Modelling of the Effect of Formulation Factors on Skin Penetration

Dr Taravat Ghafourian
Medway School of Pharmacy, Universities of Kent and Greenwich
Absorption from Skin

- Release from the vehicle
- Penetration through the skin
Release from the vehicle

- Formulation type (gel or emulsion)
- Viscosity
- Molecular size (Stokes-Einstein equation for diffusion of a particle)
- Solubility in vehicle and saturation
Penetration through the skin

- Lipid content of the stratum corneum
- Lipid pathway vs. polar pathway of the stratum corneum
- Interaction with the proteins (keratin) and lipids
Chemical penetration enhancement

Azone

Glycyrrhizin logP=4.64

Cedrene
What is the mechanism?

- Increased drug release
- Increased partitioning of drug
- Increased fluidity of SC lipids
- Increased water content of the proteins in the barrier
- Specific interactions with drug
## Glycyrrhizin in diclofenac gels and emulsions

Natural enhancer from licorice roots

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Gels</th>
<th>Emulsions (O/W)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
<td>F2</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NaCMC</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Glycyrrhizin</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Lanette O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eutanol G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arlacel 63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tween 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>66</td>
<td>65.9</td>
</tr>
</tbody>
</table>
Glycyrrhizin in diclofenac gels and emulsions

Release kinetics

Nokhodchi et al, Farmaco 57 (2002) 883/888
Glycyrrhizin in diclofenac gels and emulsions
Permeation through rat skin

Nokhodchi et al, Farmaco 57 (2002) 883/888
Enhancement ratios of 0.1%w/w glycyrrhizin

<table>
<thead>
<tr>
<th>Formulation</th>
<th>ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel</td>
<td>10.7</td>
</tr>
<tr>
<td>Emulsion</td>
<td>0.94</td>
</tr>
<tr>
<td>Applied to skin before gel</td>
<td>7.72</td>
</tr>
<tr>
<td>Applied to skin before emulsion</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Glycyrrhizin penetrates the skin and changes the barrier function of the skin.
Effect of enhancer Concentration

- Are they acting as surfactants?
- Micelle formation at higher concentrations
- CMC of glycyrrhizin in water is 0.025%w/v but it is increased due to propylene glycol vehicle by a factor of 10
Effect of concentrations of surfactants

- SLS (Sodium laureth sulfate)
- Benzalkonium chloride
- CTAB (Cetyl trimethylammonium bromide)
- Tween 80
Application of surfactants

- Emulsifiers in emulsions
- Solubilising agents in gels
- Foaming agent
- Detergent
- Wetting agent

Surfactants are found in most skin products
Lorazepam and Diazepam

<table>
<thead>
<tr>
<th>Drug</th>
<th>log P</th>
<th>Solubility in water:propylene glycol 50:50 (mg/ml)</th>
<th>kp ×10^3 (cm h^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>2.47</td>
<td>2.48</td>
<td>0.051</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2.96</td>
<td>1.53</td>
<td>0.184</td>
</tr>
</tbody>
</table>

Donor phase: saturated solution of the drugs in water: propylene glycol (50:50% v/v) with or without surfactant.
Effect on the skin penetration of diazepam

- SLS (anionic)
- Benzalkonium Chloride (cationic)
- Tween 80 (nonionic)
- CTAB (cationic)

Effect on the skin penetration of lorazepam

SLS (anionic)

CTAB (cationic)

Benzalkonium Chloride (cationic)

Tween 80 (nonionic)

Enhancement ratios (at concentrations below CMC)

<table>
<thead>
<tr>
<th>Drug</th>
<th>SLS</th>
<th>CTAB</th>
<th>Benzalkonium</th>
<th>Tween 80</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>10.05 (0.50)</td>
<td>4.67 (0.23)</td>
<td>7.66 (0.38)</td>
<td>3.75 (0.19)</td>
<td>(0.051)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5.12 (0.94)</td>
<td>1.27 (0.23)</td>
<td>7.98 (1.47)</td>
<td>5.68 (1.05)</td>
<td>(0.184)</td>
</tr>
</tbody>
</table>

(Values in brackets are kp x10^3 in cm h⁻¹)
Terpenes

- Carvone
- Menthone
- Nerolidol
- Farnesol
- Limonenoxide
Effect of concentration of terpenes

- Penetration of diclofenac sodium through rat skin
- Donor phase: saturated solutions of diclofenac in solvent mixture of ethanol: glycerin: phosphate buffer (60:10:30 ratio) with or without terpene concentrations
Estimation problems

- Large datasets are required
- The effect of enhancers are different on different penetrants
- Several possible mechanisms
Estimation by QSAR

- Quantitative Structure – Activity Relationship
- For a dataset with known skin effect (increase/ reduction of penetration of other chemicals through skin):

\[ \text{Skin effect} = f(\text{structural properties}) \]
Estimation of the effect of enhancers: Datasets

- Terpene enhancement effects on 4 penetrants
  - 5FU
  - Hydrocortisone
  - Diclofenac sodium
  - Estradiol

- Enhancement activities of pyrrolidinone derivatives towards hydrocortisone
Enhancement of diclofenac sodium penetration

\[
\log ER = 0.297 + 0.017 \, ESP^+ \\
n = 8 \quad s = 0.298 \quad r^2 = 0.554 \quad F = 7.4
\]

- Gels containing propylene glycol and 1\%(w/w) terpene
- Penetration through rat skin

**Diclofenac sodium**

- \( \log P = 4.06 \)
- \( \log D = 0.95 \)
- \( pK_a = 4.01 \)
Enhancement effect of terpenes towards 5FU

Cyclic ethers and alcohols possess the lowest and the highest EV

\[
\log ER = 0.138 - 5.79q^- - 0.46E_v
\]

\[
n = 26 \quad r^2 = 0.627 \quad s = 0.329 \quad F = 19
\]

Enhancement of Hydrocortisone penetration

Terpenes

\[ \log ER = 0.719 + 0.153 \log P \]
\[ n = 12 \quad r^2 = 0.76 \quad s = 0.089 \quad F = 32 \]

Gels with 2% terpene
Hairless mouse skin


Pyrrolidinone derivatives

\[ \log ER(Q_{24}) = 0.083 + 0.84SA^2 \]
\[ n = 16 \quad r^2 = 0.809 \quad s = 0.18 \quad F = 59 \]

\[ \log ER = 0.114 + 0.172 \log P \]
\[ n = 16 \quad r^2 = 0.621 \quad s = 0.38 \quad F = 23 \]

Hairless rat skin
Enhancement of Hydrocortisone penetration

According to Pugh et al (2005):
Hydrogen bonding has a negative effect
Number of chain carbon atoms has a positive effect

Hydrocortisone

logP = 1.43
logD = 1.43
pKa = 12.48
Enhancement of estradiol penetration

\[ \log ER = 0.743 - 0.206 S(I) - 2.91 q^- \]

\[ n = 12 \quad s = 0.232 \quad r^2 = 0.853 \quad F = 26 \]

Estradiol

- logP = 4.13
- logD = 4.13
- pKa = 10.27
Effect of solvents

- Partitioning of penetrant between solvent and SC

\[ P_{SC/\text{Vehicle}} = \frac{P_{SC/Water}}{P_{\text{Vehicle}/Water}} \]

- Diffusion of penetrant in the vehicle and the SC
  - Viscosity of vehicle
  - Penetration of vehicle into the skin
  - Effect of vehicle on the skin
Formoterol in 32 different solvents

- Terpenes, Ethyl Linoleate, Butyl myristate, n-Octanol, water, Formamide

- Rat skin, same concentration of drug in the solvents containing small fraction of ethanol

Penetration of formoterol from solvents

\[ \log Q_{24} = -0.937 \text{atoms} - 2.51^9 \chi_p^v - 1.72 \text{aromatics} - 0.177 E_{LUMO} + 1.58 \]

\[ N = 32 \quad S = 0.401 \quad R^2 = 0.611 \]

\[ \log kp = -2.87 - 9.96^9 \chi_p + 0.0191 \text{MW} + 0.0515 \text{lipole} \]

\[ n = 32 \quad s = 0.430 \quad R^2 = 0.654 \quad F = 18 \]

Formoterol
\[ \log P = 1.57 \quad pKa = 8.90 \]