IN VITRO CHARACTERIZATION OF TOPOCAL SEMISOLID DOSAGE FORMS

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U.S. Food and Drug Administration, Office of Generic Drugs
Disclaimer

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• I do not have any financial interest or conflict of interest with any pharmaceutical companies.
Impact of Product Quality Attributes

• It is widely understood that the formulation of a topical semisolid dosage form matters greatly.
• It is now increasingly clear how excipients exert their influence, by modulating the physicochemical and microstructural arrangement of matter in the dosage form.
• The resulting physical and structural characteristics of topical dosage forms, and their metamorphic properties on the skin, can directly influence topical bioavailability.
Human Skin Structure

Adapted from Cerio and Archer, 1998
Human Skin Differentiation

Adapted from Schaefer and Redelmeier, 1996
Skin Permeation Pathway

SIDE VIEW

TOP VIEW

Drawings adapted from Odland, 1971.
Micrograph accompanying “side view” from Christophers and Laurence, 1976.
Micrograph accompanying “top view” from Singh and Singh, 1995.
Diffusion of Topical Compounds

DIFFUSION PATHWAY

Drawing adapted from Odland, 1971.
Micrograph Fartasch et al., 1998.
Diffusion of Topical Compounds

- Katz & Poulsen, 1971 (Fick’s Law of Diffusion)

\[ J = \frac{P \times D \times \Delta C}{l} \]

- \( J \) = Flux (e.g. \( \mu g/cm^2/hour \))
- \( C \) = Concentration
- \( P \) = Partition Coefficient
- \( D \) = Diffusion Coefficient
- \( l \) = Length of Travel
Diffusion of Topical Compounds

• Franz & Lehman, 1995 (Finite Dose Equation)

\[ J = 2hpDC_0 \sum_{n=1}^{\infty} \frac{\alpha_n e^{-D\alpha_n^2t}}{\sin \alpha_n l} \left[ l(\alpha_n^2 + h^2) + h \right] \]

• Relevant to clinically applied thin film doses
• Accounts for the thickness of the applied dose as well as dose depletion over time
Impact of Product Quality Attributes

• Product Quality and Composition can Affect:
  o The phase states and the arrangement of matter
  o Drug diffusion within the dosage form
  o Drug partitioning from the dosage form into the SC
  o Alteration of skin structure and chemistry
  o Drug diffusion within the skin itself
  o Drug delivery & bioavailability at the target site
  o Skin (de)hydration, irritation or damage
  o Metamorphosis of the dosage form on the skin
Tests of Product Quality Attributes

• Potential CQAs and Tests:
  o Microscopic Analyses of Microstructure (e.g., Globules)
  o Rheological Analyses (incl. Texture, Tribology, etc.)
  o Dissolved vs. Undissolved Amounts of the Drug
  o Concentration of Drug in the Continuous Phase
  o Size Distribution of Globules/Particles
  o Drug Polymorphic State (Raman, XRD, etc.)
  o Drug Crystalline Habit (Optical Microscopy)
  o Drying Rate (Solvent/Water Activity)
  o Density
  o pH
  o Etc.
**IVPT: In Vitro In Vivo Correlation**

- 92 IVIVC Data Sets (Different Drugs & Formulations)

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**Fig. 1.** IVIV ratios of total absorption for all 92 data sets plotted on log-log scale. The IVIV ratios ranged from 0.18 to 19.7, with an overall mean of 1.6. Solid line: ideal 1:1 correlation. Dashed lines: ±3-fold difference from ideal.

**IVPT: In Vitro In Vivo Correlation**

- Subset of 11 **Harmonized** IVIVC Data Sets

**Fig. 2.** IVIV ratios of total absorption for 11 fully harmonized data sets plotted on log-log scale. The IVIV ratios ranged from 0.58 to 1.28, with an overall mean of 0.96. Line: ideal 1:1 correlation.

**In Vitro Release Test (IVRT)**

Image courtesy of PermeGear
IVPT vs. IVRT

**IVPT (Permeation)**
- Human Skin
- Unoccluded Dose
- Finite Dose
- Flux Profile ($J_{\text{max}}$, etc.)
- Physiological Media
- pg to ng Range
- Product stays ‘dry’
- IVIV Correlation
- Donor Variability

**IVRT (Release)**
- Synthetic Membrane
- Occluded Dose
- Infinite Dose
- Release Rate (slope)
- Alcoholic Media
- µg to mg Range
- Product-Media Interface
- Specific to the Formulation
- Relative Consistency
Can IVRT Discriminate Microstructure?

- **IVRT did discriminate** 8 formulations made with Petrolatum, USP from different sources

Data provided courtesy of Paul A. Lehman and Dr. Thomas J. Franz
Can IVRT Discriminate Microstructure?

• IVRT did not discriminate 14 formulations with substantial variations in particle size

Q3: Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

**Prof. Narasimha Murthy** FDA Award U01-FD005223

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (%w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>1</td>
</tr>
<tr>
<td>Cetostearyl alcohol</td>
<td>7</td>
</tr>
<tr>
<td>Cremophor A6</td>
<td>1.5</td>
</tr>
<tr>
<td>Cremophor A25</td>
<td>1.5</td>
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<tr>
<td>Mineral Oil</td>
<td>12</td>
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<tr>
<td>Propylene Glycol</td>
<td>8</td>
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<tr>
<td>Water</td>
<td>69</td>
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<tr>
<td>Total</td>
<td>100</td>
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</tbody>
</table>

**Manufacturing Conditions**

<table>
<thead>
<tr>
<th>RPM (min)</th>
<th>Solvent Activity $a_w$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 RPM (20 min)</td>
<td>0.950 ± 0.004</td>
</tr>
<tr>
<td>3000 RPM (20 min)</td>
<td>0.961 ± 0.006</td>
</tr>
</tbody>
</table>

Data provided courtesy of Prof. Narasimha Murthy
Q3: Dosage Form Metamorphosis

• Solvent Activity of Q1/Q2 Identical Creams

Prof. Narasimha Murthy  FDA Award U01-FD005223

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<tbody>
<tr>
<td>Cetostearyl Alcohol</td>
<td>12.5</td>
</tr>
<tr>
<td>White Wax</td>
<td>12</td>
</tr>
<tr>
<td>Mineral Oil</td>
<td>56</td>
</tr>
<tr>
<td>Sodium Borate</td>
<td>0.5</td>
</tr>
<tr>
<td>Water</td>
<td>19</td>
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<td>3500 RPM (15 min)</td>
<td>0.931 ± 0.002</td>
</tr>
<tr>
<td>7000 RPM (45 min)</td>
<td>0.875 ± 0.006</td>
</tr>
</tbody>
</table>

% Loss of contents

Data provided courtesy of Prof. Narasimha Murthy
Q3: Dosage Form Metamorphosis

• Solvent Activity \( (a_s) = \frac{\rho}{\rho_0} \)

**Prof. Narasimha Murthy** FDA Award U01-FD005223

• \( \rho \) = partial vapor pressure of Solvents in the product
• \( \rho_0 \) = vapor pressure of pure Solvent system

Data provided courtesy of Prof. Narasimha Murthy
Q3: Dosage Form Metamorphosis

• Solvent Activity and Drying Rate

Prof. Narasimha Murthy
FDA Award U01-FD005223

Data provided courtesy of Prof. Narasimha Murthy
Orthogonal In Vitro Testing Approach

- 5 Pharmaceutically Equivalent Acyclovir Creams

<table>
<thead>
<tr>
<th></th>
<th>Zovirax (USA)</th>
<th>Zovirax (UK)</th>
<th>Zovirax (Austria)</th>
<th>Aciclostad (Austria)</th>
<th>Aciclovir-1A (Austria)</th>
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<tr>
<td>Water</td>
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<tr>
<td>Propylene glycol</td>
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<td>Viscous Paraffin</td>
<td></td>
</tr>
<tr>
<td>White petrolatum</td>
<td>White soft paraffin</td>
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<tr>
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<td>SLS</td>
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</tr>
<tr>
<td>Dimethicone 20</td>
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<td>Dimethicone 20</td>
<td>Dimethicone</td>
<td></td>
<td></td>
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<tr>
<td>Arlacel 165</td>
<td>Glyceryl Mono Stearate</td>
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<td></td>
</tr>
<tr>
<td>Arlacel 165</td>
<td>Polyoxyethylene stearate</td>
<td>Macrogol stearate</td>
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Orthogonal In Vitro Testing Approach

**In Vitro Permeation Test (IVPT)**
- 6 Donors each with 6 Replicate Skin Sections

**In Vitro Release Test (IVRT)**

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- **Density (g/cc)**
  - 1.02
  - 1.02
  - 1.02
  - 1.02
  - 1.01

- **Content Uniformity (%)**
  - 97.9 ± 0.7
  - 99.6 ± 1.4
  - 100 ± 2.2
  - 99.7 ± 1.7
  - 98.3 ± 2.6

- **Polymeric Form**
  - 2,3 hydrate
  - 2,3 hydrate
  - 2,3 hydrate
  - 2,3 hydrate
  - 2,3 hydrate

- **Cristalline Habit**
  - Rectangular
  - Rectangular
  - Rectangular
  - Ovoid
  - Ovoid

- **Particle size (d50) (μm)**
  - 3.8
  - 2.5
  - 3.4
  - 6.8
  - 6

- **pH**
  - 7.74
  - 7.96
  - 7.54
  - 4.58
  - 6.05

- **Work of Adhesion**
  - 59
  - 81
  - 60
  - 17
  - 18

- **Drug in Aq (mg/g)**
  - 0.49
  - 0.75
  - 0.64
  - 0.49
  - 0.73

- **Drying Rate (T-30%)**
  - >12h
  - ~8h
  - ~7h
  - <1h
  - <1h

- **Water Activity**
  - 0.75

**Thixotropic Rheology**

**Data provided courtesy of Prof. Narasimha Murthy & Dr. Frank Sinner**
In Vivo Bioavailability/Bioequivalence

- Dermal Pharmacokinetics by dOFM (20 subjects)

Data provided courtesy of Dr. Frank Sinner

Influence of Dispensing Stress on Q3

• Influence of Dose Dispensing on Product Quality

Prof. Michael Roberts  FDA Award U01-FD005226
Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

Prof. Michael Roberts  FDA Award U01-FD005226

Comparison Zovirax UK pump and tube

Data provided courtesy of Prof. Michael Roberts & Prof. Maike Windbergs
Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

Prof. Michael Roberts  FDA Award U01-FD005226

Data provided courtesy of Prof. Michael Roberts
Summary

• All product characterization test methods, both in vitro and in vivo, have limitations ...but they don’t all have the same limitations!

• The collective weight of evidence from orthogonal assessments comparing product quality and performance is more powerful than any single test method.

• The key is to utilize tests that systematically and collectively mitigate the risk of failure modes relevant to the therapeutic performance of the drug product.
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