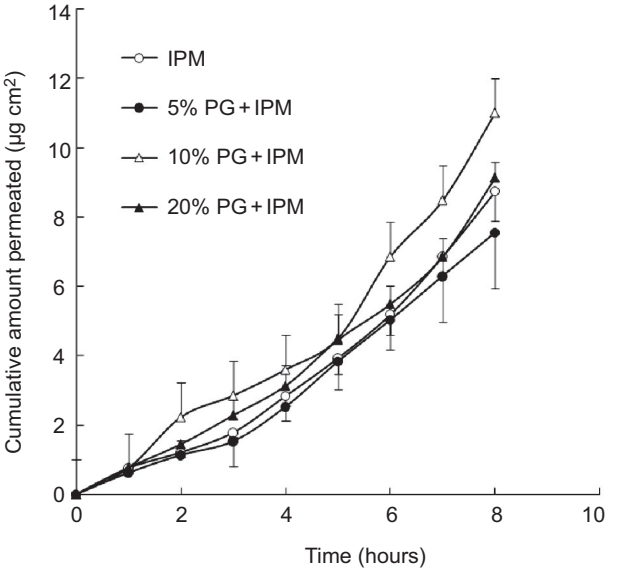

Figure 2. Effect of vehicle solution on percutaneous absorption of meloxicam. Error bars represent the SEM, $n = 3$.

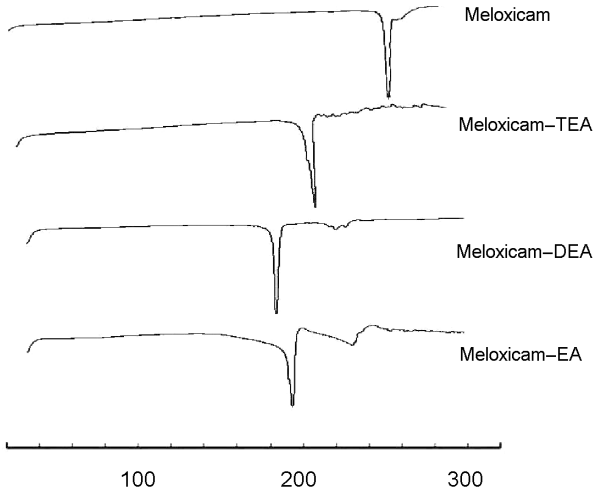

Figure 3. DSC curves of meloxicam and its complexes with alkanolamines at a scanning rate of 10°C/min.

Table 1. DSC melting characteristics of the meloxicam complexes.

Meloxicam complexes	Peak (°C)	Enthalpy (kJ/mol)
Meloxicam	264.87	43.8
Meloxicam–EA	193.72	11.7
Meloxicam–DEA	182.30	11.8
Meloxicam–TEA	214.06	22.1

enthalpy indicated that meloxicam-EAs complexes had been formed.

Because DETA/TETA/HEPP cannot form salts with meloxicam, ^{13}C-NMR spectroscopy is used to obtain evidence of an interaction between meloxicam and these counterions. The ^{13}C chemical shifts of meloxicam in $CDCl_3$ solution following the addition of different amines are given in Figure 4 and Table 2. The ^{13}C-NMR spectrum of meloxicam complexes showed a downfield shift of +8.8 (+8.4, +7.8) ppm for C(8), compared with that of meloxicam. These values strongly suggest that the charge on the enoyl group has been partially neutralized. This indicates that a hydrogen bond is formed between the oxygen of the enoyl group and the amines as the hydrogen donor.

Taken together, all this evidence shows that the physicochemical properties of meloxicam were changed by the presence of amines, resulting in enhanced penetration of meloxicam.

The influence of organic amines

Figure 5 and Table 3 show the structure and physicochemical properties of these counterions that affect the penetration of meloxicam.

Meloxicam was dispersed in donor solvents, and an equimolar amount of amine was added.

We compared the different amines as charge ions for meloxicam, as shown in Figure 6 and Table 4. The results from the transdermal experiments show that ion-pair formation with organic bases is very effective (1.39- to 5.78-fold increase) in delivering meloxicam through rat skin. As can be seen from Table 4, the solubility of meloxicam was increased markedly after adding organic bases, when the solubility of meloxicam increased from 59.38 mg/mL to 2810.23–27,088.00 mg/mL. Also the permeation coefficient of meloxicam was reduced with the solubility increasing. All the counter ions studied significantly ($P < 0.05$) promoted the in vitro transport of meloxicam across the stratum corneum, which, in terms of Q_8, occurred in the order of EA < TETA < TEA ≤ DETA ≤ DEA < HEPP. HEPP had the greatest effect on meloxicam.

As far as tertiary amines are concerned, hydroxylamines are better than alkylamines, and this is considered to be due to the structure of the counterion shown in Figure 5. This is supported by previous studies[16]. The hydroxyl groups at the end of the ethyl chains of HEPP and TEA make the ion-pairs more hydrophilic. The same also occurred with secondary amines. The values of log P and pK_a also show that the log P values of hydroxylamines are lower than those of alkylamines, and the pK_a values of hydroxylamines were higher than those of alkylamines.

All the tertiary amines exhibited a lower transdermal penetration than secondary amines except for HEPP, although the difference was not statistically significant ($P > 0.05$). The log P and pK_a values of the counterions were in the same order as above: the log P values of secondary amines were lower than those of tertiary amines, and the pK_a values of secondary amines were higher than those of tertiary amines.

As in the case of HEPP, one hypothesis is that the ring blocks the two covalent bonds attached to the nitrogen, thus improving the exposure of unshared electrons on the nitrogen atom to the solvating medium[17].

Luger et al.[5] found that, as the pH of the solvent increases, the log P value of meloxicam decreases. We determined the apparent log P value of meloxicam and its complexes in *n*-octanol-water, and found that the log P value of all the meloxicam complexes was lower, indicating that a higher hydrophilicity had been achieved (Table 5). The log P values of meloxicam complexes were not very consistent as far as the order of cumulative permeation was concerned.

Such behavior can be explained by partition between the stratum corneum (SC), epidermis, and dermis (ED)[18]. According to this theory, for lipophilic drugs, the partition from the SC into the ED becomes a rate-limiting step as far as skin penetration is concerned. The SC is essentially a lipid layer. Lipophilic drugs pass through the SC, and then they must

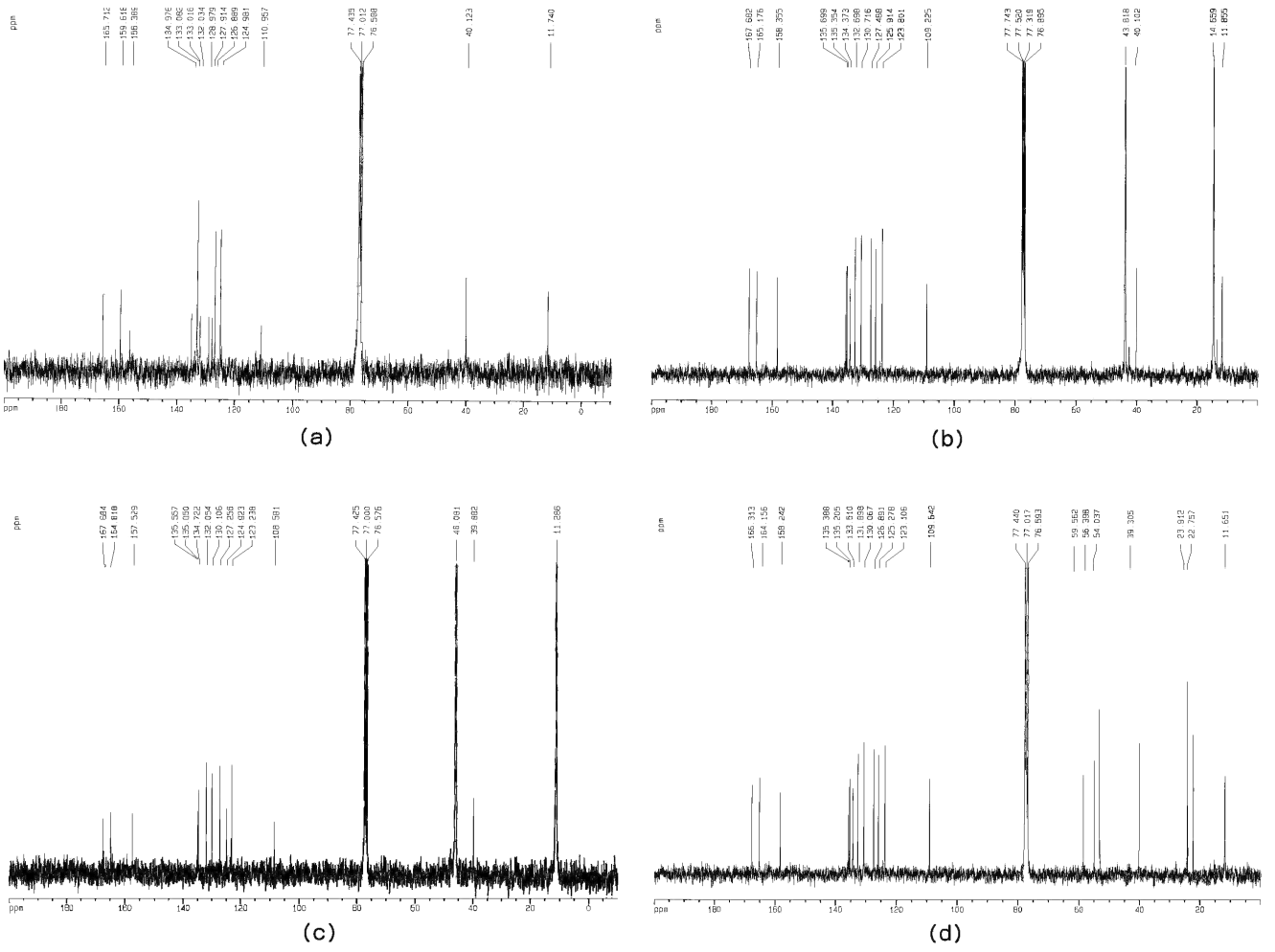

Figure 4. Spectra of ^{13}C-NMR: (A) meloxicam; (B) meloxciam-DETA; (C) meloxicam-TETA; (D) meloxicam-HEPP.

Table 2. ^{13}C chemical shifts δ (ppm) of meloxicam in $CDCl_3$ solutions adding different amines.

^{13}C	Meloxicam	Meloxicam	DETA	Meloxicam	TETA	Meloxicam	HEPP
C-2	135.0	135.7		135.6		135.4	
C-3	125.0	123.8		123.2		123.1	
C-4	129.0	130.7		130.1		130.1	
C-5	132.0	132.7		132.0		131.9	
C-6	128.0	127.5		127.2		126.9	
C-7	133.1	135.4		135.0		135.2	
C-8	156.4	165.2	+8.8	164.8	+8.4	164.2	+7.8
C-9	111.0	109.2		108.6		109.6	
C-10	40.1	40.1		39.9		39.3	
C-11	165.7	167.7		167.7		166.3	
C-13	159.8	158.3		157.5		158.2	
C-15	133.0	134.4		134.7		133.5	
C-16	126.9	125.9		124.9		125.3	
C-18	11.7	11.9		11.3		11.7	

transfer directly into the aqueous medium ED, otherwise they will remain in the SC. Therefore the affinity for the ED, in other words the hydrophilicity, is an important factor. This has also been confirmed by the study of Jiang et al.[19] Our research also supports this. From the evidence above it can be seen that, as the hydrophilicity of meloxicam increases, so does its permeability.

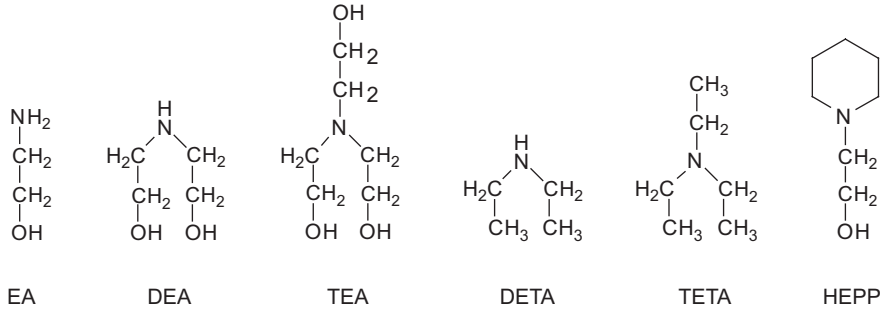

Figure 5. Structure of the organic amines as counterions.

Table 3. Physicochemical properties of various counterions.

Counterion	pK_a	log $K_{o/w}$	Molecular weight
DETA	11.1	0.58	73.14
TETA	10.8	1.45	101.19
EA	9.5	−1.31	61.08
DEA	8.96	−1.43	105.14
TEA	7.76	−1.00	149.19
HEPP	9.66	0.96	129.20

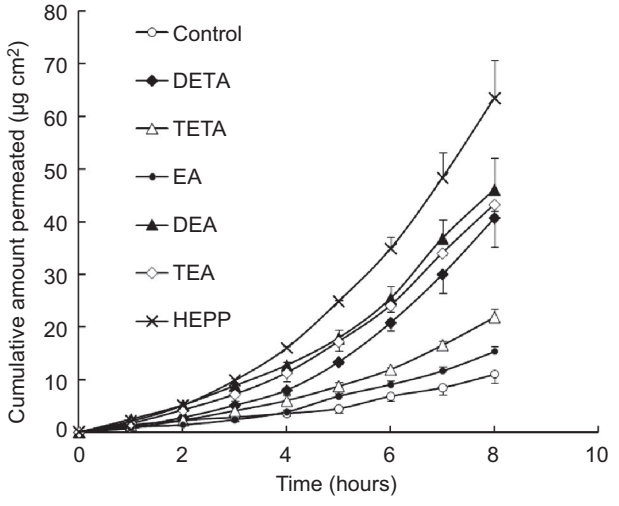

Figure 6. Effects of adding amines on percutaneous absorption of meloxicam. Error bars represent the SEM, $n = 3$.

Penetration enhancers

The effect of four frequently used chemical enhancers on the in vitro percutaneous absorption profiles of meloxicam through rat epidermis is shown in Figure 7. As can be seen from Table 6, the solubility of meloxicam was increased slightly after adding most of the permeation enhancers except for 5% NMP, when the solubility of meloxicam increased from 59.38 to 9802.53 mg/mL. No higher permeability coefficient of meloxicam was obtained in the presence of penetration enhancers. All the permeation enhancers were studied significantly ($P < 0.05$) and promoted the in vitro transport of meloxicam across the stratum corneum, which, in terms of flux, occurred in the order of 5% ME ≤ 5% OA < 5% AZ < 5% NMP. NMP clearly increases the solubility of meloxicam in the donor solution, and this is supported by previous studies[20]. The structure of NMP shows that there is a lactam group in the molecule, which is expected to exhibit H-bonding with meloxicam[21].

Although there was no significant increase in solubility, other enhancers also slightly increased the permeability of meloxicam (1.187- to 2.885-fold). According to general transdermal mechanism of these enhancers, it appears that all these improve the permeability of drugs by interacting with the stratum corneum.

Combined effects

The combined effects of NMP and HEPP are shown in Figure 8 and Table 7. Although both ion-pair formation

Table 4. The permeation parameters of meloxicam with different amines, values represent the mean ± SEM, $n = 3$.

Parameter	J (μg/cm^2/h)	T_{lag} (hours)	Q_8 (μg/cm^2)	E_R	S (μg/mL)	$P \times 10^4$ (cm/h)
Control	2.11 ± 0.35	2.85	10.99 ± 1.96	1.00	59.38	355.68 ± 18.94
DETA	9.14 ± 1.66	3.63	40.73 ± 6.37	3.71	18985.71	4.81 ± 0.87
TETA	4.40 ± 0.78	3.13	21.91 ± 2.77	1.99	23803.86	1.85 ± 0.33
EA	2.79 ± 0.10	2.66	15.29 ± 1.08	1.39	22517.59	1.24 ± 0.04
DEA	9.61 ± 1.10	3.21	46.15 ± 5.26	4.20	10231.19	6.16 ± 1.07
TEA	8.82 ± 0.56	3.13	43.32 ± 2.81	3.94	2810.23	31.39 ± 1.99
HEPP	12.94 ± 2.53	3.19	63.53 ± 9.88	5.78	27088.00	4.78 ± 0.93

J: steady-state flux, T_{lag}: lag-time, Q_8: 8-hour cumulative amount, E_R: enhancement ratio, S: solubility, P: permeation coefficient.

Table 5. Apparent log *P* values of meloxicam in *n*-octanol-water.

Meloxicam complexes	log *P*
Meloxicam	3.03
Meloxicam–EA	–0.32
Meloxicam–DEA	–0.34
Meloxicam–TEA	–0.20
Meloxicam–DETA	–0.24
Meloxicam–TETA	–0.44
Meloxicam–HEPP	–0.48

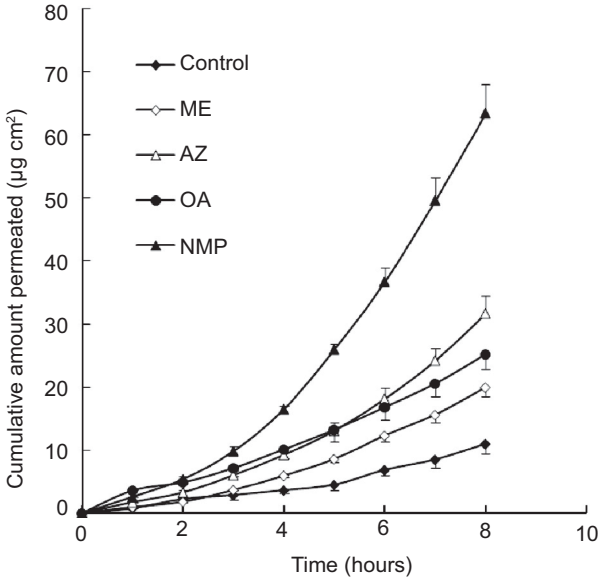

Figure 7. Effects of adding chemical enhancers on percutaneous absorption of meloxicam. Error bars represent the SEM, $n = 3$.

and chemical enhancers can clearly improve the penetration of meloxicam, there is no synergistic effect. One possible hypothesis to explain such a decrease in the cumulative amount and flux is that there is an inhibitor effect between HEPP and NMP.

As reported in the literature[22], terpenes can be used with PG to achieve a better enhancement. We added ME to donor solutions to increase the Q_8 of meloxicam. As shown in Figure 8, the flux of meloxicam was increased 8.2-fold compared to that in the control solution. The addition of ME appeared to increase the

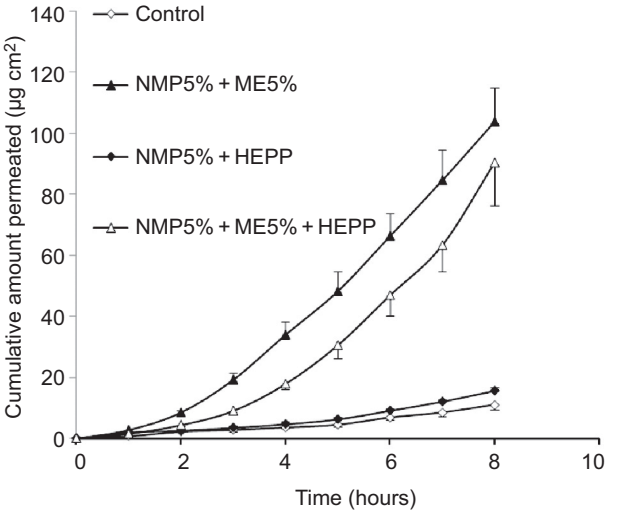

Figure 8. Percutaneous absorption of meloxicam. Error bars represent the SEM, $n = 3$.

transport of meloxicam, but this increase was not significant and was limited by the presence of HEPP. It may be that, with regard to ionic meloxicam, NMP cannot improve the solubility of the drug and, furthermore, it prevents the polarized drug from crossing the SC barrier, while ME can assist the polarized drug crossing the SC barrier[22]. This is just an initial investigation and further studies will be needed to investigate fully the transdermal behavior of meloxicam.

Conclusions

We studied the enhancing effect of organic amines on meloxicam and proved the formation of ion-pairs. Of all the amines studied, HEPP produced the greatest enhancement of meloxicam. This is expected because of its structure. We also investigated the effect of chemical enhancers on the penetration of meloxicam and found that NMP was the most promising chemical enhancer because of its ability to increase drug solubility. However, when combined with chemical enhancers, HEPP inhibited penetration. Further research into this phenomenon will be carried out in future studies.

Table 6. The permeation parameters of meloxicam with different chemical enhances, values represent the mean ± SEM, $n = 3$.

Parameter	J (μg/cm²/h)	T_{lag} (hours)	Q_8 (μg/cm²)	E_R	S (μg/mL)	$P \times 10^4$ (cm/h)
Control	2.11 ± 0.35	2.85	10.99 ± 1.96	1.00	59.38	355.68 ± 18.94
ME	3.74 ± 0.30	2.73	19.97 ± 1.85	1.82	542.71	69.01 ± 5.52
AZ	6.18 ± 0.75	2.97	31.71 ± 3.92	2.89	293.14	210.99 ± 25.58
OA	3.96 ± 0.25	1.72	25.19 ± 2.70	2.29	339.60	116.64 ± 7.36
NMP	12.53 ± 1.38	2.99	63.45 ± 6.53	5.77	9802.53	12.78 ± 1.41

J: steady-state flux, T_{lag}: lag-time, Q_8: 8-hour cumulative amount, E_R: enhancement ratio, S: solubility, P: permeation coefficient.

Table 7. The permeation parameters of meloxicam with effect of combination use of NMP and ME, NMP and HEPP, NMP and ME and HEPP, values represent the mean ± SEM, $n = 3$.

Parameter	J (μg/cm^2/h)	T_{lag} (hours)	Q_8 (μg/cm^2)	E_R	S (μg/mL)	$P \times 10^4$ (cm/h)
Control	2.11 ± 0.35	2.85	10.99 ± 1.96	1.00	59.38	355.7 ± 18.94
NMP5% + ME5%	18.48 ± 1.77	2.41	103.65 ± 13.17	9.43	540.55	341.9 ± 32.78
NMP5% + HEPP	3.10 ± 0.18	3.02	15.64 ± 1.11	1.42	480.76	64.5 ± 3.74
NMP5% + ME5% + HEPP	19.54 ± 3.03	3.55	90.17 ± 13.91	8.20	112249.9	1.7 ± 0.37

J: steady-state flux, T_{lag}: lag-time, Q_8: 8-hour cumulative amount, E_R: enhancement ratio, S: solubility, P: permeation coefficient.

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Declaration of interest: The authors report no conflicts of interest

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