Role of Regulatory Science Research Topical Product Development

Innovations in Dermatological Sciences Conference

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CDER | U.S. FDA

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Disclaimer

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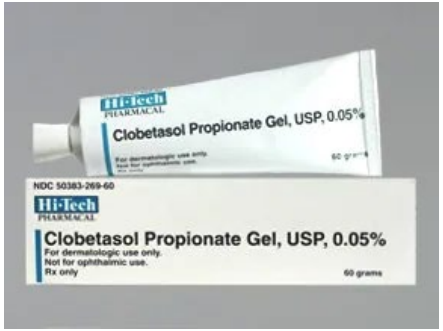
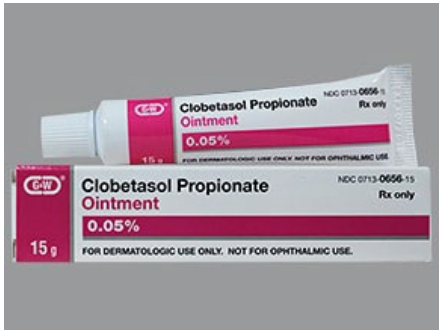
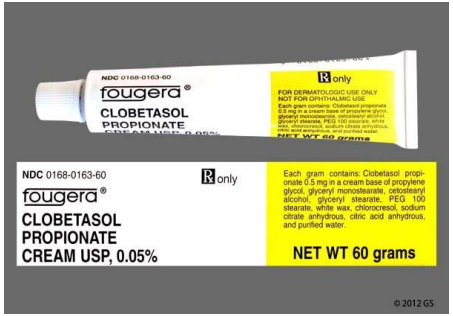






Topical Drug Products (Skin)

Understanding the Influence of Formulation

Components and Composition

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

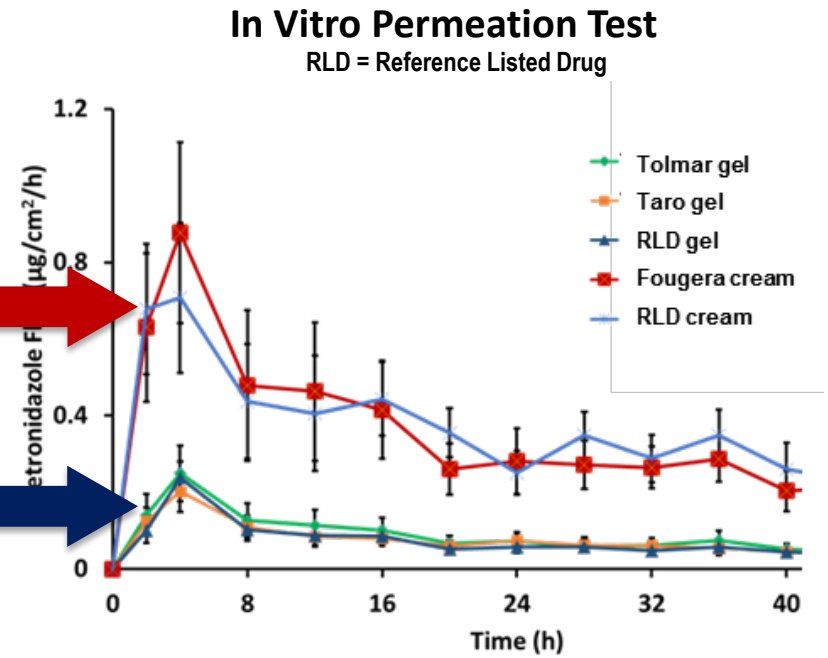
- *Characterization of the Physicochemical and Structural Properties* ***(Q3)***
- ***IVRT*** *(In Vitro Release Test)*
- ***IVPT*** *(In Vitro Permeation Test)*
- *In vivo systemic pharmacokinetic* ***(PK)*** *studies*
- *In* ***silico****-based tools (Modeling and Simulation)*

"Differences" *in Formulation*
(Currently Under Development)

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

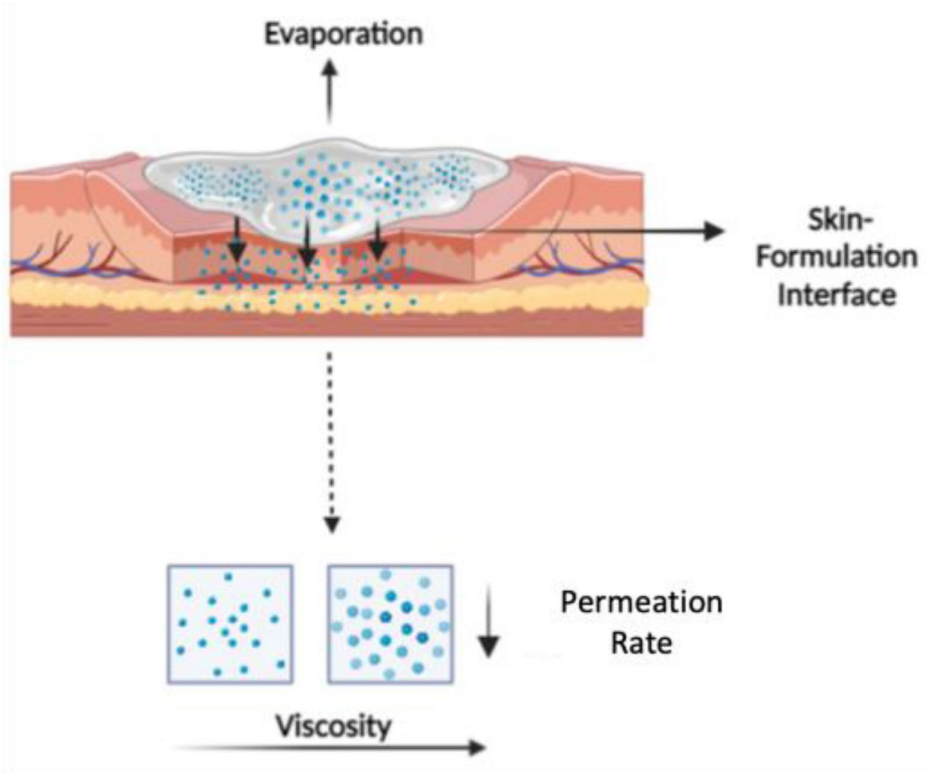
Characterization Based Approach

Quality Attribute	MetroCream® (RLD Cream)	Generic Crear (Fougera)	Metrogel® (RLD Gel)	Generic Gel (Tolmar)	Generic Ge (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingre				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
Drug in Oil (mg/g)	2.58	3.94	---	---	---
Solvent Activity	0.977	0.974	0.992	0.994	1.002
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drying, T_{30} (min)	17	11.4	5.5	4.7	6.5



Data provided courtesy of Dr. Narasimha Murthy
WOA – Work of Adhesion

Influence of Metamorphosis on Bioavailability



Jin et al. Metamorphosis of Topical Semisolid Products—Understanding the Role of Rheological Properties in Drug Permeation under the "in Use" Condition. *Pharmaceutics* **2023**, *15*, 1707. https://doi.org/10.3390/pharmaceutics15061707

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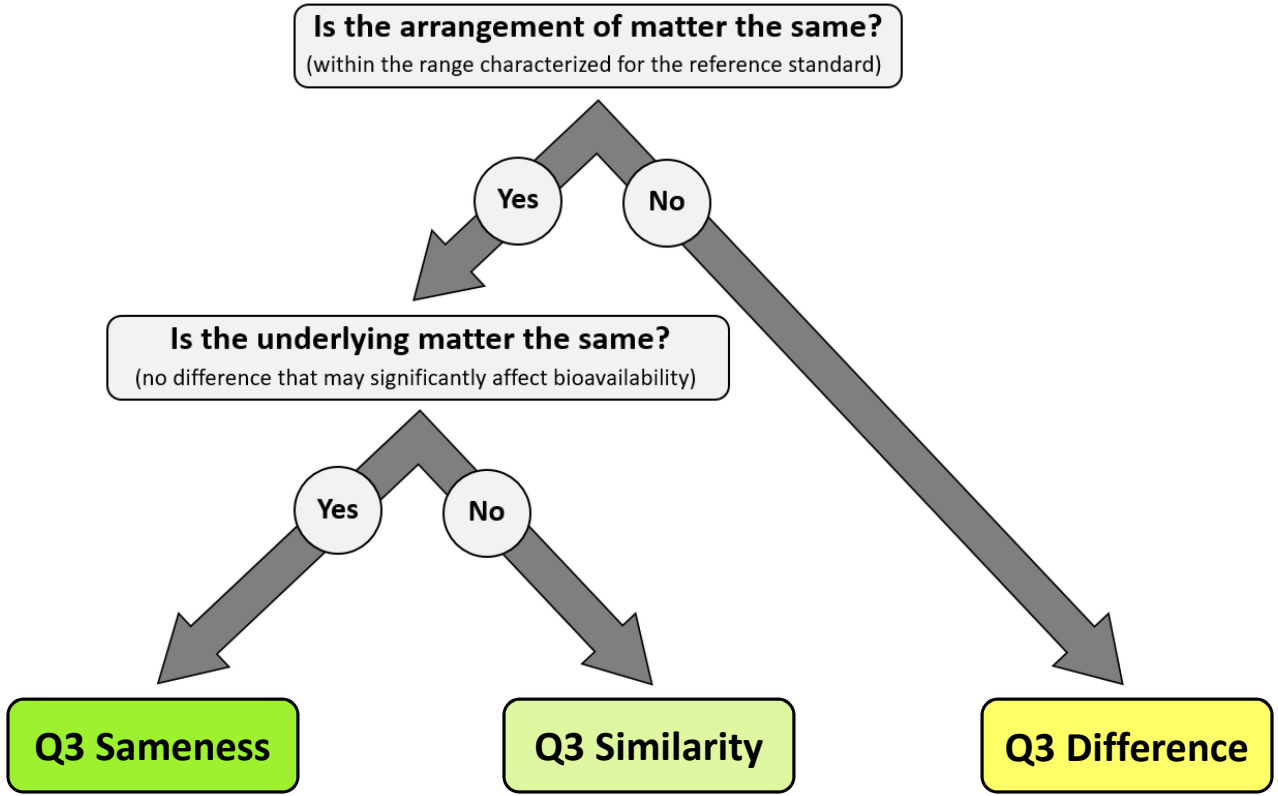
Concepts of Q3



https://www.fda.gov/media/162471/download

Understanding the Influence of Formulation

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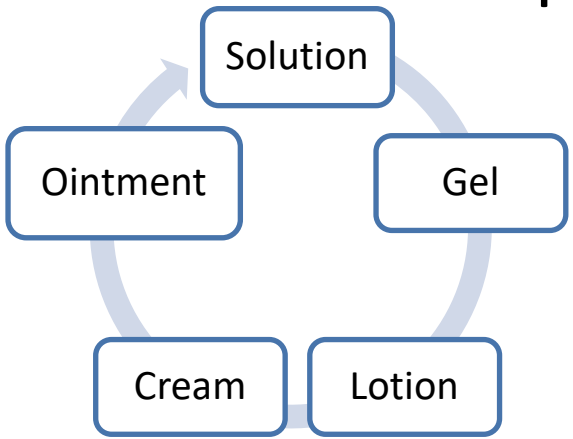
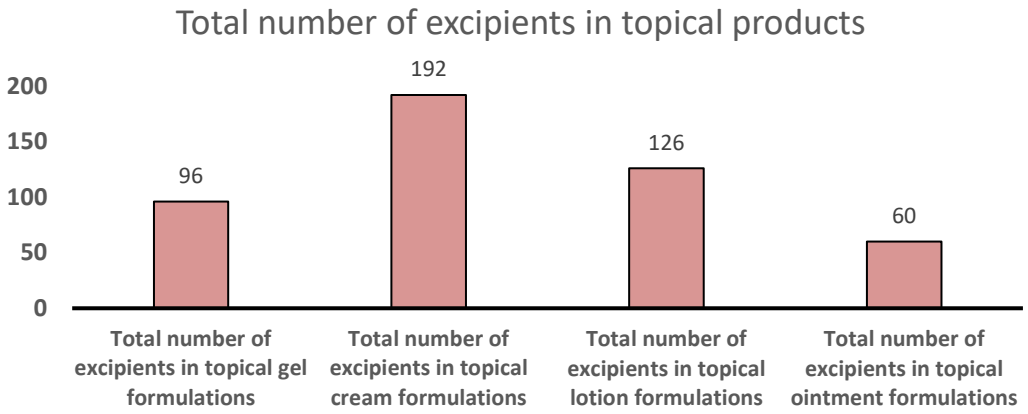
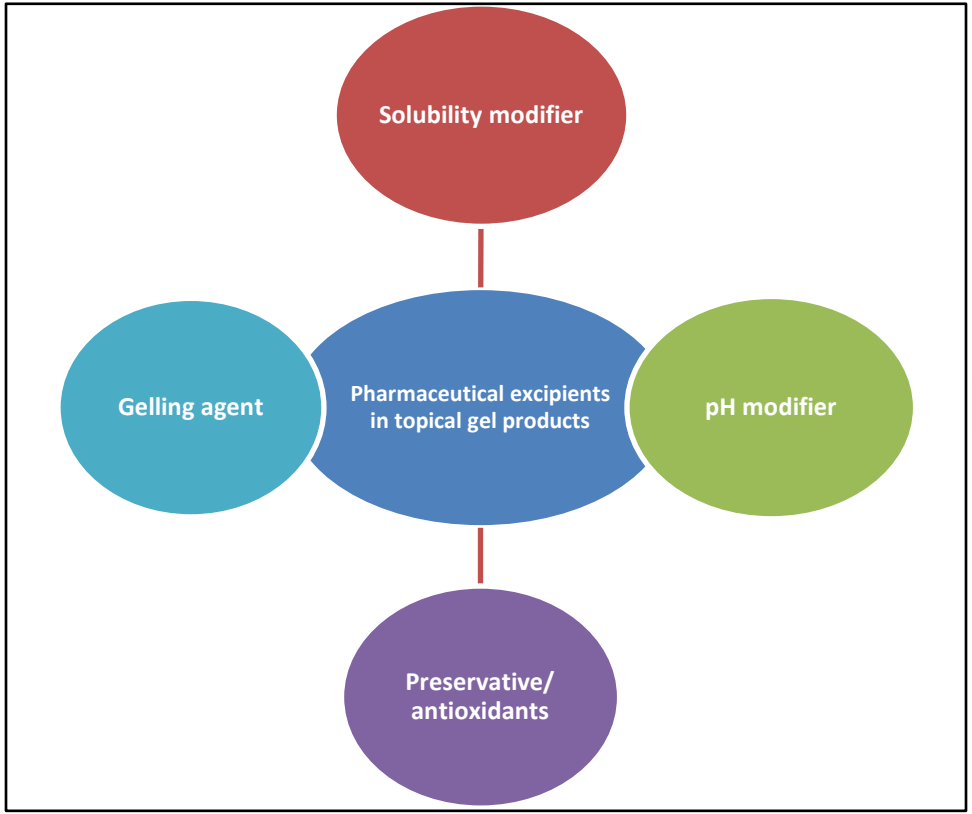
Topical Product Complexity





Unpublished Data- Office of Research and Standards, 2021

Topical Product Complexity- Gels

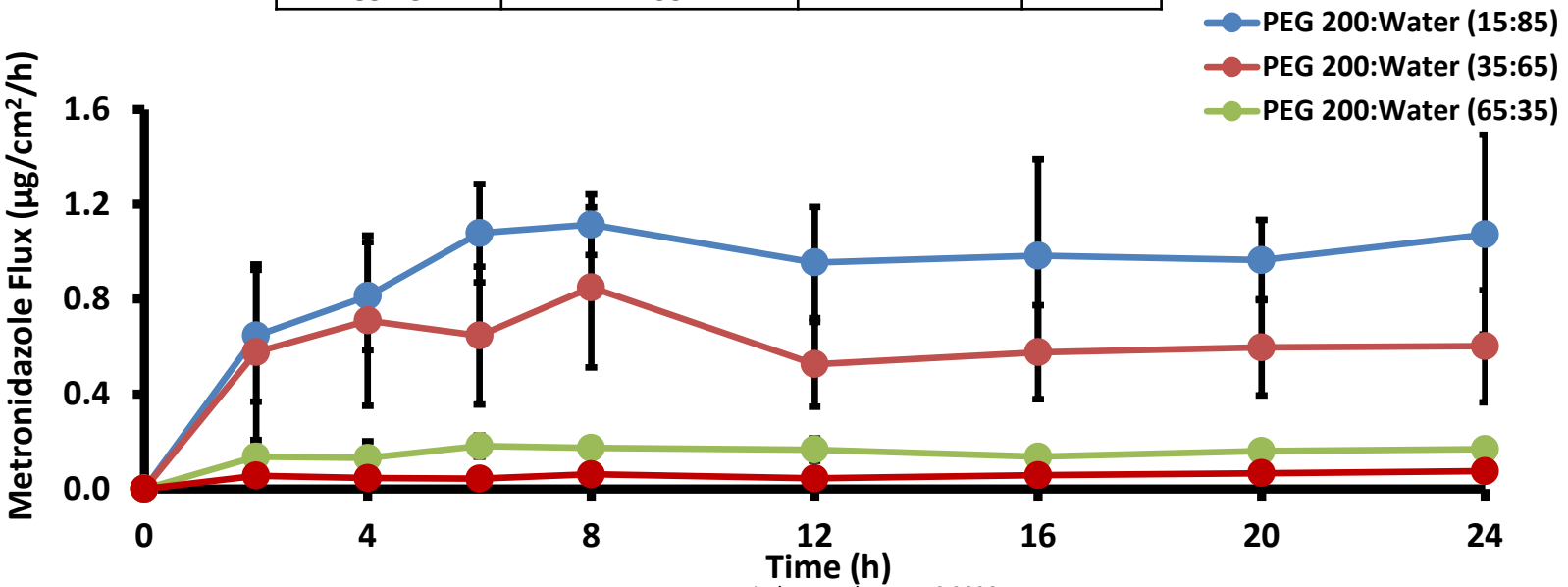


Impact on Bioavailability
Impact on Patient Perception

Unpublished Data- Office of Research and Standards

Influence of Formulation on Bioavailability

PEG 200:Water	Saturation Solubility (mg/ml)	Concentration (mg/ml)	α
15:85	10.15	7.5	0.74
35:65	11.62	7.5	0.65
65:35	14.27	7.5	0.53
85:15	22.99	7.5	0.33



Data courtesy Dr. Narasimha Murthy– AAPS 2020
PEG- Polyethylene glycol

Influence of Formulation on Bioavailability

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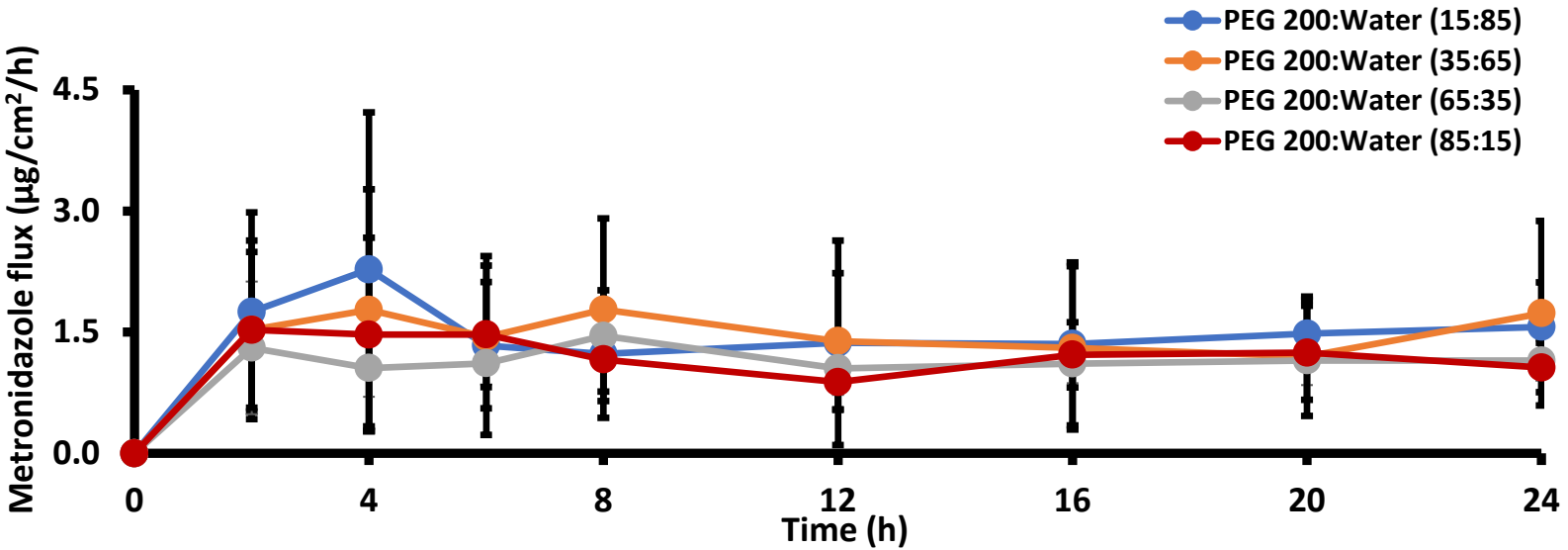


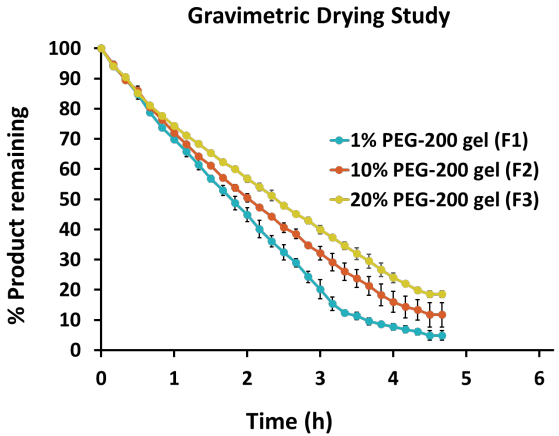
Data courtesy Dr. Narasimha Murthy– AAPS 2020

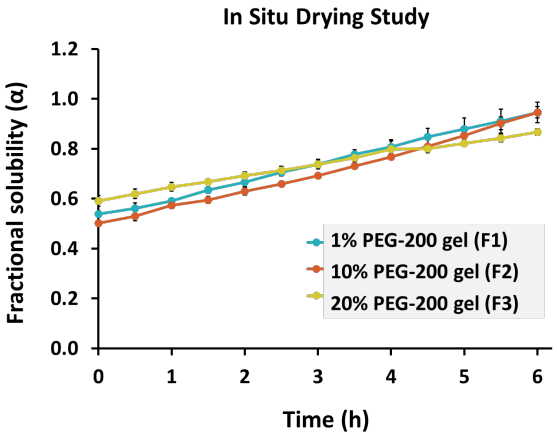
Influence of Formulation on Bioavailability

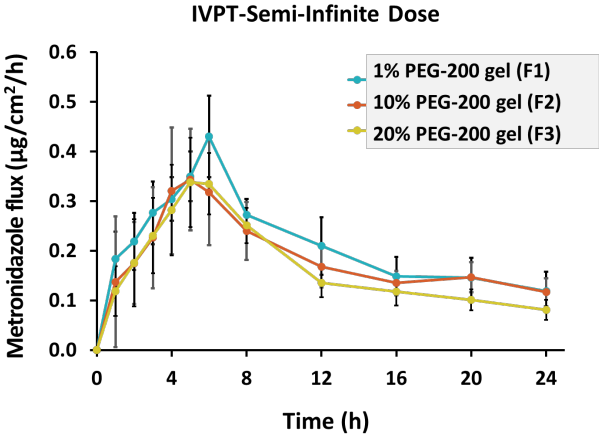
Composition (%w/w)	F1	F2	F3	F4	F5
Metronidazole	**0.5**	**0.5**	**0.5**	**0.25**	**0.75**
PEG 200	**1**	**10**	**20**	**1**	**1**
EDTA	0.01	0.01	0.01	0.01	0.01
Sodium benzoate	0.02	0.02	0.02	0.02	0.02
Hydroxy ethyl cellulose	5	5	5	5	5
Water qs	100	100	100	100	100

Data courtesy Dr. Narasimha Murthy– AAPS 2022
EDTA - Ethylenediaminetetraacetic acid

Influence of Formulation on Bioavailability







$$\alpha = \frac{\textit{Concentration of metronidazole}}{\textit{Saturation solubility of metronidazole in a given solvent}}$$

Data courtesy Narasimha Murthy– AAPS 2022

Influence of Formulation on Bioavailability

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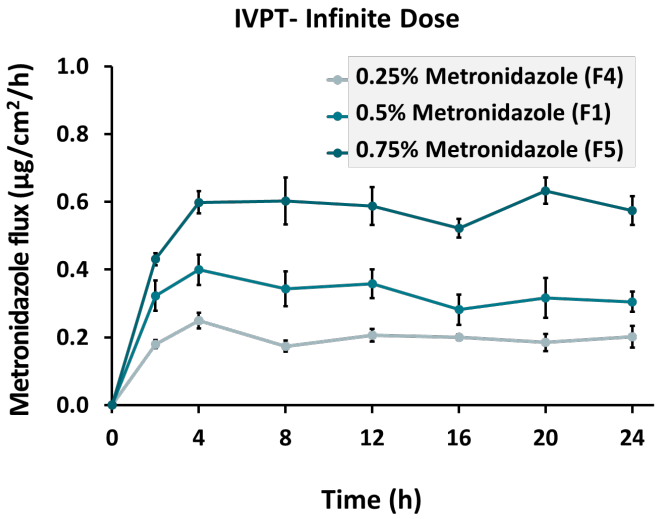
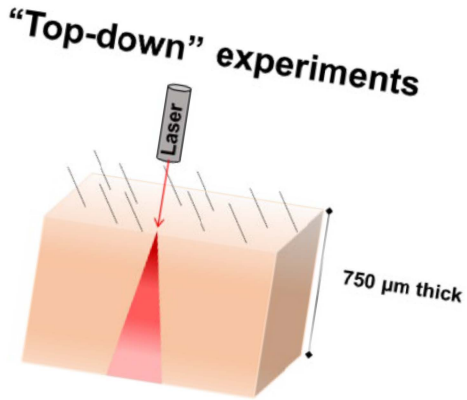
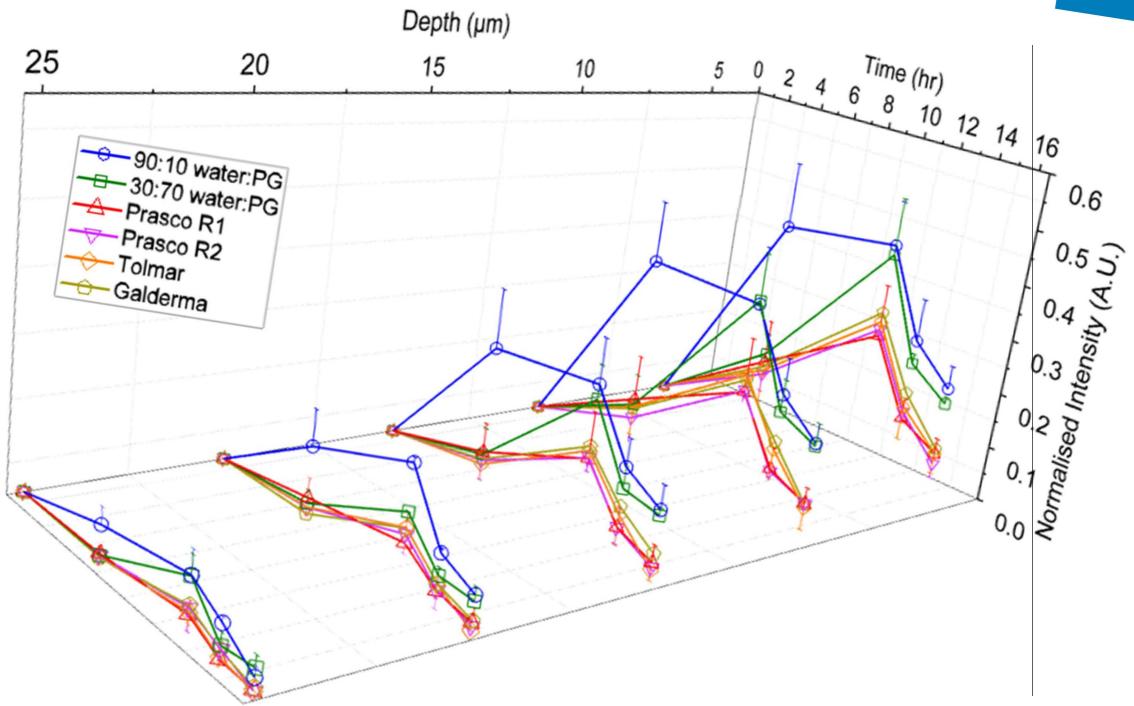
Water qs	100	100	100



Data courtesy Dr. Narasimha Murthy– AAPS 2022

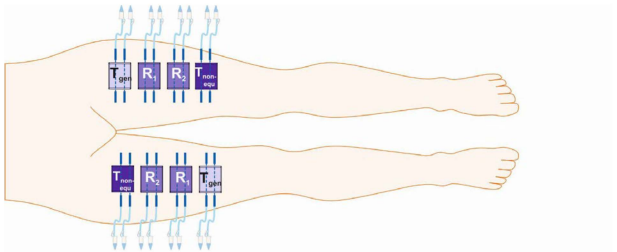
Influence of Formulation on Bioavailability

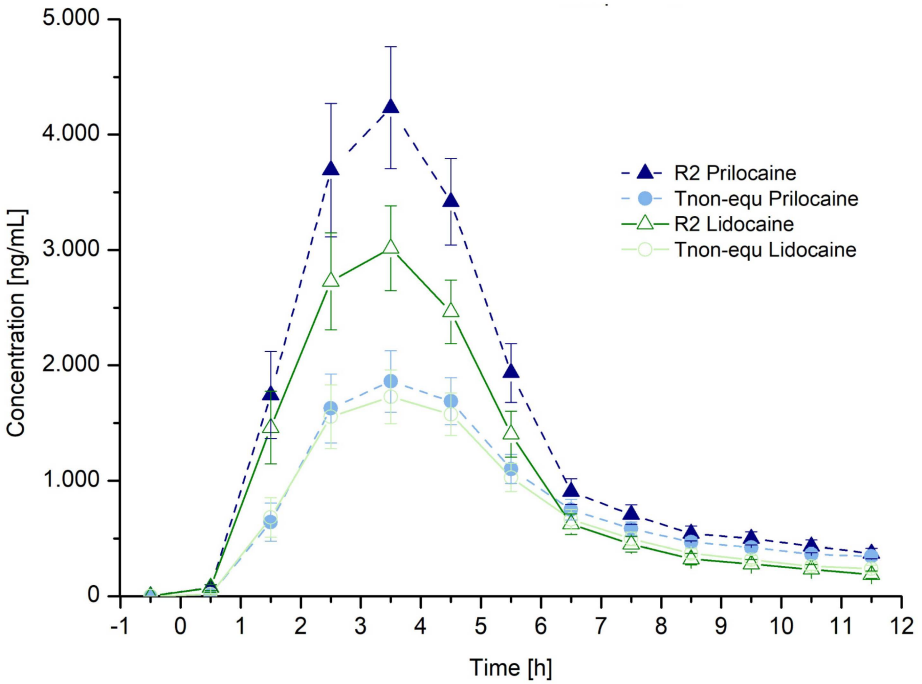




Data courtesy Prof. Richard Guy– AAPS 2022

Influence of Formulation on Bioavailability





Data courtesy Dr. Frank Sinner– AAPS 2020

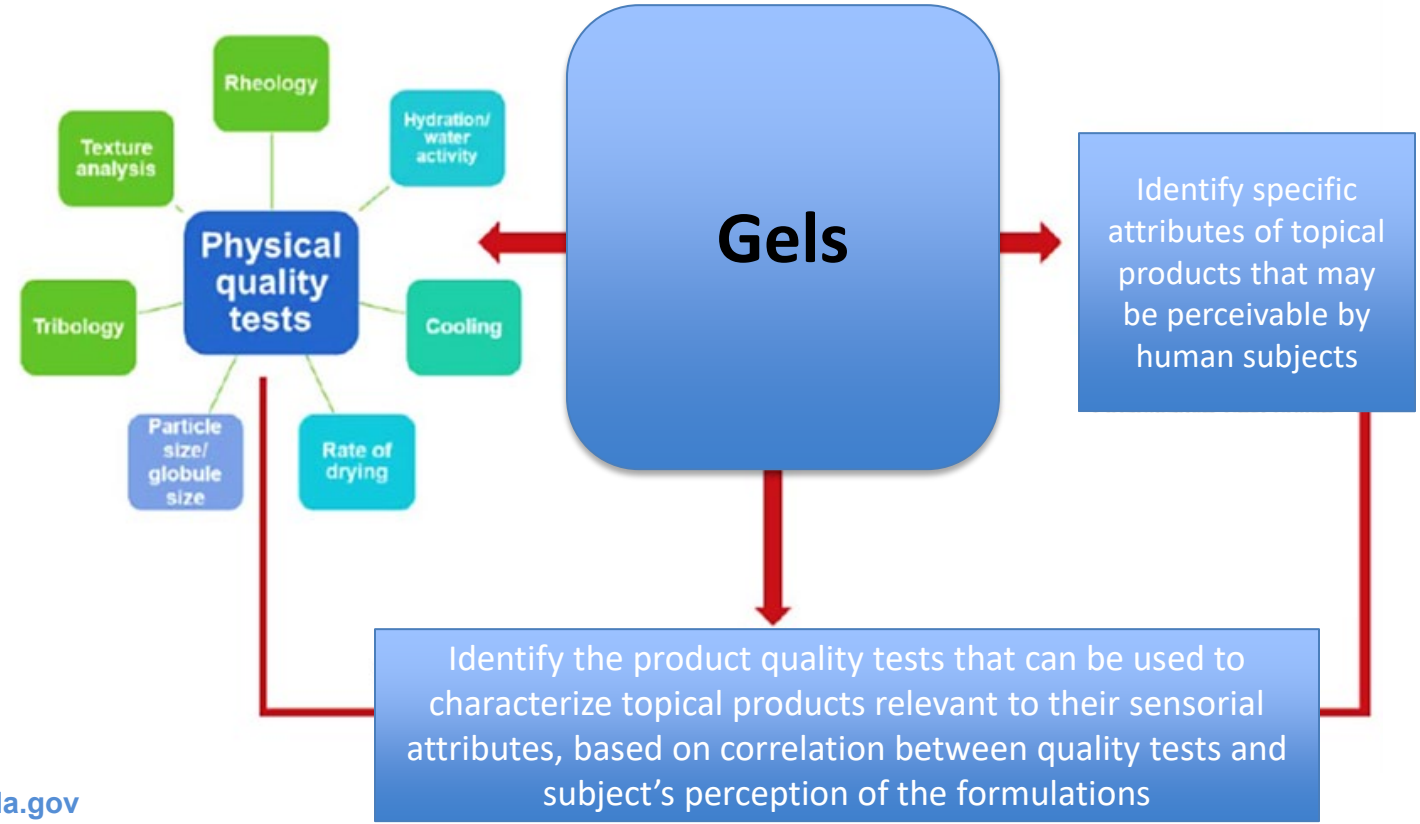
Influence of Formulation on Patient Perception

Composition (%w/w)	HEC-01	HEC-02	HEC-03	HEC-04	HEC-05	HEC-06	HEC-07	HEC-08	HEC-09	HEC-10	HEC-11	HEC-12
Hydroxyethyl cellulose	1	2.2	3	5	2.2	2.2	2.2	2.2	2.2	2.2	2.2	2.2
Ethanol	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	62.0	61.2	59.2	57.0	52.0	37.0	32.0	57.0	47.0	37.0	27.0

Composition (%w/w)	CBP-01	CBP-02	CBP-03	CBP-04	CBP-05	CBP-06	CBP-07	CBP-08	CBP-09	CBP-10	CBP-11	CBP-12	CBP-13	CBP-14
Carbopol 980	0.5	0.25	0.65	0.25	0.25	0.5	0.5	0.5	0.1	1.0	0.5	0.5	0.5	0.5
Ethanol	-	-	-	-	-	-	20	-	-	-	35	50	10	-
Propylene glycol	15	15	15	25	35	35	15	50	15	15	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	84.4	84.6	84.2	74.6	64.6	64.4	64.4	49.4	84.7	82.5	49.2	34.4	74.3	74.2

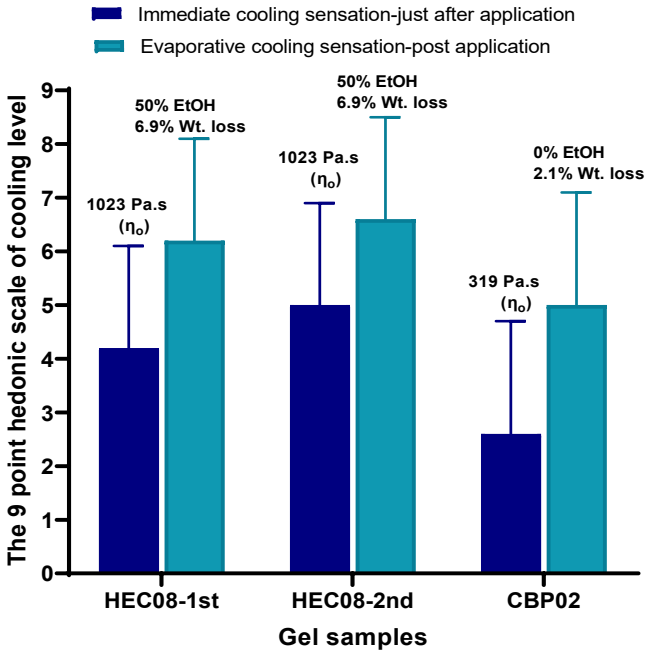
Data courtesy Dr. Yousuf Mohammed – CRS 2023 poster

Influence of Formulation on Patient Perception



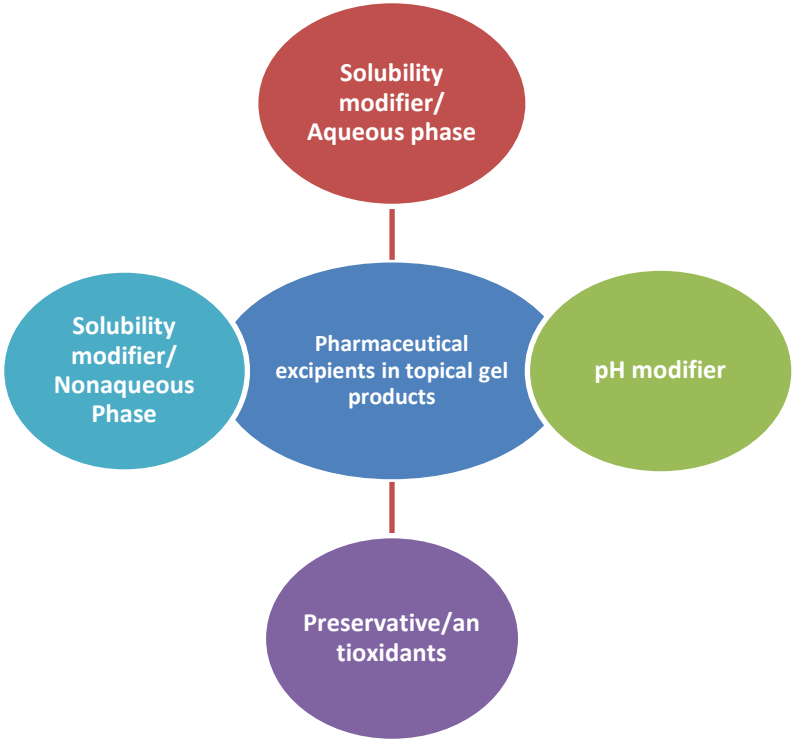
Influence of Formulation on Patient Perception

No.	Formulation	Polymer, %	Propylene glycol, %	Ethanol/iso-propanol, %	Mean temp. difference (°C)
1	CBP12 (C12)	0.5	15	50	25.23
2	HEC01 (H1)	1	15	20	14.34
3	HEC08 (H8)	2.2	15	50	**13.28**
4	HEC07 (H7)	2.2	15	45	12.99
5	HEC05 (H5)	2.2	15	25	12.18
6	HEC06 (H6)	2.2	15	30	11.43
7	CBP11 (C11)	0.5	15	35	10.69
8	HEC03 (H3)	3	15	20	9.96
9	HEC02 (H2)	2.2	15	20	9.31
10	CBP09 (C9)	0.1	15	--	9.08
11	HEC09 (H9)	2.2	20	20	8.77
12	CBP07 (C7)	0.5	15	20	8.51
13	HEC04 (H4)	5	15	20	8.42
14	HEC10 (H10)	2.2	30	20	8.12
15	HEC11 (H11)	2.2	40	20	6.87
16	CBP10 (C10)	1	15	--	6.78
17	CBP13 (C13)	0.5	15	10	6.75
18	CBP06 (C6)	0.5	35	--	6.34
19	CBP01 (C1)	0.5	15	--	5.88
20	CBP02 (C2)	0.25	15	--	**5.65**
21	HEC12 (H12)	2.2	50	20	5.47
22	CBP04 (C4)	0.25	25	--	5.30
23	CBP03 (C3)	0.65	15	--	4.86
24	CBP14 (C14)	0.5	25	--	4.65
25	CBP05 (C5)	0.25	35	--	4.48
26	CBP08 (C8)	0.5	50	--	3.03



Data courtesy Dr. Yousuf Mohammed – CRS 2023 poster

Topical Product Complexity- Creams/Lotions



Unpublished Data- Office of Research and Standards

Summary

- Topical drug products applied to the skin are generally complex dosage forms
- Understanding the behavior of a given formulation during evaporation is critical to be able to assess the bioavailability, and evaluate bioequivalence (BE), of the active ingredient from the drug product
- Differences in formulation can potentially impact both bioavailability and patient perception
- Goal of the GDUFA regulatory science and research program is to facilitate the development of tools that can enhance our understanding of how formulation may influence product performance, and thereby can be utilized to facilitate drug development/establish BE and enhance the availability of generic topical drug products

Summary

- The GDUFA regulatory science and research program is a model for research programs at the FDA
- We would love to collaborate with you
  - FDA welcomes research proposals for Grants/ Contracts/ Etc.
  - Postdoctoral Fellowship Opportunities- https://orise.orau.gov/fda/

Quick References

- Generic Drug Research Priorities & Projects
  - https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects
- Generic Drug Research Publications & Resources
  - https://www.fda.gov/drugs/generic-drugs/generic-drug-research-publications-resources
- Generic Drug Research Collaboration Opportunities
  - https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects

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- Robert Lionberger, PhD

Research Collaborators

Collaborations within FDA

All of our collaborators within the GDUFA Regulatory Science and Research Program

U.S. FOOD & DRUG ADMINISTRATION

Thank You

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Lead Pharmacologist
Office of Research and Standards (ORS), Office of Generic Drugs (OGD)
CDER | U.S. FDA