U.S. FOOD & DRUG ADMINISTRATION

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Patient-Centric Product Design, Drug Development, and Manufacturing

PQRI Product Quality Research Institute

In Vitro Release and Q3 Measurements for Semisolid Drug Products

Flavian Ștefan Rădulescu, Dalia Simona Miron

University of Medicine and Pharmacy Carol Davila, Bucharest,
Faculty Of Pharmacy, Biopharmaceutics Department / Center for Drug Sciences

Outline

- Brief introduction
- Historical perspective of the IVR methodology
- Current role of IVR. SUPAC-SS and beyond
- Validation of IVR methods
- Microstructural assessment of topical semisolids
- Role of IVR and rheological tests in TCS classification
- IVR in comparative assessment of formulations with composition or manufacturing differences
- Added value of IVR for Q3 assessment
- Conclusion

Brief introduction
Complexity of topical semisolid formulations

Drug (API)	**Impact**	
Drug - Drug product (API and excipients)	State of aggregation. Stability	**Quality** **Site of drug action** **Efficacy** **Safety**
Drug - Drug Product - Microstructure (API and excipients in specific arrangement)	Mechanism of release	
Drug - Drug Product - Microstructure - Container (API and excipients in specific arrangement and dose)	Dosing	
Drug - Drug Product - Microstructure - Container - Application (API and excipients in specific arrangement and dose, as applied onto skin)	Dose applied and in vivo delivery	

Historical perspective of the in vitro release methodology

From 1990's:

- development of methodology based on vertical diffusion cells;
- hydrocortisone 1% cream proposed for performance verification;
- comparative assessment of marketed products;
- reports on rank order relationship between the dermatopharmacokinetic. pharmacodynamic and IVR characteristics for marketed creams.

1997: Postapproval Changes: Chemistry. Manufacturing. and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (SUPAC-SS guidance): use of IVR for assessment of moderate (level 2) changes.

1998: Topical Dermatological Drug Product NDAs and ANDAs - In Vivo Bioavailability. Bioequivalence. In Vitro Release. and Associated Studies (draft guidance): development of lower strengths / screening of more extensive changes.

2013: USP chapter <1724> Semisolid drug products-performance tests: general approaches and cell models.

2016: draft guidance on acyclovir 5% creams (US-FDA).

2018: qualification and validation of IVR, acyclovir 5% cream (Tiffner KI et al).

Current role of in vitro release tests

Q1	**Qualitative equivalence**	**Same components**	**In some instances. subject to patent pending. 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 Crystal habit. density Flow / deformation**
PE	**Pharmaceutical equivalence** EMA (2018): ***Equivalence with respect to quality: Extended PE concept*** Relevant data, Relevant comparator	**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**	

Current role of in vitro release tests SUPAC-SS and beyond (1)

-performance test reflecting release rate of drug through layers of semisolids;

-high (pseudo-infinite) dose applied;

-use of inert membranes and media providing sink conditions;

-no significant changes of the formulation expected during tests;

-steady state release rates are compared.

Advantages

-reliable and reproducible;

-simple, but potentially reflecting the combined influence of several factors controlling the release (vehicle, particle / droplet size, dissolution and / or partition within heterogenous system etc.)

Limitations

-inertness of support membrane not sensitive to active excipients;

-not informative of the interactions between formulation and skin;

-unrestricted diffusion has no in vivo correspondent.

Current role of in vitro release tests SUPAC-SS and beyond (2)

A. Current applications

1. Development of generics. in selection of the optimal formulation candidate;

2. Screening defined changes in composition / manufacturing process or scale-up;

3. Comparative assessment with RLD when in vitro option available;

4. Stability studies;

5. Selection of representative batch of RLD.

B. Other (potential) applications

1. Characterization of microstructural similarity (relationship IVR - Q3);

2. Batch-to-batch consistency (EMA draft guideline, 2018).

Relevance of IVR comparison depends upon the similarity of composition.

Validation of IVR method (1)

Development	Validation (qualifications and controls)
Cell design Temperature and hydrodynamics Receptor media Membrane Pre-treatment of membrane Sampling Quantitation Data analysis	Qualification Solubility (sink), stability Inertness and compatibility Analytical method validation Linearity, range, precision. Reproducibility, recovery, mass balance, dose depletion, discrimination sensitivity, specificity and selectivity. Robustness.

US-FDA Acyclovir 5% cream draft guidance (revised Dec 2016).

Validation of IVR method (2)

Design	Validation
Choice of membrane **Choice of receptor media** • **sink conditions** (below **30%** of maximum attainable concentrations) • **back diffusion,** • **pH changes avoided.** **Ideally at least 70% of the active substance applied is released, at least 6 points.** **Amount applied (±5%) and method.** **Analytical method validation.**	**Discrimination:** • **strength** • **changes in critical quality attributes, critical manufacturing variables or quantitative composition (excipients)** **Intermediate precision.** **Robustness (stirring, temperature, media, amount applied).** **Comparison based on 90% CI for ratio means (release amount and rate, n=12), acceptance interval 90-111%.** **Similar lag time (±10%)**

Draft Guideline on quality and equivalence of topical products (EMA/CHMP/QWP/708282/2018)

Microstructural assessment of topical semisolids (1)

Rheological testing protocols including a variety of evaluations:

- Oscillatory tests (strain / stress, frequency);
- Rotational tests;
- Axial tests.

(Viscosity evaluation, part of routine QC, wide specifications).

Appropriate design of test **and evaluation** of the results. considering:

- temperature, relevant for storage conditions or site of application;
- thickness of the layer of semisolid formulation - in vivo conditions;
- changes in composition and microstructure during and after administration.

Reflective (directly or indirectly) of:

- type and intensity of internal interactions;
- response to shearing forces (before and during the application);
- stability (temperature sweep / swing test).

Microstructural assessment of topical semisolids (2)

Indications available:

- draft guidance documents (product specific or general);
- available reports (expert meetings);
- compendial chapters (USP, EP) or ISO documents.

Product variables:

- complexity composition, microstructure;
- packing (semisolids available as tubes of various sizes);
- application device (methods and means of administration);
- changes in time (within shelf life).

Adaption of testing parameters to product (non-Newtonian) characteristics.
No general approach for assessing similarity in comparative assessment.
Useful in understanding differences in performance (in vitro / in vivo).

Role of in vitro release and rheological tests in TCS classification

Comparative assessment based qualitative and quantitative composition and IVR.

IVR similarity: identification of Q1 and Q2 differences and associated risks, considering:

limitations of IVR (dose, membrane, sink)**;**

complexity of the microstructure (additional test);

impact on the skin permeability.

Evaluation of non-similarities:

functionality of excipients,

percentage and amount applied,

contribution to depth, rate and extent of penetration.

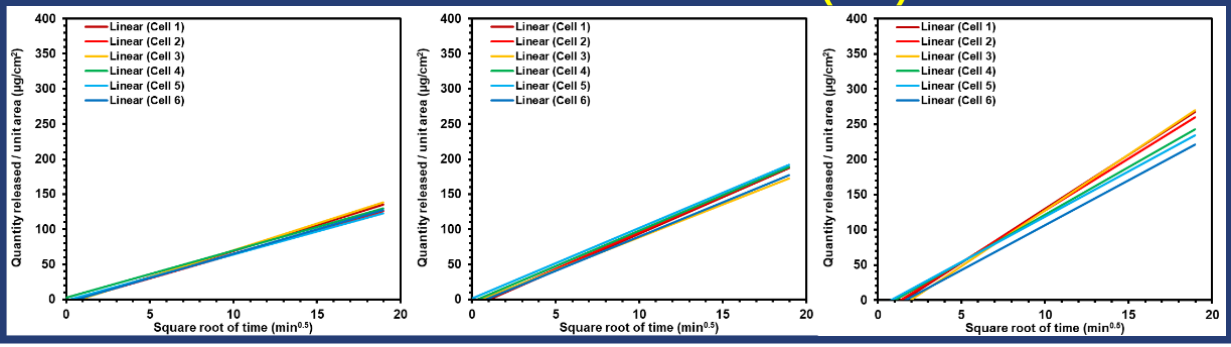
IVR differences: in vivo BE studies, independent of Q1 and Q2 similarity.

IVR in comparative assessment of formulations with manufacturing or composition differences

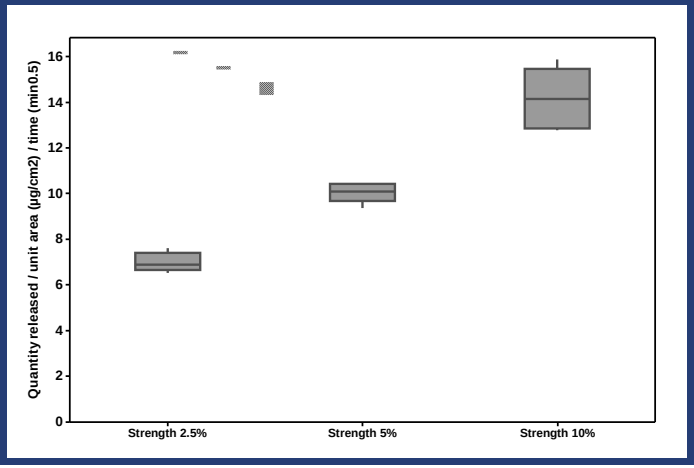
Acyclovir 5% creams

- **Solubility of acyclovir in ethanol 30%: 2.74 ± 0.04 mg/mL (32°C).**
- **Recoveries at 6, 60, 120 µg/mL: 97.18 to 107.25%.**
- **Strength discrimination (2.5%, 5%, 10%):**

Individual in vitro release (n=6)



Strength - in vitro release rate relation

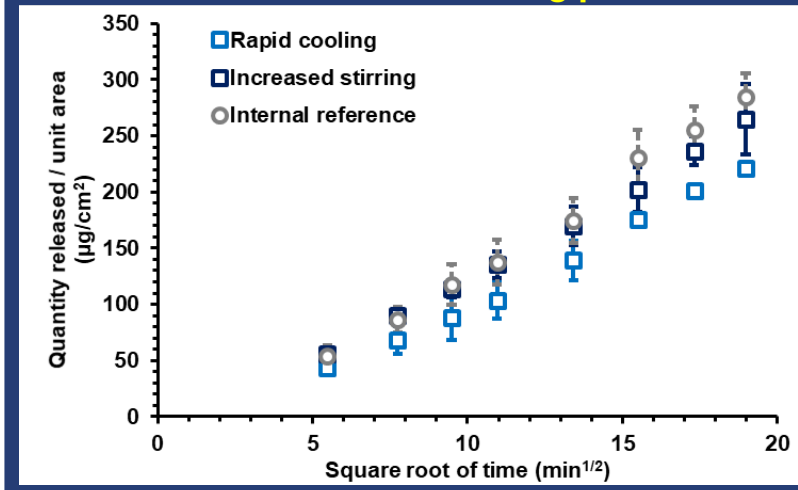


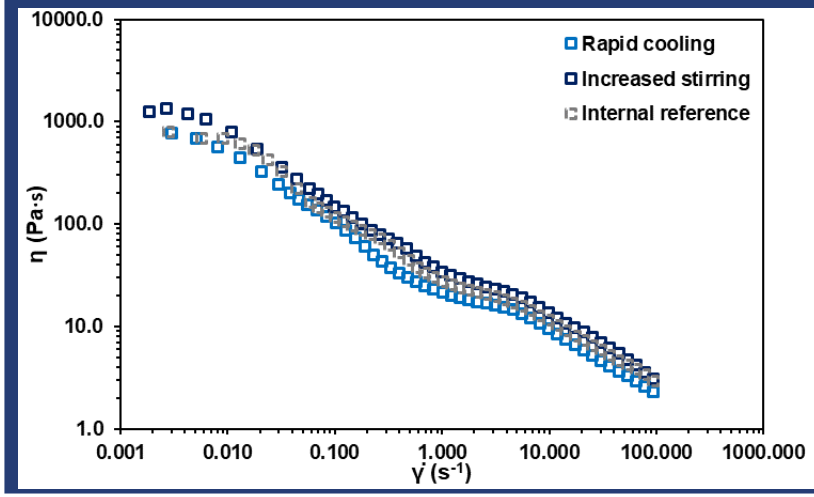
IVR in comparative assessment of formulations with manufacturing or composition differences

Acyclovir 5% creams

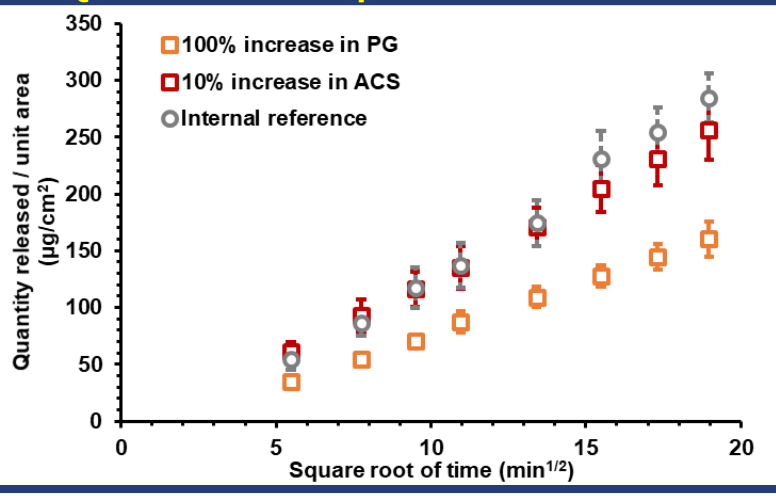
Changes

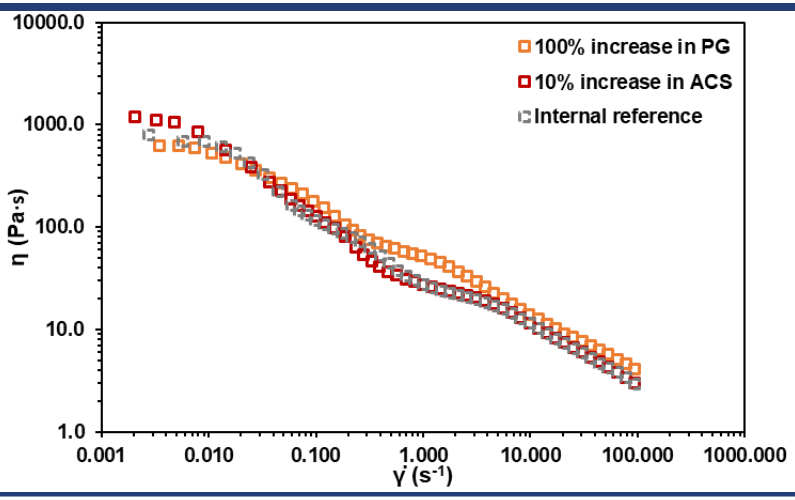
Manufacturing process





Quantitative composition



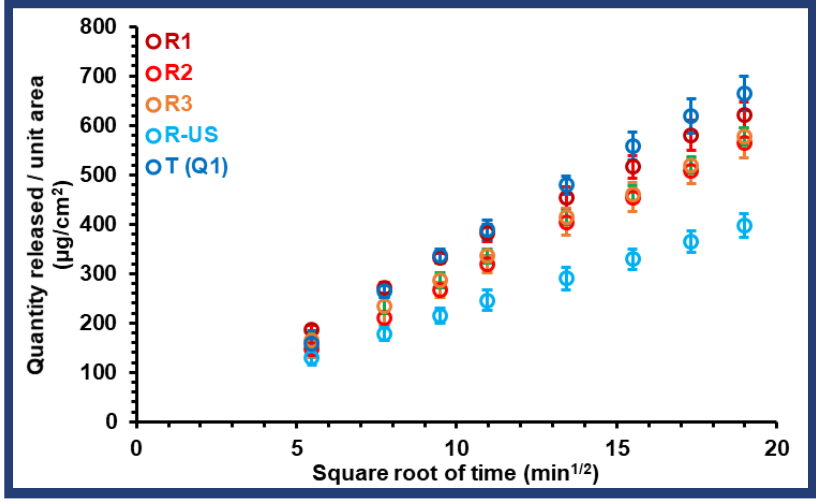


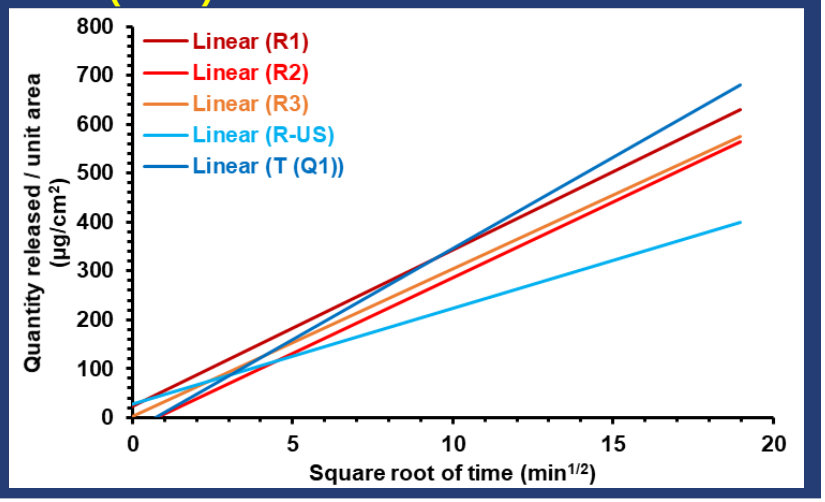
ACS – cetosearyl alcohol; PG – propylene glycol.

IVR in comparative assessment of formulations with manufacturing or composition differences

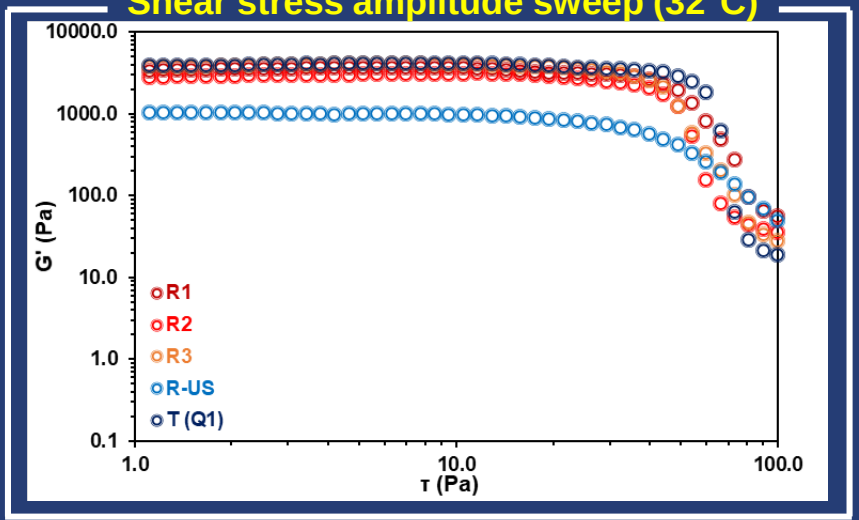
Acyclovir 5% creams

In vitro release (32°C)





Shear stress amplitude sweep (32°C)



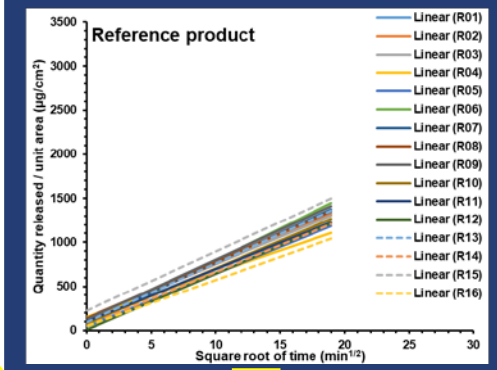
IVR in comparative assessment of formulations with manufacturing or composition differences

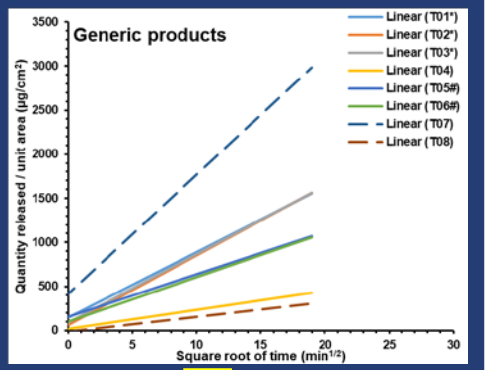
Ketoconazole 2% creams

Qualitative composition

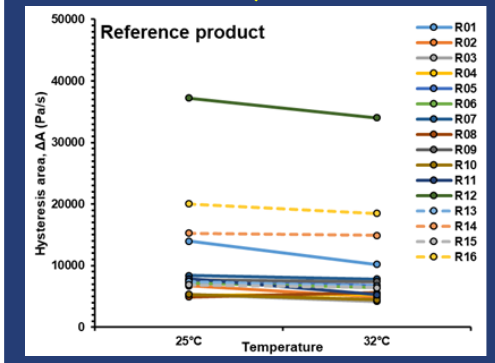
Excipient	Reference listed drug	Generic products							
		T01*	T02*	T03*	T04	T05#	T06#	T07	T08
Cetyl alcohol	✓	✓	✓	✓	✓	✓	✓	✓	✓
Stearyl alcohol	✓	✓	✓	✓	✓	✓	✓		
Sorbitan monostearate	✓	✓	✓	✓	✓	✓	✓		
Glycerol monostearate								✓	
Ceteareth-20								✓	
Octyldodecanol								✓	
White paraffin									✓
Polysorbate 60	✓	✓	✓	✓	✓	✓	✓		
Polysorbate 80	✓	✓	✓	✓	✓	✓	✓		✓
Propylene glycol	✓	✓	✓	✓	✓	✓	✓		✓
Isopropyl myristate	✓	✓	✓	✓	✓	✓	✓		
Sodium hydroxide 10% solution									✓
Sodium metabisulfite	✓	✓	✓	✓		✓	✓		
Butylated hydroxyanysole					✓				
Sodium methyl para-hydroxybenzoate								✓	
Sodium propyl para-hydroxybenzoate								✓	
Purified water	✓	✓	✓	✓	✓	✓	✓	✓	✓

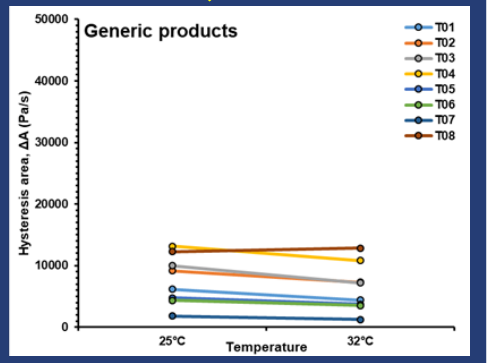
In vitro release





Rheology





Differences in age (site of manufacturing)

*** - Q1, Q2 similarity;**

 # - Q1 similarity (no information on quantitative composition available

IVR in comparative assessment of formulations with manufacturing or composition differences

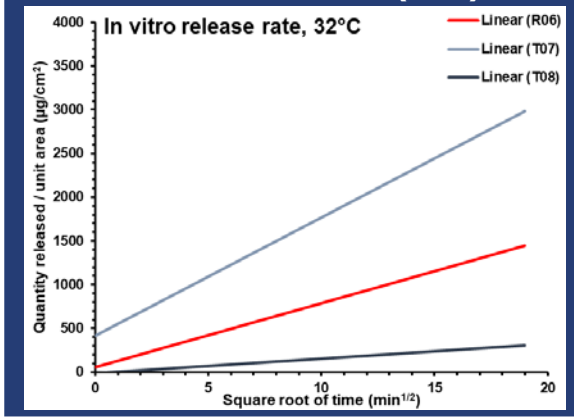
Ketoconazole 2% creams

qualitative composition

Non Q1

Excipient	Reference listed drug R06	Generic products T07	Generic products T08
Cetyl alcohol	✓	✓	✓
Stearyl alcohol	✓		
Sorbitan monostearate	✓		
Glycerol monostearate		✓	
Ceteareth-20		✓	
Octyldodecanol		✓	
White paraffin			✓
Polysorbate 60	✓		
Polysorbate 80	✓		✓
Propylene glycol	✓		✓
Isopropyl myristate	✓		
Sodium hydroxide 10% solution			✓
Sodium metabisulfite	✓		
Butylated hydroxyanysole			
Sodium methyl para-hydroxybenzoate		✓	
Sodium propyl para-hydroxybenzoate		✓	
Purified water	✓	✓	✓

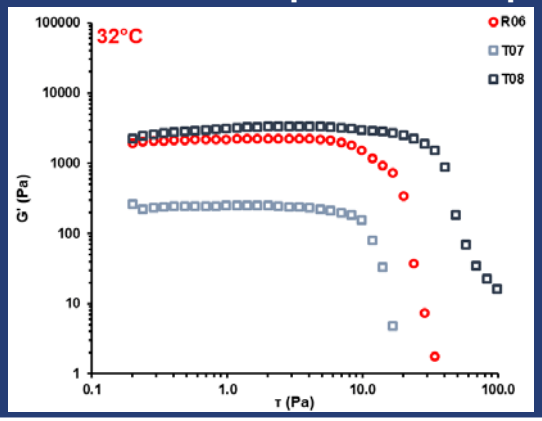
in vitro release (n=6)



Non Q3

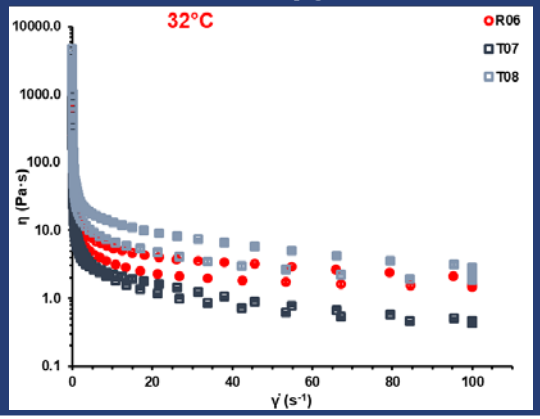
shear stress amplitude sweep

Oscillatory



thixotropy test

Rotational



Discriminative IVR

Reflecting the overall effect

Distinct

Inner interactions
Responses to stress
Spreadability
Structure recovery

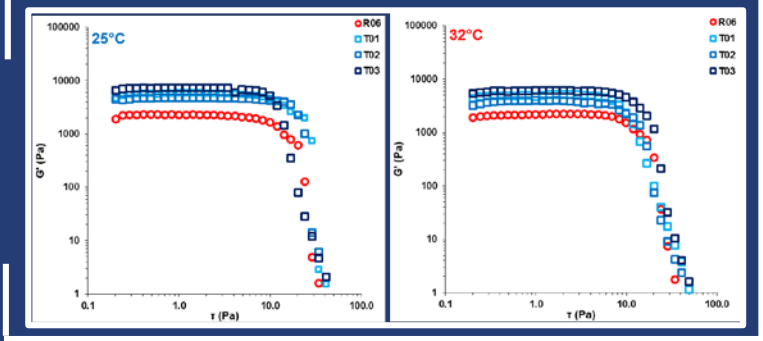
IVR in comparative assessment of formulations with manufacturing or composition differences

Ketoconazole 2% creams

Mild differences in rheology

oscillatory

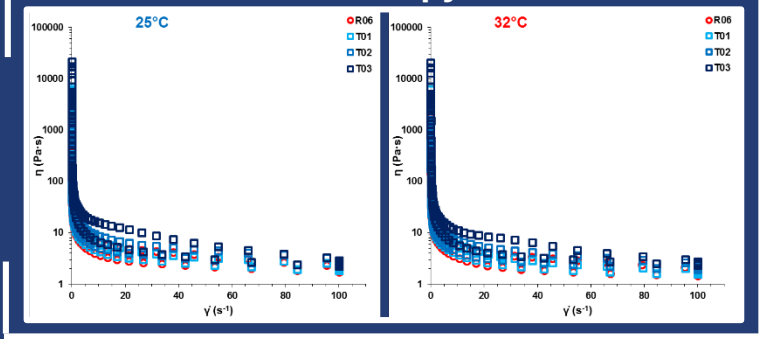
Yield stress



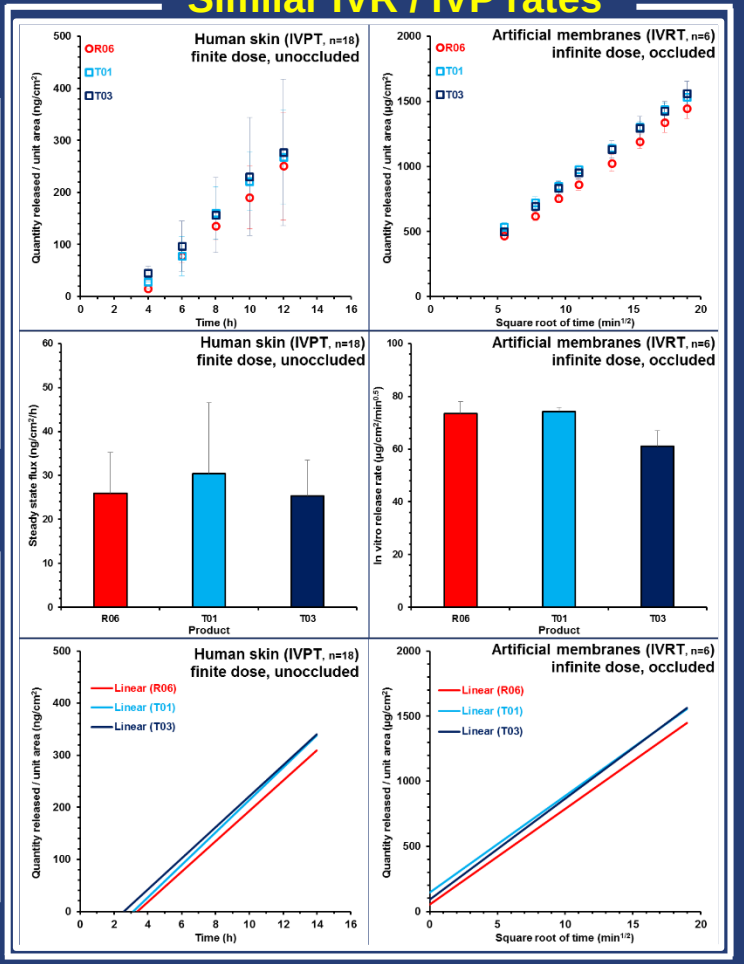
Mild differences in rheology

rotational

Thixotropy test



Similar IVR / IVP rates

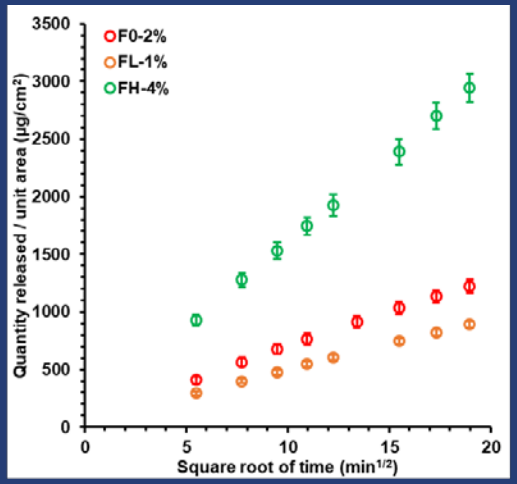


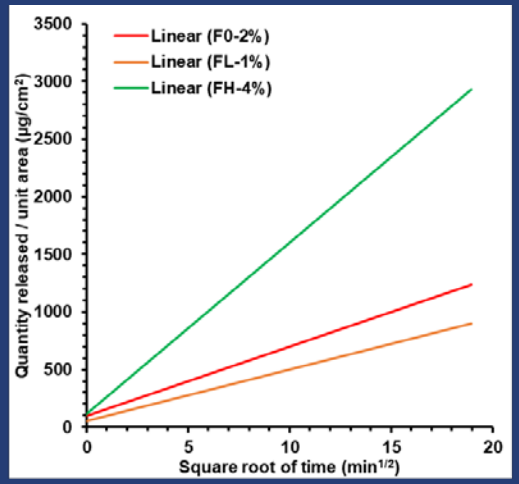
IVR in comparative assessment of formulations with manufacturing or composition differences

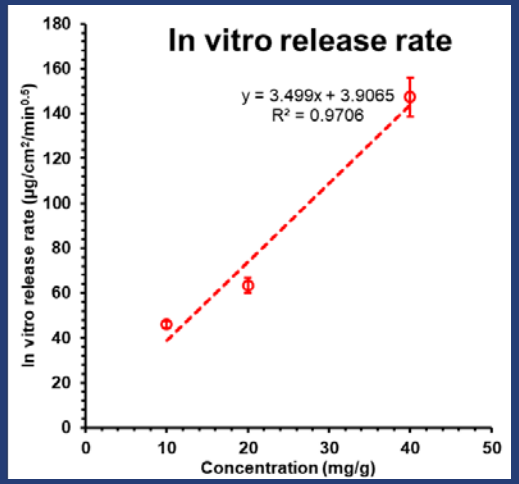
Ketoconazole 2% creams (pilot scale)

IVR profile, strengths discrimination (50, 100 and 200%; n=6)

Manufacturing at different scale (different stirring pattern) may impact in vitro release rate, the microstructure being slightly different.







Note:

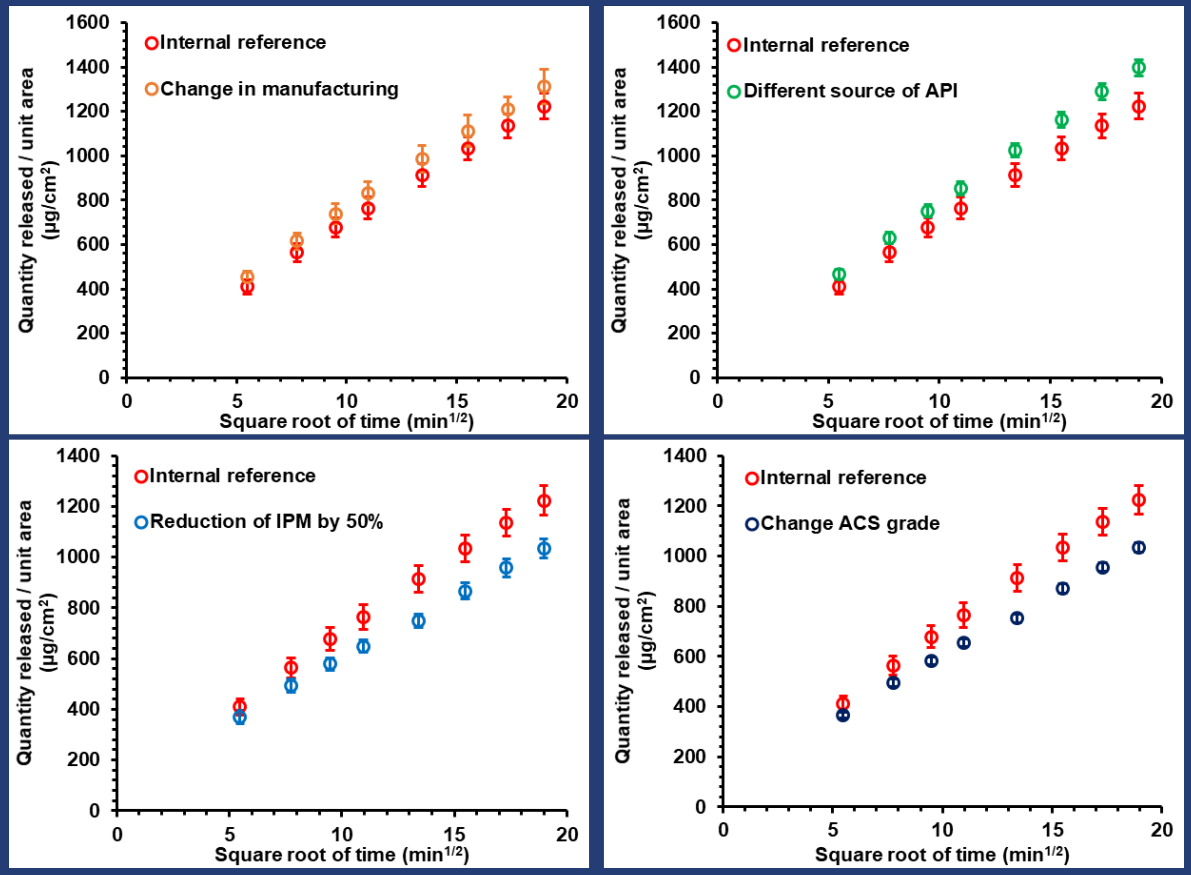
Lower strength used for strength discrimination may not have the same state of aggregation as target and higher strength (distinct IVR rate - strength relation).

IVR in comparative assessment of formulations with manufacturing or composition differences

Ketoconazole 2% creams (pilot scale)

Formulations prepared by controlled changes in manufacturing process or composition.

First stage in selection of candidates for in vivo study (TCS validation).

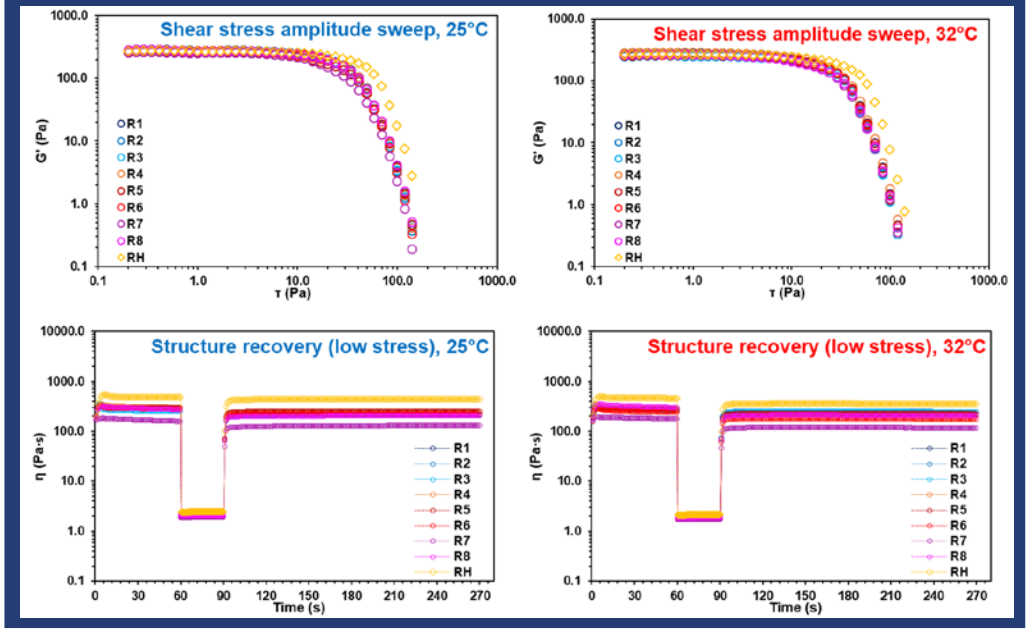


ACS – cetosearyl alcohol; IPM – isopropyl myristate; API – active pharmaceutical ingredient.

IVR in comparative assessment of formulations with manufacturing or composition differences

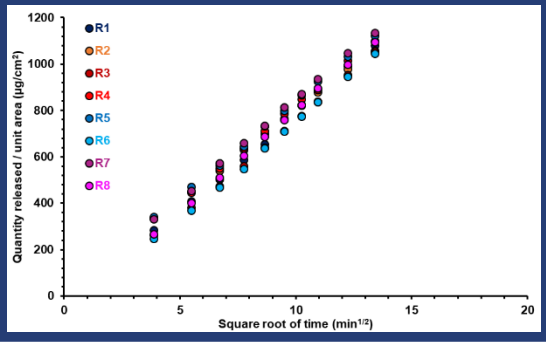
Drug product X

Rheology



In vitro release

Q3



Q1, Q2, Q3 products

RH, higher strength of RLD;

R7, use of applicator.

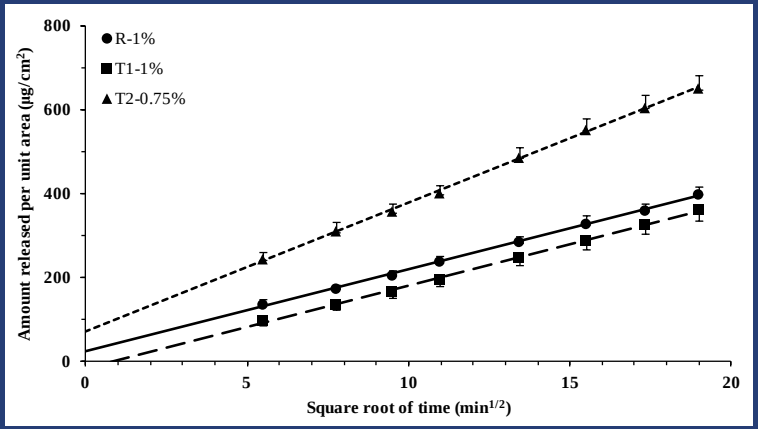
No significant changes in microstructure for the squeezed dose.

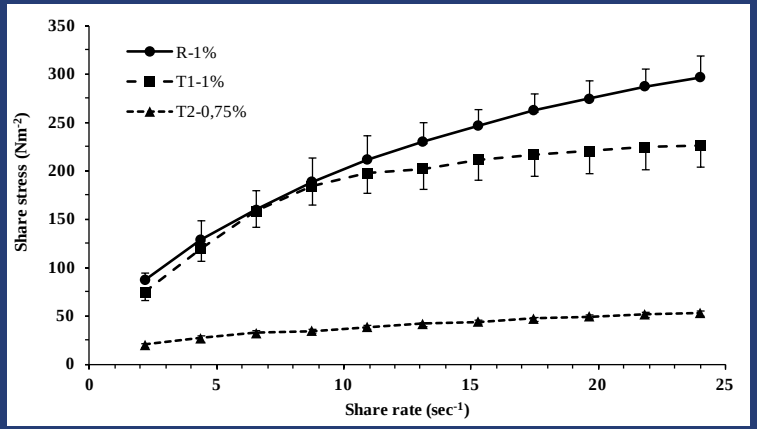
Similar in vitro release (n=6, stage 1).

IVR in comparative assessment of formulations with manufacturing or composition differences

Metronidazole 0.75-1.00% creams (Miron DS et al, 2014)

IVRT-Rheology-DMD-DPK





In vitro release parameters

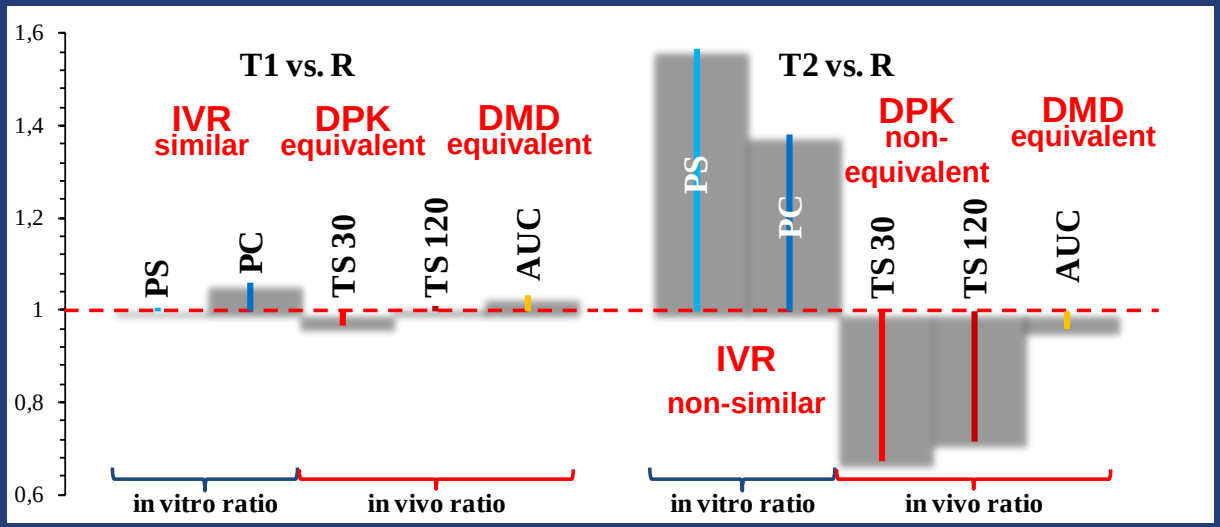
Parameter	Product		
	R	T1	T2
Release rate (µg/cm²/min^0.5)	19.52 ± 0.8	19.65 ± 1.31	30.63 ± 1.05
Cumulative amount released after six hours (µg)	704.64 ± 30.84	639.54 ± 40.02	1150.8 ± 49.14
Correlation coefficient	>0.99		

Rheological parameters

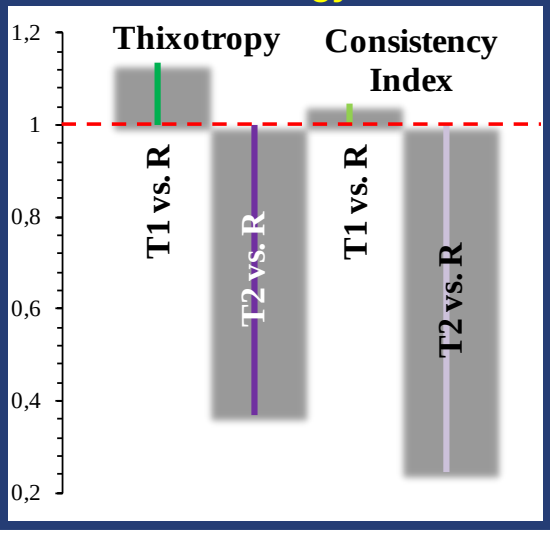
Parameter	Product		
	R	T1	T2
Flow consistency index, m	58.85	61.74	14.47
Flow behavior index, n	0.50	0.44	0.41
Correlation coefficient	>0.99		
Thixotropy area (Pa/sec)	202.86	230.44	74.94

IVR in comparative assessment of formulations with manufacturing or composition differences

Ratio of In vitro release* – In vivo (DPK / DMD) parameters**



Rheology*



In vivo parameters**

Parameter	Product		
	R	T1	T2
AUC_{DMD} (ng/ml min)	533 ± 231	552 ± 222	512 ± 280
$TS_{30\ min}$ (μg/cm²)	33.6 ± 8.4	32.6 ± 6.1	22.7 ± 40
$TS_{120\ min}$ (μg/cm²)	32.9 ± 9.5	33.3 ± 8.5	23.6 ± 5.2

*Miron DS et al, 2014;
**Garcia-Ortiz P et al, 2011

Added value of IVR

- **IVR** is a **comparative,** steady state release measurement performed in **well-defined conditions.**
- **IVR** is a **good indicator** of the combined influence of **composition** and **microstructural characteristics.**
- **IVR** depends on the **degree of similarity of composition (Q1, Q2), the arrangement of the components and their interactions.**
- **IVR provides an objective measurement of similarity.**
- **Adequate interpretation of IVR** requires details on role, type and quantities of excipients, **criteria used by TCS.**
- **IVR** may be **combined with other in vitro methodologies** when complexity of the dosage form and of the in vivo delivery process are high**.**
- **IVR** is **not directly reflecting** the **transformation** of the product which occurs onto the **skin.**
- **IVR** is **not directly reflecting** the **changes in skin permeability** resulting from interactions with **excipients.**
- However, **IVR non-similarity** indicates risks of non-equivalent in vivo performance.

Conclusions

- **IVR reflects Q3.**
- **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 and current version of EMA draft guidance (2018).
- In vitro release tests are powerful tools in **quality assessment and comparative performance testing** for semisolid dosage forms.
- **IVR results provide an objective way of assessing similarity.**
- **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.

Acknowledgements

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

THANK YOU FOR YOUR ATENTION!