Transdermal Administration of Emedastine

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Transdermal administration of emedastine was tested in vitro and in vivo. In the diffusion cell method in vitro, emedastine free base was more permeable by transdermal administration than emedastine difumarate. Emedastine had higher permeability in hydrophobic vehicles than in hydrophilic vehicles, and was most permeable in fatty acid monesters. It was suggested that the change in permeability of emedastine from these vehicles was dependent on the change in its partition from the vehicle to the skin. In studies using rabbits in vivo, emedastine had high permeability from fatty acid monesters and fatty acid diesters as found in in vitro studies, and bioavailability of the drug after transdermal administration was greater than that after peroral administration. The flux of emedastine in vitro was correlative with the pharmacokinetic parameters in vivo. Consequently, it is clear that transdermal permeability of emedastine is very high and that the drug may be efficacious in the system after administration by these means.

Keywords emedastine; fatty acid ester; transdermal administration; vehicle; permeability coefficient; hydrophobicity

1-(2-Ethoxyethyl)-2-(hexahydro-4-methyl-1H,4-diazepin-1-yl)-1H-benzimidazole (hereafter referred to as emedastine) is a compound of the following formula:

![Chemical structure of Emedastine]

which has a strong antihistaminic activity, and is useful for the prophylaxis and treatment of diseases caused by histamine such as allergic bronchial asthma, allergic dermatitis, and allergic rhinitis.\(^1\) Due to its high aqueous solubility, difumarate salt of emedastine was chosen for peroral administration, however emedastine difumarate exhibits extensive first-pass effect. If given transdermally, emedastine would bypass the gastrointestinal tract, thereby circumventing the first-pass metabolism. Consequently, a lower dose could be given, and the associated side effects of the drug would be reduced.

The penetration of drugs through the intact human skin has generally been shown to be very poor. The composition of the vehicle is believed to affect significantly the ability of a drug in a topical formulation to penetrate the skin.\(^2\)\(^-\)\(^5\) Release of a drug from the vehicle is thought to be influenced by drug-vehicle, drug-skin and vehicle-skin interactions. Thus, the purpose of this report is to describe the effect of vehicle composition on the penetration of emedastine and its difumarate salt.

Materials and Methods

Materials Emedastine difumarate and its related compound, 1-(2-ethoxyethyl)-2-(4-methyl-1-piperazinyl) benzimidazole 3:2 fumarate (KB-1088) were synthesized by Kamebo. Emedastine difumarate was a white to light yellow crystalline powder. It has weak base with molecular weight of 534.57, a melting point of 148 to 152°C and pKₐ of 4.5 and 8.5. Emedastine free base (M.W.: 302.42) was extracted with ethyl acetate from emedastine difumarate solution at pH 11. It was a light yellow oily liquid and freely soluble in ether, octanol and ethanol. Fatty acid monester and fatty acid diesters were used as vehicles for transdermal administration of emedastine. The fatty acid monesters were as follows: ethanol hexanoate \([\text{CH}_2(\text{CH}_2)_n\text{COOCH}_3\text{H}_2]_n\), ethyl octanoate \([\text{CH}_2(\text{CH}_2)_n\text{COOCH}_3\text{H}_2]_n\), ethyl decanoate \([\text{CH}_2(\text{CH}_2)_n\text{COOCH}_3\text{H}_2]_n\), ethyl laurate \([\text{CH}_2(\text{CH}_2)_n\text{COOCH}_3\text{H}_2]_n\), isopropyl myristate \([\text{CH}_3(\text{CH}_2)_n\text{COOCOOCH}_3\text{H}_2]_n\), butyl stearate \([\text{CH}_2(\text{CH}_2)_n\text{COOCH}_3\text{H}_2]_n\), and ethyl oleate \([\text{CH}_2(\text{CH}_2)_n\text{CH}_3\text{COOCH}_3\text{H}_2]_n\). The fatty acid diesters were as follows: diethyl succinate \([\text{CH}_2(\text{OOCCH}_3\text{H}_2)_n\text{COOCH}_3\text{H}_2]_n\), diethyl adipate \([\text{CH}_2(\text{OOCCH}_3\text{H}_2)_n\text{COOCH}_3\text{H}_2]_n\), dioctyl sebacate \([\text{CH}_2(\text{OOCCH}_3\text{H}_2)_n\text{COOCH}_3\text{H}_2]_n\), diethyl sebacate \([\text{CH}_2(\text{OOCCH}_3\text{H}_2)_n\text{COOCH}_3\text{H}_2]_n\), the carboxyls, propylene glycol, ethanol, octanol, isopropyl alcohol, and formamide were obtained commercially from Wako Pure Chemical Ind., Osaka. Hydrophilic ointment and macrogel ointment were prepared in accordance with the Pharmacopeia of Japan XIII. All reagents were of analytical grade. Poloid \(^6\) which was prepared with liquid paraffin gelled by polyethylene resin was purchased from Ishihamo Pharmaceutical Co., Ltd., and white petrolatum was purchased from Nikko Rica Co. as Sun White (P-1)\(^8\).

In Vitro Diffusion Cell Study The diffusion cell (Kerceo Engineering Consultants, Palo Alto, California, U.S.A.) was the same as that used by Sloan et al.\(^7\) It consisted of a plexiglass chamber (45 ml) with a side arm to allow sampling of the receptor phase, a polyfot lid, and a rubber gasket. Male Wistar rats (185—260 g) were anesthetized with ether, and their abdominal hair clipped with electric hair clippers one day before the experiment. The abdominal skin was excised, and stretched over the lower opening of the lid of a diffusion cell, and secured with a rubber gasket. After securing the skin, the lid was placed firmly on the lower chamber with screws. The area available for diffusion was 8.04 cm². The dermal side was in contact with a receptor solution. The receptor chamber was filled with 45 ml isotonic phosphate buffer solution (pH 7.4) and the receptor compartment was agitated with a magnetic stirrer. The diffusion cell was placed in a 37°C air bath. Concentration of the test formulations were 20.0% of emedastine equimolar to 35.4% of emedastine difumarate in phosphate buffer (pH 3.0, 6.4, 10.3), and was 20.0% of emedastine for formulations in the following vehicles: ethanol, propylene glycol, octanol, isopropyl alcohol, formamide, isopropyl myristate, diethyl sebacate, white petrolatum, Poloid,\(^6\) hydrophilic ointment, macrogel ointment, fatty acid monesters, and fatty acid diesters. One gram of the test formulation was applied to the epidermal side. Samples of 0.1 ml were removed periodically from the receptor phase via the side arm and were analyzed by high performance liquid chromatography (HPLC).

HPLC Analysis of Emedastine for In Vitro Study To determine the concentration of emedastine by HPLC, the chromatograph used was model LC-5A (Shimadzu, Kyoto) equipped with a UV detector (SPD-2A, Shimadzu) operated at 280 nm. Adsorbent column (ODS column (5 μm; 150 mm, Shimadzu, Kyoto) was used at a reversed phase mode phase. A mixture of acetonitrile and 0.025 M phosphate buffer (pH 2.4) containing 0.25% sodium lauryl sulfate (5:5 by volume) was the mobile phase at a flow rate of 1.4 ml/min.

In Vivo Administration Study with Rabbits Male Japanese white rabbits (2.5—3.5 kg) were used.

1) Intravenous Administration (20 mg of Emedastine Difumarate/kg Body Weight): A solution containing 66.7 mg/ml of emedastine difumarate in distilled water was used for intravenous injection. The rabbits were injected with 0.3 ml/kg body weight of emedastine difumarate solution into the left auricular vein with a syringe.

2) Peroral Administration (20 mg of Emedastine Difumarate/kg Body Weight):
Weight): A solution containing 10 mg/ml of emedastine difumarate in distilled water was used for peroral administration. The rabbits were given 2 ml/kg body weight of emedastine difumarate solution orally into the stomach using a polyethylene tube.

3) Transdermal Administration (11.3 mg of Emedastine/kg Body Weight): The formulation containing 200 mg/g of emedastine in the vehicle was applied to the left hairless scapula of rabbit (3 x 5 cm² area).

Following the administration, 1 ml of blood was collected from the right auricular vein at appropriate intervals. Blood samples were centrifuged, and 0.4 ml of plasma sample was withdrawn for measurement of emedastine.

Determination of Emedastine in Plasma: Measurement of emedastine concentration in plasma was achieved by gas liquid chromatography (GC) using a nitrogen sensitive detector.7 A plasma of 0.4 ml was mixed in a 10 ml glass-stoppered centrifuge tube with 1 ml of 0.2 N sodium hydroxide and 6 ml of benzene. The mixture was vigorously shaken for 10 min and centrifuged for 10 min at 3000 rpm. Five milliliters of the organic layer was transferred into another centrifuge tube containing 2 ml of 1 N hydrochloric acid, and the mixture was shaken and centrifuged under the same condition as described above. The organic layer was carefully discarded with an aspirator, and the remaining aqueous phase was alkalinized again by adding 0.5 ml of 5 N sodium hydroxide. The mixture was re-extracted with 6 ml of benzene by shaking and centrifuging in the same manner as described above. The 5 ml of the organic layer was transferred to another centrifuge tube and 20 mg of KG-1688 dissolved in ethanol (1 mg/ml) was added as an internal standard. After being stirred for 3 h, the mixture was evaporated to dryness under a steam of nitrogen at about 40°C. The residual was redissolved in 50 μl of methanol:25—28% ammonia water mixture (50:1) and 1 μl aliquot was injected onto the column. A Shimadzu GC-7A gas chromatograph equipped with a nitrogen sensitive detector (model FTD-8, Shimadzu, Kyoto, Japan) and a moving needle solvent cut sample injector (Shimadzu) was used for the analysis.

The column used was a flexible fused silica capillary column coated with OV-1701 (25 m x 0.2 mm i.d., Shimadzu). The injector port and column oven were maintained at 300 and 250°C, respectively. Helium was used as the carrier gas and make-up gas at a flow rate of 1.4 and 40 ml/min, respectively. The detector output was set at 10—20% and flow rate of air and hydrogen were adjusted to 110 and 2.8 ml/min, respectively.

Pharmacokinetic Analysis: The moments were computed by fitting a polynomials function ($C(t) = \sum C_i \exp(-\lambda_i t)$) to the discrete time course data of plasma concentration ($C(t)$) using the iterative least squares method.8 The mean residence time (MRT) was determined using equations described by Gibaldi and Perrier.9

Results and Discussion

Effect of the Applied Solution pH on the Penetration of Emedastine: The receptor phase concentration—time curves obtained by the application of several pH solutions to the rat skin are shown in Fig. 1. The receptor phase concentration of emedastine appeared to increase with increasing pH of the solution. The permeability of emedastine was relatively lower after application of emedastine difumarate in different pH buffer than after application of emedastine free base in water, and was highest after application of emedastine free base in water. The dissociation constants ($pK_a$) of emedastine are 4.5 and 8.5. Therefore, the ratio of non-ionized form to ionized form increased with increasing pH, and it seemed that pH dependence of the permeability was related to the concentration of non-ionized emedastine in the applied solution. The permeability after application of emedastine difumarate in pH 10.3 buffer was relatively lower than that after application of emedastine free base in water (pH 10.6). The solubilities of emedastine difumarate and emedastine free base in buffer pH 10 were measured at 37°C, and that of emedastine difumarate proved to be the lower of the two. Further, the solubility of emedastine free base in buffer pH 10 decreased with the addition of fumaric acid or sodium chloride. The high concentration of fumaric acid or other ions reduced the emedastine solubility in the donor phase and caused a reduction in the permeability of the drug in the emedastine difumarate solution.

Thus, emedastine free base was more permeable by transdermal application than emedastine difumarate.

Effect of the Vehicle Composition on the Penetration of Emedastine: Vehicles commonly employed for topical formulations were used for application of emedastine in diffusion cell studies. The test formulation contained 20% of emedastine in macrogel ointment, white petrolatum, hydrophilic ointment, and Poloid® (liquid paraffin gelled with 5% of polyethylene resin). Figure 2 shows the time course of penetration of emedastine through rat skin from test formulations. The least penetration was achieved with the macrogel ointment, and the amount penetrated from hydrophobic vehicles (Poloid®) seemed to be more than from hydrophilic vehicles (macrogel ointment).

Effect of the Vehicle Composed of One Component on the Penetration of Emedastine: Poloid® and hydrophilic ointment consist of two or more components and it is difficult to determine which component is responsible for the penetration of emedastine in the formulation. To examine the effect of a simple vehicle on the permeability, penetration of the drug from simpler formulations of 20% emedastine and 80% of the single component studied. Isopropyl myristate, diethyl sebacate, octanol, isopropyl alcohol, ethanol, propylene glycol, and formamide were chosen as single components have different lipophilicities each other. The results illustrated in Fig. 3 show that the amount of emedastine penetrated from hydrophobic
vehicles (isopropyl myristate, diethyl sebacate) seemed greater than from hydrophilic vehicles (ethanol, propylene glycol).

Consequently, more hydrophobic vehicles were examined. Isopropyl myristate of fatty acid monooester group and diethyl sebacate of fatty acid diester group were chosen as the other hydrophobic vehicles. The fatty acid monoesters (C_{8-20}) were as follows: ethyl hexanoate (C_8), ethyl octanoate (C_{10}), ethyl decanoate (C_{12}), ethyl laurate (C_{14}), isopropyl myristate (C_{17}), and ethyl oleate (C_{20}). The fatty acid diesters (C_{8-14}) were: diethyl succinate (C_8), diethyl adipate (C_{10}), diisopropyl adipate (C_{12}), diethyl suberate (C_{12}), and diethyl sebacate (C_{14}). The results of test with the hydrophobic vehicles are shown in Fig. 4 and all of them enhanced the penetration of emedastine. Especially, the permeability from ethyl decanoate was about 60 that of hydrophilic vehicles such as ethanol and propylene glycol.

To investigate the relationship between the hydrophobicity of the vehicle and the permeability of emedastine in the vehicle, the permeability coefficient (Table I) was plotted as a function of vehicle carbon number in Fig. 5. The permeability in the fatty acid monoesters was higher than that in the fatty acid diesters. In the latter, the maximum permeability occurred with the vehicle whose carbon number was about 12. It seems that the vehicle must have an optimum hydrophobicity in order to have a maximum permeability of emedastine. On the other hand, the penetration of emedastine from formamide was relatively high in spite of the hydrophilicity of formamide, and the penetration of emedastine from some hydrophobic vehicles such as diethyl adipate and diethyl succinate were relatively low. Thus the penetration of the drug cannot be explained only by the hydrophilicity or hydrophobicity of the vehicle.

**Determinaton of Penetrant Characteristics.** There are several properties of penetrants that influence rates of skin absorption. These include structure, molecular weight, pK, volatility, solubility, partition coefficient, and diffusivity. Diffusivity is measured by kinetic studies. The method involves simply measuring the transdermal flux at early time until a steady-state flux is reached. In this case, the flux in this simple form is valid only (1) for homogeneous membrane, (2) where the concentration difference is constant with time and (3) where the diffusion is not dependent on concentration. The time lag before the steady state is reached is characteristic of the diffusivity of the penetrant in the membrane, and can be used to calculated the diffusivity. The time lag (L) is the time obtained extrapolating the steady-state portion of the curve back to from abscissa, and is defined by the following equation;

\[ L = h^2/(6D) \]

where \( h \) is the thickness of the membrane in cm and \( D \) is the diffusion coefficient in \( \text{cm}^2/\text{s} \). The \( D \) is easily estimated, provided that the membrane thickness is known, (\( h \) is about 0.08 cm). The flux (\( dM/dt \)) can be expressed by the following equation from Fick’s First Law

\[ dM/dt = DC_0/h \]

where \( C_0 \) is the penetrant concentration at the membrane surface. \( C_0 \) can be calculated because steady state flux (\( dM/dt \)) and \( D \) were measured experimentally. The concentrations are typically related by

\[ C_0 = C_0 K \]

where \( C_0 \) is the concentration in the donor phase which bathes the membrane and \( K \) is the partition coefficient of the solute between membrane and bathing solution. Thus \( K \) can be also calculated experimentally.

The permeability coefficient (\( P \)), diffusion coefficient (\( D \)) and partition coefficient (\( K \)) from each vehicle are shown in Table I. Many transdermal preparations of nitroglycerin are on the world market because this substance is highly permeable by this means. The permeability coefficient of nitroglycerin was about \( 110 \times 10^{-4} \text{cm/h} \) which is near the
permeability coefficient of emedastine from ethyl decanoate. It is clear that the permeability of emedastine was very high and that the drug may be effective in the system after transdermal administration.

Generally enhancers and vehicles increase drug permeability by altering the diffusivity in skin and/or partitioning of drugs. Azone (1-dodecylazacycloheptan-2-one) enhances intercellular drug diffusion. Water alters markedly the diffusional resistance of the intracellular contents by skin hydration. Dimethylsulfoxide and its analogues, the pyrrolidones, and propylene glycol may increase drug partitioning into skin. To investigate which parameter has greater influence on emedastine permeability in carbomates, the diffusion coefficient and partition coefficient are plotted as a function of the permeability coefficient in Fig. 6. The permeability coefficient relatively correlated with the partition coefficient and it was suggested that the change in permeability was largely dependent on the change in the partition from the vehicle to the skin. In this case, the diffusion coefficient for ethyl octanoate was significantly higher than those of other vehicles. Ethyl octanoate may affect the diffusivity of emedastine in the skin by acting on the skin.

In Vivo Administration Study with Rabbit In Vivo transdermal administration was investigated with rabbits. The test formulations contained 20% of emedastine in Poloid, hydrophilic ointment, macrogol ointment, diethyl

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>P (cm/h, (10^{-9}))</th>
<th>D ((\text{cm}^2/\text{s}, 10^{-9}))</th>
<th>K ((\text{cm}^2/\text{h}, 10^{-9}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl succinate</td>
<td>8.27 ± 1.08</td>
<td>1.41 ± 0.14</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td>Diethyl adipate</td>
<td>5.25 ± 1.24</td>
<td>1.83 ± 0.29</td>
<td>0.070 ± 0.017</td>
</tr>
<tr>
<td>Diethyl suberate</td>
<td>28.22 ± 9.18</td>
<td>0.63 ± 0.03</td>
<td>1.02 ± 0.33</td>
</tr>
<tr>
<td>Diethyl sebacate</td>
<td>31.64 ± 1.05</td>
<td>2.44 ± 0.59</td>
<td>0.299 ± 0.064</td>
</tr>
<tr>
<td>Diisopropyl adipate</td>
<td>10.52 ± 2.71</td>
<td>1.68 ± 0.11</td>
<td>0.141 ± 0.04</td>
</tr>
<tr>
<td>Ethyl oleate</td>
<td>60.85 ± 7.16</td>
<td>0.92 ± 0.15</td>
<td>1.713 ± 0.44</td>
</tr>
<tr>
<td>Ethyl hexanoate</td>
<td>81.63 ± 5.05</td>
<td>0.73 ± 0.11</td>
<td>2.52 ± 0.30</td>
</tr>
<tr>
<td>Ethyl octanoate</td>
<td>69.85 ± 11.81</td>
<td>10.5 ± 8.00</td>
<td>0.2 ± 0.14</td>
</tr>
<tr>
<td>Ethyl decanoate</td>
<td>92.09 ± 10.33</td>
<td>2.42 ± 0.41</td>
<td>0.83 ± 0.23</td>
</tr>
<tr>
<td>Ethyl laurate</td>
<td>88.81 ± 10.73</td>
<td>1.74 ± 0.57</td>
<td>1.23 ± 0.39</td>
</tr>
<tr>
<td>Isopropyl myristate</td>
<td>78.68 ± 3.95</td>
<td>1.03 ± 0.01</td>
<td>1.6 ± 0.06</td>
</tr>
<tr>
<td>Octanol</td>
<td>21.09 ± 1.25</td>
<td>2.52 ± 0.48</td>
<td>0.19 ± 0.02</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1.38 ± 0.30</td>
<td>1.92 ± 0.35</td>
<td>0.017 ± 0.005</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>1.49 ± 1.32</td>
<td>1.68 ± 0.44</td>
<td>0.021 ± 0.007</td>
</tr>
<tr>
<td>Formamide</td>
<td>30.64 ± 5.09</td>
<td>1.67 ± 0.07</td>
<td>0.410 ± 0.078</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>2.70 ± 0.53</td>
<td>1.95 ± 0.56</td>
<td>0.032 ± 0.007</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.E. of 5 determinations.

Here is a table summarizing the parameters characterizing the absorption of transdermal emedastine and peroral emedastine difumarate:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Peroral</th>
<th>Transdermal</th>
<th>IPM</th>
<th>DES</th>
<th>Poloid®</th>
<th>HO</th>
<th>MO</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.29 ± 0.02</td>
<td>3.00 ± 0.59</td>
<td>1.63 ± 0.28</td>
<td>1.63 ± 0.28</td>
<td>0.405 ± 0.224</td>
<td>0.322 ± 0.092</td>
<td>0.090 ± 0.016</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.625 ± 0.125</td>
<td>0.83 ± 0.17</td>
<td>1.17 ± 0.44</td>
<td>1.17 ± 0.44</td>
<td>3.00 ± 0.58</td>
<td>4.12 ± 2.13</td>
<td>4.76 ± 3.67</td>
</tr>
<tr>
<td>MRT</td>
<td>1.25 ± 0.03</td>
<td>2.77 ± 0.33</td>
<td>5.14 ± 0.17</td>
<td>5.14 ± 0.17</td>
<td>10.3 ± 2.0</td>
<td>10.9 ± 3.5</td>
<td>13.3 ± 0.7</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0−5&lt;/sub&gt;</td>
<td>22.7 ± 3.0</td>
<td>437.3 ± 45.3</td>
<td>542.4 ± 104.5</td>
<td>542.4 ± 104.5</td>
<td>213.8 ± 93.9</td>
<td>179.1 ± 37.4</td>
<td>89.8 ± 9.8</td>
</tr>
<tr>
<td>B.A.</td>
<td>1.93 ± 0.25</td>
<td>37.1 ± 3.8</td>
<td>46.0 ± 8.9</td>
<td>46.0 ± 8.9</td>
<td>18.1 ± 8.0</td>
<td>15.1 ± 3.2</td>
<td>7.61 ± 0.83</td>
</tr>
</tbody>
</table>

C<sub>max</sub> (nmol·ml<sup>-1</sup>), maximum plasma concentration; T<sub>max</sub> (h), time required to reach C<sub>max</sub>; MRT (h), mean residence time; AUC<sub>0−5</sub> (nmol·ml<sup>-1</sup>·min<sup>-1</sup>), area under the blood concentration time curve from 0−25h after administration; B.A. (%), bioavailability (percentage of AUC in transdermal or peroral administration versus AUC in intravenous injection); IPM, isopropyl myristate; DES, diethyl sebacate; HO, hydrophilic ointment; MO, macrogol ointment. Each value is the mean ± S.E. of three animals.

The permeability coefficient is plotted versus diffusion coefficient and partition coefficient in Fig. 6. A plot of permeability coefficient versus diffusion coefficient (A) and partition coefficient (B). The permeability coefficient varies from 0.32 to 0.090, and the partition coefficient from 0.032 to 0.090. The plasma concentration-time curve following transdermal administration of emedastine is shown in Fig. 7. The plasma concentration-time curve for emedastine following oral administration is also shown. The blood concentration time curve for emedastine following oral administration is shown. The peak concentration is higher than that of transdermal administration. The area under the blood concentration time curve is lower for oral administration.
administration than emedastine difumarate. The transdermal permeability of emedastine was remarkably enhanced by using hydrophobic vehicles, though the hydrophobicity of the vehicle alone could not account for the permeability. The in vitro steady state flux correlated with the in vivo parameter. It is clear that transdermal permeability of emedastine is very high, this is a suitable drug for transdermal administration because its in vivo parameters can be controlled by use of the appropriate vehicle, the dosage can be lower, and the associated side effects reduced.

References

Conclusions
Emedastine free base was more permeable by transdermal