TRANSDERMAL FLUX PREDICTIONS FOR HIGHLY LIPOPHILIC COMPOUNDS: COMPARISON WITH EXPERIMENTAL RESULTS

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BACKGROUND & AIMS

- To evaluate the feasibility of delivering transdermally a series of highly lipophilic compounds (log P ~ 4-7), comprising several selective estrogen receptor modulators (SERMs) and a modified testosterone (danazol).
- To explore whether the fluxes achieved might be sufficient to allow for ‘local’ application and drug delivery to underlying subcutaneous tissues, avoiding thereby undesirable systemic side-effects when treating breast cancer.
- To compare the in vitro experimental fluxes of the drugs considered with their predicted transport using the Potts & Guy algorithm.

Methods

**Prediction model & experimental studies**

**Step 1:** Calculation of lipophilicity and aqueous solubility of compounds

Log P<sub>o/w</sub> and aqueous solubilities (log S) of the drugs were estimated with the “ALOGPS 2.1 Programme” [1].

**Step 2:** Prediction of maximum drug flux (J<sub>max</sub>) across skin

\[ J_{max} \approx \frac{D \times K_{skin/vehicle} \times C_{rat/vehicle}}{h} \]

Calculate permeability coefficient (K<sub>P</sub>) of each drug across skin from aqueous solution using the Potts & Guy equation [2]:

\[ \log K_P = -2.7 + 0.71 \times \log P - 0.0061 \times MW \]

Calculate corrected permeability coefficient (K<sub>pcorr</sub>) following Cleek & Bunge [3] for highly lipophilic species for which viable epidermis can contribute to rate-control:

\[ K_{pcorr} = \frac{K_p}{1 + \frac{K_p \times MW}{2.6}} \]

**Step 3:** Determine J<sub>max</sub> from K<sub>p</sub> x estimated solubility of drug in water

**Step 4:** In vitro permeation studies

In vitro experimental fluxes (J<sub>exp</sub>) from saturated hydroalcoholic solutions (70:30; ethanol:water) were determined in side-by-side diffusion cells (area: 0.71 cm²; volume: 3.2 ml) through dermotomed (750 µm) pig skin at 37±0.5°C. Samples were analyzed by HPLC.

**Table:** Estimated physicochemical properties and predicted skin permeability parameters of the compounds considered.

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW (g.cm⁻²)</th>
<th>K&lt;sub&gt;p&lt;/sub&gt; (cm.h⁻¹)</th>
<th>J&lt;sub&gt;max&lt;/sub&gt; (µg.cm⁻².h⁻¹)</th>
<th>J&lt;sub&gt;exp&lt;/sub&gt; (µg.cm⁻².h⁻¹)</th>
<th>J&lt;sub&gt;exp&lt;/sub&gt;/J&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomiphene</td>
<td>343.49</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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<tr>
<td>Danazol</td>
<td>357.49</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Droloxifene</td>
<td>387.52</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Endoxifen</td>
<td>375.52</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>4-OH Tamoxifen</td>
<td>387.52</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>371.52</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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<tr>
<td>Toremifene</td>
<td>405.91</td>
<td>0.01</td>
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<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Theoretical calculations presented are based only on parent drug.

**CONCLUSIONS**

- Fluxes of highly lipophilic compounds can be reasonably predicted.
- From previous clinical studies [4, 5] and experimental fluxes observed, topical delivery of therapeutically useful doses of certain compounds to cancerous breast tissue and/or to treat benign breast diseases (such as mastalgia) may be feasible.

REFERENCES


ACKNOWLEDGEMENTS

We thank Ascend Therapeutics, Inc. and the Scientific and Research Council of Turkey (TÜBİTAK) for financial support.

Skin and Formulation, 3rd Symposium & Skin Forum, 10th Annual Meeting, March 9-10, 2009, Versailles, France