In vitro drug release from semisolid dosage forms and its regulatory applications

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Drug delivery from special vehicles through complex barrier

I) Drug characteristics
Physicochemical properties (relevant for biological interactions)
Particle size, polymorph etc.

II) Drug product (formulations) characteristics
- composition
  (macromolecules, complex mixtures), hydro-lipophilic nature
- state of aggregation of drug
  (dissolved, distributed in two or more phases, suspended), ratio
- pH (bulk, aqueous phase), buffer capacity, water activity etc.
- different (contextual) role of excipients
  (formulation factor - penetration enhancer)
- solubility: within product and within barrier, both changing after application (co-diffusing excipients, evaporation loss, pH changes, temperature changes).
Drug delivery from special vehicles through complex barrier

III) Microstructure
- Formulation factors (qualitative and quantitative composition)
- Manufacturing process (parameters: batch size, order of operations, phase ratio, temperature profile etc.)
- History of formulation
- Changes in particle or globule size during manufacturing or shelf-life
- Specific changes at application (shearing forces): dispensing & application stress, temperature shift
- Dose delivered (density) - multiple dose
  (air entrapment; Murthy SN, 2015)

IV) Container
single or multiple dose, diameter of dispenser, closure system.

Considering ALL these characteristics, individually and correlated!
Bioequivalence

**BE General approaches**
- **PK** endpoint studies

**Topical BE approaches**
- Lidocaine patches (2006),
- Diclofenac Sodium 1% gel (2011),
- MUst

**DPK (JP)**
- VCA for corticosteroids

**Gold standard**
- 3 draft guidances (*in vitro option*)
- Topical solution (Q1, Q2)

(proportionality, self-evident, BCS)

When / how clinical studies can be replaced by adequate procedures?

**Alternatives:**
- DPK, DMD, NIR/Raman/TEWL.

**Unacceptable** (ethics - invasive, reproducibility):
- skin biopsy, suction blisters, surface recovery etc.
IVR methodology - Timeline

1980’s - 1990’s Shah VP: development and standardization of IVR.


1998 DPK draft guidance


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.

2013: Chapter <1724> - USP36/NF31, first supplement
Semisolid drug products-performance tests

- AAPS/FIP meeting reports - IVR Testing of Novel/Special Dosage Forms
Current regulatory applications

1. Selection of the optimal formulation candidate
   (available reference product)
   drug polymorph, particle size etc.
2. Testing the impact of moderate (level 2) changes in composition / manufacturing process (US: SUPAC / EU: variations)
3. Waiving the in vivo studies (topical solutions, 3 draft guidance US/FDA)
4. Stability studies (microstructural / thermodynamic activity)
5. JP: Selection of batch for the reference (innovator) product:
   Selected RLD batch - intermediate IVR rate

Other (potential) applications
1. Characterization of microstructural similarity
   (relationship between IVR and Q3 similarity, TCS)
2. Batch-to-batch consistency
   (routine QC, batch release)
Method development - selection of testing parameters

0. Cell design
   (preference, difficulties, sink conditions!)
1. Composition of receptor media
   (sink conditions: composition, volume, temperature)
2. Membrane
   (nature, pore size, porosity, thickness, tortuosity)
3. Membrane and media
   adequate contact angle with semisolid donor
4. Pre-treatment of membrane
   (soaking in receiver / other media)
5. Assessment of adsorption and compatibility profiles
   (media and membrane)
6. Temperature and hydrodynamics in the receiver
   (stirrer, rotation speed/flow rate 32/37°C, tolerance)
7. Sampling schedule
   (steady state release, 5 data points in the linear region, depletion)
8. Analytics
   (concentration in receiver, strength, volumes, pattern, lag time)
9. Data analysis (calculation of rate - model dependent, CI90%)
Method validation

Variability of experimental data
reproducibility

Discrimination for different strengths of the same product
dissolved or dispersed drug
distinct relationship between strength and release rate
different strengths,
same composition,
same manufacturing process and parameters,
same state of aggregation.

Consistent IVR data for similar microstructure
accuracy (batch sameness)

Sensitivity to controlled changes
composition and / or microstructure (process, stress etc.)
(Thakker KD et al, 2003)
In vitro release vs. dissolution tests

Similarities

1. Total quality control tools
   (reflecting in aggregate the influence of various factors)

2. Screening the impact of defined changes in composition / manufacturing process (SUPAC)
   (decision on in vivo BE studies)

3. Testing conditions fitted to characteristics drug, drug product

4. Addressed by dedicated compendial chapters
   (<1724> / <711>, <1092>, <1094> etc.)

5. Partially, common instrumental platforms
   (adapted dissolution equipment: USP2/USP4)

6. Characterization during R&D Phase

7. Characterization of clinical batches
   (assessment / understanding of product failure modes)
In vitro release vs. in vitro dissolution tests

Differences (1)

1. IVIVC (prospectively) more difficult to develop
   1.a. No extensive experience in terms of in vivo (PK) BE studies
   1.b. Complexity and specificity of:
       - biological barrier (physiology, pathology)
       - composition of semisolids (dissolved/dispersed drug)
       - dosing conditions (no unitary doses, region, area, shear)
   1.c. Active role of excipients in:
       - delivery release / penetration / permeation
       - pharmacodynamics

2. Diversity of experimental devices - specific:
   <1724> diffusion cells (horizontal/vertical; static/flow-through)

3. No regulatory requirement for routine QC.
4. No proportionality waivers.
In vitro release vs. in vitro dissolution tests
Differences (2)

5. Methodological particularities:
   sink conditions and media degassing are mandatory;
   infinite dose, occluded conditions;
   sampling has limited hydrodynamic impact
   but may contribute significantly to sink conditions
   stirring is critical, but the rate has lower impact on release
   no limit of CV (%)
   model dependent approaches in data analysis;
   preventing significant changes of product by receiver (back-diffusion).

6. Two stages of comparison (S1: n=6, S2: n=6+12), SUPAC only!

7. Individual (not mean) profiles are compared

8. No PVT available (hydrocortisone 1% cream)
# In Vitro Release vs. In Vitro Permeation Tests (1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IVPT</th>
<th>IVRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equipment</strong></td>
<td>Diffusion cells</td>
<td>Occluded</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Occluded / un-occluded</td>
<td>Infinite dose</td>
</tr>
<tr>
<td></td>
<td>Finite dose</td>
<td>Leave-on</td>
</tr>
<tr>
<td></td>
<td>Leave-on</td>
<td></td>
</tr>
<tr>
<td><strong>Interface (membrane)</strong></td>
<td>Natural (animal / human), torso</td>
<td>Artificial</td>
</tr>
<tr>
<td></td>
<td>Full / split-thickness</td>
<td>Reproducible characteristics</td>
</tr>
<tr>
<td></td>
<td>Reactive</td>
<td>Inert (mechanical support)</td>
</tr>
<tr>
<td></td>
<td>Compatibility assessment</td>
<td>Compatibility assessment</td>
</tr>
<tr>
<td></td>
<td>Integrity assessment</td>
<td></td>
</tr>
<tr>
<td><strong>Receiver</strong></td>
<td>Sink conditions (modified) PBS pH=7.4, SBF, BSA</td>
<td>Sink conditions pH=5.5 or hydro-alcoholic</td>
</tr>
<tr>
<td></td>
<td>32°C (surface)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37°C (receiver)</td>
<td>32°C (skin products)</td>
</tr>
<tr>
<td></td>
<td>Antimicrobial agent</td>
<td>37°C (vaginal products)</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>24 hours</td>
<td>Sufficient for accurate evaluation of steady state release (4-6 hours)</td>
</tr>
<tr>
<td></td>
<td>More if necessary and integrity is maintained</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less (rinse-off)</td>
<td></td>
</tr>
</tbody>
</table>
## In Vitro Release vs. In Vitro Permeation Tests (2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IVPT</th>
<th>IVRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery</strong></td>
<td>Variable lag time</td>
<td>Limited lag time (&lt;10%)</td>
</tr>
<tr>
<td></td>
<td>Steady state</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Donor depletion</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Critical region</th>
<th>4-12-18 (24h)</th>
<th>1-4 (6) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>(detailed sampling from receiver, at steady state)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Samples</th>
<th>Receiver</th>
<th>Receiver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surface (wash, strip)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Separated compartments</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Main process</th>
<th>Diffusion and distribution in various layers</th>
<th>Unrestricted diffusion form donor to the receiver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Receiver recovery</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Reflecting distinct pathways (bulk / shunt route)</td>
<td>Reflecting release from semisolid toward the skin</td>
</tr>
</tbody>
</table>
## In Vitro Release vs. In Vitro Permeation Tests (2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IVPT</th>
<th>IVRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data analysis</strong></td>
<td>Total recovery (90-110%) Compartment distribution (incl. receiver)</td>
<td>Apparent amount (&lt;30%)</td>
</tr>
<tr>
<td></td>
<td>Flux ($J$, $\mu g/cm^2/h$) and partition coefficient ($K_p$)</td>
<td>Rate (square root law), $\mu g/cm^2/h^{0.5}$</td>
</tr>
<tr>
<td><strong>Similarity</strong></td>
<td>Various statistical methods: Donor effects Product effects</td>
<td>Nonparametric statistical method for log slopes</td>
</tr>
<tr>
<td></td>
<td>Donor*Product interactions</td>
<td>Two stages with acceptance interval 75-133.33%</td>
</tr>
<tr>
<td><strong>(Bio) Relevance</strong></td>
<td>Predictive</td>
<td>*</td>
</tr>
<tr>
<td><strong>Sensitivity to microstructural differences</strong></td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>
Current regulatory attitude

Not appropriate test for BA assessment or BE demonstration ..
   .. as a single test, but essential component of aggregate weight of evidence.

Nor for comparison of formulation across manufacturers ..
   .. if significant differences in qualitative and quantitative composition.
   .. but useful for in depth understanding of formulation (and its failure mode/risk).

Proportionality waivers? Non-linear PK/PD profiles ..
   .. although initially considered for lower / intermediate strengths (1998).

Arguments / questions:

Reduced (bio)relevance (IVIVC more difficult to achieve)?
Consistency of results and setting (meaningful) acceptance criteria (routine QC & stability testing)?
Using individual results of general quality tests or performance test (aggregate outcome)?
### IVR Test: 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>
<tbody>
<tr>
<td>Q1</td>
<td>Same components</td>
<td>Same components</td>
<td>Same arrangement</td>
<td>Same:</td>
<td>Meet compendial &amp; other appl. requirements.</td>
</tr>
<tr>
<td></td>
<td>In some instances, subject to patent requests</td>
<td>Same quantities</td>
<td></td>
<td>-API</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>Qualitative equivalence</td>
<td>Same components</td>
<td>IVRT</td>
<td>-Strength</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>Quantitative equivalence</td>
<td>Same quantities</td>
<td>Rheological behaviour</td>
<td>-Dosage form (definition)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Micro) Structure similarity</td>
<td></td>
<td>Globule / particle size</td>
<td>-Route</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Same</td>
<td></td>
<td></td>
<td>Comparable:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>arrangement</td>
<td></td>
<td></td>
<td>-Labeling</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>Pharmaceutical equivalence</td>
<td></td>
<td></td>
<td></td>
<td>TE = PE + BE</td>
</tr>
<tr>
<td>TE</td>
<td>Therapeutic equivalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Q3
microstructural similarity

Relevant evaluations should be conducted in relevant test conditions.
The microstructural similarity must be assessed:
  at relevant temperature
    storage: 20-25°C,
    application: 32 or 37°C;
  under controlled and relevant stress:
    Q3a: similarity of static (unstressed) layers
    Q3b: similarity of thick (squeezed) layers (compression and shearing)
    Q3c: similarity in thin (spread and heated) layers

Estimated shear stress 20 sec\(^{-1}\), 5mm vs. 3333 sec\(^{-1}\) 30 μm (Murthy NS, 2015).
Changes are more likely to occur during the initial storage period (Boylan C, 1966)

Mucosal products (dilution effect of body fluids, shear stress, temperature).
Recent developments

1) US-FDA - Draft Guidance with in vitro option:
   1.1. Draft guidance on acyclovir ointment; Mar 2012.
   1.2. Draft guidance on cyclosporine ophthalmic emulsion; Jun 2013.
   1.3. Draft guidance on difluprednate ophthalmic emulsion; Jan 2016.

2) PQRI meeting:
   “Evaluation of Topical Drug Products-Current Challenges in Bioequivalence, Quality, and Novel Assessment Technologies”
   Rockville, Maryland (US) Mar 2013.
   2.1. The “one-size fits all” model - outdated.
   2.2. Several methods need to be implemented in a correlated manner “complimentary toolkit of methods”.

3) EMA/CHMP/QWP/558185/2014; Dec 2014
   Concept paper on the development of a guideline on quality and equivalence of topical products
   Developing an extended concept of pharmaceutical equivalence:
   .. suitable in vitro and in vivo models and methods ..
Conclusions

• Powerful tools in quality assessment for semisolid dosage forms.
• Specific test for evaluation of the impact of Level 2 changes, in SUPAC-SS.
• Encouraging number of draft guidance with in vitro options.
• Essential for future biowaiver procedures (extrapolation to lower strength, once BE for higher strength has been proven / TCS-based biowaiver).
• Tailoring to drug, drug product, microstructure and dosing conditions is critical.
• Discriminatory or overly discriminatory for the impact of various changes.
• Pharmaceutical equivalence is mandatory.
• Combined methodologies (aggregate weight of evidence / advanced pharmaceutical equivalence) 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.
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