The influence of a binary solvent system on the dermal delivery of lidocaine hydrochloride in human skin

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Objectives
The binary combination composed of polar and non-polar vehicles has been demonstrated as one of the approaches to enhance the permeation of drugs. In this study the effect of binary vehicles of Transcutol® (TC) as a polar solvent and isopropyl myristate (IPM) as a non-polar solvent on the enhancement of permeation of Lidocaine hydrochloride (LID-HCL) through human skin was determined.

Materials and Methods
In vitro infinite dose studies with female abdominal human skin were performed using Franz diffusion cells containing PBS pH 7.4 with 0.1% sodium azide as the receptor solution. Saturated LID-HCL solutions of neat vehicles and the various combinations were used to maintain an equal (and unit) thermodynamic activity of LID-HCL. The binary combination composed of polar and non-polar vehicles has been demonstrated as one of the approaches to enhance the permeation of drugs. In this study the effect of non-polar solvent on the enhancement of permeation of Lidocaine hydrochloride (LID-HCL) through human skin was determined.

Results and Discussion
Permeation profiles of LID-HCL through human skin with various binary combinations of TC and IPM are shown in Fig.1. The permeability coefficient was calculated from equations 2 and 3.

The maximum enhancement for TC:IPM=75:25 showed a 1000-fold increase compared with neat solvents.

The solubility of LID-HCL in the formulations increased significantly as the concentration of TC increased.

The results confirm the importance of determining the optimum balance between the activity of penetration of solvents and subsequent alteration of skin integrity appears to play an important role in drug partitioning.

Conclusions
- The thermodynamic activity of TC and/or IPM may be altered with different concentrations of LID-HCL in binary mixtures.
- Binary solvents systems composed of TC and IPM have a synergistic effect on the permeation of LID-HCL across the skin.
- The results confirm the importance of determining the optimum balance between the activity of LID-HCL and the activity of the solvents in the binary system to obtain the maximum flux.

Reference

Acknowledgments
We are grateful to Gattefossé Ltd. for providing Transcutol®. We thank Maruho Co. Ltd. (Japan) for financial support.

Table 1 Relative composition of TC-IPM binary solvents, mole fractions of LID-HCL and solvents; LID-HCL solubility at 32°C, LID-HCL steady state flux, apparent partition coefficient, apparent diffusion coefficient, permeability coefficient. Each data point represents the mean ± S.D. (n = 5)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Mole fraction</th>
<th>Solubility</th>
<th>LID-HCL properties</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(μmol/mL)</td>
<td>(μmol x 10^-1/cm^2/h)</td>
<td>(cm x 10^-3)(x10^-2/min)</td>
</tr>
<tr>
<td>IPM</td>
<td>1.000</td>
<td>0.350</td>
<td>3.1 ± 0.5</td>
</tr>
<tr>
<td>TC:IPM=25:75</td>
<td>0.400</td>
<td>0.850</td>
<td>80 ± 2</td>
</tr>
<tr>
<td>TC:IPM=50:50</td>
<td>0.659</td>
<td>0.437</td>
<td>189 ± 179</td>
</tr>
<tr>
<td>TC:IPM=75:25</td>
<td>0.708</td>
<td>0.130</td>
<td>581 ± 68</td>
</tr>
<tr>
<td>TC</td>
<td>0.872</td>
<td>0.000</td>
<td>1506 ± 13</td>
</tr>
</tbody>
</table>

Fig. 1 Permeation profile of LID-HCL with Transcutol - IPM mixtures. Each data points represents the mean ± S.D. (n = 5)

Fig. 2 Steady state fluxes of LID-HCL through human skin from the saturated Transcutol-IPM mixtures. Each data points represents the mean ± S.D. (n = 5)

The maximum enhancement for TC:IPM=75:25 showed a 1000-fold increase compared with neat solvents.