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

- **PD** endpoint studies
- **Clinical** endpoint studies
- IV**R**T
- **Waiver**

(proportionality, self-evident, BCS)

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)

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.

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.** *Pharmacopeial Forum*; 35(3):750-64.

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:

Guideline for Bioequivalence Studies of Generic Products for Topical Use (July 7, 2003).

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. <u>Individual</u> (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 characteristics 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
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

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	*
Sensitivity to microstructural 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.

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/risks).*

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

Q1	Qualitative equivalence	Same components	In some instances, subject to patent requests **Q1 & Q2 =/≠ Q3!**
Q2	Quantitative equivalence	Same components Same quantities	
Q3	(Micro) Structure similarity	Same arrangement	IVRT Rheological behaviour Globule / particle size
PE	Pharmaceutical equivalence	Same: -API -Strength -Dosage form (definition) -Route Comparable: -Labeling Meet compendial & other appl. requirements.	
TE	Therapeutic equivalence	TE = PE + BE	

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 <u>in vitro option</u>:

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 "**<u>one-size fits all</u>**" model - **<u>outdated</u>**.

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:

*.. **<u>suitable in vitro</u>** 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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