Locally applied, locally acting products
Topicals – in vitro comparison

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BioBridges

Outline

Drug delivery from special vehicles through complex barrier
Drug, drug product, microstructure, container, application

Bioequivance of topical dosage forms
~~Clinical studies~~, Alternative approaches

In vitro release testing (IVRT)
Timeline, current applications
Similarities and difference vs. dissolution
In vitro release vs. permeation (IVRT/IVPT)
Q1 / Q2 / Q3 / Q4, Topical drug Classification System (TCS)

Case studies (erased from the original presentation)
Current developments
Conclusions

Drug delivery from special vehicles through complex barrier

I) Drug characteristics

Physicochemical properties (relevant for biological interactions):

Molecular determinants

- water / lipid solubility,
- acidobasic characteristics (pKa values; molecular species / solubility)
- n-octanol / water partition or distribution coefficient (logP, $logD_{5.5}$),
- molecular weight / molecular volume (MW/MV),
- polar surface area (PSA)
- ability to develop hydrogen bonds (donor / acceptor groups, HBD/HBA).

Particle size and shape,

Polymorph,

Crystal habit.

Drug delivery from special vehicles through complex barrier

II) Drug product (formulations) characteristics

- **composition**
  (macromolecules, complex mixtures), hydro-lipophilic nature
  sometimes anhydrous formulations (e.g. PEG ointments)
- **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 / temperature changes.

Drug delivery from special vehicles through complex barrier

III) Microstructure

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

Drug delivery from special vehicles through complex barrier

IV) Container (very important, frequently ignored)

nature (plastic, aluminium), size (2-100 g),
single or multiple dose (e.g. testosterone gel 5%, 5 g, single dose),
diameter of dispenser (e.g. acyclovir creams EU market: 0.1-0.5 mm),
closure system,
application device (shearing forces; e.g. no mess applicator),
dosing (e.g. progesterone 10mg/g gel, spoon).

V) Application

Changes of the product during:
- dosing (amount, stress applied),
- spreading (shear, heating, changes in thickness of the layer),
- residence at the site of application,
- during the permeation / penetration processes (for drug).

Drug delivery from special vehicles through complex barrier

Considering ALL these characteristics (I to V)

Assess their significance individually and correlated, in terms of:

Quality;
Efficacy;
Safety.

Importance of visual observations:

- **first (visual) assessment of difference in yield stress / spreadability when two products are analysed comparatively;**
- **squeeze the tube, observe the flow pattern;**
- **obvious when semisolid products are applied onto membranes (in vitro release) or on plates of equipment (rheological assessment);**
- **patient perception, acceptance and compliance to treatment.**

Pharmaceutical equivalence (PE) Bioequivalence (BE)

BE General approaches

- **PK** endpoint studies

- **PD** endpoint studies
- **Clinical** endpoint studies
- In vitro studies (IV**P**T, IV**R**T)
- **Waiver**

(proportionality, self-evident, TCS?)

Topical BE approaches

Lidocaine patches (2006),
Diclofenac Sodium 1% gel (2011),
MUsT

DPK (JP)

VCA for corticosteroids

Gold standard

FDA-Draft guidances (*in vitro option*)
Topical solution (Q1, Q2)

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

Alternatives:

- DPK, DMD, OFM, 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.

1993 **Shah VP et al.** In vitro release measurement for topical Glucocorticoid Creams. *Pharmacopeial Forum*; 19(2):5048-60.
1997 **Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation** *(***SUPAC-SS***).*
1998 **DPK** *draft guidance*
2010 **Ueda CT et al.** The *Topical/Transdermal Ad Hoc Advisory Panel for the USP Performance Tests of Topical and Transdermal Dosage Forms: Topical and Transdermal Drug Products, Stimuli for the Revision Process. Pharmacopeial Forum*; 35(3):750-64.
2013 **USP-***Chapter 1724 Semisolid drug products-performance tests*
Detailed description of general test conditions:
- Cell design (Vertical Diffusion Cell, VDC, 7 ml; models described in USP),
- Test conditions - Receptor media (composition, degassing), membrane,
- Profile comparison, stages and acceptance criteria,
- "**Reference standard**" dosage form: Hidrocortisone cream 1% (*Pharmacia*). Performance Verification Test.

- **AAPS/FIP** *meeting reports* **- IVR Testing of Novel/Special Dosage Forms**

1998: Topical Dermatological Drug Product NDAs and ANDAs - In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies (Draft guidance)

"..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.**

$$\frac{\text{IVR rate } (R_{HS})}{\text{IVR rate } (R_{LS})} \approx \frac{\text{IVR rate } (T_{HS})}{\text{IVR rate } (T_{LS})}$$

Intermediate strengths and extended applications also mentioned!

R – reference listed drug; T – tested product (generic);
HS / LS – higher / lower strength;
IVR – in vitro release rate.

2013: Chapter <1724> - USP36/NF31, first supplement 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 *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***, 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 (1997).

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, draft guidances US/FDA)

4. Stability studies

5. JP: **Selection of batch for the reference** (innovator) product (July 7, 2003): Guideline for Bioequivalence Studies of Generic Products for Topical Use

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

Cell design
(preference, skils, sink conditions)

Composition of receptor media
(sink conditions: composition, volume, temperature)

Membrane
(nature, pore size, porosity, thickness, tortuosity)

Membrane and media
adequate contact angle with semisolid donor

Pre-treatment of membrane
(soaking in receiver / other media)

Temperature and hydrodynamics in the receiver
(stirrer, rotation speed/flow rate 32/37°C, tolerance)

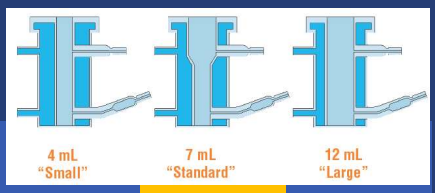
Sampling schedule
(steady state release, 5 data points / linear region, depletion)

Analytics
(concentration in receiver, strength, volumes, pattern, lag time)

Data analysis
calculation of rate - model dependent, CI90%, 2 stages

Cell design.
Vertical diffusion cells

Example:
Hanson Microette,
Hanson Research Inc.

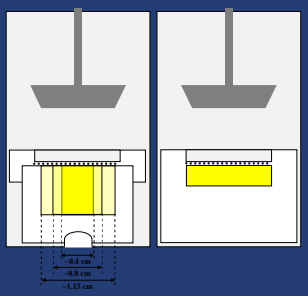


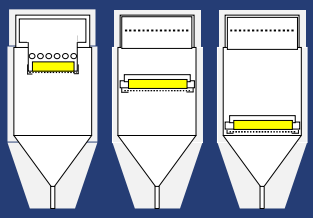
Diameter (mm)	4 mL "Small"	7 mL "Standard"	12 mL "Large"
Top	9	15	15
Bottom	9	9	15
Height (mm)	61	61	61
Volume (ml)	4	7	12
Surface, top (cm^2)	0,636	1,767	1,767
Height / Diameter (stirring efficiency)	6,78	4,07	4,07
Surface / volume (cm^{-1})	0,16	0,25	0,15
Thickness of dosage wafer (mm)	1.5	1.5	1.5
Quantity of product accommodated (mg)	~100	~300	~300
Sampled (0.5/1 ml) /total volume (%)	25	14,285	8,33

Data from Vertical Diffusion Cells - The Hanson VDC (http://www.hansonresearch.com/, accessed April 12th, 2014)
Images from Hanson Research Inc., with permission.

Cell design. Immersion cells

-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 more easily.





Method validation

Variability of experimental data
- reproducibility

Discrimination for different strengths
- 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.)

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. **Assessment during design of the formulation**
7. **Characterization of clinical batches**
   (assessment / understanding of failure modes for a product)

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 (rarely unitary doses, region, area, deformation)
   - **1.c. Active role of excipients in:**
     delivery release / penetration / permeation
     pharmacodynamics (safety and efficacy)
2. **Diversity of experimental devices - specific:**
   diffusion cells (horizontal / vertical; static / flow-through)
3. **No regulatory requirement for routine quality control.**
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)

7. Individual (not mean) profiles are compared

8. No PVT available (hydrocortisone 1% cream)

In Vitro Release vs. In Vitro Permeation Tests (1)

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

In Vitro Release vs. In Vitro Permeation Tests (2)

Parameter	IVPT	IVRT
Delivery	Variable lag time Steady state Donor depletion	Limited lag time (<10%) Steady state Preventing advanced depletion of donor (<30%)
Critical region (detailed sampling from receiver, at steady state)	4-12-18(24h)	1-4(6) h
Samples	Receiver Surface (wash, strip) Separated compartments	Receiver* - -
Main process	Diffusion and distribution in various layers Receiver recovery Reflecting distinct pathways (bulk / shunt route)	Unrestricted diffusion form donor to the receiver - Reflecting release from semisolid toward the skin

*** Recovery, Mass Balance & Dose Depletion assessment in Acyclovir 5% cream draft guidance.**

In Vitro Release vs. In Vitro Permeation Tests (2)

Parameter	IVPT	IVRT
Data analysis	Total recovery (90-110%) Compartment distribution (incl. receiver) Flux (J, µg/cm^2/h) and partition coefficient (Kp)	Apparent amount (<30%) - Rate (square root law), µg/cm^2/h$^{0.5}$
Similarity	Various statistical methods: Donor effects Product effects Donor*Product interactions	Nonparametric statistical method for log slopes Two stages with acceptance interval 75-133.33%
(Bio) Relevance	Predictive (biological membrane) Qualification / integrity check	*Dependent on the degree of similarity of qualitative and quantitative composition* **(Q1&Q2)**
Sensitivity to microstructural (Q3&Q4) differences	+	+++

Current Regulatory attitude

Not appropriate test for BA assessment or BE demonstration ..

.. as a single test, but essential component of aggregate weight of evidence.

Not 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/risks).*

Not for 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)?

Current Industry attitude

Innovator:

-not real (diseased) skin;

-increased risks of inadequate BE conclusion;

-excipients contribute to both efficacy and safety (all are non-inert);

-artificial membranes have no sensitivity for the specific effects;

-IVIVC not possible due to complexity, therefore not biorelevant.

Generics:

-utilized in assessment of OOS;

-overestimate the results when in vitro similarity is concluded;

-underestimate when in vitro outcome is not in line with routine QC;

-IVIVC not expected due to complexity.

Both:

-screening of variations (SUPAC-SS);

-applied in design of formulation and selection of optimal candidates.

IVR Test: addressing Q1, Q2, Q3 (Q4)

Q1	Qualitative equivalence	Same components	In some instances, subject to patent requests **Q1 & Q2 =/≠ Q3!**
Q2	Quantitative equivalence (±5%; US-FDA)	Same components Same quantities	
Q3 / Q4	(Micro) Structure similarity Methods and means of application	Same arrangement Similar (device)	IVRT Rheological behaviour Globule / particle size Flow / deformation
PE	Pharmaceutical equivalence EMA (2014): *Extended PE*	Same: -Drug -Strength / Concentration -Dosage form (Complexity) -Route (methods and means?) Comparable (adequate) labeling Meet compendial & other applicable requirements.	
TE	Therapeutic equivalence	TE = PE + BE	

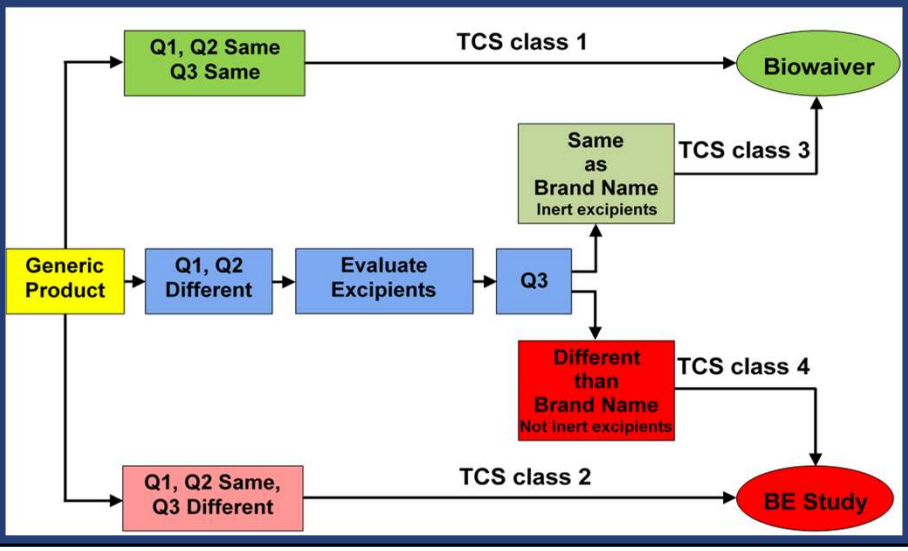
Topical drug Classification System (TCS)

Shah VP. *et al*, Int J Pharm. 2015, 2016

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

Topical drug Classification System (TCS)

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



Q3
microstructural similarity

Particle / droplet size measurement – similar distribution
Polymorphism, crystal habit
Rheological behavior
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 (σ_0) – inversely proportional to spreadability.

Many topical semisolids – non-Newtonian behavior (apparent viscosity)
Vane method (Kryscio DR et al, 2008),
Oscillatory, rotational and axial measurements.

Validation of Q3: must be related to TE
(Yu L., 2003. Advisory Committee for Pharmaceutical Science Meeting)

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).

US-Food and Drug Administration
Draft guidance documents - general approach

Classify drug products based on their (assumed) complexity (Raney S, 2016)

Less complex

(in vitro methodologies are considered as part of the comparative physicochemical assessment)

Moderately complex

(in vitro release and other complementary tests)

e.g. ointments in PEG mixtures (Acyclovir ointment 5%);

Draft guidance on silver sulfadiazine cream (in vitro study, not an option).

(Highly) complex

(combinations of in vitro permeation / release tests, complex microstructural characterization, including particle size distribution, rheology, solvent activity, pH, density, antimicrobial activity, appropriate ex vivo assay *with relevant controls* etc.)

e.g. Acyclovir cream 5%, Benzyl alcohol topical lotion.

Systemic PK approaches are included in some cases.

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"

EMA/CHMP/QWP/558185/2014 (02.12.2014)

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,

(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.

Conclusions

- **Tailoring the in vitro approach** to **drug, drug product, microstructure and dosing conditions** is essential.
- **Combined methodologies (aggregate weight of evidence / extended pharmaceutical equivalence)** are recommended by an encouraging number of draft guidance.
- In vitro release tests are powerful tools in **quality assessment and comparative performance testing** for semisolid dosage forms. The results should not be over or underestimated.
- **TCS** is under validation using three model drugs, emphasizing on **IVRT** as main approach for **Q3** similarity assessment.
- The **adequate design and interpretation** of the in vitro comparative assessment should consider the **complexity** of the dosage form.
- **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. **Still feasible!**