Approaches for Evaluation of Formulation Differences on Performance of Topical Products

Advancing Generic Drug Development 2024:
Translating Science to Approval

Day 1, Session 2:
Research to Support Guidance Development for Topical Drug Products

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Learning Objectives

- Describe considerations for formulation development of a test product that does not meet the “no significant difference” criterion compared to the reference standard
- Evaluate the impact of compositional differences in topical gels on bioavailability (BA)
- Evaluate the impact of compositional differences in topical gels on sensory perception of the product

Bioequivalence (BE) for Topicals

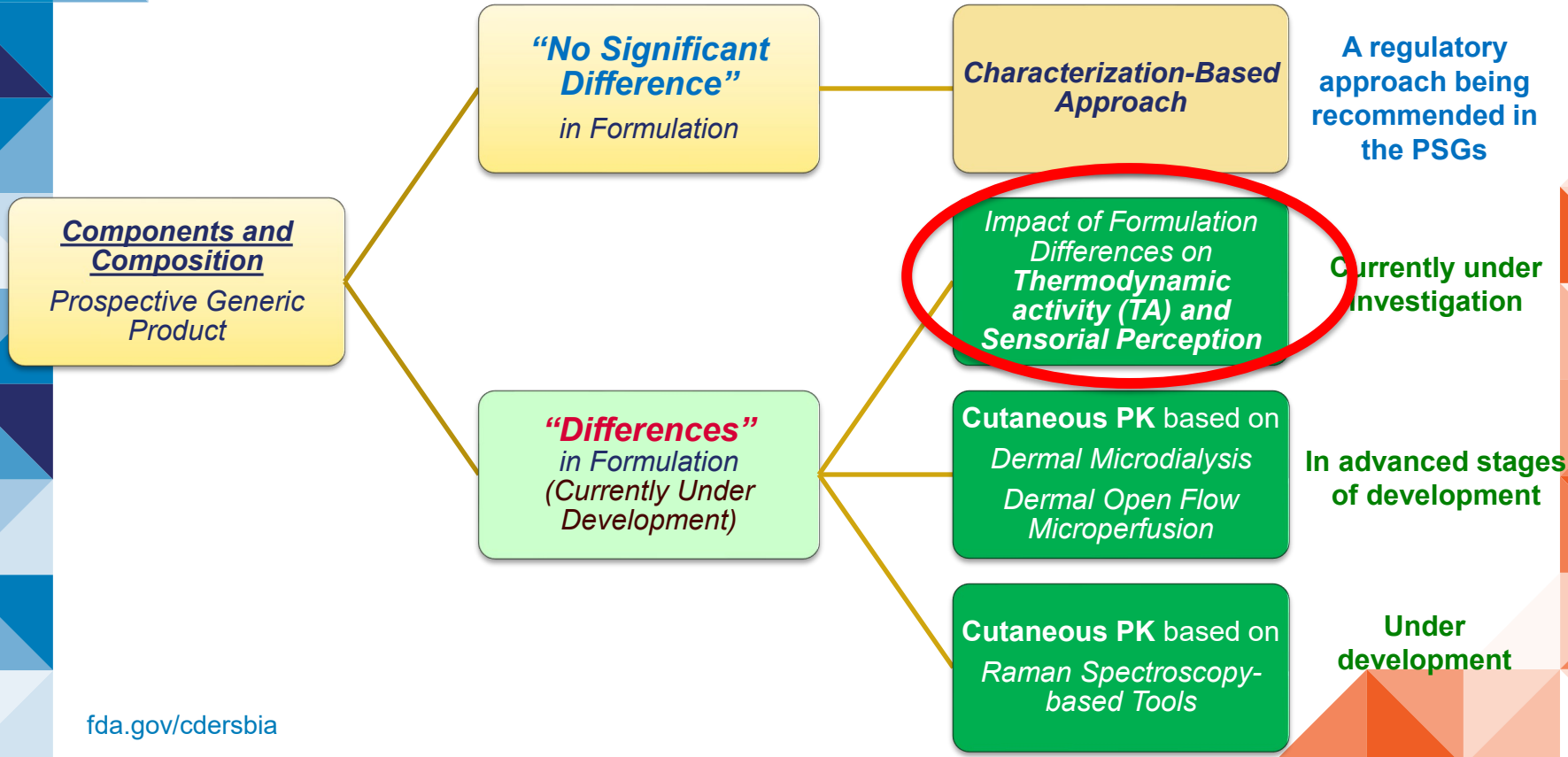
Establishing equivalent performance, conventionally via:

- Comparative in vivo BE studies
  - Clinical endpoint
  - Pharmacodynamic endpoint (e.g., vasoconstrictor (VC) studies)

Developing more efficient BE approaches:

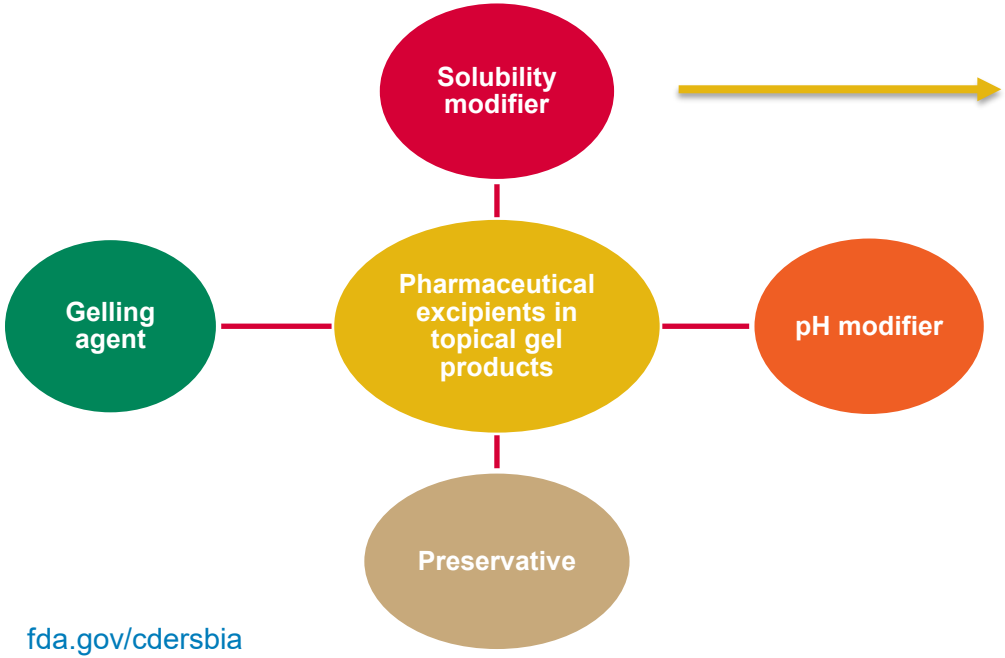
- In vitro characterization and performance tests
- Cutaneous pharmacokinetic studies

Potential Strategies for BE



Single Phase Gels

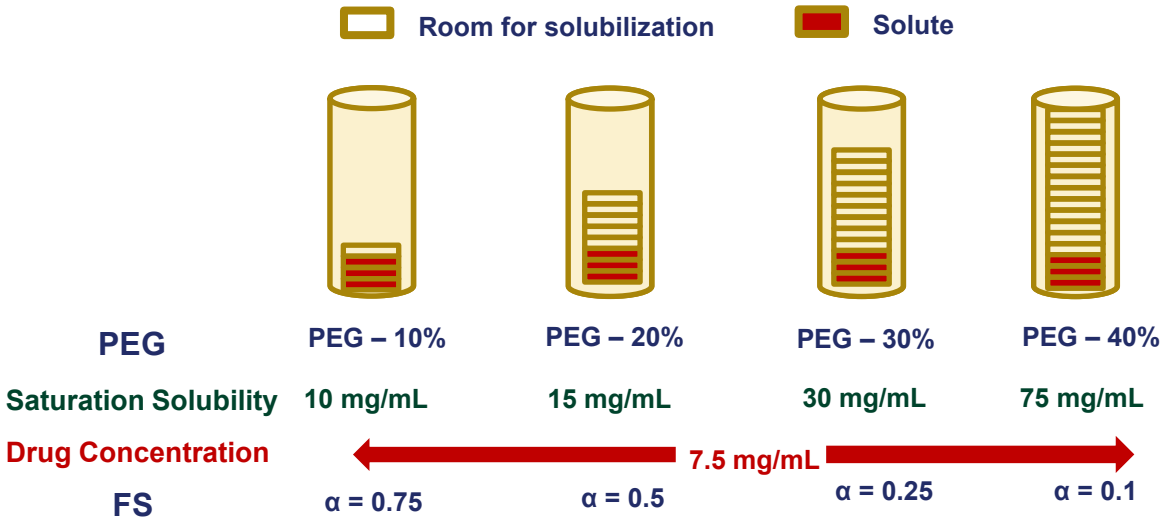
Understanding the function of excipients and their impact on thermodynamic activity (TA) of the drug in the topical formulations.



Most common solubility modifiers:
Propylene glycol (PG)
Polyethylene glycols (PEG)
Glycerin

Fractional Solubility

$$Fractional\ Solubility\ (FS)\ ,\alpha = \frac{Conc.\ of\ Solute}{Saturation\ solubility\ of\ solute\ in\ the\ solvent}$$



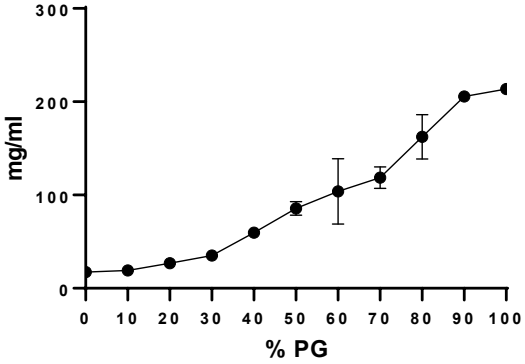
- Fractional solubility is often predictive of TA of the drug in the formulation

2020 AAPS Rapid Fire Talk by Srinivas Ajjarapu, FDA Award U01FD006507

FS and BA

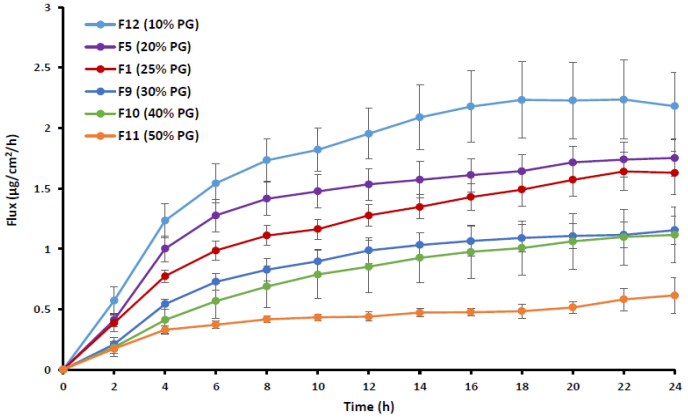
Diclofenac sodium in PG:water formulations

Drug Solubility in PG-water



Data are presented as mean±SD, n=3

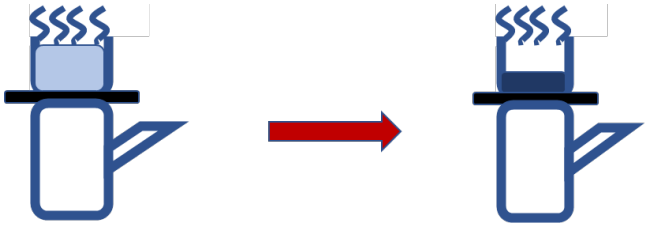
IVPT (infinite dose)



Data are presented as mean±SE, 3 donors 3 replicates

Courtesy of Dr.Mike Roberts and Dr.Yousuf Mohammad, FDA award U01FD006496

Metamorphosis and Change in FS



- Solvent evaporation during metamorphosis of the formulation can lead to
  - Change in drug solubility at the application site

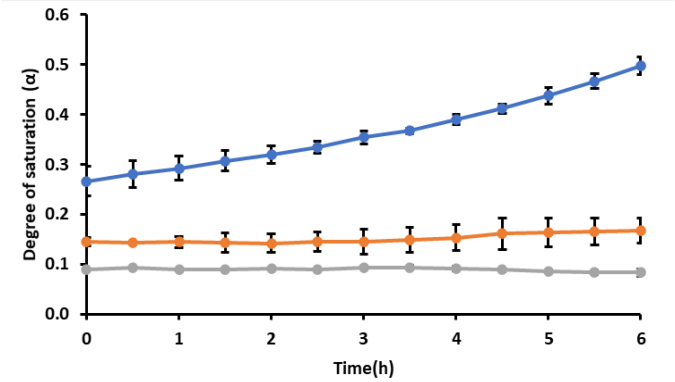
  (can be monitored by measuring drug concentration in the donor compartment)
  - Change in microstructure/Q3 properties

  May lead to change in drug permeation and BA

Q2 Differences and BA- PEG 200

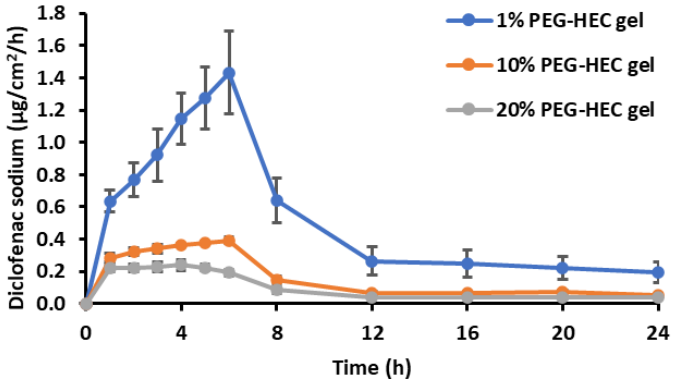
Diclofenac sodium gels with different amounts of PEG 200

FS vs time



Data are presented as mean±SD, n=3

IVPT (semi-finite dose)



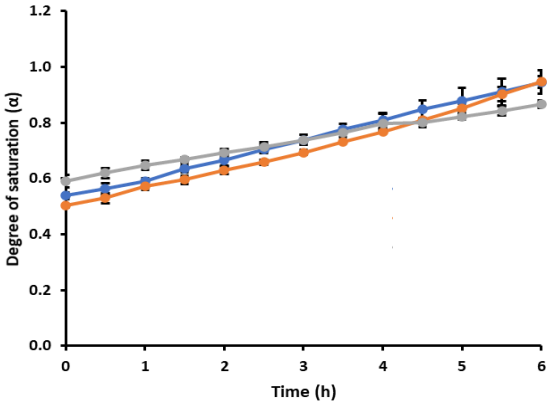
Data are presented as mean±SE, 3 donors 6 replicates

Rangappa et al. 2021 AAPS Poster, FDA Award U01FD006507

Q2 Differences and BA- PEG 200

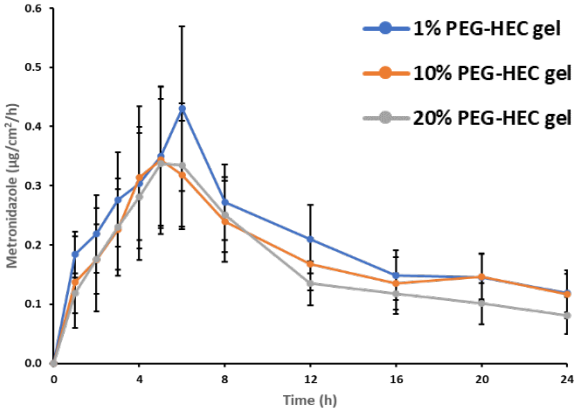
Metronidazole gels with different amounts of PEG 200

FS vs time



Data are presented as mean±SD, n=3

IVPT (semi-finite dose)

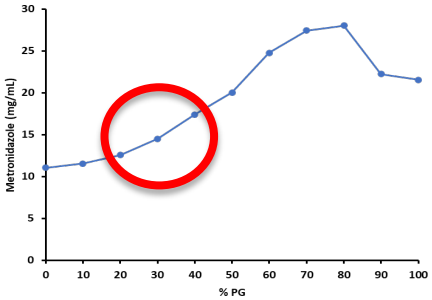
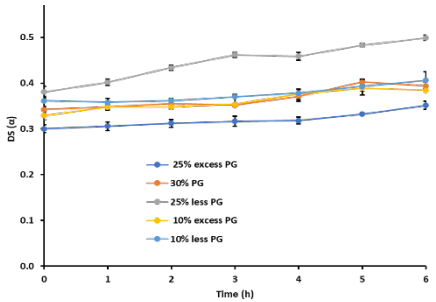
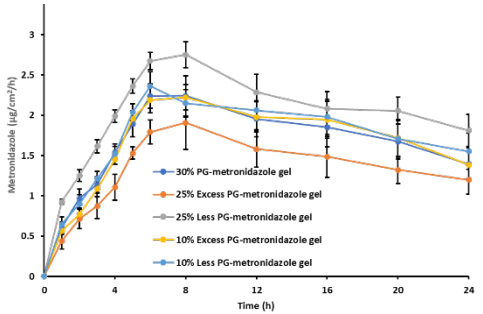
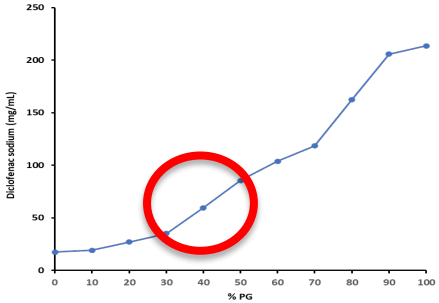
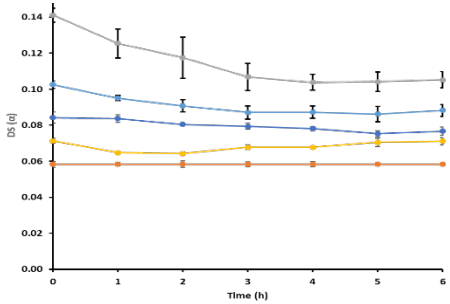
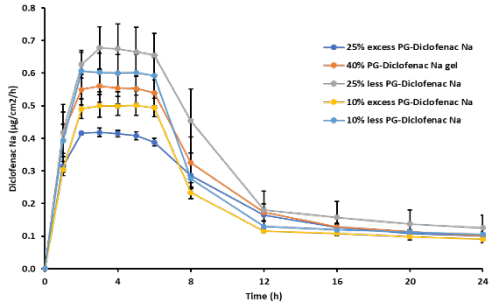


Data are presented as mean±SE, 3 donors 6 replicates

Rangappa et al. 2022 AAPS Poster, FDA Award U01FD006507

Q2 Differences and BA- PG

Composition	(Reference)				
% change in PG	+25	+10	0	-10	-25

Drug	Solubility Data	FS	IVPT Data
Metronidazole			
Diclofenac sodium			

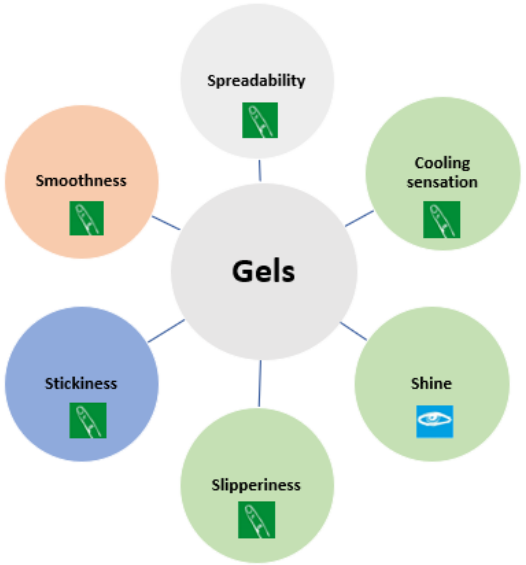
Courtesy of Dr. Narasimha Murthy, FDA Award U01FD006507

Differences Beyond BA

- Would differences in Q1/Q2/Q3 of topical products result in differences in the feel of the topical drug product and subsequently in therapeutic equivalence (TE)?
  - Establish a correlation between Q2, Q3 and sensory perception
- Can characterization of the arrangement of matter, (e.g., rheological characterizations) correlate with and/or be predictive of sensorial differences perceived by human subjects?
  - Develop objective instrumental tests measuring some Q3 attributes that can provide prediction of sensory perception of topical products

Sensory Attributes and TE

Potential sensory attributes of gels that may impact TE



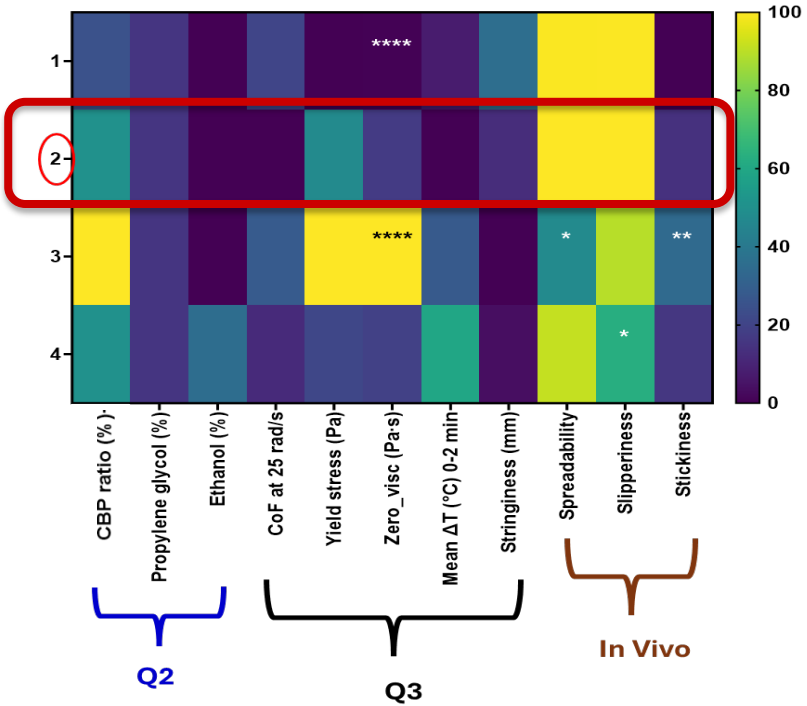
Sensory attributes	Instrumental technique	Formulation variables	Q3 attributes
Cooling sensation	Gravimetric measurement of drying rate/ corneometer	Amount of solvent/cosolvent (e.g., water, alcohol, etc.)	Evaporation of volatile components
Firmness/ stickiness	Texture analyzer	Amount of gelling agent(s)	Zero sheer viscosity, yield stress, adhesiveness
Spreadability	Rheometer	Amount of gelling agent(s)	Zero sheer viscosity, yield stress, adhesiveness

Courtesy of Dr.Yousuf Mohammad FDA Award U01FD006700

Sensorial Studies of the Gels

Gels made using Carpool 980 (CBP) with different compositions of the gelling agent and alcohol

Reference formulation

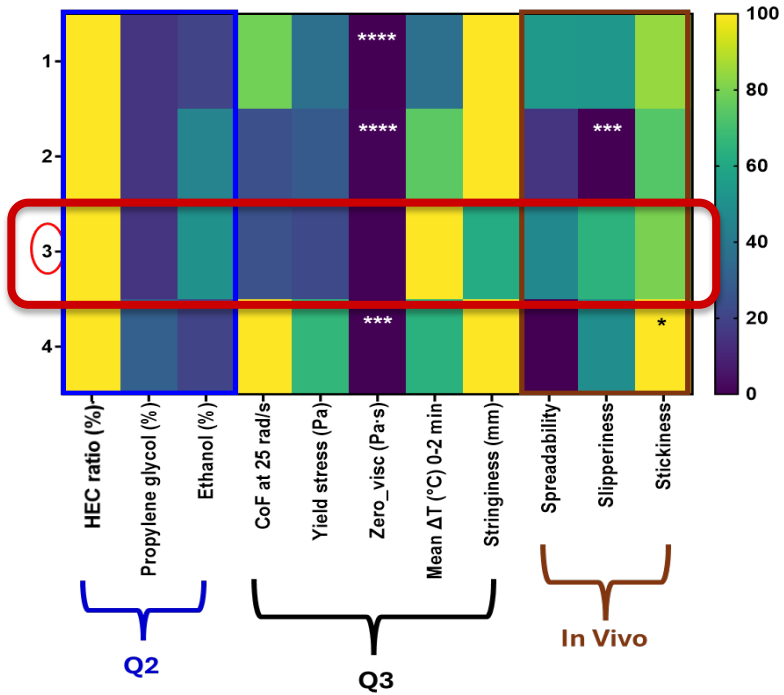


Phan et al. CRS poster 2024, FDA Award U01FD006700

Sensorial Studies of the Gels

Gels made using hydroxyethyl cellulose (HEC) with different compositions and PG and alcohol.

Reference formulation



Phan et al. CRS poster 2024, FDA Award U01FD006700

Summary and Next Steps

- FDA is investigating alternative, scientifically valid methods, including in vitro approaches, to support the assessment of BE for topical drug products that have compositional differences compared to the reference standard.
- The current research data suggests that when there are differences in FS-time profiles and TA, such differences may result in differences in BA of the topical drug as evaluated using IVPT.
- The Q3 properties assessed instrumently, in vitro, may be valuable in understanding most of the sensorial differences among topical gels assessed in vivo.
- Current data suggests that large differences in Q3 attributes, such as rheological, tribological behavior and texture properties are likely to be perceptible to human subjects.
- Research is underway to further evaluate impact of Q2 differences on BA and product perception of topical gel formulations.

Challenge Question #1

Which statement is NOT correct?

A. Q2 differences would always result in changes in performance of topical products

B. It may be feasible to assess fractional solubility of the drug in conjunction with IVPT to assess the impact of Q2 changes on the performance of topical products

C. Significant Q3 differences may result in changes in performance of topical products

D. Metamorphosis of a formulation following topical application may change the microstructure of the product

Challenge Question #2

Which of the following Q3 attributes is more likely to correlate with spreadability and stickiness of topical gels?

A. Friction of coefficient (texture)

B. Zero shear viscosity

C. Drying rate

D. All of the above

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- **Dr. Yousuf Mohammad**

Questions?

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