Correlation between rheology, in-vitro release and in-vivo performance of topical dosage forms

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Skin - the particularities of a complex biological barrier

Large, efficient, multilayered and self-repairing barrier

Complexity of the structure and functions

Several pathways of absorption for an active pharmaceutical ingredient

**trans-epidermal (bulk) route:** transcellular, intercellular;
*brick* (corneocytes) *and mortar* (lipid ordered domains) *model*;

**trans-appendageal (shunt) route:** sweat glands, hair follicles;

Relative contribution:
- molecular determinants (API), area of specific route, facilitation.

The barrier function can be changed / compromised by various pathological processes.

Specific issues:
- metabolic capacity, immunological response, underlying blood flow pattern.

The extrapolation from animal skin is difficult or impractical (nature of interface, composition, appendages).

Difficult to simulate in-vitro the overall process, even where excised healthy skin is considered.

Large intra (site-specific) and inter-individual variability in humans (hydration, thickness, lipid composition, pH, temperature etc.).
Nonsterile semisolid dosage forms

- Complex composition and structure, specific release mechanism.

- Highly variable qualitative and quantitative composition
  - homogenous or heterogeneous systems

- Active pharmaceutical ingredient - dissolved or dispersed

- Specific issues:
  - particle size, interfacial and partition phenomenon, (micro)structure etc.

- Differences in (micro) structure – viscosity/rheology – variable release parameters across formulations and manufacturers.

- Local, product specific phenomenon influence the release / skin penetration (spreading, mechanical stress, temperature changes etc.).

- Material attributes and process parameters are frequently subject to various levels of changes, with different prospected impact on quality and/or performance.
Drug delivery from a complex vehicle through a complex barrier

3 stages process of penetration through a highly specialized interface

1. Release of API from the formulation to stratum corneum (SC),
   Physico-chemical properties of API (MW (MV), LogP/LogD₅.₄, HBD/A, PSA etc.)
   Solubility and dispersion / distribution in the vehicle (thermodynamic activity),
   Diffusion resistance of the vehicle (micro-structure spreadability/viscosity) etc.

2. Penetration through the SC (brick and mortar model, limiting step?)
   Various pathways, different contribution, specific rates
   Physiological or pathological status, site, integrity, hydration, composition
   Alterations induced by the formulation (co-diffusing excipients)
   Binding potential to endogenous substrates
   In-situ crystallizing (?)

3. Distribution from SC to the site of action (PD effect).
   Selection of testing methodology depends on the site of action (SC/deeper layers) and purpose (quality control / product performance test)

(Shah VP, 2005)
Specific issues of BE for topical semisolids

(1) Clinical end-points studies for locally acting dermatological products
Costly, time consuming, high variability, but with increased clinician confidence
Three-arm studies (test, reference > placebo) in patient population (large no. 400-700 for antifungal drugs, Lionberger R, 2004)
Comparison of %cure rate for test and reference population (-20; 20%). (Draft Guidance on Fluorouracil - 5% cream, 2011).

Unnecessary testing in humans

High costs - studies addressing each dose strength (waiver?)

Failure rate in demonstrating BE

Sensitivity to formulation variables

Less reliable,

Self administration (patient) – not standardized in terms of dose, application area and conditions (mechanical stress).
Specific issues of BE for topical semisolids

(2) Vasoconstrictor assay (VCA) - corticosteroids
   (Stoughton-McKenzie vasoconstrictor assay)

- considerable experience, correlation of PD profile with exposure, consistent IVRT reports;
- evaluation of dose-related vasoconstrictor response (periodic assessment, 24 hours; 90% CI for AUEC_{0-24h});
- relative small number of subjects.

- Limited to a specific class, displaying a particular PD effect;
- Some issues regarding inter-individual variability (>50%; n=100);
- Problems with dosage forms containing a completely dissolved API (solutions, gels).

(Yacobi A et al, 2014)
(3) Pharmacokinetic studies

- Low (inaccessible, undetectable) concentration at the site of action – assessment of the concentrations at the systemic level for an apparent dose delivered (safety, beside specific Skin irritation/sensitization study; Draft Guidance on Lidocaine patches, 2006): plasma level is proportional to the concentration at the site of action (beneath SC).

- In some instances, combined approaches: pharmacokinetic and clinical end-point studies.

- Draft Guidance on Diclofenac Sodium (gel 1%, 2011) - effects believed to be due to local (soft tissue – clinical end-point study) and systemic exposure (pharmacokinetic study).

(4) Biowaiver grating - topical solutions

- Same active ingredient, same concentration, no composition factors susceptible to change the penetration (promoters)
The need for alternative, scientifically based methodologies

There are concerns regarding:

- products improvement process (SUPAC),
- guiding the selection in R&D,
- availability of generics (high quality, adequately tested, all therapeutic classes).

**Goal:** identifying when and how clinical studies can be replaced by adequate testing procedures.

- Several promising techniques are available. The extensive and successful use of dissolution tests for oral solid dosage forms encourages the development of in-vitro release tests for topical semisolids
- Indicator of BA **IF appropriate IVIVC has been demonstrated.**

**Alternatives:**

- DPK – dermatopharmacokinetics (skin stripping),
- DMD – dermal microdialysis,
- **IVR – in vitro drug release** *(Draft Guidance on Acyclovir Ointment 5%, 2012)*
- NIR/Raman/TEWL,
- Unacceptable: Skin biopsy, suction blisters, surface recovery etc.
In-Vitro Drug Release Methodologies (IVR)


- **Detailed description of general test conditions:**
  - Cell design (Vertical Diffusion Cell, VDC, 7 ml HR),
  - Receptor media (composition, degassing),
  - Membrane type and conditioning,
  - Profile comparison and acceptance criteria,
  - Stages of comparison,
  - A “reference standard” dosage form: Hidrocortisone cream 1%.

Performance Verification Test.

- Mentioned in several AAPS/FIP meeting reports on In Vitro Release Testing of Novel/Special Dosage Forms
Chapter <1724> - USP36/NF31, first supplement

Semisolid drug products-performance tests

- General information on the assessment of in-vitro performance for topical semisolids
- Drug release from semisolid matrix, related to the in-vivo performance.
- Topical semisolids – *may be considered as ER formulations* (release process dependent on formulation and manufacturing).
- The barrier properties of SC prevent a direct correlation between in-vitro release rate and in-vivo performance.

- **Multiple options** in terms of testing equipment:
  - vertical diffusion cells (3 models),
  - immersion cells (2 models),
  - specific flow-through cell design (1 model, with various design across equipment manufacturers, closed loop).

- **Multiple parameters** to be selected and validated (API and/or product specific).
# Integration of IVR into SUP AC framework

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Level</th>
<th>Impact on quality / performance</th>
<th>Scale UP</th>
<th>Post Approval Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compendial</td>
<td>1</td>
<td>unlikely</td>
<td>≤ 10x</td>
<td>Quantitative (any excipient or collectively) ≤ 5 % (not for diluents)</td>
</tr>
<tr>
<td>Compendial + IVRT</td>
<td>2</td>
<td>could be influenced</td>
<td>&gt; 10x</td>
<td>Supplier of structure forming agent (mixture) # API Particle size ≥ 5 and &lt; 10 % (not for diluents)</td>
</tr>
<tr>
<td>Compendial + BE IVRT - support</td>
<td>3</td>
<td>likely</td>
<td>-</td>
<td>API Crystalline form &gt; 10 %</td>
</tr>
</tbody>
</table>

- **Scale UP**: Batch size Scale-Up Scale-down
- **Composition**: Supplier of:
  - non-structure forming agent - structure forming agent (single, ≥ 95%)
  - Technical grade of supplier of other excipients
- **Process**: Operating Principles, Equipment Design
- **Site**: Compendial + IVRT, Compendial + BE

*Based on approved target composition, not on previous level 1 or 2 changes; *
*#incl. technical grade of structure forming agent (single agent).*
In Vitro Test: Diffusion vs. Dissolution
Evaluation of release profiles (1)

- Samples
  - Concentration
    - Amount released

\[ Q_t < 30\% Q_V \]
Amount released/area vs. sqrt

Linear regression on individual diffusion profiles:
- Suspensions: \( Q_t = (2 \times C_0 \times C_s \times D \times t^{1/2}) \)
- Solutions: \( Q_t = (2 \times C_0 \times C_s \times D \times t/\pi)^{1/2} \)

Nonparametric statistical method for log slopes
(Wilcoxon Rank Sum/Mann Whitney rank test)

Fraction released vs. t
Analysis of data variability (CV%)

Compendial metrics applied to mean dissolution profiles
- Difference factor, \( f_1 (<15) \)
- Similarity factor, \( f_2 (>50) \)
**In Vitro Test: Evaluation of release profiles (2)**

**Diffusion vs. Dissolution**

**Model dependent approach**
- 5 points;
- 6 hours (recommended).

**Model independent approach**
- 3 points (zero excluded; one > 85%);
- time dependent on release mechanism.

**N = 12**

- CV < 20%
- < 10%

**N = 6**

- Qt < 30%

---

**Graphs and Data: (Images containing graphs and data points)**
In Vitro Test: Diffusion vs. Dissolution
Evaluation of release profiles (3)

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Test</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
<th>T6</th>
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<tbody>
<tr>
<td>Reference</td>
<td>R/T</td>
<td>282.38</td>
<td>284.81</td>
<td>286.32</td>
<td>258.79</td>
<td>257.09</td>
<td>217.06</td>
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<tr>
<td>R1</td>
<td>216.41</td>
<td>1.3049</td>
<td>1.3161</td>
<td>1.3231</td>
<td>1.1959</td>
<td>1.1880</td>
<td>1.0030</td>
</tr>
<tr>
<td>R2</td>
<td>204.05</td>
<td>1.3839</td>
<td>1.3958</td>
<td>1.4032</td>
<td>1.2683</td>
<td>1.2599</td>
<td>1.0638</td>
</tr>
<tr>
<td>R3</td>
<td>216.04</td>
<td>1.3071</td>
<td>1.3183</td>
<td>1.3254</td>
<td>1.1979</td>
<td>1.1900</td>
<td>1.0048</td>
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<tr>
<td>R4</td>
<td>242.69</td>
<td>1.1636</td>
<td>1.1735</td>
<td>1.1798</td>
<td>1.0664</td>
<td>1.0593</td>
<td>0.8944</td>
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<tr>
<td>R5</td>
<td>213.40</td>
<td>1.3233</td>
<td>1.3346</td>
<td>1.3418</td>
<td>1.2127</td>
<td>1.2048</td>
<td>1.0172</td>
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<tr>
<td>R6</td>
<td>226.16</td>
<td>1.2486</td>
<td>1.2593</td>
<td>1.2660</td>
<td>1.1443</td>
<td>1.1367</td>
<td>0.9598</td>
</tr>
</tbody>
</table>

First stage (6 + 6) cells
36 IVR ratios

Second stage + 2 x (6 + 6) cells
324 IVR ratios

8th - 29th within 75 - 133.33%
Passed?
No

110th - 215th within 75 - 133.33%

0.5 0.75 1.0 1.333 1.5
In Vitro Test: Diffusion vs. Dissolution

IVRT – developed in analogy with USP dissolution methodologies for oral solid dosage forms

**Similar purpose:**
- total quality control test;
- accurately guiding of development phase (reverse engineering);
- assessment of the impact for various SUPAC changes;
- biowaiver for lower strengths, based on in vitro methodology; (BE for higher strengths established)

**Particularities:**
- not part of routine quality control;
- diversity of experimental devices (limited data on inter-comparability);
- composition and structural characteristics of the semisolid dosage forms;
- properties of the biological barrier (different pathways, distinct hydro-lipophilic affinities);
- excipients - actively involved in the release and absorption (penetration) process (no inert excipients, some display distinct PD effects).
- IVIVC/biorelevant conditions - more difficult to develop (supportive, not surrogate) e.g. divergent reports on the in-vivo relevance of IVRT/other specific evaluations (e.g. rheology).
In Vitro Diffusion Test - General description

- Use of diffusion cell systems
- Principle: static / flow-through; horizontal / vertical;
- Special devices / adaption to the standard dissolution equipment (immersion cells).

**Common features:**
- 3 compartments apparatus: donor, membrane, receptor;

**Differences:**
- Material
- Design
- Volume
- Application of drug product (surface, conditions)
- Hydrodynamics (stirring equipment, rate)
- Sampling (manual, automated, on-line)
IVRT – design of diffusion cells: donor

**Donor compartment:**

- Occluded / opened (constant/variable composition during test)
- Accommodates various quantities of drug product
  - up to 500 mg or 6 ml
  - finite / (pseudo)infinite dose test conditions
- Static or stirred (side-by-side)
- Directly or indirectly temperature-controlled
- Application: syringe or spatula

dosage wafers / low viscosity adaptor;

- Distinct assembly procedures (flat surface / special devices)
- Protective against photo-degradation (amber glass)
- Different direction of diffusion processes:
  VDC/USP4 – immersion – side-by-side cells
Membrane compartment:

- For QC purposes: inert, mechanical support of the drug product;
- Non-adsorptive, non rate-limiting.

- Animal/human skin – not viable for QC
  - variability, sources etc.; integrity test; complex, reactive support;
  - in-vivo relevance–questionable (lack of underlying tissue structure).

- Alternative: artificial membranes
  Porous (micro/ultra-filtration) / non-porous
  Self-supported / additional elements / coated

Differences in pore size and density ($\varepsilon$), thickness ($h$), tortuosity ($\tau$).

\[
J = K \frac{C}{v} / h \\
J = D_v K' \varepsilon / \tau h
\]

- Without membrane: concerns on direct, considerable changes of formulation (channels).
### IVRT – design of diffusion cells: membrane

Gel product containing two hydrophobic API (4% xiline and 2% phenylbutazone);
Receptor media: 30% absolute ethanol in water;
8 types of membranes:
- different pore size: 0.20, 0.40, 0.45 μm;
- hydrophilic (cellulose esters, polysulfone, polysulfone ether, polyamide);
- hydrophobic (polycarbonate).

<table>
<thead>
<tr>
<th>Type</th>
<th>Pores size (μm)</th>
<th>Thickness (μm)</th>
<th>Trade name</th>
<th>Part.no.</th>
<th>Batch no.</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose mix ester (MC)</td>
<td>0.45</td>
<td>?</td>
<td>Teknokroma® membrane filters</td>
<td>TR-200240</td>
<td>133895</td>
<td>Teknokroma</td>
</tr>
<tr>
<td>Polysulfone (PS)</td>
<td>0.45</td>
<td>145</td>
<td>Tuffryn®, HT-450 membrane filters</td>
<td>66221</td>
<td>T82215</td>
<td>Pall Life Sciences</td>
</tr>
<tr>
<td>Polysulfone ester (PSE)</td>
<td>0.45</td>
<td>114.3-165.1</td>
<td>Supor®-450</td>
<td>60172</td>
<td>T80222</td>
<td>Pall Life Sciences</td>
</tr>
<tr>
<td>Polyamide (NY)</td>
<td>0.45</td>
<td>?</td>
<td>Teknokroma® membrane filters</td>
<td>TR-200120</td>
<td>123781</td>
<td>Teknokroma</td>
</tr>
<tr>
<td>Polycarbonate (PCo.2)</td>
<td>0.20</td>
<td>?</td>
<td>Polycarbonate 0.2</td>
<td>K02CP02500/1215611</td>
<td>202119</td>
<td>GE Water&amp;Process Technologies</td>
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<td>Polycarbonate (PCo.4)</td>
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<td>K04CP02500/1215614</td>
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<td>GE Water&amp;Process Technologies</td>
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<td>Cellulose acetate (ACo.2)</td>
<td>0.20</td>
<td>?</td>
<td>Millipore White GSWP, 142 mm</td>
<td>GSWP14250</td>
<td>H1NN04263</td>
<td>Milipore Corporation, Bedford, MA 01730</td>
</tr>
<tr>
<td>Cellulose nitrate (NCo.2)</td>
<td>0.20</td>
<td>?</td>
<td>Sartorius AG</td>
<td>11107-142N</td>
<td>1097-11107-9604603</td>
<td>Sartorius AG, 37070 Goettingen</td>
</tr>
</tbody>
</table>
IVRT – design of diffusion cells: membrane

- IVR profiles - dependent on membrane characteristics;
- The API ratio: 2; IVR rate ratio: 0.7 (influence of LogP, solubility difference);
- Reduced influence of pore size for hydrophobic membranes;
- Adsorption - various concentration levels, throughout expected interval.
- Lag-time (initial resistance) – limited to 10% of test duration.
IVRT – design of diffusion cells: receptor

**Receptor compartment:**

- **Fluid composition:**
  - sink conditions, membrane-compatible (adequate wetting).
- **Preferred composition:** phosphate buffer (60%) or normal saline (15%)
- **The majority of API – lipophilic** (permeability–required characteristic)
- **Extensive use of solubility** – increasing agents (sink conditions):
  - Tensioactives; BSA; cyclodextrins; Lower alkanols (mainly ethanol), propylene glycol, polyethylene glycols etc.
- **Special issues:**
  - gastro-intestinal absorption: bile acids (synthetic tensioactive accepted);
  - increased solubility while maintaining the discriminatory power;
  - excised skin – removal of several biological components;
  - wetting of hydrophobic membranes by aqueous buffer systems;
  - retro-diffusion (fraction dissolved, phase ratio, micro-structure etc.);
  - **Quality control vs. in-vitro performance test:**
    - Special issues: degassing
      - difficult with tensioactive agents, loss of alcoholic components;
      - mandatory (air bubbles on membrane–reduced diffusion surface).
**IVRT – design of diffusion cells: receptor**

**Receptor compartment:**

- **Difference in:**
  - **Shape**
    - cylinder
    - funnel
    - combined
  - **Volume**
    - Flow through cells: minimum (cell body);
      - *e.g.* <142 µl, 1 ml/h, 7 replacements/h. (Wiechers JW., 2005);
    - VDC: 4-7-12 ml;
    - Immersion cells: 100-150 ml.
  - **Stirring** (50 – 800 rpm)
    - Magnetic bars,
    - With or without additional stainless-still helix,
    - Mini-paddles.

Influence on dimensions of unstirred layer (diffusion coefficient, lag time)

**Parameters:** stirring efficiency (height/diameter); surface/volume.
**IVRT – design of diffusion cells: receptor**

**Example:**
Hanson Microette,
Hanson Research Inc.

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>4 mL “Small”</th>
<th>7 mL “Standard”</th>
<th>12 mL “Large”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top</td>
<td>9</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Bottom</td>
<td>9</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Height (mm)</td>
<td>61</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>4</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Surface, top (cm²)</td>
<td>0.636</td>
<td>1.767</td>
<td>1.767</td>
</tr>
<tr>
<td>Height / Diameter (stirring efficiency)</td>
<td>6.78</td>
<td>4.07</td>
<td>4.07</td>
</tr>
<tr>
<td>Surface / volume (cm⁻¹)</td>
<td>0.16</td>
<td>0.25</td>
<td>0.15</td>
</tr>
<tr>
<td>Thickness of dosage wafer (mm)</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Quantity of product accommodated (mg)</td>
<td>~100</td>
<td>~300</td>
<td>~300</td>
</tr>
<tr>
<td>Sampled (1 ml) / total volume (%)</td>
<td>25</td>
<td>14.285</td>
<td>8.33</td>
</tr>
</tbody>
</table>

Data from Vertical Diffusion Cells - The Hanson VDC (http://www.hansonresearch.com/, accessed April 12th, 2014)
Images from Hanson Research Inc., with permission.
IVRT – design of diffusion cells: receptor design and volume

**Impact of differences in design on IVR profiles**

- 5 formulations,
- 0.75% metronidazole.
- Gel, Emulsion, Cream

- 4, 7, 12 ml VDC;
- PS, 25 mm, 0.45 μm;
- 400 rpm;
- N=6.

<table>
<thead>
<tr>
<th>Product</th>
<th>Rozex® Gel 0.75%</th>
<th>Rozex® Emulsion 0.75%</th>
<th>Rozex® Crème 0.75%</th>
<th>Rosiced® Cream 0.75%</th>
<th>Rosaced® Cream 0.75%</th>
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<tr>
<td>Manufacturer</td>
<td>s.a. Galderama Belgilux n.v.</td>
<td>Pierre Fabre Benelux</td>
<td>Pierre Fabre Hellas A.E.</td>
<td></td>
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<tr>
<td>Carbomer</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Liquid paraffine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclomethicone</td>
<td></td>
<td>✓</td>
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<td></td>
<td></td>
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<tr>
<td>Glycerol stearate &amp; PEG 100 stearate</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Glycerol monolaurate</td>
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<td>✓</td>
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<tr>
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<tr>
<td>Steareth-21</td>
<td></td>
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<tr>
<td>Sorbitol (70%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Emulsifying cera</td>
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<tr>
<td>Methyl parahydroxibenzoate (E218)</td>
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<tr>
<td>Lactic acid</td>
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<td>Citric acid anhydrous</td>
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<tr>
<td>Sodium hydroxide</td>
<td></td>
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<td></td>
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<td>Purified water</td>
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<td>Batch no.</td>
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<td>8076021</td>
<td>8075011</td>
<td>M801A</td>
<td>N903A</td>
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</table>
IVRT – design of diffusion cells: receptor shape and volume
IVRT – design of diffusion cells: VDC vs. immersion cells

Ointment cells (OC), Hanson Research:
- 150 ml, 50 rpm, same protocol (membrane, duration, sampling times) for G, E, C;
- Sampled volume: 1 ml (replacement).
  - Higher IVR rate in OC, lower variability,
  - Similarity concluded for creams.
IVRT – design of diffusion cells: immersion cells

Ointment cells (OC, model A), Hanson Research

Enhancer cells (EC, model B), Agilent / Varian Technologies

Differences:
- Design – concerns on dead volume.
- Initially: vessel shape: flat bottom (A); round bottom (now, flat, special peak).
- Quantity of formulation: fixed (A: approx. 500 mg); variable (B).
- Membrane surface: fixed, 1 design (A): 1,767 cm²; variable, 3 designs (B): 0.5-2-4 cm².
- Assembling procedure: adapted alignment tools (including adjustment tool and plates; variable ease of use, some requesting skills.
Advantages:
- large availability of standard dissolution equipment;
- can beneficiary partially from existing qualification procedures;
- existing automation equipment;
- sampling procedure similar to dissolution methodologies;
- lower costs of the system (immersion cells and vessels / mini-paddles);
- inert materials (PTFE) – lower reactivity compared to standard glass;
- higher volume-sink conditions achieved with lower quant. of ethanol etc.;
- tensioactives can be used without increasing the risk of air-bubbles.

Disadvantages:
- request for increased sensitivity of analytical methodology;
- poor heat transfer profile (longer time for temperature equilibrations);
- risk of quantitatively significant loss of receptor media (hydro-alcoholic mixtures).

Comparative studies with VDC needed
(Various formulations, API, experimental conditions).
(Zatz JL, 1998; Rege PR et al, 1998)
Impact of the alcohol content on similarity evaluation of IVR:

2 Ibuprofen 5% topical gels;
Receptor media: 3 hydro-alcoholic mixtures
33, 50 and 67% absolute ethanol, v/v;
2 experimental devices:
OC, 150ml, 50rpm, 32°C / VDC 12ml, 400rpm, 32°C. PS membranes.

Structural evaluation (deformation profiles 0-25 sec\(^{-1}\), rump up/down, at 25-32°C).

<table>
<thead>
<tr>
<th>Product</th>
<th>Reference, R</th>
<th>Test, T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyethylcellulose</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>Triethanolamine</td>
<td></td>
<td>V</td>
</tr>
<tr>
<td>Benzylic alcohol</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>Ethanol 96%</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td></td>
<td>V</td>
</tr>
<tr>
<td>Batch</td>
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<td>2021006</td>
</tr>
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</table>
IVRT

design of diffusion cells and receptor media composition

R, VDC

T, VDC

R, OC

T, OC
IVRT design of diffusion cells and receptor media composition

- **Back-diffusion possible** (no changes reported by visual inspection);
- **Similarity conclusions:** dependent on quantity of ethanol in receptor media;
- Discriminatory character of the methodology;
- Lower variability; higher release rates for OC.
### IVRT – addressing Q1, Q2, Q3

<table>
<thead>
<tr>
<th></th>
<th>Qualitative equivalence</th>
<th>Quantitative equivalence</th>
<th>(Micro) Structure similarity</th>
<th>Pharmaceutical equivalence</th>
<th>Therapeutic equivalence</th>
</tr>
</thead>
</table>
| Q1 | Same components | Same components | Same arrangement | Same:  
  - API  
  - Strength  
  - Dosage form (definition)  
  - Route  
  - Labeling  
  Fulfill compendial + other applicable requirements. | TE = PE + BE |
| Q2 | Q1 + Q2 =/≠ Q3! | Same quantities | Vane method?  
  Complete rheological profile? |  |
| Q3 | In some instances, subject to patent requests |  |

**Table: Equivalence and Methodology**

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>IVRT</th>
<th>BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>TE</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Legend:**
- ✓: Present
- -: Absent
- ~: In some instances
IVRT – addressing Q1, Q2, Q3

Case 1: various types of dosage forms—non-similar structure and IVR (mechanism)
Same antifungal API’s available in various liquid and semisolid formulations
Special issues for shampoo’s – particular release kinetics
(high quantities of tensioactives)

(Manescu O et al, 2013)
IVRT – addressing Q1, Q2, Q3

Case 2: Q1 equivalent, Q2 differences – non-similar structure Q3 and IVR
Changes – 1-4% concentration of structure forming agent (cellulose derivative)
Linear dependence of diffusion coefficient (structural resistance, thermodynamic activity of API)

(Manescu O et al, 2013)
IVRT – addressing Q1, Q2, Q3

Case 3: different Q1, Q2, Q3, similar IVR

Single point viscosity evaluation - replaced by full deformation profiles:
Concentric cylinder, at 25° or IVR testing temperature (32°, 37°, other?)
IVRT

Q1, Q2, Q3: guiding the selection of optimal formulation

Case 4: different Q1, Q2, IVR, similar Q3

Structural differences

- the same structure forming agent, two types of neutralizing agent;
- triethanolamine (B1, B2), sodium hydroxide (B3);
- with or without tensioactive agent;

Comparison with RLD (gel-emulsion; R), BE gel (A) and cream (C)
IVRT

**Q₁, Q₂, Q₃:** guiding the selection of optimal formulation

**Case 5:** different Q₁, Q₂, correlation of IVR with Q₃

Rheological profile – fitted with Ostwald de Waele model (power low)

Correlation of IVR rate with flow consistency index, m (R²>0.99)

<table>
<thead>
<tr>
<th>Excipient</th>
<th>R</th>
<th>T₁</th>
<th>T₂</th>
<th>T₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbomer 940</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbomer 980</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxy-ethyl cellulose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrogol 7 glycerol cocoate</td>
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<tr>
<td>Ethanol</td>
<td></td>
<td></td>
<td>√</td>
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<tr>
<td>Isopropanol</td>
<td></td>
<td></td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Propylenglycol</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triethanolamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diisopropanolamide</td>
<td></td>
<td>√</td>
<td></td>
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</tr>
<tr>
<td>Sodium hydroxide</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Potassium dihydrogen phosphate</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Methyl p-hydroxybenzoate</td>
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<td></td>
<td></td>
<td>√</td>
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<tr>
<td>Sodium metabisulfite</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purrified water</td>
<td></td>
<td></td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

**Miron DS et al (2010)**

\[
\tau = m(\dot{\gamma})^n
\]
Case 6: similar $Q_1$, $Q_2$, $Q_3$, similar IVR (batch to batch, site to site)

<table>
<thead>
<tr>
<th>Code</th>
<th>Batch no.</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>80367A</td>
<td>Testosterone 50 mg</td>
</tr>
<tr>
<td>B</td>
<td>80498A</td>
<td>Carbomer 980, Ethanol 96%, Isopropylmyristate</td>
</tr>
<tr>
<td>C</td>
<td>80466</td>
<td>Sodium hydroxide, Purified water ad 100g</td>
</tr>
</tbody>
</table>
IVRT
Q₁, Q₂, Q₃
Case 6: similar Q₁, Q₂, Q₃, similar IVR (batch to batch, site to site)

Temperature:
- 25°C
- 32°C
Potential IVIVR/IVIVC

In vitro – in vivo relations / correlation

- In-vitro property: IVR rate, rheological measurement;
- In-vivo property: PD, DPK, DMD etc.

Different requirements for QC / biorelevant tests?

Reported rank-order relationships:
- IVR rate - PD, skin blanching effect (betamethasone valerate, Shah VP et al, 1992),
- IVR rate - potency (betamethasone dipropionate, Shah VP et al, 1999),
- DPK - PD, skin blanching effect (hydrocortisone, Caron D et al, 1990),

Prospective limitations of IVRT in IVIVC (release – absorption)
- Design as total QC test, potentially supportive, not surrogate of BA/BE,
- Occlusive conditions <-> composition/structural changes after application,
- Thickness of formulation layer: 20 µm <-> 1500 µm,
- (Pseudo)infinite dose <-> finite dose,
- Interface: inert (QC), lacking essential physiological elements/properties (skin samples),
  <-> complex, dynamic, reactive biological barrier, various pathways (in-vivo).
  Sink <-> Non-Sink; Inert <-> Binding; Spreadability.

The impact of absorption promoters – accurately reflected in limited number of cases: increase of solubility in SC / lipid fluidity of bilayers.

(Shah VP., 2005)
Draft Guidance on Acyclovir ointment  (March 2012)

Recommended study: 2 Options - *In Vitro* or *In Vivo* Study

**In-vitro option**

i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same ($Q_1/Q_2$).

ii. **Acceptable comparative physicochemical characterization** of the test and RLD formulations.

iii. **Acceptable comparative in vitro drug release rate tests** of acyclovir from the test and RLD formulations.

**In-vivo option**: BE Study with Clinical Endpoint

Randomized, double-blind, parallel, placebo-controlled in vivo

**Petition**: *unprecedented, scientifically unsupportable, risk of approving non-equivalent products.*

**Response**: *the in vitro study is equally (or more) sensitive, accurate, and reproducible than conducting an in vivo study with clinical endpoint comparing two products.*

1. formulation simplicity (one API suspended in one ingredient vehicle)

2. **Important physicochemical characteristics affecting BA** – well established
PQRI meeting (Yacobi A et al, Pharm. Res. 2014)

“Evaluation of Topical Drug Products-Current Challenges in Bioequivalence, Quality, and Novel Assessment Technologies”

March 12–14, 2013, Rockville, Maryland, USA

Product Quality Research Institute (PQRI), cosponsored by AAPS, EUFEPS, FIP, USP

Re-evaluation of available methods and approaches to determine BE
Need for new approaches to optimize available methods
Draft Decision Tree Strawman for Determination of Topical BE

Requirement for a multi-faceted approach, tailored to:

- drug,
- disease,
- product interface.

The “one-size fits all” model - outdated.

Several methods need to be implemented in a correlated manner

“complimentary toolkit of methods”
Evaluation of IVR profiles:
three semisolid dosage forms (creams),
metronidazole (0.75 – 1%),
BE previously concluded, based on DMD, DPK.

Membranes:
hydrophilic (polysulfone, 0.45μm),
hydrophobic (polycarbonate, 0.40μm).

Sampling: 30, 60, 90, 120, 150, 180, 210, 240, 300 and 360 min.

Structural differences: flow curves comparison / modeling.

Correlation with DPK and DMD data
(Garcia Ortiz P. et al, Skin Pharmacol Physiol. 2011;24(1):44-53),
using the same batches of drug products.

Miron DS et al (Pharm.Dev.Tech, 2014)
## Qualitative composition

<table>
<thead>
<tr>
<th>Product</th>
<th>Rozex®-Gel 0.75%</th>
<th>Rozex®-Emulsion 0.75%</th>
<th>Rozex®-Crème 0.75%</th>
<th>Rozex®-Kräm 0.75%</th>
<th>Rosiced® Cream 0.75%</th>
<th>Rosaced® Cream 0.75%</th>
<th>Flagyl® 1% R-1.0%</th>
<th>Metronidazole 1% T1-1.0%</th>
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<tbody>
<tr>
<td>Carbomer</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
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<tr>
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<tr>
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<td>Emulsifying cera</td>
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<tr>
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<td>V</td>
<td>V</td>
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<tr>
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<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
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<tr>
<td>Sodium cetyl- and stearylo sulphate</td>
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<td>V</td>
<td>V</td>
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<tr>
<td>Alcohol cetyllicus and stearylicus emusificans B</td>
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<td></td>
<td>V</td>
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<td>V</td>
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<tr>
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<td>V</td>
<td>V</td>
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<td>Sodium hydroxide</td>
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<td>V</td>
<td>V</td>
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<tr>
<td>Purified water</td>
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<td>V</td>
<td>V</td>
<td>V</td>
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</tr>
</tbody>
</table>
IVRT – DMD / DPK

IVRT results:

**PS membranes** (0.45 μm, hydrophilic)
- Diffusion coefficient (μg/cm²/min¹/₂): R-1% 19.52, T1-1% 19.65, T2-0.75% 30.63
- Amount released (μg):
  - 30 min: 241.38, 176.13, 392.14
  - 120 min: 422.26, 347.86, 682.77
  - 360 min: 704.64, 639.54, 1150.80

**PC membranes** (0.40 μm, hydrophobic)
- Diffusion coefficient (μg/cm²/min¹/₂): R-1% 23.05, T1-1% 24.48, T2-0.75% 31.90
- Amount released (μg):
  - 30 min: 288.28, 236.74, 392.14
  - 120 min: 508.09, 469.68, 682.77
  - 360 min: 839.95, 825.01, 1144.67
Rheological profile:
- Lower flow resistance for T2-0.75% (higher IVR rate)
- Pseudoplastic behavior confirmed (flow behavior index < 1)

**Ostwald de Waele model**

- Flow consistency index, $m$
  - $R - 1\%$: 58.85
  - $T1 - 1\%$: 61.74
  - $T2 - 0.75\%$: 14.47

- Flow behavior index, $n$
  - $R - 1\%$: 0.50
  - $T1 - 1\%$: 0.44
  - $T2 - 0.75\%$: 0.41

- Correlation coefficient
  - $R - 1\%$: >0.995
  - $T1 - 1\%$: 0.44
  - $T2 - 0.75\%$: 0.41

**Pseudoplastic behavior**

- Thixotropy area (Pa/sec)
  - $R - 1\%$: 202.86
  - $T1 - 1\%$: 230.44
  - $T2 - 0.75\%$: 74.94
“IVIVC – feasible, but not essential” (Shah VP, 2005)
Conclusions - IVRT

- Powerful tools for evaluation of quality for semisolid dosage forms.
- Specific test for evaluation of the impact of Level 2 changes, in SUPAC-SS.
- Essential for biowaiver procedures (extrapolation to lower strength, once BE for higher strength has been proven).
- Key decision test on QbD, similar to solid oral dosage forms (build-in quality)
- Tailoring based on API physico-chemical properties and formulations characteristics is critical.
- Discriminatory or overdiscriminatory for the impact of various type of changes.
- Pharmaceutical equivalence – mandatory.
- Supplementary test/methodologies could be useful for accurate interpretation.
- IVIVR / IVIVC are more difficult to develop, specific properties of the biological barrier and its interaction with formulation components leading to discrepancies between release and absorption kinetics.
- Special cases need specific assessment (foams, shampoos, non-Higuchi release).
Organizing Committee of Disso Asia 2014
Dr. Vinod P. Shah.
Dr. Eva Benfeldt.
Dr. Lakshmanan Ramaswamy.
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