Therapeutic Equivalence of Compositionally Different Topical Products: Correlation of Product Characteristics with Sensorial Attributes

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Dermatological Drug Products

https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

The Concepts of Q1, Q2, Q3

Q1: Components in a topical product

- Q1 characterization of a topical product provides a profile of the qualitative components (ingredients) in that product

Q2: Composition of a topical product

- Q2 characterization of a topical product provides a profile of the quantitative formulation composition of that product

Q3: Arrangement of matter in a topical product

- Q3 characterization of a topical product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that product

Potential Strategies for Bioequivalence (BE)

Components and Composition

Prospective Generic Product

"No Significant Difference" in Formulation
(Characterization Based Approach)

- *Characterization of the Physical and Structural Properties **(Q3)***
- ***IVRT** (In Vitro Release Test)*
- ***IVPT** (In Vitro Permeation Test)*
- *In vivo systemic pharmacokinetic **(PK)** studies*
- *In **silico**-based tools (Modeling and Simulation)*

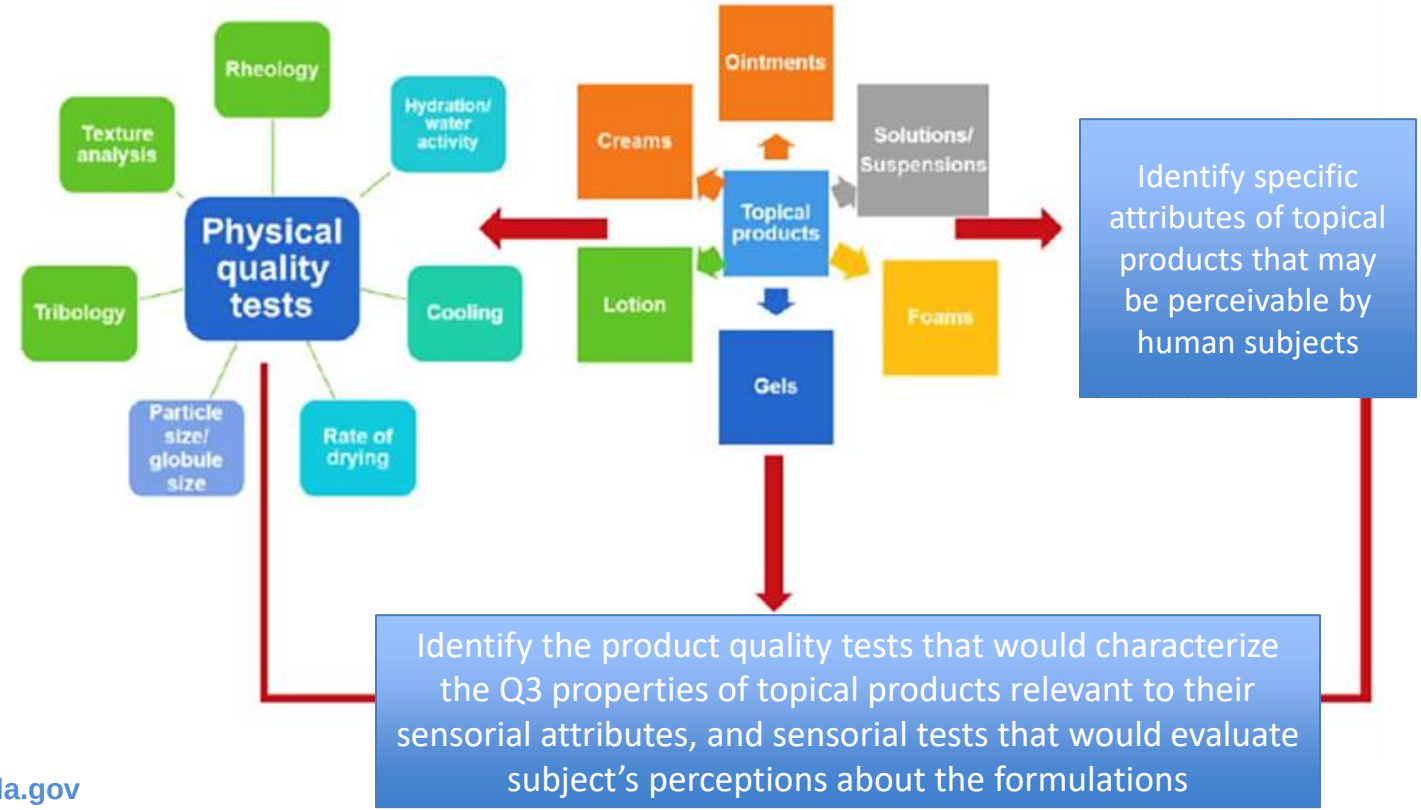
"Significant Differences" in Formulation
(Currently Under Development)

- *Comparative Clinical Endpoint Studies*
- *Impact of Formulation Differences on **Thermodynamic** activity*
- ***Cutaneous PK** Approaches*
  - *Dermal Microdialysis*
  - *Dermal Open Flow Microperfusion*
  - *Raman Spectroscopy-based Tools*

Differences Beyond Bioavailability

- Would differences in Q1/Q2/Q3 result in differences in the feel of the topical drug product?
- Can characterization of the arrangement of matter, (e.g., rheological characterizations) correlate with and/or be predictive of sensorial differences perceived by human subjects?
- *Grant 1U01FD006700: Elucidating the Sensorial and Functional Characteristics of Compositionally Different and Differently Aged Topical Formulations, awarded to Dr. Yousuf Mohammad at University of Queensland.*

Quality and Sensorial Properties



Sensory Attributes Versus Q3 Attributes

Dosage form	Sensory attributes	Classification as per Senses	Instrumental technique	Q3 attributes
Gels	Odour		Gas chromatography/e-nose	Evaporation of volatiles
	Colour		Spectrophotometer/Visual assessment	Uniformity and consistency
	Grittiness/ Texture		Microscopy/Tribometer	Particle size and hardness, crystal habit and aspect ratio, coefficient of friction
	Quick drying		Gravimetric/TEWL measurement/Corneometer	Evaporation of volatiles and drying, Hydration
	Speed of absorption		Time for absorption	?
	Greasiness (non-greasy)		Sebumeter/Tribometer	Coefficient of friction
	Stringiness		Rheometer/Texture analyser/Tribometer	Viscosity, yield stress, coefficient of friction
	Cooling sensation		Gravimetric/TEWL measurement/TiVi/ Corneometer	Evaporation of volatiles and drying, Hydration
	Firmness/Stickiness		Texture analyser/Rheometer	Zero shear viscosity, adhesiveness and yield stress
	Spreadability		Rheometer	Zero shear viscosity, Yield stress

Touch Visual Hearing Smell Hybrid

Courtesy of Dr.Yousuf Mohammad FDA Award U01FD006700

Impact on Therapeutic Equivalence (TE)

– Potential sensory attributes of gels that may impact therapeutic equivalence (TE)

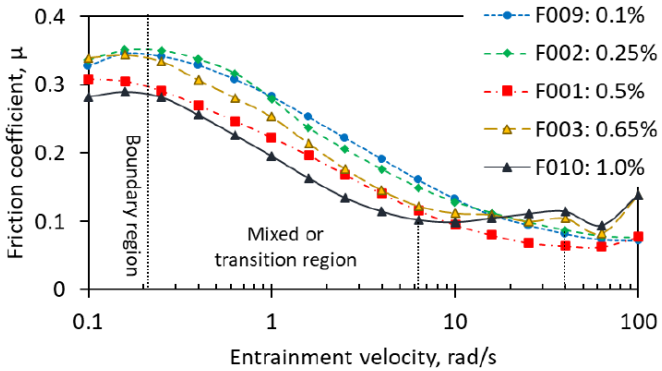
Sensory attributes	Instrumental technique	Formulation variables	Q3 attributes
Time to dry	Gravimetric measurement of drying rate/ corneometer	Amount of solvent/cosolvent (e.g., water, alcohol, etc.)	Evaporation of volatile components
Cooling sensation	Gravimetric measurement of drying rate/ corneometer	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

Gel Formulations with Q2 Variants

Gel formulations made using hydroxy ethyl cellulose (HEC) and different compositions

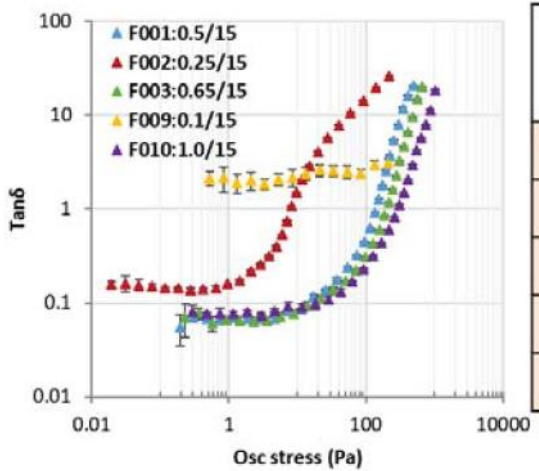
Composition (%w/w)	F001	F002	F003	F009	F010	F004	F005	F006	F007	F008	F011	F012	F013	F014
Carbopol 980	**0.5**	**0.25**	**0.65**	**0.1**	**1.0**	**0.25**	**0.25**	**0.5**	**0.5**	**0.5**	0.5	0.5	0.5	0.5
Ethanol	-	-	-	-	-	-	-	-	20	-	**35.0**	**50.0**	**10.0**	-
Propylene glycol	15	15	15	15	15	**25**	**35**	**35**	**15**	**50**	15	15	15	**25**
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Propyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	84.37	84.62	84.22	84.72	82.47	74.62	64.62	64.37	64.37	49.37	49.21	34.36	74.27	74.22

Rheological and Textural Attributes



Friction profiles of gels with variation in the amount of CBP

CBP gels during texture analysis



Gels	CBP, %	PG, %	CBP/H_2O fraction (R)	Plateau elastic modulus (G'_p), Pa	Yield stress, (τ_y) Pa	Critical strain (γ_c)
F009	0.10	15	0.12	0.015	NA	NA
F002	0.25	15	0.30	51.79	3.08	0.28
F001	0.5	15	0.59	303.99	52.22	0.68
F003	0.65	15	0.77	352.48	66.44	0.83
F010	1.0	15	1.21	469.70	98.74	0.84

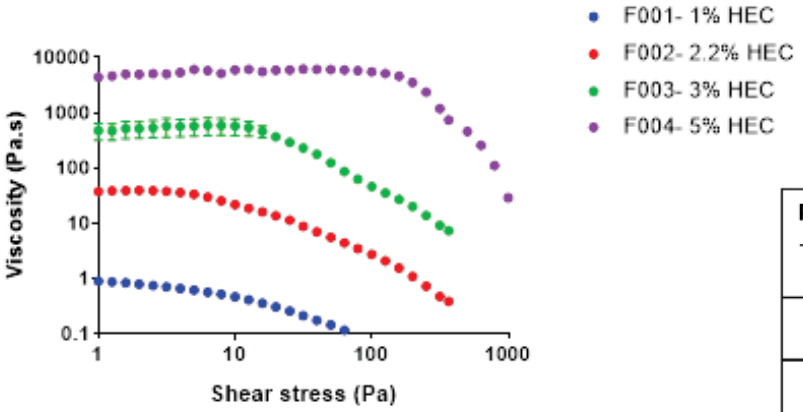
Courtesy of Dr.Yousuf Mohammad FDA Award U01FD006700

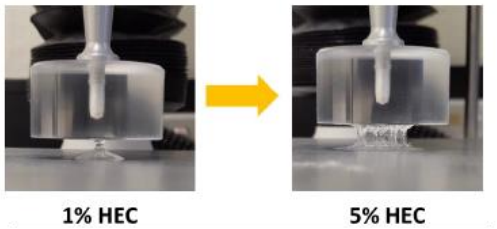
Gel Formulations with Q2 Variants

Gel formulations made using Carpool 980 (CBP) and different compositions

Ingredients (%, w/w)	F01	F02	F03	F04	F05	F06	F07	F08	F09	F10	F11	F12
Hydroxy ethyl cellulose	**1**	**2.2**	**3**	**5**	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Iso-propyl alcohol	20	20	20	20	**25**	**30**	**45**	**50**	20	20	20	20
Propylene glycol	15	15	15	15	15	15	15	15	**20**	**30**	**40**	**50**
2-Phenoxyethanol	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Water	63.2	62	61.2	59.2	57	52	37	32	57	47	37	27

Rheological and Textural Attributes





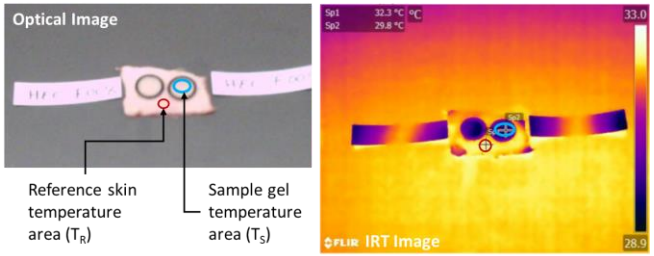
HEC gels during texture analysis

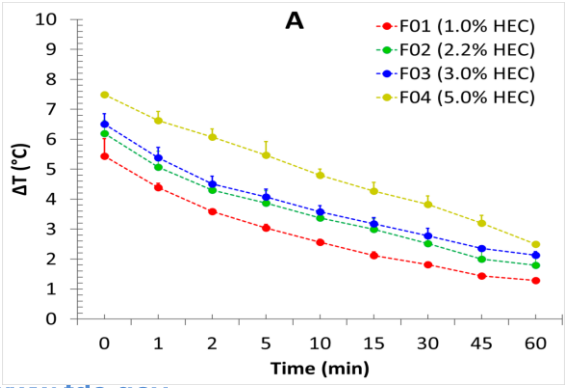
Formul -ations	HEC, %	HEC/ H_2O fraction	Firmness (N)	Work of shear (N·s)	Adhesiveness (N·s)	Stringiness (mm)
F001	1.0	1.58	0.30±0.06	0.04±00	0.12±0.02	5.1±0.1
F002	2.2	3.54	1.70±0.06	0.42±0.04	0.38±0.01	15
F003	3.0	4.90	3.58±0.04	0.95±0.01	0.77±0.01	15
F004	5.0	8.45	10.81±0.6	3.74±0.16	3.02±0.30	10.9±0.9

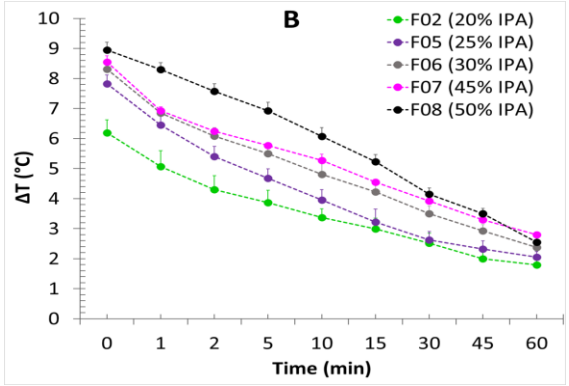
Courtesy of Dr.Yousuf Mohammad FDA Award U01FD006700

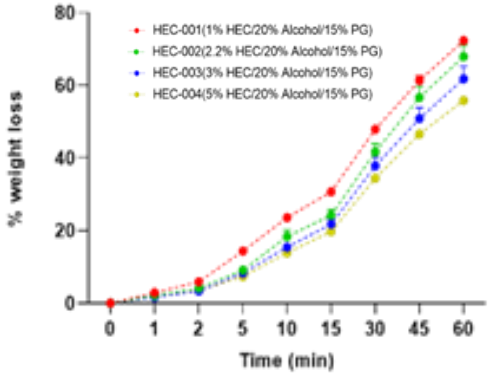
Cooling Potential

Use of infrared thermal imaging (IRT)-based technique for in vitro assessment of the cooling potential (measured as ΔT), of topical gel formulations









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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.
- Significant compositional changes may impact sensorial attributes of a topical product.
- In vitro instrumental techniques were developed and optimized to predict sensorial properties of topical gel products.
- A sensorial panel test is underway to assess whether the differences observed in Q3 attributes of the HEC and CBP gels are perceivable by human subjects.

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