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에탄올아민염형성이메록시캄의 경피흡수에미치는영향

朝鮮大學校 大學院

藥 學 科

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The Effect of Salt Formation with Ethanolamines on the Percutaneous Absorption of Meloxicam

2006年 2月 24日

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Frankly speaking, two years as a graduated student was sometimes tough for me, but it has also been the greatest time in my life, especially because there has always been someone I could depend on just beside me.

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기 한 뫼

지도 교수 : 최후균

조선대학교 대학원 약학과

메록시캄은 비스테로이드성 소염진통제 (NSAID) 중의 하나로서 골관절염, 류마티스성 관절염 및 다양한 근골격계 장애로 인한 급성 및 만성 통증에 매우 효과적이다. 또한 diclofenac, naproxen, piroxicam 등의 다른 NSAIDs에 비해 더 높은 약리 활성을 가졌다고 보고된다. 경구투여가 가장 일반적으로 사용되지만 장기 투여시 소화성 궤양 등의 위장장애를 일으키고 First-pass metabolism을 받는다. 따라서 meloxicam을 경피를 통해 흡수 시킬 수 있다면 위의 문제점을 개선 할 수 있고 환자의 편의성을 도모 할 수 있으므로 더 높은 효과를 기대할 수 있을 것이다.

메록시캄은 두 개의 pKa (pKa_1=1.09, pKa_2=4.18)를 가지고 있는 양쪽성 이온으로서 높은 융점 및 낮은 용해도 등에 의해 낮은 피부 투과도를 나타내므로 물리화학적인 성상을 향상시킨 meloxicam salt를 이용하여 피부를 통한 약물 흡수를 증진하는 동시에 그 기전을 밝히고 piroxicam의 경우와 비교 해 보고자 하였다. 적절한 상대 이온의 선택과 그 구조에 의한 영향을 파악하기 위해 일차아민, 이차아민, 삼차아민 중

ethanolamine, diethanolamine, triethanolamine을 선택하여 salt를 제조하고 물리화학적 특성을 파악하며 그들의 피부투과도에 미치는 영향을 살펴보았다.

염의 형성은 분배계수의 변화에 영향을 미치지 않았으나 메록시캄 모노에탄올아민염과 메록시캄 디에탄올아민염의 경우 시험한 대부분의 용매에서 메록시캄보다 높은 용해도와 투과도를 나타내서 피록시캄의 모노에탄올아민 및 디에탄올아민 염과 같은 영향을 보였다. 하지만 메록시캄 트리에탄올아민염의 경우 대부분의 용매에서 낮은 용해도를 보였던 반면 투과도는 메록시캄보다 높아서 용해도와 투과도가 모두 감소했던 피록시캄 트리에탄올아민염과는 다른 영향을 보였다. 염을 형성함으로서 융점을 낮추는 효과가 있었으며 메록시캄 디에탄올아민염이 가장 낮은 융점을 나타냈다. 다양한 흡수 촉진제 중 비이온성 계면 활성제에서의 메록시캄 및 메록시캄 염의 경피 플럭스를 살펴볼 때 중등도의 HLB와 알킬 chain 길이 C_{18}을 가지고 있는 비이온성 계면 활성제가 각질층을 변형하여 투과하는 능력이 다른 것에 비해 우수하였다.

에탄올아민류를 이용하여 메록시캄의 염을 형성하였고 FT-IR, DSC, 그리고 용해도의 변화를 통해서 염의 형성을 확인 할 수 있었다. 염을 형성함으로써 메록시캄의 용해도가 크게 증가하였고 피부 투과도를 높이는 효과를 보였다. 따라서 ethanolamine을 이용한 메록시캄의 염은 transdermal delivery system을 개발하는 데 응용될 수 있을 것으로 기대된다.

The Effect of Salt Formation with Ethanolamines on the Percutaneous Absorption of Meloxicam

Abstract

The purpose of this study is to prepare meloxicam-ethanolamine salts (MX-EAs) to improve the physicochemical properties for enhanced transdermal delivery of meloxicam. The physicochemical properties of MX-EAs were investigated by Differential Scanning Calorimetry (DSC) and Infrared Spectroscopy (FT-IR). The effect of various vehicles on the percutaneous absorption of meloxicam and its salts across the hairless mouse skin were evaluated using flow-through diffusion cell system at 37°C. The salt formation lowered the melting point of meloxicam and slightly decreased the octanol/water partition coefficient. Meloxicam-monoethanolamine salt (MX-MEA) and meloxicam-diethanolamine salt (MX-DEA) had higher solubility and higher permeation rate across the skin than meloxicam in various vehicles. Even though the solubility of meloxicam-triethanolamine salt (MX-TEA) was lower than that of meloxicam, the permeation rate was higher. The relationship between physicochemical properties of various surfactants and measured flux showed that non-ionic surfactants with medium HLB and alkyl chain length of C_{18} were effective for transdermal delivery of meloxicam and MX-EAs. The results suggest that MX-EAs can be utilized in the development of transdermal delivery system.

1. Introduction

Meloxicam is a non-steroidal anti-inflammatory drug, which is very effective against various arthritic conditions and inflammations. It is reported to have higher inflammatory efficacy than other NSAIDs, such as diclofenac, naproxen, or piroxicam [1]. It has been generally administered orally, however, its use was often limited because of its potential to cause gastro-intestinal adverse effects. First-pass hepatic metabolism and patient non-compliance are also common problems in the chronic use of oral administration [2]. In order to improve therapeutic efficacy and patient compliance of meloxicam, transdermal administration can be an alternative route of administration. However, delivering meloxicam through the skin has its own problem due to the physicochemical nature of meloxicam. As shown in Fig. 1, meloxicam is a zwitterionic drug with two pKa values (pKa_1=1.09, pKa_2=4.18) [3]. Most of zwitterionic drugs have relatively high melting point, low solubilities in polar and non-polar media and low lipophilicity due to its large intramolecular multipole moment [4]. These physicochemical properties make the zwitterionic drugs very hard to be used in the transdermal delivery.

Several approaches for enhancing the permeation of ionic drugs were investigated including ion pair formation [5-9]. Some of them have been applied to transdermal delivery of zwitterionic drugs [10, 11]. By adding oppositely charged species, the drug can form a lipophilic ion pair [12]. Theseion-pair formations generally have smaller dipoles and lower crystalline lattice energy, resulting in higher solubilities in both polar and non-polar

solvents [4]. These changes in the physicochemical properties can improve the skin transport of zwitterionic drug without modification of the drug structure [13]. In our previous study on piroxicam, which is also a zwitterionic drug and structurally related to meloxicam, the solubility and skin permeability were dramatically increased by forming salt with ethanolamines [14].

In the present study, ethanolamine, diethanolamine, and triethanolamine were used to prepare meloxicam salts in order to improve skin permeation of meloxicam and to compare the results with those obtained from piroxicam ethanolamine salts. Differences in the physicochemical characteristics between meloxicam and its salts were evaluated using DSC, FT-IR and Elemental Analysis. In addition, the effect of salt formation of meloxicam with ethanolamines on the percutaneous absorption of meloxicam from various vehicles was investigated.

2. Materials and Methods

2-1. Materials

Meloxicam was obtained from Hana Phrarmaceutical Co. (Seoul, Korea). Monoethanolamine, diethanolamine, triethanolamine, polyethylene glycol 300 (PEG 300) and glycerol formal were purchasedfrom Sigma Chem. Co. (St. Louis, MO). PEG-8 glyceryl caprylate/caprate (Labrasol®), PEG-8 glyceryl linolate (Labrafil® WL 2609), polyglyceryl-3 oleate (Plural oleique® CC 497) and propylene glycol caprylate/caprate (Labrafac® PG) were obtained from Gattepose Korea (Seoul, South Korea). Isopropyl myristate (Crodamol® IPM), PEG-2 almond glyceride (Crovol® A 40), PEG-60 almond glyceride (Crovol A®70), PEG-20 evening primrose glyceride (Crovol® EP 40), and PEG-12 palm kernel glyceride (Crovol® PK 40) were obtained from Croda (Parsippanym NJ, USA). Sorbitan monooleate (Span® 80), polyoxyethylene sorbitan monooleate (Tween® 80), polyoxyethylene sorbitan monolaurate (Tween® 20), n-octanol, and polypropylene glycol 400 (PPG 400) were purchased from Junsei Chemical Co. (Japan). Cineole was purchased from Aldrich Chem. Co. (Milwaukee, WS, USA). All other chemicals were of reagent grade or above and were used without further purification.

2-2. Preparation and Identification of MX-EAs

Preparation of MX-EAs

Meloxicam was dispersed in organic solvent (ethanol, acetone and

methanol for MX-MEA, MX-DEA and MX-TEA, respectively) and an equi-molar amount of monoethanolamine, diethanolamine, or triethanolamine was added. The precipitated salt was collected by filtration. The filtrate was washed with n-hexane several times. Light yellow solid residue was dried in vacuum for 3 h.

Thermal Analysis

Thermograms were recorded from room temperature to 300°C using a differential scanning calorimeter (DSC 50, Shimadzu Scientific Instrument, MD) at a scan rate of 10°C/min.

IR Spectroscopy

FT-IR spectra of meloxicam and MX-EAs were recorded using a FT-IR spectrophotometer (LX30-7012, Perkin Elmer, IL, USA) in the 4000-2000 cm^{-1} range. Powdered samples were prepared with KBr to make pellets.

Elemental Analysis

Elemental analysis was performed by Chns-o Analayzer Automatic (EA1108, Carlo Erba, Italy). The criterion used for the analysis acceptance was les than 0.3% deviation for each atom (C, H, N, S).

2-3. HPLC Methodology

Meloxicam and its salts were analyzed by a HPLC system (Shimadzu Scientific Instruments, MD, USA) comprising a UV detector (SPD-10A), a

pump (LC-10AD), and an automatic injector (SIL-10A). The wavelength of UV detector was set at 320 nm. A reversed phase column (Luna 5μm C8, 4.6*150mm, Phenomenex) was used for the analysis. The column temperature was maintained at 30℃ using a thin foil temperature controller (CH 1445, SYSTEC, MN). The mobile phase used was methnaol/water/phosphoric acid (700/299/1) and the flow rate was 1ml/m. The salts of meloxicam would be dissociated into meloxicam and ethanolamine under our analytical conditions of pH 3.0. Therefore, the salt samples were analyzed as meloxicam.

2-4. Solubility and Partition Coefficient

Equilibrium solubility was measured by adding excess amount of the drug (meloxicam, MX-MEA, MX-DEA, and MX-TEA) to various solvents in 20ml vials. The solvents used in the present study are listed in Table I and Table II. The contents were stirred by magnetic bar at room temperature for 24 h. The saturated solution was then filtered with a syringe filter (0.45 μm). After appropriate dilution, the concentration of meloxicam was measured by HPLC.

The apparent partition coefficients of meloixcam and its salts (MX-EAs) were measured using n-octanol and phosphate buffer (50 mM, pH 7.4). Meloxicam or each MX-EA was dissolved in pH 7.4 phosphate buffer (60 μg/ml) saturated with n-octanol. Meloxicam or MX-EA solutions in phosphate buffer (10 ml) were equilibrated with 10 ml of n-octanol at room temperature. After centrifugation and separation, the concentration of meloxicam in aqueous phase was measured by HPLC. The concentration of

the drug in organic phase was determined by subtracting the amount of drug in aqueous phase from the total amount. The pH of the solution was measured by a pH meter (Sartorious Professional Meter PP-15, Sartorious AG, Germany).

2-5. Transdermal Diffusion Cell system

Flow through diffusion cell system comprising a multi-channel peristaltic pump (IPC-24, Ismatec, Switzerland), a fraction collector (Retriever IV, ISCO, NE), a circulation water bath (CW-20G, JeioTech, Korea), and flow-through diffusion cells was used. The flow-trough diffusion cell consisted of two side arms, which enabled conduction of receiver cell media from a peristaltic pump to a fraction collector. The temperature was maintained at 37°C by circulating water at constant temperature through the outer jacket of the receiver cell. The surface area of the receiver cell opening was 2 cm^2, and the cell volume was 5.5 ml.

2-6. Procedure and Data Reduction

The preparation of the hairless mouse skins, the penetration study procedure and data reduction methods have been described in an earlier study [15]. 300 μl of saturated suspension in each test vehicle was applied on the skin. Samples were collected every 4 h for 36 h.

3. Results and Discussion

3-1. Characterization of MX-EAs

Monoethanolamine (MEA), diethanolamine (DEA), or triethanolamine (TEA) was used to prepare a salt of meloxicam. When meloxicam was added into the solvent, it was not completely dissolved in the solvent due to its low solubility in each solvent. However, as soon as MEA or DEA was added, the suspension became clear for a moment and then a precipitate was formed. At first, meloxicam dissolved completely because of the high pH induced by MEA or DEA, however, it started to precipitate after forming a salt with MEA or DEA due to the low solubility of meloxicam monoethanolamine (MX-MEA) and meloxicam diethanolamine salts (MX-DEA) in each solvent, which is an indirect evidence of salt formation. Although initial dissolving phenomenon was not observed when TEA was added, the color of the dispersed drug in methanol was changed, which indicated that some change of physicochemical property may have occurred. It seemed that dissolution of meloxicam and precipitation of meloxicam-triethanolamine salt (MX-TEA) might have occurred simultaneously, which made it hard to observe the initial dissolving effect. Meloxicam is also known to form a salt with ammonia by the addition of ethanolic ammonia and subsequent crystallization from water-isopropanol [3].

In order to confirm salt formation of meloxicam with ethanolamines, FT-IR spectrum was compared and is shown in Fig. 3. The strong and

narrow absorption peak at 3291cm^{-1} is attributed to N-H or O-H stretching vibration of meloxicam. Similar peak was observed with piroxicam [16]. In the case of MX-EAs, the characteristic peak of N-H or O-H vibration was shifted and broadened. These results indicate that strong intermolecular interaction has occurred between meloxicam and EAs. In the case of piroxicam, the negative charge on O (17) of piroxicam and the positive charge on the N atom of the EAs were expected to interact electrostatically [14] and similar mechanism is expected for meloxicam.

DSC thermograms for meloxicam and its salts are shown in Fig. 4 and the melting points of each compound are listed in Table 3. Zwitterionic drugs including meloxicam generally have high melting point. The melting point for meloxicam measured by DSC was 256.2°C, but after forming salt with EAs, the endothermal melting peaks were significantly shifted to lower temperature. This result is in good agreement with the report that salt of a zwitterion would have a lower melting point than the parent compound due to lower crystalline lattice energy [4]. Interestingly, two endothermal peaks were observed for MX-MEA. Narrow peak was appeared at 193.4°C and broad peak was appeared at 225°C. Similar DSC peak was observed in other report, which studied complexation of mefenamic acid with alkanolamines [16]. Melting point of mefenamic acid was also decreased after forming salts with alkanolamines and broad peak after the melting peak was due to complex decomposition. So, the large and narrow peak of MX-MEA at 193.4°C might be the melting point and the broad peak might be due to the decomposition of MX-MEA. In order to confirm whether the broad peak at 225°C is due to decomposition or not, additional experiment was conducted. If MX-MEA is decomposed at 225°C, endothermal melting

peak of the same compound will disappear when the DSC thermogram of the same compound is reprocessed. DSC thermogram was processed until the temperature reaches each of the endothermic temperature for MX-MEA and then cooled sufficiently until it becomes solid. DSC thermogram was reprocessed to figure out each of the peak still appears or not. As shown in Fig. 5, after the temperature was raised up to the first peak, it disappeared and only the second peak appeared. After raising the temperature up to the second peak, both of the peaks were disappeared. Melting Point Apparatus was also used to observe the state of MX-MEA at each of the endothermic temperature. As the temperature reached 193.4°C, only some part of MX-MEA melted and then was burnt black. Other part melted slowly until the temperature reached 250°C. At the temperature of 250°C, the color of melted MX-MEA was completely turned into black, which means that it was decomposed completely. These results indicate that both of the peaks are the melting peaks and so that there might be two different crystal forms exist for MX-MEA, which decompose as they melt.

The lipophilicity of an ionic drug is usually increased after formation of ion pair with counterions. The partition coefficients of quarternary ammonium compounds were increased by the lipophilic counter ions, such as n-alkylsulfonates and n-alkylcarbonates [5]. It was also reported that salt formations display enhanced partition towards n-octanol [17]. The apparent partition coefficients (APC) of meloxicam and MX-EAs between n-octanol and phosphate buffer (pH 7.4) are shown in Table 1. The partition coefficients of meloxicam salts were slightly lower than meloxicam and these results are not in accordance with other studies. Similar results

were obtained in a study with piroxicam ethanolamine salts and it was attributed to pH effect induced by ethanolamine [14]. The partition coefficient can be viewed approximately as the ratio of saturation solubility between two immiscible phases. Although the solubility of meloxicam in aqueous phase increased more than ten folds owing to the salt formation with ethanolamines, that in octanol did not change as much. If we focus only on the saturation solubility data, significant decrease in partition coefficient is expected by the formation of ethanolamine salts. However, it should be noted that the unusual high solubility in aqueous phase may be due to the pH effec tas mentioned before since the final pH values after reaching the saturation solubility was 8.44, 8.26 and 7.97 for MX-MEA, MX-DEA and MX-TEA, respectively. The extent of pH change is afunction of meloxicam salt concentration. Since the more meloxicam salt is dissolved in water, the more ethanolamine is available in the water and will increase the pH. In case of partition coefficient study, 60 μg/ml solution was used and the actual solubility will be lower due to the lower pH of the solution. The pH values of the aqueous phase from the determination of the partition coefficients did not increase for all the salts.

The solubilities of meloxicam and MX-EAs in various vehicles are summarized in Table II. After meloxicam formed a salt with MEA, the solubility of the drug was significantly increased up to 64 fold higher than meloxicam itself with an exception of cineole, Crovol® A 70, Tween® 20, Crodamol® IPM and Labrafac® PG in which the solubility did not change significantly or slightly decreased. The solubility of meloxicam was also increased after forming salt with DEA in many of the vehicles tested. However, the solubility of the drug was rather decreased after forming salt

with DEA in Crovol® PK 40, Crovol® EP 40, Crovol® A 70, Labrafil® 2609, Crodamol® IPM, Labrafac® PG and PPG 400. Although the solubilities of MX-MEA and MX-DEA salts were higher than that of meloxicam in many vehicles, the solubility of MX-TEA was lower than that of meloxicam in most of the vehicles except for Crovol® A 40 and propylene glycol. It has been claimed in the literature that the solubilities of certain groups of salts display an inverse relationship with melting point [18-20]. However, in the case of meloxicam, no relationship could be found between melting point and solubility since solibility of MX-MEA generally had higher solubility than others, even though MX-DEA had lowest melting point among MX-EAs. In addition, solubility of MX-TEA was lower than that of meloxicam, in spite of the fact that melting point of MX-TEA was lower than that of meloxicam. This result is similar with our previous study of piroxicam where the trend of solubility of piroxicam ethanolamine salts (PX-EAs) did not correlate with the order of melting points. So, it seems that other independent variables may be involved in the change of solubility after forming salts with EAs.

3-2. Effect of the Enhancers

Chemical enhancers are commonly incorporated in the transdermal formulations as one of the effective approaches to overcome the skin barrier. A vast array of chemical enhancers has been evaluated as penetration enhancers. They may increase the diffusion coefficient of the drug in the stratum corneum, may act to increase the effective concentration of the drug in the vehicle or could improve partitioning

between the formulation and the stratum corneum [8]. Since their mechanism of action in general are complex and they may have different enhancing effect depending on the physicochemical properties of penetrants as well as the enhancer itself [21], it is very important to select the proper enhancer for the model drug. So as to compare the enhancing effect of various vehicles and to compare permeability of meloxicam and its salts, the permeation of meloxicam and MX-EAs from saturated solutions in various vehicles across hairless mouse skin was investigated. An excess amount of solute was placed in each vehicle to maintain a constant donor concentration during the experiment. A saturated solution of a drug would maintain unit activity, therefore, all the saturated solutions of the same permeant in any solvent systems should produce an equal flux through the membrane in the absence of solvent-induced skin damage [15]. The vehicles used in the study include non-ionic surfactants, fatty acid esters, fatty acids, terpene and alcohols. They are known to enhance the transdermal delivery of many drugs through various mechanisms [8]. The average flux of meloxicam and MX-EAs across hairless mouse skin over 36h is shown in Table IV, and physicochemical properties of surfactants used in the study are shown in Table V. Meloxicam showed very low permeation across hairless mouse skin in most of the vehicles tested probably due to the zwitterionic nature of meloxicam. However, it was interesting to note that the flux of meloxicam from saturated solution in cineole showed significantly higher flux than all other vehicles tested although the solubility of meloxicam was the least in cineole solution. Cineole has been used to promote the percutaneous absorption of several lipophilic drugs through hairless mouse skin [22]. Terpenes including

cineole are reported to have effect on polar head groups of stratum corneum and break inter- and intralamellar hydrogen bonding network [23]. As shown in Table IV, the flux generally increased after forming salt with MEA and DEA. Especially when vehicle including Crovol® A 40, PEG 300, Labrasol® or Tween® 80 was used, the permeation across hairless mouse skin was remarkably increased by forming salt with MEA. This might be due to increased solubility of MX-MEA in those vehicles, since 10 to 64 fold higher solubility was observed after forming salt with MEA. It is interesting to note that the flux was also increased after forming salt with TEA, even though MX-TEA had lower solubility than that of meloxicam. This result is somewhat different from the study of piroxicam where both of the flux and solubility were decreased after forming salt with TEA [14]. So, this result shows that the increased permeability may be partly due to the increased solubility attained by forming salt with MEA or DEA and that, there are also some other factors affecting the enhanced flux across hairless mouse skin. Although meloxicam and piroxicam are both oxicam derivatives, salt formation with TEA showed some different effects on the permeation of parent compound.

Surfactants are reported to have structure-dependent effect on the enhancing capability. So, the percutaneous absorption can be different depending on the length of alkyl chain and polyoxyethylene chain of the surfactants [24, 25]. Our previous study indicated that non-ionic surfactants with medium HLB, an alkyl chain length of C_{18} and an EO chain shows better enhancing effect for piroxicam [14]. In the case of meloxicam, when surfactants which have same alkyl chain length with different ethylene oxide (EO) chain length are compared, Crovol® A 40 (EO

= 20, C_{18}) showed highest enhancing effect among the surfactants. However, Crovol® A 70 (EO = 60, C_{18}) and Tween® 80 (EO = 20, C_{18}) showed much lower flux, so it was not possible to find any trend between the EO chain length and the measured flux. Labrasol® (C_8, C_{10}), Labrafac® PG (C_8, C_{10}), and Tween® 20 (C_{11}) which have shorter alkyl chain length provided rather lower enhancing effect than others which have alkyl chain length of C_{16}-C_{18}. HLB can also affect the percutaneous absorption of a drug. The results showed that, Crovol® A 40 (HLB 10) had higher enhancing effect than Labrasol® (HLB 14), Tween® 80 (HLB 15), Tween® 20 (HLB 16.5) and Crovol® A 70 (HLB 15) which are more hydrophilic surfactants. They also showed higher enhancing effect than Labrafac® PG (HLB 2) which is more hydrophobic vehicle. Although it may be too soon to draw a conclusion, the permeation data indicates that nonionic surfactants with moderate HLB and alkyl chain length of C_{18}, which were effective for piroxicam may also be effective for meloxicam and MX-EAs.

3-3 Conclusions

The MX-EA salts were obtained by simply mixing meloxicam with ethanolamines in organic solvent and the salt formations were confirmed by DSC, FT-IR and solubility measurements. The solubilities of meloxicam in various vehicles and the permeability across hairless mouse skin were increased after forming salt with ethanolamines. The results suggest that MX-EAs can be utilized in the development of transdermal delivery system.

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Table I. Apparent partition coefficient and solubility of of meloxicam or MX-EAs.

	APC	Solubility (mg/ml)[a]	Solubility (mg/ml)[b]
Meloxicam	1.42 ± 0.02	0.15 ± 0.01	0.74 ± 0.06
MX-MEA	1.39 ± 0.01	0.90 ± 0.02	8.36 ± 0.44
MX-DEA	1.40 ± 0.02	0.06 ± 0.001	8.23 ± 1.61
MX-TEA	1.40 ± 0.01	0.09 ± 0.001	4.36 ± 0.09

APC = apparent partition coefficient between n-octanol and phosphate buffer 7.4.

a = solubility in n-octanol.

b = solubility in phosphate buffer 7.4.

Each value represents the mean ± SD (n = 3).

Table II. Comparison of the solubility of meloxicam and MX-EAs in various vehicles (Measured as the amount of meloxicam dissolved).

Vehicle	meloxicam	MX-MEA	MX-DEA	MX-TEA
	Solubility(mg/ml)			
cineole	0.07 ± 0.01	0.10 ± 0.01	0.10 ± 0.02	0.06 ± 0.01
crovol® EP 40	7.26 ± 0.73	9.28 ± 1.54	7.10 ± 0.29	3.64 ± 0.11
crovol® A 40	3.10 ± 0.21	79.61 ± 2.35	8.88 ± 0.93	5.02 ± 0.34
propylene glycol	0.28 ± 0.05	10.02 ± 0.59	17.13 ± 0.43	5.18 ± 0.36
crovol® A 70	8.45 ± 0.31	8.45 ± 0.1	7.72 ± 0.04	4.86 ± 0.01
PEG 300	3.62 ± 0.06	144.70 ± 0.63	30.00 ± 1.76	2.86 ± 0.01
tween 20	8.17 ± 0.76	8.67 ± 2.22	9.71 ± 0.90	4.07 ± 0.006
Crodamol® IPM	0.08 ± 0.0005	0.01 ± 0.0003	0.002 ± 0.0007	0.0002 ± 0.0001
labrafac® PG	0.27 ± 0.01	0.20 ± 0.004	0.003 ± 0.0005	0.002 ± 0.0008
labrasol®	2.75 ± 0.03	175.77 ± 15.39	4.29 ± 0.09	0.95 ± 0.10
tween® 80	5.42 ± 0.03	137.54 ± 2.39	8.45 ± 0.001	3.18 ± 0.001
PPG 400	0.74 ± 0.05	6.51 ± 0.52	0.18 ± 0.06	0.16 ± 0.007

Each value represents the mean ± SD (n = 3).

Table III. Melting points of meloxicam and MX-EAs.

	Melting point (°C)
meloxicam	256.2
MX-MEA	193.4
MX-DEA	181.3
MX-TEA	213.6

Table IV. Effect of various vehicles on the permeation of meloxicam and MX-EAs from saturated solution.

Enhancer	meloxicam	MX-MEA	MX-DEA	MX-TEA
	Flux (μg/2cm^2/h)			
Cineole	6.48 ± 0.88	13.87 ± 0.81	47.14 ± 1.17	13.73 ± 0.62
Crovol® EP40	0.20 ± 0.04	2.47 ± 0.80	2.09 ± 0.33	0.54 ± 0.14
Crovol® A 40	0.41 ± 0.01	20.65 ± 8.22	5.30 ± 1.02	1.45 ± 0.34
Propylene glycol	0.18 ± 0.10	0.40 ± 0.07	1.09 ± 0.46	0.17 ± 0.01
Crovol® A 70	0.051 ± 0.01	0.30 ± 0.03	0.04 ± 0.008	0.09 ± 0.08
PEG 300	0.048 ± 0.006	0.32 ± 0.07	0.05 ± 0.001	0.07 ± 0.05
Tween® 20	0.042 ± 0.010	0.12 ± 0.05	0.02 ± 0.009	0.03 ± 0.01
Crodamol® IPM	0.15 ± 0.01	0.99 ± 0.24	0.53 ± 0.17	0.46 ± 0.12
Labrafac® PG	0.08 ± 0.01	0.50 ± 0.14	0.31 ± 0.10	0.08 ± 0.04
Labrasol®	0.02 ± 0.004	0.45 ± 0.15	0.033 ± 0.006	0.04 ± 0.03
Tween® 80	0.03 ± 0.002	1.62 ± 0.74	0.11 ± 0.07	0.13 ± 0.08
PPG 400	0.03 ± 0.007	0.08 ± 0.02	0.106 ± 0.06	0.02 ± 0.01

The amount permeated is expressed as the amount of meloxicam in all cases.
Each value represents the mean ± SD (n = 3).

Table V. Physicochemical information of the surfactants used in this study.

Enhancer	hydrophobic portion	EO chain length	Number of double bonds	HLB
Crovol® EP40	Linoleate (C_{18}) ɣ-Linolenic acid (C_{18})	20	2 (cis), 3	10
Crovol® A 40	Oleate (C_{18})	20	1 (cis)	10
Crovol® A 70	Oleate (C_{18})	60	1 (cis)	15
Labrasol®	Caprylate (C_8) Caprate (C_{10})	8	saturated	14
Tween® 80	Oleate (C_{18})	20	1 (cis)	15
Tween® 20	Laurate (C_{11})	20	1 (cis)	16.7
Labrafac® PG	Caprylate (C_8) Caprate (C_{10})	-	-	2

EO = ethylene oxide.
HLB = hydrophile lipophile balance.

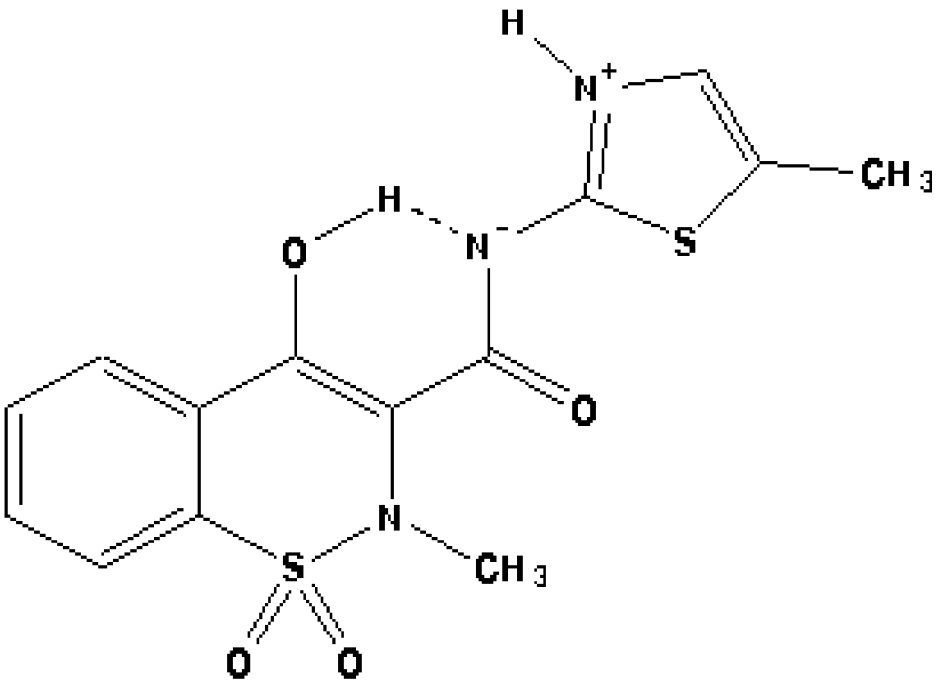

Fig. 1. The structure of the zwitterion form of meloxicam.

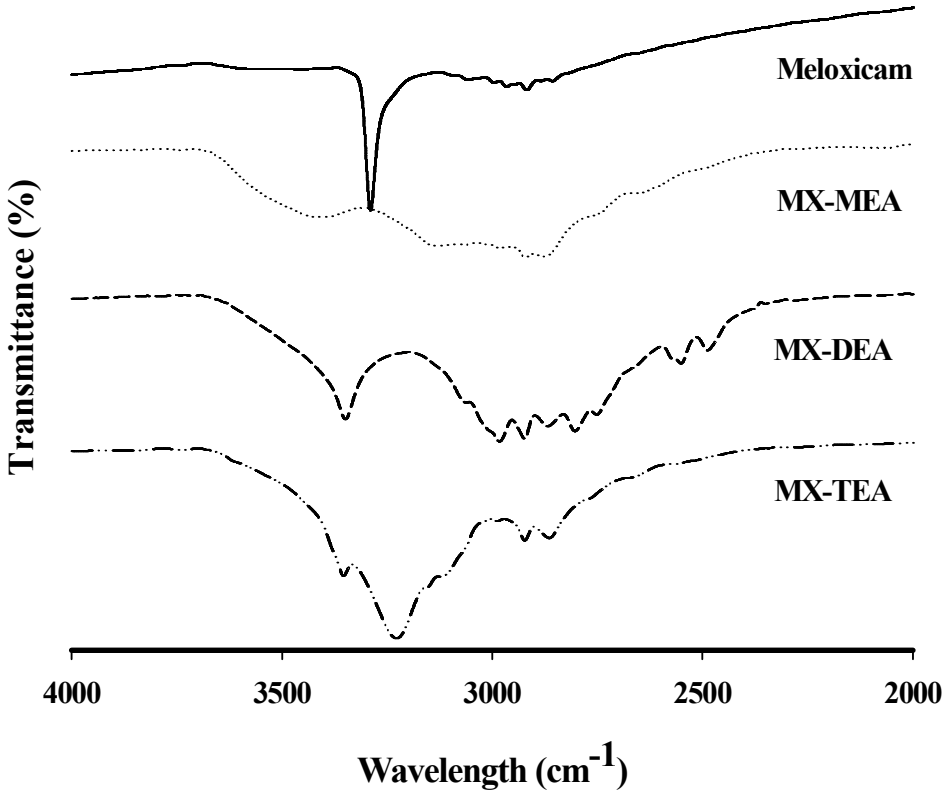

Fig. 2. FT-IR spectra of meloxicam and meloxicam ethanolamine salts.

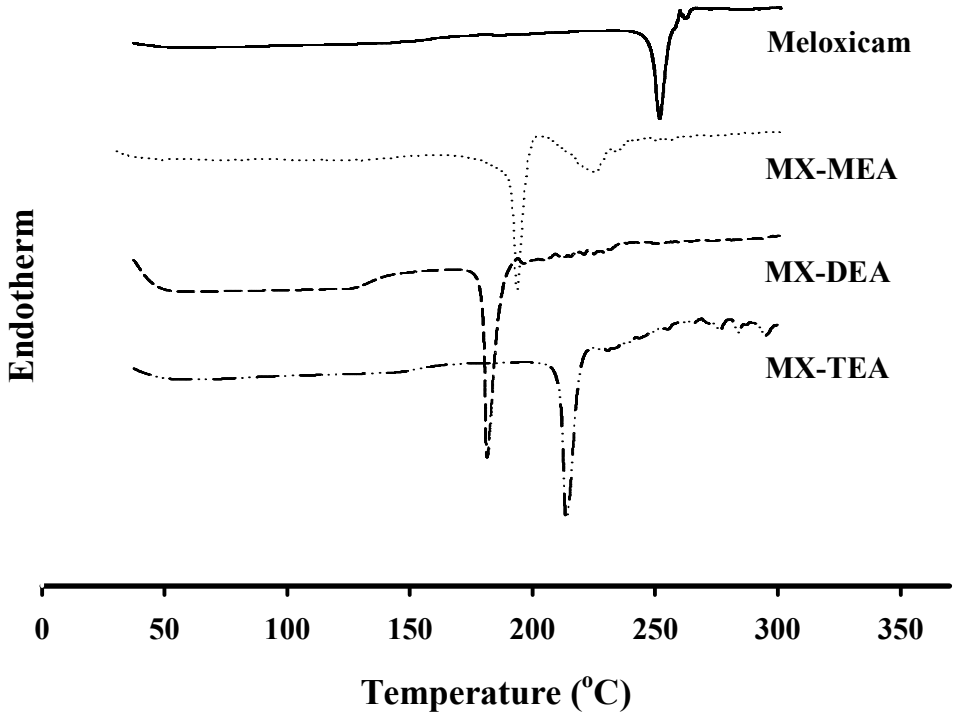

Fig. 3. DSC thermograms of meloixcam and meloxicam ethanolamine salts.

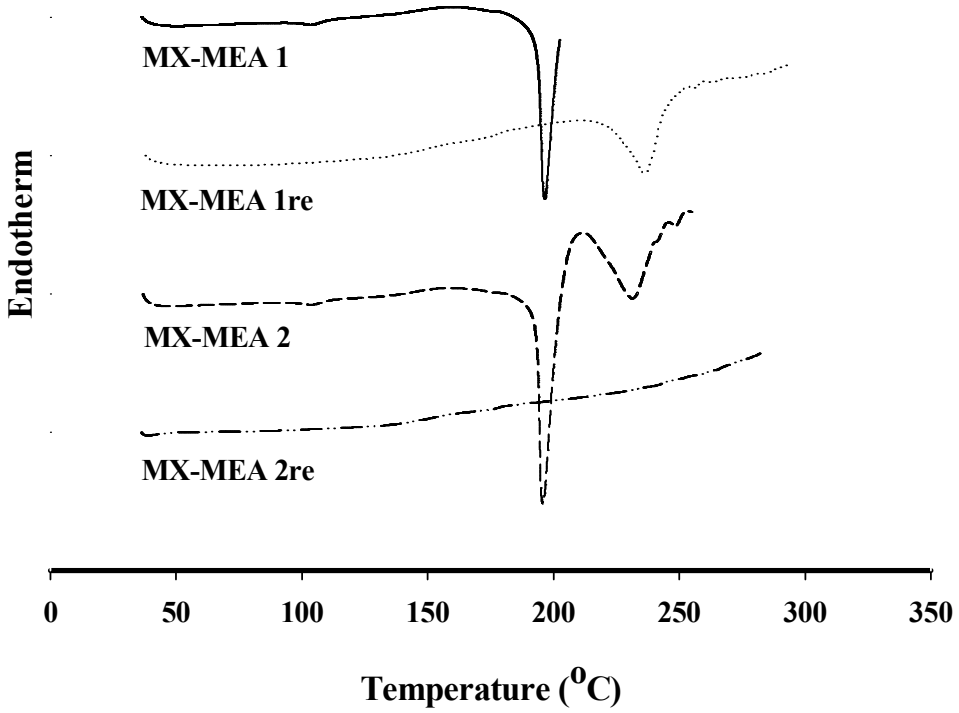

Fig. 4. DSC thermograms of meloxicam monoethanolamine salt to confirm the decomposition at different temperature.