Physicochemical Characterization of Acyclovir Topical Semisolid Dosage Forms Towards TCS Validation

Flavian Ștefan Rădulescu, Dalia Simona Miron
University of Medicine and Pharmacy Carol Davila, Bucharest, Faculty Of Pharmacy, Biopharmaceutics Dept.
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

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

Considering ALL these characteristics, individually and correlated!

*Murthy SN, 2015*
### IVR Test: addressing Q1, Q2, Q3

<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</td>
<td>Q1 &amp; Q2 =/≠ Q3!</td>
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<td></td>
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<td>Same quantities</td>
<td></td>
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<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>Same:</td>
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<td>- API</td>
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<td>- Strength</td>
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<td>- Dosage form (definition)</td>
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<td>- Route</td>
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<td>Comparable:</td>
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<td>- Labeling</td>
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<td>Meet compendial &amp; other appl. requirements.</td>
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<tr>
<td>TE</td>
<td>Therapeutic equivalence</td>
<td>TE = PE + BE</td>
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</tbody>
</table>
Relevant evaluations - relevant test conditions.

The microstructural similarity - 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, 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).
Topical *drug* Classification System (TCS)

Comparative evaluation of qualitative and quantitative composition

Classification of excipients into two groups based on their inert / non-inert character

Use of IVR (and other relevant tests) for Q3 assessment

Biowaiver

In vivo study

Significance of comparison of formulations across manufacturers
Oscillatory tests
- Deformation amplitude sweep
  (controlled stress mode for evaluation of linear viscoelastic region);
- Shear stress amplitude sweep
  (controlled stress mode for the evaluation of LVR and yield stress).

Rotational tests
- Creep and recovery;
- Yield stress determination using a shear stress ramp;
- Hysteresis loop test;
- Structure recovery (at low shear rate; temperature ramp).

Tests performed at two temperatures: 25 and 32/37°C.
Topical drug Classification System (TCS)


- **TCS class 1**
  - Q1, Q2 Same
  - Q3 Same

- **TCS class 2**
  - Q1, Q2 Same
  - Q3 Different

- **TCS class 3**
  - Q1, Q2 Different
  - Q3 Same

- **TCS class 4**
  - Q1, Q2 Different
  - Q3 Different
Topical drug Classification System (TCS)

Acyclovir cream 5%

> 40 topical creams on EU market;
significant differences in Q1 / Q2 / Q3;
different formulations of the same MAH in different countries.

Qualitative composition (excipients grouped into categories):

<table>
<thead>
<tr>
<th>Code</th>
<th>R01</th>
<th>R02</th>
<th>R03</th>
<th>R04</th>
<th>R05</th>
<th>R06</th>
<th>R07</th>
<th>T01</th>
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<td>Esters of fatty alcohols with fatty acids&lt;sup&gt;1)&lt;/sup&gt;</td>
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<td>Fatty alcohols / Fatty acids&lt;sup&gt;6)&lt;/sup&gt;</td>
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<td>Preservative&lt;sup&gt;8)&lt;/sup&gt;</td>
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</table>
IVR Test: Comparison across manufacturers

Acyclovir creams 5% (EU/US)
6 batches of RLD

- RLD from two regions (EU: R01-R04, R07; US: R06)
- Q1 differences
- IVR non-similar - Q3 different: microstructural discrimination
  30.21-34.56 vs. 19.65 µg/cm²/min⁰/⁵
IVR Test: Comparison across manufacturers

Acyclovir creams 5% (EU market)
21 generic formulations (Q1/Q3/Q3 non-similar)

Propylene glycol
Mineral oil / Liquid paraffin
Petrolatum / White soft paraffin
Cetyl alcohol
Dimeticone
Cetostearyl alcohol
Sodium lauryl sulfate
Glyceryl monostearate
Macrogol stearate
Poloxamer 407
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Glycerol
Dimethicone 350
Polysorbate 80
Stearyl macrogol glycerides
Poloxamer
PEG-5-Glycerol-Stearate
Octyl dodecanol
Stearyl alcohol
Benzyl alcohol
Pheny ethanol alcohol
Citric acid
Sodium citrate
Triethanolamine
Dimeticone 20
Macrogol stearate 1500
PEG-100 stearate
PEG-6 stearate
Dodecyl oleate
Beeswax
Cera carnauba
Stearic acid
Semisynthetic glycerides
Castor oil
Vanilla flavor
Chlorocresol
Butylhydroxytoluene
Sodium edetate
Carbomer
PEG-esters with fatty acids
Macrogol cetosteareate
Glyceryl stearate 100
Glyceryl stearate
PEG-32 stearate
Macrogol 4000
Macrogol 400
Cetostearyl alcohol (type B)
Paraffin
Poloxamer 188
Monocetyl ether
Cera lanette
Water

<25%
1.5-5%
Q3 assessment - Oscillatory tests

- Q3 non-similarity between US and EU RLD confirmed by IVR and rheological evaluations (distinct LVR).
- EU RLD: consistent IVR and microstructure between the 5 batches.
- Complex relationship between rheology and IVR for multisource drug products (differences in qualitative composition – microstructure - IVR).
Q3 assessment – Rotational tests

The amplitude of deformations and structural recovery:
- dependent upon the stress profile and temperature,
- related to composition and manufacturing process (history).
IVR - changes in non-inert excipients

Preliminary study

Microstructural impact of PG is reflected by IVR
Manufacturing of semisolid formulations

- Scale down from industrial manufacturing process; (marketed product)
- Changes to the approved composition by addition of 20% propylene glycol (PG) – formulation F0;
- Illustrating the non-inert group of excipients:
  - impact on microstructure (reflected by IVRT),

Changes in manufacturing process or composition (F1-F12).

Scope
- formulations corresponding to TCS classes 1, 2 and 3;
- comparative testing: IVRT (n=12), IVPT (n=6), DPK (n=4);
- complementary tests for assessing Q3.
# Formulations under evaluation

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Code of the formulation</th>
<th>Ingredient / Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (manufacturing variables)</td>
<td>F1</td>
<td>Order of addition for phases</td>
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<tr>
<td></td>
<td>F2</td>
<td>Cooling procedure (stirring)</td>
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<td></td>
<td>F3</td>
<td>Cooling procedure (temperature)</td>
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<tr>
<td></td>
<td>F4</td>
<td>Mixing procedure</td>
</tr>
<tr>
<td>B (sources of row material)</td>
<td>F5</td>
<td>Cetostearylic alcohol (inert excipient)</td>
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<td></td>
<td>F6</td>
<td>Polisorbate 80 (non-inert excipient)</td>
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<td></td>
<td>F7</td>
<td>Acyclovir (active ingredient)</td>
</tr>
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<td></td>
<td>F8</td>
<td>Petrolatum / White soft paraffin (inert excipient)</td>
</tr>
<tr>
<td>C (quantities / grade)</td>
<td>F9</td>
<td>Propylene glycol, 5% (non-inert excipient)</td>
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<td>F10</td>
<td>Propylene glycol, 40% (non-inert excipient)</td>
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<td></td>
<td>F11</td>
<td>Cetostearylic alcohol (30:70) (inert excipient)</td>
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<td>F12</td>
<td>Cetostearylic alcohol (110%) (inert excipient)</td>
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</tbody>
</table>

**Drug / Excipient**
- Acyclovir
- Cetostearylic alcohol (50:50)
- Mineral oil / Liquid paraffin
- Petrolatum / White soft paraffin
- Polisorbate 80
- Sorbitan oleate
- Benzylic alcohol
- Purified water
- Propylene glycol
IVR and rheological evaluations

Subgroup A (F1-F4) - Candidates for TCS class 1

IVR

Yield stress

LVR

25°C

32°C
IVR and rheological evaluations

Subgroup A (F1-F4) - comparison with F0

Candidates for TCS class 1 (Q1, Q2, Q3)
IVR and rheological evaluations

Subgroup A (F1-F4) - Candidates for TCS class 1
IVR and rheological evaluations

Subgroup B (F5-F8) - Candidates for TCS class 2

IVR

Yield stress

LVR

F7 (different source of API): Q1, Q2, Q3
IVR and rheological evaluations
Subgroup B (F5-F8) - Candidates for TCS class 2
IVR and rheological evaluations

Subgroup C (F9-F12) - Candidates for TCS class 3 (F9)

IVR

Yield stress

LVR

25°C

32°C
IVR and rheological evaluations

Subgroup C (F9-F12)
Developments – Relevant documents

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.
   1.4. Draft guidance on acyclovir cream; Dec 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

IVR

- IVR is a powerful tool for *TCS classification* and for biowaiver procedures (TCS classes 1 and 3).
- Evaluation of the impact of **Level 2 changes**, in SUPAC-SS.
- Encouraging number of draft guidance with in vitro options.
- **Tailoring** to *drug, drug product, microstructure and dosing conditions*.
- **Discriminatory or overly discriminatory** for the impact of various changes and microstructural non-similarities.
- **Pharmaceutical equivalence** is mandatory.
- **Combined methodologies** could be useful for accurate interpretation.
Acknowledgements

Part of this work was supported by a grant from Product Quality Research Institute.

THANK YOU FOR YOUR ATTENTION!