Topical & Transdermal drug delivery

Superficial = exterior only
Topical = into the skin
Regional = through the skin to concentrate locally
Transdermal = through the skin for systemic availability
Why Transdermal Delivery?

- Avoid gastrointestinal tract
- Avoid first pass hepatic metabolism
- Maintain constant therapeutic level
- Avoid need to swallow pills
- Avoid unpleasant administration
- Better immune response in case of vaccines

Drug Permeation Pathways

Transfollicular
- Transapendageal
- Transcellular

Intracellular
Passive vs Active Technologies

- Molecular permeation Enhancers (MPE™)
- Iontophoresis
- Electroporation
- Ultrasonication
- Jet injection

Skin permeability enhancement

Development of Skin-Applied Product

- Preferences in drug selection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Should be low (&lt;20 mg/day)</td>
</tr>
<tr>
<td>Half-life in h</td>
<td>10 or less</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt;500</td>
</tr>
<tr>
<td>Partition coefficient (Log P)</td>
<td>Between -1.0 and 4</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>Non irritating and non-sensitizing</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>Low</td>
</tr>
<tr>
<td>Therapeutic index</td>
<td>Low</td>
</tr>
</tbody>
</table>

- Development of analytical method (HPLC, LCMS)
- Solubility studies
- Short term stability studies in solvents
Role of Molecular Permeation Enhancers (MPE™s)

- Various excipients (all at <5 wt%) added to a base 50/50 water/ethanol chassis (leftmost bar is flux from chassis + API only)
- Translation from one active to another is rare


HTE Platform Development

(HTE = High Throughput Experimentation)
(FUROR™ = Flow-through cells system with Robotic metRology)
(TORNADO™ = high Throughput skin permeation And Dermal uptake Observation)
Skin Applied Dosage Forms

- Liquids: solutions, foams, ointments, pastes, creams, gels, lotions
  - pH measurement
  - % Loss on Drying
  - Wet-ability
  - Rheological study
  - Stability

- Semi-solids: pastes, creams, gels
  - pH measurement
  - Particle
  - Size distribution
  - % Loss on drying
  - Polymorphism
  - Wet-ability
  - Zeta Potential
  - Rheological study
  - Spreadability
  - Stability
  - Drug content uniformity test

- Solids: powders, patches, films
  - pH measurement
  - Rheological study
  - Adhesively
  - Stability
  - Release studies
  - Drug content uniformity test
  - Drying time
  - Washability

Estimation of drug retained in Epidermis & Dermis

Tap stripping method

Complete separation of epidermis
Stability studies

<table>
<thead>
<tr>
<th>Long-term/Accelerated conditions</th>
<th>Conditions</th>
<th>Minimum time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term Testing</td>
<td>25°C ± 2°C/60% RH ± 5%</td>
<td>12 Months</td>
</tr>
<tr>
<td>Accelerated Testing</td>
<td>40°C ± 2°C/75% RH ± 5%</td>
<td>6 Months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accelerated conditions</th>
<th>Conditions</th>
<th>Minimum time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated Testing</td>
<td>low temperature (4-8°C) ambient temperature (25°C) high temperature (40°C or 45°C) freeze–thaw cycles (-10°C to +40°C)</td>
<td>Two cycles every 24 h for 7 days</td>
</tr>
</tbody>
</table>

Trans-Nail Delivery of AR-12, A Novel Antifungal Drug

**Onychomycosis**: is an infection in the toe and finger nails that is mainly caused by keratinophilic fungus.

The amount of AR-12 retained in the nail plates (ng/mg)

Results of TranScreen-N for identifying the potential enhancers: CS 20 (Kolliphor® CS 20), TPGS (Vitamin E TPGS), Dex (Dexpanthenol), RH 35 (Kolliphor® EL), RH 40 (Kolliphor™ RH 40), PEG 400 (Polyethylene glycol), HS 15 (Kolliphor™ HS 15). The data represent mean ± SD of three determinations. *p (0.009) < 0.05, **p (0.002) =< 0.05

Work performed at Department of Pharmaceutics, University of Mississippi, prior to joining Tioga Research
**Treatment of Hypertrophic Scar**

- Scar is a skin fibrotic condition that can be caused by minor insults to skin, such as acne or ear piercing, or by severe injuries such as burns.
- Scar is mainly formed due to extra deposition of collagen type I and III and reduction in level of collagenase enzyme inhibitor.

**Conclusion**

- Screening of effective MPE™s
- Selection of an appropriate topical dosage form
- Proper characterization of dosage form
- Stability of drug in formulation
- Translation of *in vitro* data into *in vivo* studies
Skin Delivery Innovations

Chosen globally for topical & transdermal product services

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