Formulation Strategies to overcome the skin’s defence

Skin – Target or Barrier?
SCI Meeting, London, 1st November 2007
The Skin’s Defence Barrier
Barriers: GI tract versus Skin!
Drug permeability coefficient: Caco-2 versus human skin

Fig. 1. Plot of observed log $K_p$ values versus predicted log $K_p$ values using Eq. (6).

Patel, Cronin et al. 2002
Phenylcarbamic acid permeability coefficient: Caco-2 versus human skin

<table>
<thead>
<tr>
<th>Compound #</th>
<th>C&lt;sub&gt;n&lt;/sub&gt; =</th>
<th>Pc Caco-2 *10&lt;sup&gt;-6&lt;/sup&gt;cm/sec</th>
<th>Pc human skin *10&lt;sup&gt;-6&lt;/sup&gt;cm/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>-C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>28</td>
<td>0.01</td>
</tr>
<tr>
<td>V111</td>
<td>-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>27</td>
<td>1.86</td>
</tr>
<tr>
<td>XI</td>
<td>-C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>26</td>
<td>2.19</td>
</tr>
<tr>
<td>XIV</td>
<td>-C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>17</td>
<td>2.14</td>
</tr>
<tr>
<td>XV11</td>
<td>-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;</td>
<td>3.3</td>
<td>2.14</td>
</tr>
<tr>
<td>XX</td>
<td>-C&lt;sub&gt;7&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;</td>
<td>Not detected</td>
<td>1.42</td>
</tr>
<tr>
<td>XX111</td>
<td>-C&lt;sub&gt;8&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

Fig. 1. Structure of the phenylcarbamic acid esters studied. R = C<sub>n</sub>H<sub>2n+1</sub>, when n = 1–10. In compound II the n = 1, and in V–XXIX the n = 2–10, respectively (see also Table I).

Gyurosliova et al. Pharm. Res. 19(2); 162-168: 2002
Pharmacokinetics: areas and volumes

GI tract: 1cm² area supplies 0.05cm³ volume
Pharmacokinetics: areas and volumes

**Skin:** 1cm² area supplies 0.05cm³ volume
The Skin is a Viable Target not an impenetrable Barrier
Formulation Strategy 1: Choose the right drug
Choose the right drug to get effective levels to the target site in the Skin

Stratum Corneum

Epidermis

Dermis

Keratolitics
Antifungals
Antipsoriatics
Antiviral
Superficial itch and pain
Anti-inflammatory
- Eczema
- Dermatitis
- Muscle Pain
Drug Potency and Skin Penetration are equally important

Hydrocortisone

Triamcinolone

Fluocinonide
The ratio of Penetration / Potency allows Efficacy Ranking

\[
\text{Flux / Potency} = \text{Efficacy} * \{\text{PK black box}\}
\]

\[
\frac{J}{C_{\text{plasma effective}}} = EI \{\text{Cl/A}\}
\]
Formulation Strategy 1: 
Choose the right drug

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Flux, J,ug/cm²/hr</th>
<th>IC 50 (COX-2), uM</th>
<th>EI (COX-2)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>1.4</td>
<td>0.03</td>
<td>46.7</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>13</td>
<td>0.38</td>
<td>34.2</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>16</td>
<td>0.74</td>
<td>21.6</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>0.7</td>
<td>0.16</td>
<td>4.4</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>0.7</td>
<td>55.26</td>
<td>0.01</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0.08</td>
<td>34.9</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Penetration to Potency ratio may predict Topical Efficacy : NSAIDs

\[
\text{Flux/Potency} = \text{Efficacy} \times \{ \text{black box} \}
\]

\[
\frac{J}{IC_{50}} = \text{Efficacy} \times \{ \frac{2D_d}{h_d} \}
\]

\[
\text{ITAA} = \frac{J}{IC_{50}} \times \frac{h_d}{2D_d}
\]

<table>
<thead>
<tr>
<th>NSAID</th>
<th>J (ug/cm²/hr)</th>
<th>IC 50 (COX-2), uM</th>
<th>EI (COX-2)*</th>
<th>ITAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>1.4</td>
<td>0.03</td>
<td>46.7</td>
<td>43.8</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>13</td>
<td>0.38</td>
<td>34.2</td>
<td>37.2</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>16</td>
<td>0.74</td>
<td>21.6</td>
<td>23.6</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>0.7</td>
<td>0.16</td>
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<td>Piroxicam</td>
<td>0.08</td>
<td>34.9</td>
<td>0.002</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Penetration and Potency may predict Topical Efficacy: TIMS

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MW</th>
<th>Potency (nM)</th>
<th>Flux (in AD) (ng/cm²/hr)</th>
<th>Efficacy Index</th>
<th>Systemic Safety Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin A</td>
<td>1203</td>
<td>14</td>
<td>&lt; 1.25</td>
<td>&lt; 0.04</td>
<td>96</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>804</td>
<td>0.17</td>
<td>1.25</td>
<td>5.5</td>
<td>252</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td>810</td>
<td>0.23</td>
<td>~ 0.65</td>
<td>~ 2.1</td>
<td>~ 960</td>
</tr>
</tbody>
</table>

Formulation Strategy 2: Get an idea of the drug dose (because design is drug and dose specific)
Calculation of topical dose from flux

\[ \text{Flux/Potency} = \text{Efficacy} * \{ \text{black box} \} \]

\[ C_{\text{free}} = \frac{J * h_d}{2D_d} \]

\[ \frac{C_{\text{free}}}{C^\#} = \frac{J * h_d}{C^\# * 2D_d} \]

\[ J^\# = \frac{2C^\# D_d}{h_d} \quad \text{Equ. 1} \]
## Prediction of minimum dose

<table>
<thead>
<tr>
<th>Drug potency: ng/cm³ (5000 range)</th>
<th>Flux, J#, for efficacy in dermis: ng/cm²/hr</th>
<th>Dose/cm²/10hr: ng</th>
<th>% in product @2mg/cm² (A) (/20,000)</th>
<th>Drug % in typical products (B)</th>
<th>Estimate of bioavailability % (A) / (B) *100</th>
<th>Drug example with this potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0.1</td>
<td>1</td>
<td>0.00005%</td>
<td>0.005-0.05%</td>
<td>1.0-0.1%</td>
<td>Fluticasone propionate (Cutivate)</td>
</tr>
<tr>
<td>0.1</td>
<td>0.2</td>
<td>2</td>
<td>0.0001%</td>
<td>0.025-0.1%</td>
<td>0.4 - 0.1%</td>
<td>Retinoic acid (Retin-A)</td>
</tr>
<tr>
<td>0.25</td>
<td>0.5</td>
<td>5</td>
<td>0.00025%</td>
<td>1.0%</td>
<td>0.025%</td>
<td>Diclofenac (Volterol)</td>
</tr>
<tr>
<td>0.5</td>
<td>1.0</td>
<td>10</td>
<td>0.0005%</td>
<td>0.03 – 0.1%</td>
<td>1.67 – 0.5%</td>
<td>Tacrolimus (Elidel)</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>100</td>
<td>0.005%</td>
<td>0.5-1.0%</td>
<td>1.0 – 0.5%</td>
<td>Hydrocortisone (Generic)</td>
</tr>
<tr>
<td>250</td>
<td>500</td>
<td>5,000</td>
<td>0.25%</td>
<td>5%</td>
<td>5%</td>
<td>Ibuprofen (Generic)</td>
</tr>
</tbody>
</table>
Formulation Strategy 3:
Design for the drug and its dose:
residual phase solubility / saturation
Formulation Design

Pharmaceutical Quality:
- Drug stability
- Preservation
- Physical stability

Drug Delivery:
- Drug physicochemistry
- Vehicle effects
  - Partitioning
  - Diffusivity
- Dose

Aesthetic Quality
- Ease of use
- Meaning in use
Formulation Design: Whole vehicle effects

Pharmaceutical Quality:
- Drug stability
- Preservation
- Physical stability

Drug Delivery:
- Drug physicochemistry
- Vehicle effects
  - Partitioning
  - Diffusivity
- Dose

Aesthetic Quality
- Ease of use
- Meaning in use
Formulation Design: Residual Phase effects

Pharmaceutical Quality:
- Drug stability
- Preservation
- Physical stability

Drug Delivery:
- Drug physicochemistry
- Vehicle effects
  - Partitioning
  - Diffusivity
- Dose

Aesthetic Quality
- Ease of use
- Meaning in use
Residual phase as formulation basis

- drug in solution (saturation or >)
- non volatile solvent phase

+ water, surfactants, waxes
+ volatile solvent, polymer
+ patch (Alza, Cygnus)

Cream  |  Spray / Gel  |  Patch
Degree of saturation, not concentration, drives penetration

Relative vasoconstrictor response from subsaturated solutions (open symbols) and saturated solution and suspension (filled symbols) formulations of betamethasone benzoate in mineral oil/myglyol.
Lotion 0.005%

- Calcipotriene 50 ug/g
- isopropanol (51% v/v)
- propylene glycol and water
- menthol
- hydroxypropyl cellulose
- sodium citrate

Fig. 7. Linear relationship between transport of hydrocortisone acetate and degree of saturation over the range of subsaturated to supersaturated systems. Combined data from Figs. 4–6. Mean ($n = 3$ or $6$) ± S.E.
Formulation Strategy 4: Choose the right enhancer system: if you need one!
The Higuchi Physical Model (1960): In vitro Transport

\[
F = \frac{C_v \times P_c}{D_c \times h}
\]
Alcohol/Glycol–Fatty acid derivative co-enhancers

\[ F = C_v \times \frac{P_c}{D_c} \times h \]
Isopropyl myristate-propylene glycol: Nicorandil

Propylene glycol-Oleic acid co-enhancer


Propylene glycol-Oleyl alcohol co-enhancer


Transcutol-Oleic acid co-enhancer


Basic co-enhancer residual phase

- drug in solution (saturation or >)
- polar solvent (propylene glycol) \( \text{Pc} \)
- polar lipid (glycol monolaurate) \( \text{Dc} \)

+ water, surfactants, waxes

+ volatile solvent, polymer

+ patch (Alza, Cygnus)

Cream  Spray / Gel  Patch
Formulation Strategy 5:
Get an idea of the dose of the polar solvent enhancer:
Loperamide penetration is propylene glycol dose dependent
Aciclovir penetration is propylene glycol dose dependent

Trottet L et al.  
International Journal Pharmaceutics.  
2005; 304(1-2): 63-71

Diez-Sales O et al.  
Journal Pharmaceutical Sci.  
2005; 94(5): 1039-47
Formulation Strategy 6:
Design the formulation to deliver the polar lipid co-enhancer
Effect of vehicle on partitioning of fatty acid co-enhancers into skin

Penetration of morphine depends upon that of menthol and ethanol and their partitioning

Phase diagram for ethanol-menthol-water. Data from Wada 1994.

Wada Y et al.
Formulation Strategy 7: Design the formulation to deliver the drug, also.
Lotion 0.005%

- Calcipotriene 50 ug/g
- isopropanol (51% v/v)
- propylene glycol and water
- menthol
- hydroxypropyl cellulose
- sodium citrate

Fig. 7. Linear relationship between transport of hydrocortisone acetate and degree of saturation over the range of subsaturated to supersaturated systems. Combined data from Figs. 4–6. Mean (n = 3 or 6) ± S.E.
Liquid Crystal Residual Phase with drug supersaturation

PEG-glycerol monooleate 3 parts
Caprylic-capric acid glycerol esters 7 parts

Muller BW. US Patent 4,719239
Formulation strategy

DRUG AND DOSE SELECTION
- Choose best drug (and form) based on penetration / potency
- Get an idea of the drug dose

RESIDUAL PHASE and SATURATION
- Design solution system around residual phase
- Drug at saturation or higher

ENHANCEMENT
- Consider co-enhancer system
  - Consider dose of polar (Pc) enhancer
  - Consider saturation-partitioning of lipid co-enhancer in residual
  - Consider saturation-partitioning of the drug in residual

FORMATING
- Disguise the residual phase as appropriate for indication
Strategies to overcome barriers