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Effect of Ethanolamine Salts and Enhancers on the Percutaneous Absorption of Meloxicam from a Pressure Sensitive Adhesive Matrix

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ABSTRACT – The purpose of this study was to investigate the effect of salt formation on the percutaneous absorption of meloxicam through hairless mouse skin from a pressure sensitive adhesive (PSA) matrix. In addition, the influences of enhancers on the permeation of meloxicam or meloxicam-ethanolamine (MX-EA) salts across the hairless mouse skin were evaluated using a flow-through diffusion cell system. The salt formation of meloxicam resulted in lower permeation rate than the parent drug. Span® 80 provided the highest enhancing effect for meloxicam and meloxicam monoethanolamine salt. The maximum amount of the drug that can be loaded without retarding permeation rate was different depending on the compound. No relationship was found between the fluxes of meloxicam or MX-EA salts from saturated solutions and those from PSA matrices containing the same enhancer.

Key words – Salt, Meloxicam, PSA matrix, Enhancer, Skin permeability

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for various arthritic conditions and inflammations including rheumatoid arthritis, osteoarthritis, and other joint diseases. Oral administration of NSAID is generally used to reduce the symptoms of such diseases. However, its use is often limited by gastro-intestinal (GI) adverse effects.[1] One promising method to avoid the GI adverse effects, minimize systemic toxicity and achieve a better therapeutic effect is administering the drug via skin.[2] Because of these benefits, many NSAIDs have been used as candidates for transdermal delivery and some of them have already been developed and marketed for many years. However, due to the lack of systemic efficacy, patients still need a medication having higher anti-inflammatory and analgesic effect.

Meloxicam has low daily dose (7.5 - 30 mg/day) and higher anti-inflammatory effect than usual NSAIDs and has been used as a model drug to treat arthritis and rheumatism.[3,4] Since meloxicam is a zwitterionic drug, it has extremely low solubility, low lipophilicity and low skin permeability.[5] In order to increase solubility and skin permeability of meloxicam, we used the concept of ion-pair formation. Ethanolamines were used as a counter ion for meloxicam to form an ion-pair. The physicochemical properties and percutaneous absorption of meloxicam-ethanolamine salts from saturated solutions across hairless mouse skin were studied in our previous work.[6] The solubility and skin permeation of meloxicam were increased by forming salt with monoethanolamine and diethanolamine. Although the solubility of meloxicam-triethanolamine salt was lower than that of meloxicam, its permeation rate was higher.

The majority of recently approved transdermal delivery system in the USA is drug-in-adhesive type, suggesting that this type of delivery is very attractive to patients.[7] Selection of a pressure sensitive adhesive matrix and an effective permeation enhancer are very crucial to the development of a transdermal drug delivery system. Even though enhancers could be selected based on the solution formulation study, the enhancing effect may or may not be achieved when they are incorporated in a PSA matrix.

In this study, the effect of MX-EA salts in combination with various enhancers on the percutaneous absorption of meloxicam from a PSA matrix across hairless mouse skin was investigated. Also, the influence of the functional groups of PSA matrices and drug loading amount on the permeability of meloxicam or MX-EA salts through hairless mouse skin from PSA were evaluated. In addition, the fluxes of meloxicam or MX-EA salts from saturated solutions and those from PSA matrices were compared.

Materials and Methods

Materials

Meloxicam was obtained from Hana Pharmaceutical Co. (Seoul, Korea). Monoethanolamine, diethanolamine and triethanolamine were purchased from Sigma Chem. Co. (St. Louis, MO, USA). PEG-8 glyceryl linolate (Labrafil® WL 2609) and polyglyceryl-3 oleate (Plural oleique® CC 497)

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were obtained from Gattepossе Korea (Seoul, Korea). PEG-2 almond glyceride (Crovol® A 40), 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) and polyoxyethylene sorbitan monolaurate (Tween® 20) were purchased from Junsei Chemical Co. (Tokyo, Japan). Cineole was purchased from Aldrich Chem. Co. (Milwaukee, WS, USA). Acrylic adhesives were obtained from National Starch & Chemical (Bridgewater, NJ, USA). All other chemicals were of reagent grade or above and were used without further purification.

Preparation of MX-MEA (meloxicam-monoethanolamine salt), MX-DEA (meloxicam-diethanolamine salt and MX-TEA (meloxicam-triethanolamine salt)

The method used for the preparation of piroxicam ethanolamine salts were used with minor modifications.[8] Briefly, meloxicam was dispersed in organic solvent and an equi-molar amount of each ethanolamine was added. The solutions were stirred for 24 hr. The salts precipitated and were collected by filtration. The filtrate was washed with n-hexane several times. Light yellow solid residues were dried in vacuum for 3 hr.

HPLC Methodology

Meloxicam and its salts were analyzed by a HPLC system (Shimadzu Scientific Instruments, MD, USA), which consisted of an UV detector (SPD-10A), a pump (LC-10AD), and an automatic injector (SIL-10A). The wavelength of UV detector was set at 320 nm and the retention time of the meloxicam was 3.25 min. A reversed phase column (Luna 5 μm C8, Phenomenex) was used for the analysis. The column temperature was maintained at 30°C using a thin foil temperature controller (CH 1445, SYSTEC, MN, USA). The flow rate was 1 ml/min. and methanol/water/phosphoric acid (700/299/1) was used as the mobile phase. 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.

Preparation of the PSA matrix formulation

Acrylic adhesive solution in organic solvent mixture was mixed with meloxicam or each of MX-EA solution with or without an enhancer according to the study protocol. PSA matrix was prepared by casting the above solution on the release liner coated with silicone using a casting knife. It was set at room temperature for 20 min and dried in the oven at 80°C for 30 min and 110°C for 5 min to remove the residual organic solvents. The dried film was laminated onto a backing film. The thickness of dried film was 160 μm. No crystal was observed at the time of in vitro diffusion study.

In vitro transdermal Diffusion Cell system

Flow through diffusion cell system, consisting of a multi-channel peristaltic pump (IPC-24, Ismatec, Switzerland), a fraction collector (Retriever IV, ISCO, NE, USA), a circulation water bath (RB-10, JeioTech, Korea), and flow-through diffusion cells were 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.

Procedure and Data Reduction

The preparation of the hairless mouse skins, the penetration study procedure and data reduction methods have been described in previous study.[9] Samples were collected every 4 hr for 28 hr.

Results and discussion

Effect of meloxicam salt formation in the PSA matrix on the percutaneous absorption of meloxicam

The effect of the chemical nature of acrylic adhesive matrix on the permeation of meloxicam was investigated. Figure 1 shows the permeation profile of meloxicam across hairless mouse skin from acrylic PSA matrix with hydroxyl, carboxyl,

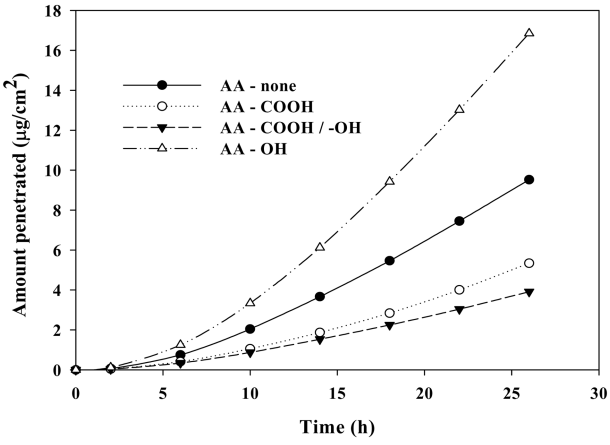

Figure 1–Effect of functional group of acrylic adhesive on the permeation of meloxicam and MX-EAs across the hairless mouse skin. AA-none = acrylic adhesive without functional group, AA-COOH = acrylic adhesive with carboxyl functional group, AA- COOH / -OH = acrylic adhesive with carboxyl and hydroxyl functional group, AA-OH = acrylic adhesive with hydroxyl functional group.

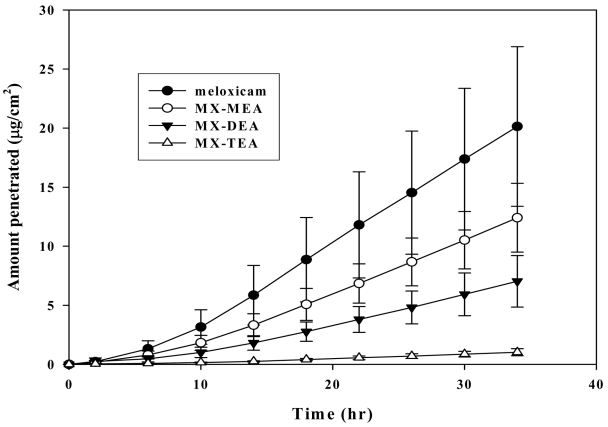

Figure 2–Cumulative amount of meloxicam and MX-EAs permeated from an adhesive matrix. The amount permeated is expressed as the amount of meloxicam in all the cases. Each point represents an average of three measurements.

or no functional group. The flux of meloxicam from the acrylic adhesive with hydroxyl functional group was higher than those from other matrices. The flux from acrylic PSA with carboxyl functional group was the lowest. The penetration of the drug across the skin could have been hindered due to the interaction between the carboxyl functional group in the acrylic PSA and the amine group of meloxicam, resulting in the lower permeation rate. Based on this flux result, acrylic adhesive with hydroxyl functional group was selected for the further study.

The penetration profiles of meloxicam and its salts across hairless mouse skin from the PSA matrix are shown in Fig. 2. Penetration of meloxicam and its salts were compared to investigate the effect of salt formation on the skin permeation rate of meloxicam. Since salt formation provided higher skin permeation rate than that of parent drug in the previous study using solution formulations[6], it was expected that the salt formations would also provide higher skin permeation rate than the parent drug from adhesive matrix. However, as can be seen in Fig. 2, the results were different from our previous results obtained using solution formulations. Meloxicam showed the highest permeation rate followed by MX-MEA, MX-DEA, and MX-TEA.

Since the maximum amount of drug that can be loaded into PSA matrix can be different depending on the physicochemical properties of the drug, the effect of drug loading was investigated using meloxicam and its ethanolamine salts. Fig. 3 shows the effect of drug loading on the flux of meloxicam and ethanolamine salts across the hairless mouse skin. The permeation rate of meloxicam increased with increasing the amount of meloxicam loaded in PSA matrix up to 3.5% of total weight of matrix layer. The flux of meloxicam significantly retarded when over 4.0% of the drug was loaded in the

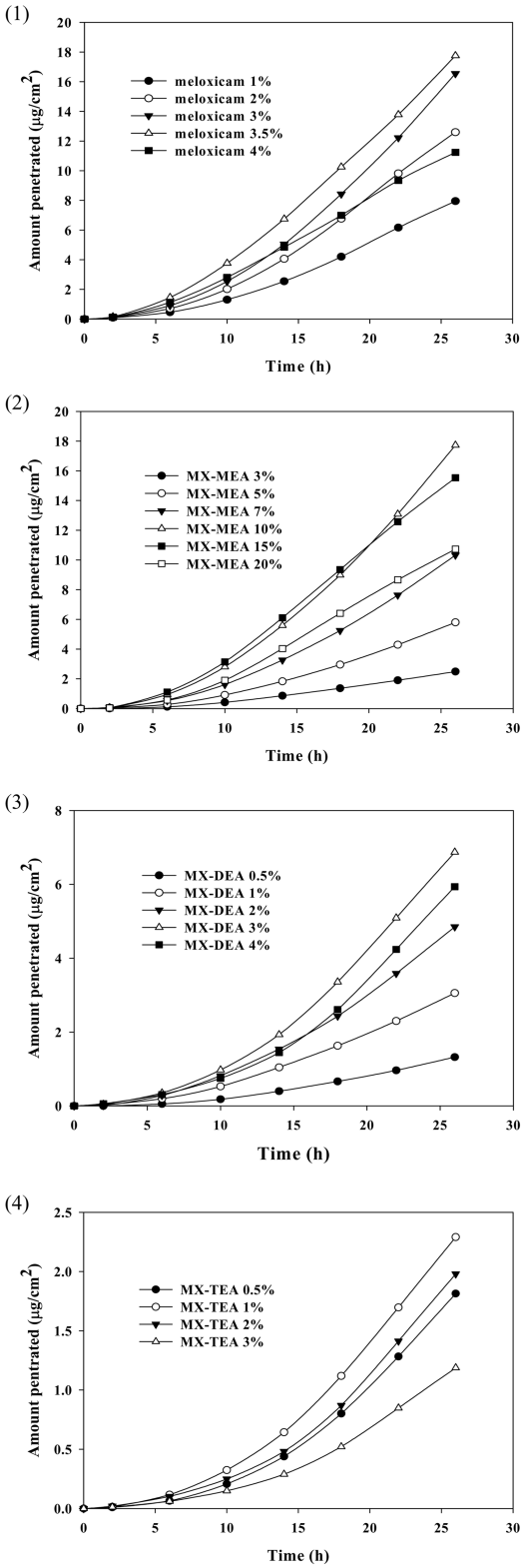

Figure 3–Effect of drug loading on the permeation of meloxicam across the hairless mouse skin from acrylic adhesive matrix. The percentage in the legend represents amount of meloxicam loaded in acrylic adhesive polymer (% w/w). Each point represents average of three measurements.

Table I–*Effect of Various Enhancers on the Permeation of Meloxicam and MX-EA Salts from PSA Matrix Across the Hairless Mouse Skin When 20% of Each Enhancer is Incorporated*

Enhancer	meloxicam	MX-MEA	MX-DEA	MX-TEA
	Flux ($\mu g/cm^2/h$)			
Span® 80	3.91 ± 0.77	3.23 ± 0.33	1.37 ± 0.24	0.30 ± 0.06
Plural oleique®	2.63 ± 0.27	2.04 ± 0.11	1.12 ± 0.32	0.25 ± 0.04
Labrafil® 2609	1.75 ± 0.45	0.93 ± 0.19	0.92 ± 0.01	0.44 ± 0.05
Crovol® PK 40	2.12 ± 0.44	1.80 ± 0.52	0.86 ± 0.06	0.57 ± 0.03
Crovol® EP40	1.29 ± 0.03	1.26 ± 0.30	0.40 ± 0.15	0.14 ± 0.03
Crovol® A 40	1.86 ± 0.47	2.23 ± 0.42	0.37 ± 0.09	0.56 ± 0.11
Cineole	0.50 ± 0.11	0.46 ± 0.14	0.34 ± 0.06	0.11 ± 0.01
Tween® 20	0.75 ± 0.05	0.40 ± 0.09	0.10 ± 0.04	0.08 ± 0.04
Oleic acid	0.31 ± 0.06	3.12 ± 0.30	2.32 ± 0.40	0.28 ± 0.09
Control	0.56 ± 0.12	0.55 ± 0.14	0.25 ± 0.04	0.07 ± 0.002

PSA matrix, indicating that meloxicam was already saturated at 3.5% level. In the case of MX-MEA, they seemed to have higher solubility in PSA matrix than meloxicam. The flux of MX-MEA increased up to 10% loading and decreased when the loading content was higher than 10%. It seemed that the lower flux of MX-MEA than meloxicam in the previous study might be due to its high solubility in the PSA matrix. Although 3.5% meloxicam and 10% MX-MEA showed similar flux at the end of the permeation study, initial flux was higher in case of meloxicam. The permeation profile of MX-DEA and MX-TEA showed that maximum flux was obtained at 3% of MX-DEA and 1% of MX-TEA, indicating relatively low solubility of both compounds. Theoretically, the flux from adhesive matrix should increase until the content of a drug reaches saturation solubility in the adhesive matrix and remain unchanged beyond saturation solubility. It is not clear why the flux decreased when the loading content exceeded a certain point. One of the reasons for the decreased flux is that the diffusion pathway of the drug may be blocked by the drug crystals present in the matrix.

Unlike solution formulation, the flux of meloxicam from PSA matrix was decreased after forming a salt with ethanolamines, which is different from the results obtained using piroxicam.[8] The permeation rates of piroxicam monoethanolamine and diethanolamine salt through hairless mouse skin from both saturated solution and PSA matrix increased when compared with that of piroxicam. Although both compounds are oxicam derivatives, the effect of salt formation was quite different.

Effects of enhancers on the permeability of meloxicam and MX-EA salts across hairless mouse skin

Chemical enhancers are usually required in the development of a matrix type transdermal delivery system. Most enhancers are known to interact with the intercellular lipid domain of the stratum corneum and act by increasing the diffusivity or thermodynamic activity of the drug in the vehicle and the skin.[10] However, none has been proved to be an ideal enhancer to date[11] due to the fact that the effect of enhancer can be different depending on drugs and other additives used. To investigate the effect of various enhancers on the permeation of meloxicam and its salts across the hairless mouse skin, various enhancers were incorporated into the acrylic adhesive matrix. In addition, fluxes from PSA matrices were compared with those from saturated solutions. Since the solubility of meloxicam and its salts in PSA were different, the loading content showing the highest flux for each compound was chosen and various enhancers were added to PSA matrix at 20% level. The fluxes of meloxicam and MX-EA salts are shown in Table 1. The order of the permeation rate from the PSA matrix was meloxicam>MX-MEA>MX-DEA>MX-TEA, except when Crovol® A40 or oleic acid was used as an enhancer. It is quite similar to the results obtained without enhancer. However, the effectiveness of the vehicles on the permeation rate was different depending on the compound used. In the case of meloxicam, Span® 80 was the most efficient vehicle followed by Plural oleique® CC 497, Crovol® PK40, and Crovol® A40. Although Span® 80 was the most efficient vehicle for MX-MEA, the second most efficient enhancer was oleic acid. In case of MX-DEA, oleic acid showed the highest flux followed by Span® 80, Plural oleique® CC 497, and Labrafil® WL 2609.

The effect of concentration of enhancers in PSA matrix on the permeation rate of meloxicam across the hairless mouse skin was investigated and the results are shown in Fig. 4. When the amount of enhancer added to the PSA matrix was

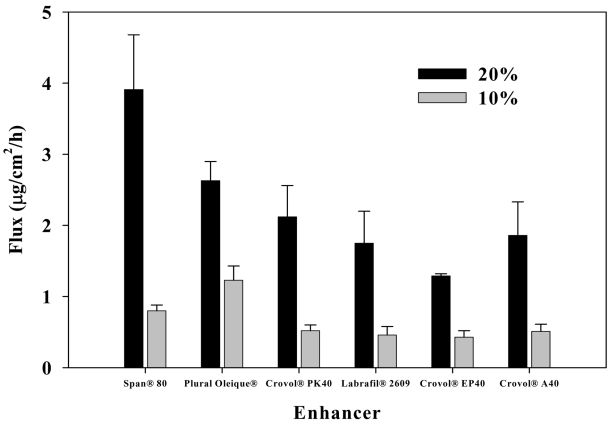

Figure 4–Effect of concentration of various enhancers on the permeation of meloxicam from PSA matrix across the hairless mouse skin.

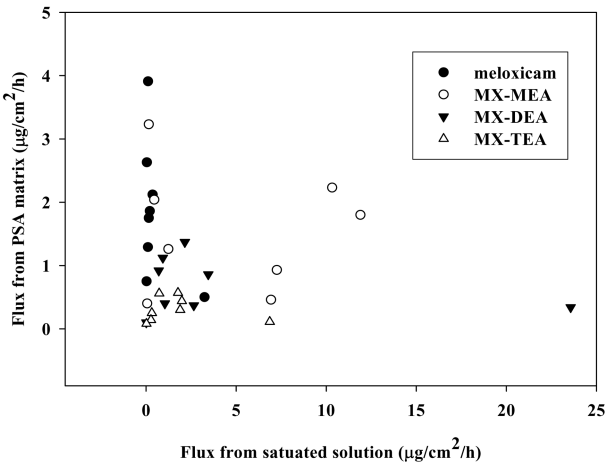

Figure 5–Relationship between the flux from a saturated solution and that from a PSA matrix.

reduced from 20% to 10% level, the flux of the meloxicam decreased at a different rate depending on the enhancer incorporated. While the enhancing effect of Span® 80 was reduced by 80% when compared to the flux obtained using 20% of Span® 80, that of Plural oleique® CC 497 was reduced by approximately 50%.

The enhancing effects of vehicles incorporated in PSA matrix were different from those obtained in the previous study using saturated solutions.[6] Cineole, which showed the highest flux in saturated solution, showed relatively low flux in PSA matrix. The relationship between fluxes from saturated solutions and those from the PSA matrix containing the same vehicles is compared in Fig. 5. There was no correlation between the flux from saturated solution and that from PSA matrix through hairless mouse skin for all the compounds tested. The correlation coefficients were – 0.49, – 0.05, – 0.27 and – 0.17 for meloxicam, MX-MEA, MX-DEA and MX-TEA respectively. The results indicated that the flux data obtained from solution formulation should not be extended to predict the flux from PSA matrix.

Axknowledgements

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