A Novel Science Based Approach for Topical Drug Classification System (TCS)

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Outline

- Principle of TCS
- Q1, Q2, and Q3
- SUPAC-SS
- In Vitro Release (IVR)
- Classification of TCS
- BCS and TCS comparison
- Impact of TCS
- Conclusions

Topical Drug Products Bioequivalence

- Determination of BE of most topical drug products is challenging, cumbersome, time consuming and often requiring comparative **clinical studies**. These clinical trials with vigorous statistical requirements are associated with high degree of variability and low sensitivity to formulation factors.
- There are some exceptions –
  - PD approach: Glucocorticoids; Guidance, 1997
  - In vitro approach (Draft Guidance):
    Acyclovir ointment; Mar 2012.
    Cyclosporine ophthalmic emulsion; Jun 2013.
    Difluprednate ophthalmic emulsion; Jan 2016.
    Acyclovir cream; Dec 2016

Topical Drug Classification System (TCS)

- **TCS** is a framework for classifying topical drug products based on its qualitative and quantitative composition, microstructure arrangements of matter and *in vitro* release (IVR).
- **TCS** is a classification system of topical drug products, which when applied will help in approval of generic topical drug products, without conducting *in vivo* studies, but assuring product efficacy.
- It is a drug development tool to justify 'biowaiver' in conjunction with the *in vitro* drug release of the topical dosage form.

Topical Drug Classification System (TCS)

- **TCS** is based on established scientific principles specifically developed for semisolid topical products (**SUPAC-SS**) and is combined with the **IVR** of the drug product.

- **TCS** considers the qualitative (**Q1**) and quantitative (**Q2**) composition, the role of inactive ingredients and microstructure arrangement of topical semisolid products (**Q3**). **Q3 → IVR.**

Generic Topical Drug Product

- According to 21 CFR 314.94 the generic topical drug product will need to have the same excipients, qualitatively (Q1) and quantitatively (Q2) as the Reference Listed Drug (brand name drug) (RLD).

- If the generic product is not Q1 and Q2 compared to RLD, the applicant must provide adequate proofs that the differences will not impact the safety and efficacy profiles of the product.

SUPAC - SS

- The SUPAC-SS guidance was developed to address:
  - Changes in the component or composition,
  - Changes in the manufacturing process and equipment,
  - The scale-up/scale-down of manufacture, and/or
  - Change in site of manufacture.

SUPAC - SS

- ***Level 1 Changes***: Changes in excipients up to 5% - unlikely to have detectable impact on quality/performance
- ***Level 2 Changes*** include:
  - (i) changes of > 5 and ≤ 10% of excipients,
  - (ii) change in equipment to a different design / different operating principles; process changes including changes in rate of mixing, rate of cooling, operating speeds and holding time,
  - (iii) change in batch size beyond a factor of 10.

SUPAC - SS

- *"The physical properties of the dosage form depend upon various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient, between the phases, and product rheology. These factors combine to* ***determine the release characteristics*** *of the drug, as well as other characteristics, such as viscosity."* … **SUPAC-SS**
- *"An in vitro release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form."* … **SUPAC-SS**

Q1, Q2 and Q3. In vitro Release

- Q1 – Same ingredients/components as RLD
- Q2 – Same ingredients/components in the same concentration as RLD
- Q3 – Same ingredients/components/in the same concentration with same arrangement of matter (microstructure) as RLD →Same IVR
- Acceptable comparative physicochemical characterization (Q3) and equivalent in vitro release to RLD
- Biowaiver may be granted with supportive data to demonstrate Q1 and Q2 same and similar physicochemical characteristics (Q3 → IVR)

Ref: R-K Chang, A Raw, R Lionberger and L Yu. AAPS Journal, 15 (1), 41-52, 2013.

IVR and Q3

- Adequately developed and validated, IVR methodology can provide information on the combined role of several physico-chemical characteristics, including the particle or droplet size, viscosity and diffusional resistance of the vehicle.
- The IVR reflects the microstructure, arrangement of the matter and the state of aggregation of the dosage form (Q3). **Q3 → IVR**
- IVR methodology for the evaluation of Q3 similarity is used in TCS classification for application of biowaiver.

Microstructural Similarity(Q3)

- Microstructure similarity: Particle/droplet size measurements - similar distribution, similar rheological properties
- Microstructure non-similarity: differences in physical characteristics, in rheology (even for similar particle size) and in IVR rates

Rheology:

- Oscillatory measurements:
  Evaluation of linear viscoelastic response;
- Rotational tests:
  Shear stress (viscosity) vs. strain rate measurements;
  Yield stress (σ_0) - inversely proportional to spreadability.
- Validation of Q3 must be related to Therapeutic Equivalence

Excipients in Topical Drug Products

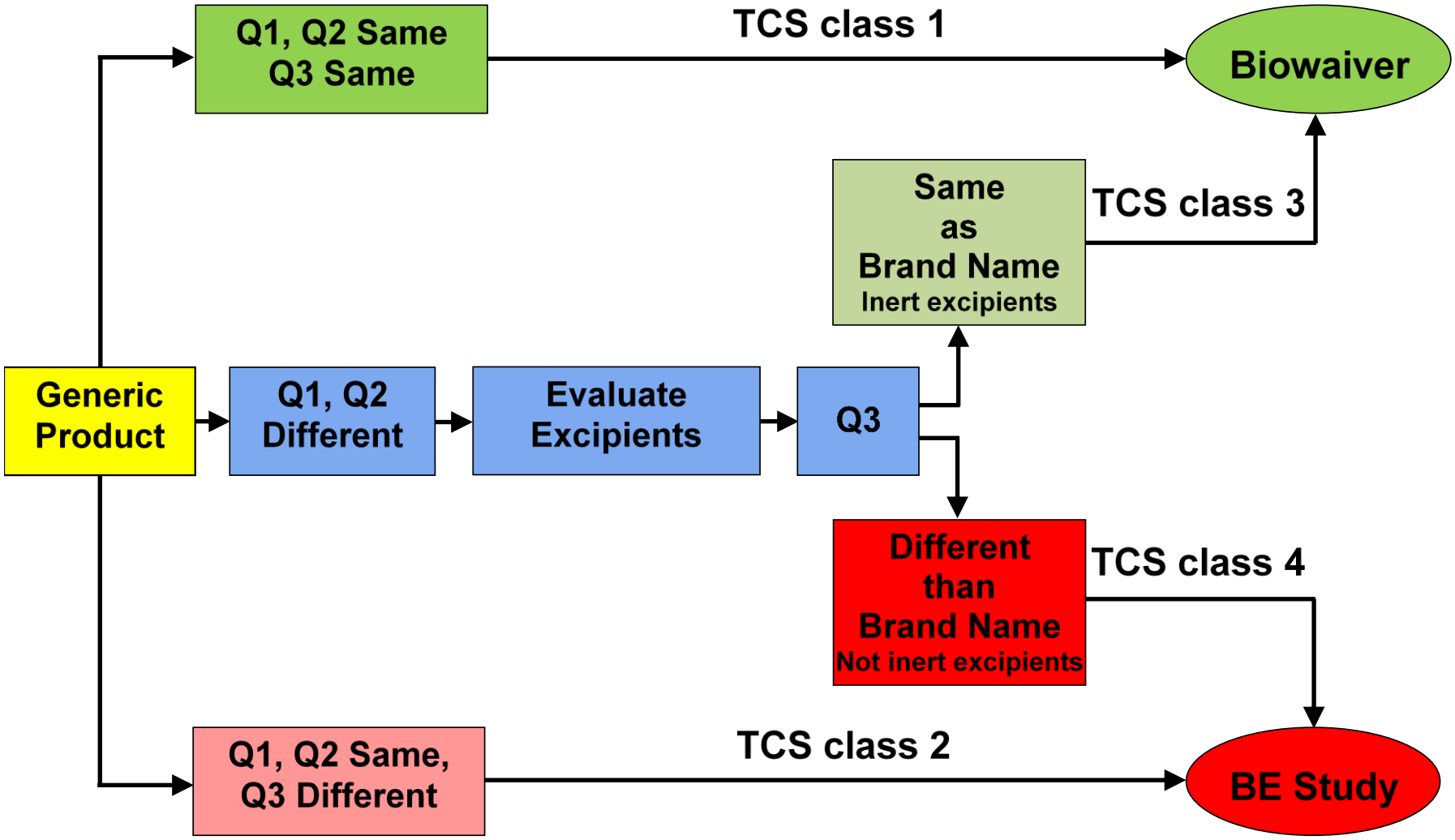
- Excipients may have significant impact on drug release from topical dosage form, skin barrier properties and/or drug penetration directly affecting rate and extent of exposure at site of action, and may have an effect on *in vivo* performance of the product, thereby changing the safety and efficacy profiles.

- Excipients are classified as '***inert***' and '***non-inert***', depending upon their potential effect on the permeability of skin (beyond assumed sensitivity of **IVR**).

Topical Drug Classification System - TCS

- Based on composition (**Q1** and **Q2**) and **IVR** properties, the topical drug products are classified as **TCS** class **1**, **2**, **3** and **4**.
- Under the proposed classification:
  - ❑Only **TCS class 1** and **TCS class 3** drug products are eligible for biowaiver;
  - ❑ **TCS class 2** and **TCS class 4**, are not eligible for biowaiver and will require *in vivo* BE studies for drug approval;
  - ❑The nature and type of *in vivo* BE study will depend on the therapeutic class and dosage form category.

Topical Drug Classification System, TCS



Ref: VP Shah et al., Int J of Pharmaceutics. 491: 21-25, 2015.

Topical Drug Classification System - TCS

Biowaiver

- **TCS Class 1:**
  Q1, Q2 and Q3 same → IVR
- **TCS Class 3:**
  Q1 and Q2 different, Q3 same → IVR

- **May require additional in vitro studies**
  (e.g., particle size, pH, globule size, rheology)
- Excipient evaluation

Bioequivalence Study

- **TCS Class 2:**
  Q1, Q2 same but Q3 different → BE studies
- **TCS Class 4:**
  Q1, Q2, Q3 different → BE studies

Topical Drug Classification System, TCS

Q1, Q2 Same Q3 Same	Q1, Q2 Same Q3 Different
TCS class 1	TCS class 2
Q1, Q2 Different Q3 Same	Q1, Q2 Different Q3 Different
TCS class 3	TCS class 4

Ref: VP Shah et al., Int J of Pharmaceutics. 491: 21-25, 2015.

Topical Drug Classification System (TCS)

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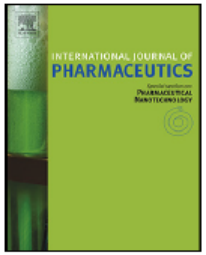

Review

A science based approach to topical drug classification system (TCS)

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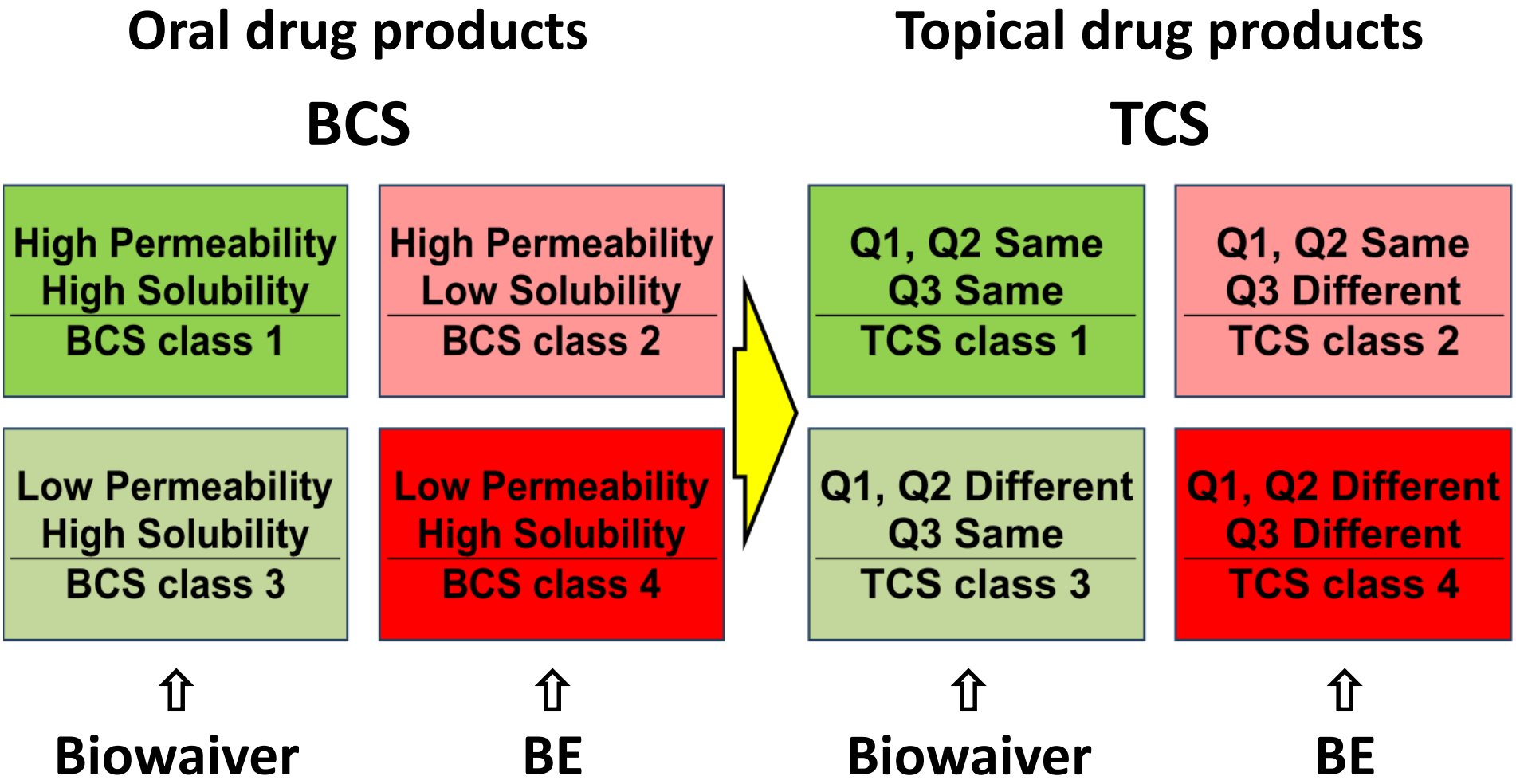
ABSTRACT

The Biopharmaceutics Classification System (BCS) for oral immediate release solid drug products has been very successful; its implementation in drug industry and regulatory approval has shown significant progress. This has been the case primarily because BCS was developed using sound scientific judgment. Following the success of BCS, we have considered the topical drug products for similar classification system based on sound scientific principles.

BCS and TCS

- **BCS** is based on the solubility and permeability characteristics of the drug substance.
- **TCS** system is based on established scientific principles specifically developed for semisolid topical products (**SUPAC-SS**) and is combined with **IVR** of the drug product.
- **TCS** considers the qualitative and quantitative composition of inactive ingredients and microstructure arrangement of topical semisolid products.
- In both the classification systems, **BCS** and **TCS**, their applicability for biowaiver granting **relies on the use of *in vitro* testing** as key decision tools.

BCS and TCS



Ref: VP Shah et al., Int J of Pharmaceutics. 509: 35-40, 2016.

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Mini review

Commonality between BCS and TCS

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ABSTRACT

Both biopharmaceutics classification system (BCS) and topical drug classification system (TCS) are based on sound scientific principles with the aim of providing biowaiver and reducing regulatory burden without lowering the quality requirements and standards of approval for the drug products. BCS is based on the solubility and permeability properties of the active pharmaceutical ingredient (API, or drug substance) whereas the TCS is based on the qualitative and quantitative composition of the dosage form and the in vitro release rate of the active ingredient as key decision tools. Both BCS and TCS take drug release and dissolution as their guiding principle for providing biowaiver, increasing the availability and affordability of safe and effective medicines to the consumers and at the same time maintaining the drug product quality.

Acyclovir Cream

Current Study Findings

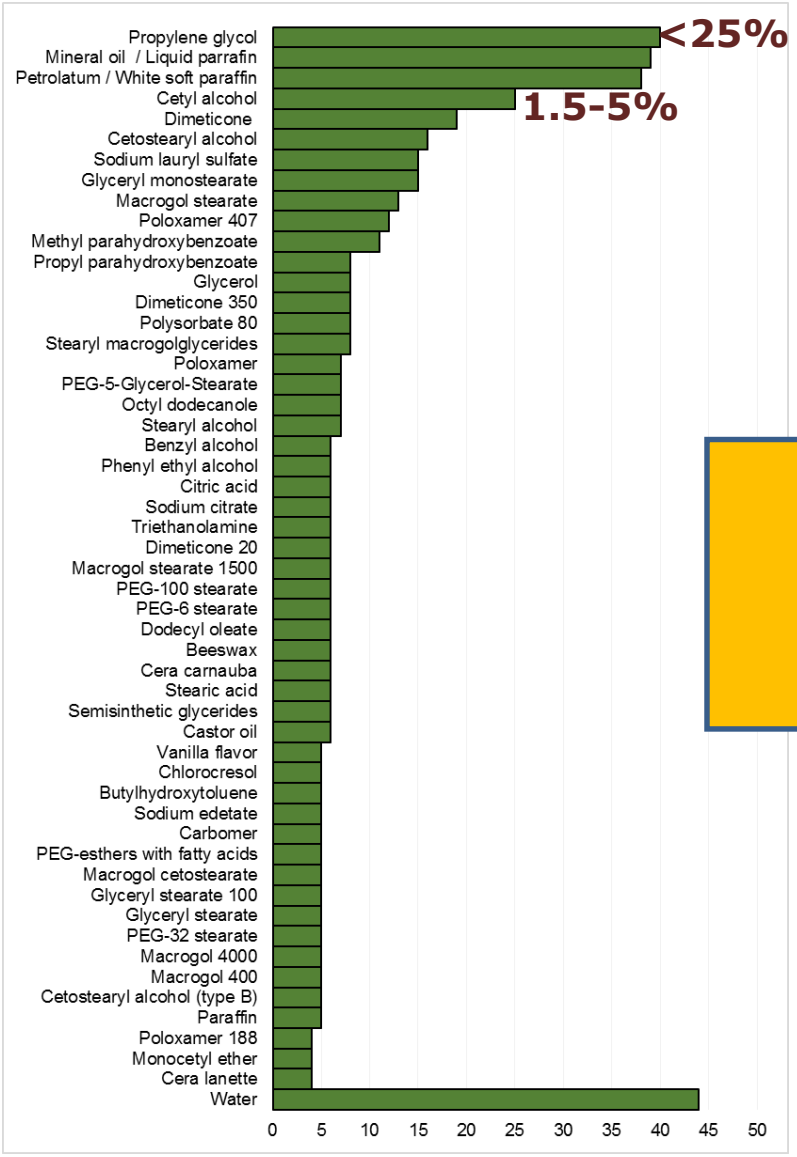
- 21 generic products and 6 RLD (from Europe, US) were analyzed.

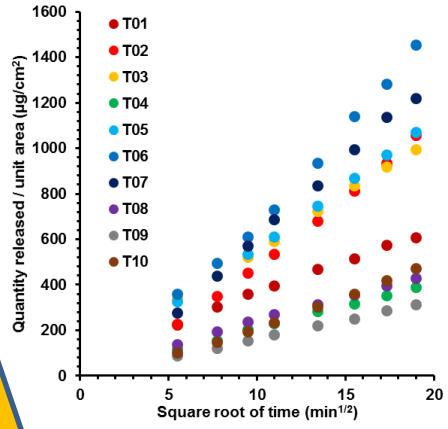
Findings indicate that:

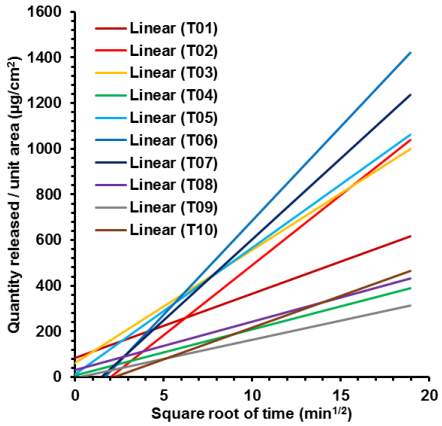
- The formulations (excipients/composition) are markedly different, the *in vitro* release and microstructure, rheology are all different.
- A good relationship was observed in these studies between microstructure (Q3) (rheology) and *in vitro* release. Changes in microstructure reflected in different release rate. **Q3 → IVRT**

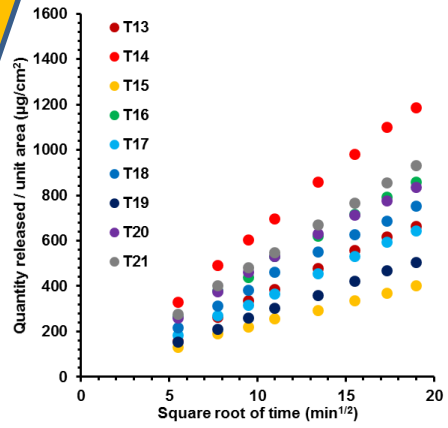
IVR Test: Comparison across manufacturers

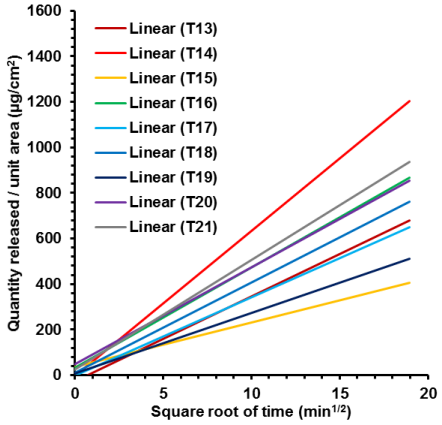
Acyclovir creams 5% (EU market)
21 generic formulations (Q1/Q3/Q3 non-similar)





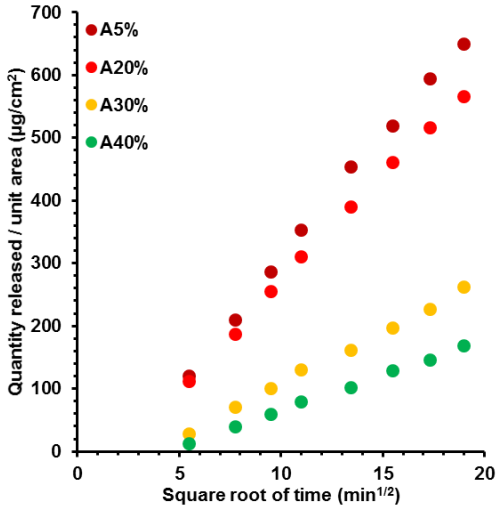


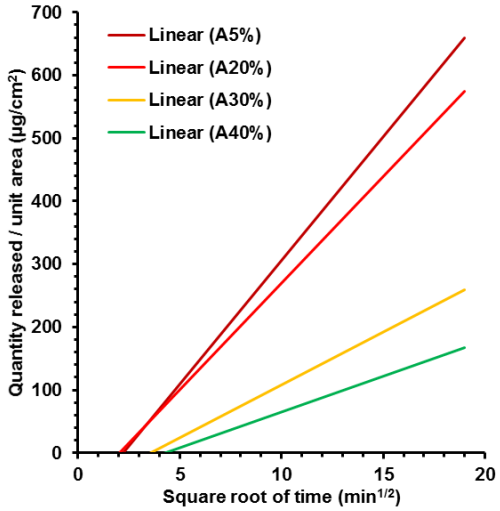




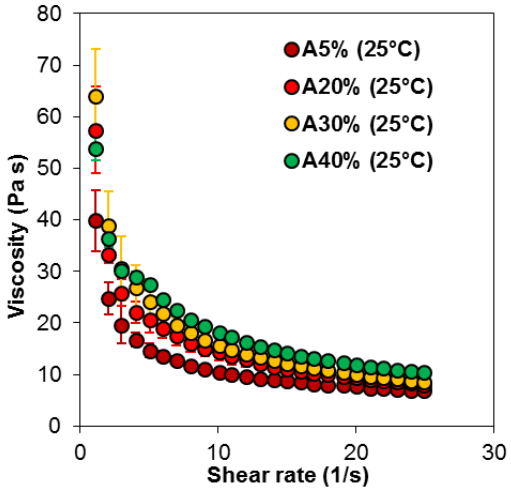
Acyclovir Cream

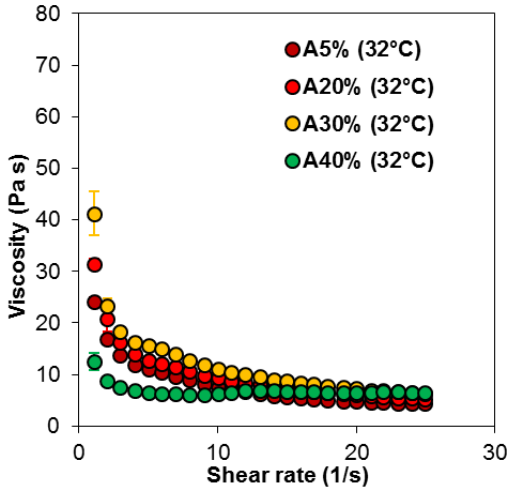
IVR - changes in non-inert excipients

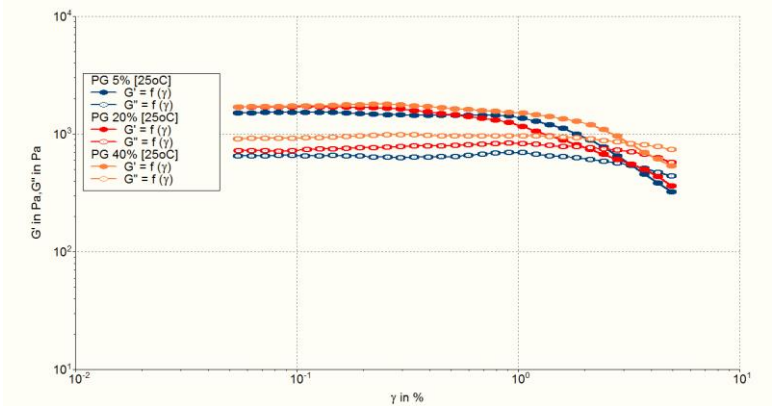




Microstructural impact of propylene glycol (non-inert excipient) is reflected by IVR







Acyclovir Cream

Studies in Progress to validate TCS

- 12 formulations are prepared with changes in manufacturing process or composition to yield drug products in **TCS class 1, 2 or 3**.
- We will be conducting
  - *in vitro* release tests (IV**R**T), *in vitro* permeation test (IV**P**T),
  - Assessment of Q3, Microstructure measurements, Rheology.
  - *In vivo* testing – Pilot study using DPK

Formulations under evaluation

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

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

Impact of TCS

- It will help in developing appropriate regulatory guidance.
- It will help in updating/modifying existing guidance.
- It will validate the application of IVR beyond the current SUPAC-SS framework.
- It will facilitate in product development, reduce regulatory burden and assure product quality.
- It will increase the availability of topical drug products to patients and consumers at a more affordable cost.

Conclusion

- **A practical and science based classification system, TCS, for topical drug products is proposed.**

- TCS will facilitate:
  - ❑ Generic product development, reduce the regulatory burden and assure product quality across all therapeutic classes.
  - ❑ Availability of topical drug products to patients and consumers at a more reasonable cost.

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Thank you for your Attention