In vitro release methodologies as performance tests for topical semisolids

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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 complex vehicles through complex barrier

3 stages process - highly specialized interface

1. Release of API from the formulation to stratum corneum (SC)
   - Physico-chemical properties of API
   - Solubility and dispersion / distribution in the vehicle
   - Diffusion resistance, vehicle microstructure

2. Penetration through the SC (rate limiting step)
   Various pathways, different contributions, specific rates
   - Physiological/pathological state, 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) and aim (quality control/product performance test).
BE for topical semisolids

(1) Clinical end-points studies for locally acting dermatological products
   - Costly, time consuming, high variability, but increased clinician confidence;

(2) Vasoconstrictor assay (VCA) - corticosteroids
   (Stoughton-McKenzie vasoconstrictor assay)
   - Limited to a specific class, some issues on inter-individual variability;

(3) Pharmacokinetic studies
   - Draft Guidance on Diclofenac Sodium (gel 1%, 2011);
   - Draft Guidance on Lidocaine patches, 2006;

(4) Biowaiver granting - topical solutions
   - Same active ingredient, same concentration,
   - No composition factors susceptible to change penetration (promoters).
The need for alternatives

Scientifically based methodologies for:

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

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

Indicator of BA IF appropriate IVIVC has been demonstrated.

Several promising techniques are available:

- DPK - dermatopharmacokinetics (skin stripping) (June 1998)
- DMD - dermal microdialysis
- IVR - in vitro drug release (2 Draft Guidance with IVR option)
- NIR/CRS/TEWL

Unacceptable: Skin biopsy, suction blisters, surface recovery etc.
In-Vitro Drug Release Methodologies (IVR)

Shah VP: development and standardization of IVR.


Detailed description of general test conditions:
- Cell design (Vertical Diffusion Cell, VDC, 7 ml HR),
- Test conditions - Receptor media (composition, degassing), membrane,
- Profile comparison, stages and acceptance criteria,
- “Reference standard” dosage form: Hidrocortisone cream 1%.
  Performance Verification Test.

- AAPS/FIP meeting reports - IVR Testing of Novel/Special Dosage Forms
## IVR in SUPAC-SS (1997)

<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></td>
<td></td>
<td></td>
<td>Batch size</td>
<td>Composition*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Scale-up</td>
<td>Qualitative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Scale-down</td>
<td>(any excipient or collectively)</td>
</tr>
<tr>
<td>Compendial</td>
<td>1</td>
<td>unlikely</td>
<td>≤ 10x</td>
<td>Supplier of: -non-structure forming agent -structure forming agent (single, ≥95%)</td>
</tr>
<tr>
<td>Compendial</td>
<td>2</td>
<td>could be influenced</td>
<td>&gt; 10x</td>
<td>Supplier of structure forming agent (mixture)# API</td>
</tr>
<tr>
<td>Compendial</td>
<td>3</td>
<td>likely</td>
<td>-</td>
<td>API</td>
</tr>
</tbody>
</table>

- Based on approved target composition, not on previous level 1 or 2 changes;
- # incl. technical grade of structure forming agent (single agent).

### Notes:
- Supplier of: non-structure forming agent -structure forming agent (single, ≥95%)
- Technical grade of supplier of other excipients
- API
- Particle size
- API
- Crystalline form
- Operating Principles
- Design
- Supplier of:
  - non-structure forming agent
  - structure forming agent (mixture)
- Outside anterior application ranges
- Different phase combining
- Different site (no IVRT, no BE)
- Outside anterior application ranges
- Different facility, Same site (no IVRT, no BE)
- Different site (no IVRT, no BE)
- Supplier of:
  - structure forming agent (mixture)
  - structure forming agent
- Supplier of: non-structure forming agent -structure forming agent (single, ≥95%)
- Supplier of:
  - non-structure forming agent -structure forming agent (single, ≥95%)
- Technical grade of supplier of other excipients
- API
- Particle size
- API
- Crystalline form
- Supplier of: non-structure forming agent -structure forming agent (single, ≥95%)
- Supplier of:
  - non-structure forming agent -structure forming agent (single, ≥95%)
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

Linera regression on individual diffusion profiles:
- Suspensions: \[ Q_t = (2 \, C_0 \, C_s \, D \, t)^{1/2} \]
- Solutions: \[ Q_t = (2 \, C_0 \, C_s \, D \, t/\pi)^{1/2} \]
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: Diffusion vs. Dissolution
Evaluation of release profiles (2)

N=6
Qt<30%

Model dependent approach
• 5 points (in the linear region);
• adequate duration.

N=12
CV<20%
<10%

Model independent approach
• 3 points (zero excluded; one > 85%);
• time dependent on release mechanism.
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>
</tr>
</thead>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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%
III. INACTIVE INGREDIENTS

B. Waiver of Bioequivalence

- topical solution drug product - in vivo BE may be waived;
- Q1 identical, Q2 essentially the same to RLD;
- evidence that difference does not affect safety and/or efficacy.

IV. BA & BE APPROACH

D. In Vitro Release Approaches (Lower Strength)

- Strengths: usually 1, sometimes 2, rarely 3,
- Small amounts of the active drug substance (≤5%, usually ≤1%).

The lower strength(s) - small changes in formulation (inactive ingredients);
- NO changes in manufacturing process.
“...for an ANDA, when BE has been documented for the HS, IVR may also be used to waive in vivo studies to assess BE between these LS and the corresponding strengths of the RLD”.

- Establish BA of LS in an NDA or to document BE of LS in an ANDA:
  - For the two strengths:
    - Formulations should differ only in API concentration and equivalent amount of the diluent;
    - No differences in manufacturing process and equipment.
  - For an ANDA:
    - RLD should be marketed at both HS & LS;
    - HS of the test product should be BE to the HS of RLD.

\[
\begin{align*}
\text{IVR rate (RHS)} & \approx \text{IVR rate (THS)} \\
\text{IVR rate (RLS)} & \approx \text{IVR rate (TLS)}
\end{align*}
\]
New Intermediate Strengths

- Development of an intermediate strength, after approval of two strengths;
- Differ in API concentration, not in manufacturing processes and equipment;
- IVR rate should fall between the IVR of HS and LS.

IVR: Extension of the Methodology

- release rate – a property of the dosage form;
- acceptable regulatory measure to signal inequivalence;
- replacing a series of tests assessing in aggregate product quality & release;
- optimization of IVR tests, similar to dissolution tests;
- more extensive postapproval changes in formulation +/- manufacturing.
Semisolid drug products-performance tests

- General information on assessment of in-vitro performance for topicals
- 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 IVR 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, various designs across equipment manufacturers, closed loop).

- **Multiple method development parameters** to be selected and validated (API and/or product specific).

Profile comparison, stages and acceptance criteria – SUPAC-SS.
IVR Test: Diffusion vs. Dissolution

IVRT – developed in analogy with dissolution methodologies

Similar purpose:
- release specification (total QC test);
- accurately guiding the development phase (reverse engineering);
- assessment of the impact for various SUPAC changes (level 2) & stability;
- biowaiver for lower strengths (feasible).

Particularities:
- not part of routine QC (batch to batch consistency);
- diversity of experimental devices;
- composition and structural characteristics of topical semisolids;
- properties of the biological barrier;
- excipients - actively involved in the release and absorption (penetration)
  (no inert excipients, some display distinct PD effects).
- IVIVC/biorelevant conditions – prospectively, more difficult to develop:
  - supportive, not surrogate;
  - divergent reports on in-vivo relevance of IVR/other specific evaluations
    (e.g. rheology).
IVR Test: General description

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

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

- **Animal/human skin – not viable for QC**
  - variability, sources etc.; integrity test; complex, reactive support;
  - in-vivo relevance (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 ($\tau$).

- $J = K C_v / h$
- $J = D_v K' \varepsilon / \tau h$

- **Without membrane:** concerns on direct, considerable changes of formulation (channels).
IVR Test: Membrane

IVR profiles - dependent on membrane characteristics;
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.
IVR Test: Receptor composition

**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:**
- 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).
IVR Test: Receptor composition

- Weak basic drug
- Receptor media: pH=1.2 / ethanol 30%
**IVR Test: Receptor compartment**

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

<table>
<thead>
<tr>
<th></th>
<th>4 mL &quot;Small&quot;</th>
<th>7 mL &quot;Standard&quot;</th>
<th>12 mL &quot;Large&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<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 (0.5/1 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.
IVR Test: Receptor compartment

- C1: 4 ml vs. 12 ml
- C1: 7 ml vs. 12 ml
- C1: 4 ml vs. 7 ml

- C2: 4 ml vs. 12 ml
- C2: 7 ml vs. 12 ml
- C2: 4 ml vs. 7 ml

- C3: 4 ml vs. 12 ml
- C3: 7 ml vs. 12 ml
- C3: 4 ml vs. 7 ml

- E: 4 ml vs. 12 ml
- E: 7 ml vs. 12 ml
- E: 4 ml vs. 7 ml

- G: 4 ml vs. 12 ml
- G: 7 ml vs. 12 ml
- G: 4 ml vs. 7 ml
Ointment cells (OC, model A), c. of Hanson Research

Enhancer cells (EC, model B), c. of 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).

IVR Test: Receptor compartment
IVR Test: immersion cells vs. VDC

**Advantages:**
- Large availability of standard dissolution equipment;
- Existing qualification procedures and 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 (preferred system - adequate experience) (various formulations, API, experimental conditions).

(Zatz JL, 1998; Rege PR et al, 1998)
IVR Test: immersion cells vs. VDC

Non-similarity of IVR profiles - difference of composition
Same discriminatory character (VDC, OC, EC)
<table>
<thead>
<tr>
<th>Q1</th>
<th>Qualitative equivalence</th>
<th>Same components</th>
<th>In some instances, subject to patent requests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2</td>
<td>Quantitative equivalence</td>
<td>Same components Same quantities</td>
<td>Q1 &amp; Q2 $\neq$ Q3!</td>
</tr>
<tr>
<td>Q3</td>
<td>(Micro) Structure similarity</td>
<td>Same arrangement</td>
<td>IVRT Rheological behaviour Globule / particle size</td>
</tr>
<tr>
<td>PE</td>
<td>Pharmaceutical equivalence</td>
<td></td>
<td>Same: API Strength Dosage form (definition) Route</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Comparable: Labeling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Meet compendial &amp; other appl. requirements.</td>
</tr>
<tr>
<td>TE</td>
<td>Therapeutic equivalence</td>
<td>TE = PE + BE</td>
<td></td>
</tr>
</tbody>
</table>
Q3 microstructural similarity

Particle / droplet size measurement – similar distribution

Rheological behaviour

Microstructural non-similarity – differences in:
- physical characteristics – rheology (even for similar particle size)
- IVR rates.

Rheology:
1) Shear stress vs. strain rate measurements;
2) Evaluation of linear viscoelastic response;
   (storage and loss modulus vs. frequency; $G'$, $G''$);
3) Yield stress ($\sigma_0$) – inversely proportional to spreadability.

Many topical semisolids – non-Newtonian behavior (apparent viscosity)
Vane method (Kryscio DR et al, 2008),
Hysteresis loop test.

Validation of Q3: must be related to TE

(Yu L., 2003. Advisory Committee for Pharmaceutical Science Meeting)
IVR Test: Q1, Q2, Q3

Application 1: guiding selection of optimal formulation candidates
IVR Test: Q1, Q2, Q3

Application 1: guiding selection of optimal formulation candidates

Addition of critical excipient
IVR Test: Q1, Q2, Q3

Application 2: monitoring batch to batch consistency
3 consecutive batches

32°C
IVR Test: Q1, Q2, Q3

Application 3: monitoring site to site consistency

Intercomparability of results on different cell models (VDC)
**IVR Test: Q1, Q2, Q3**

**Application 3: monitoring site to site consistency**

Intercomparability of results on different cell models (IC)
IVR Test: Q1, Q2, Q3

Application 3: monitoring site to site consistency

25°C

32°C
IVR Test: Q1, Q2, Q3

Application 4: evaluation of level 2 changes / stability studies

Graphs showing the relationship between quantity released/unit area (µg/cm²) and square root of time (min^1/2) at 25°C and 32°C. The graphs compare different linear models (R (Zovirax), Linear (T1), Linear (T2 (10.5%)), Linear (T3 (11.0%))).
IVR Test: Q1, Q2, Q3

Application 5: development of lower strength hydrocortisone creams (0.25-0.5-1.0%)

- IVR rate proportional to $\sqrt{C_0}$ for drug in suspension, with Q1, Q2 and Q3 similar vehicles

Co – total concentration of drug in the vehicle (dissolved and disperse)
IVR Test: Q1, Q2, Q3

Application 5: development of lower strength dispersed drug

- IVR rate proportional to $\sqrt{Co}$ for drug in suspension, with Q1, Q2 and Q3 similar vehicles

Co – total concentration of drug in the vehicle (dissolved and disperse)
IVR Test: Q1, Q2, Q3

Application 5: development of lower strength dissolved drug

- IVR rate proportional to Co for drug in the matrix (dissolved), with Q1, Q2 and Q3 similar vehicles

Co – total concentration of drug in the vehicle
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 (*Q1/Q2*).

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”
IVRT – DMD / DPK

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

"IVIVC – feasible, but not essential " (Shah VP, 2005)
Concept paper on the development of a guideline on quality and equivalence of topical products

.. the vehicle itself may influence the condition to be treated ..

Clinical trials are in principle necessary to demonstrate therapeutic equivalence, but other models may be used, if adequately validated. In many cases, these other models have exhibited poor accuracy, sensitivity, reproducibility, in vitro in vivo correlation and have been unable to provide convincing evidence to predict therapeutic equivalence.

Developing an extended concept of pharmaceutical equivalence:
(1) suitable in vitro and in vivo models and methods,
(2) appropriate and representative comparative quality data (T vs. RLD),
(3) adequate acceptance (equivalence) criteria.

The concept of pharmaceutical equivalence for topical products should be developed and extended to include e.g. qualitative and quantitative equivalence of formulation, physical properties and microstructure, administration and in vitro drug release properties.
Topical drug Classification System (TCS)

Shah, V.P., et al, Int J Pharm. 2015

Q1, Q2 Same
Q3 Same
TCS class 1

Q1, Q2 Same
Q3 Different
TCS class 2

Q1, Q2 Different
Q3 Same
TCS class 3

Q1, Q2 Different
Q3 Different
TCS class 4
Conclusions

- 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 / **TCS-based biowaiver**).
- Part of 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, anhidrous).
Acknowledgements

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THANK YOU!