U.S. FOOD & DRUG ADMINISTRATION

Physicochemical, Structural, and Performance Characterization of Topical Semisolid Products

Florida Chapter Society of Cosmetic Chemists

Sunscreen Symposium 2021

Sam Raney, PhD
Associate Director for Science
Office of Research and Standards
Office of Generic Drugs| CDER | U.S. FDA
September 25, 2021

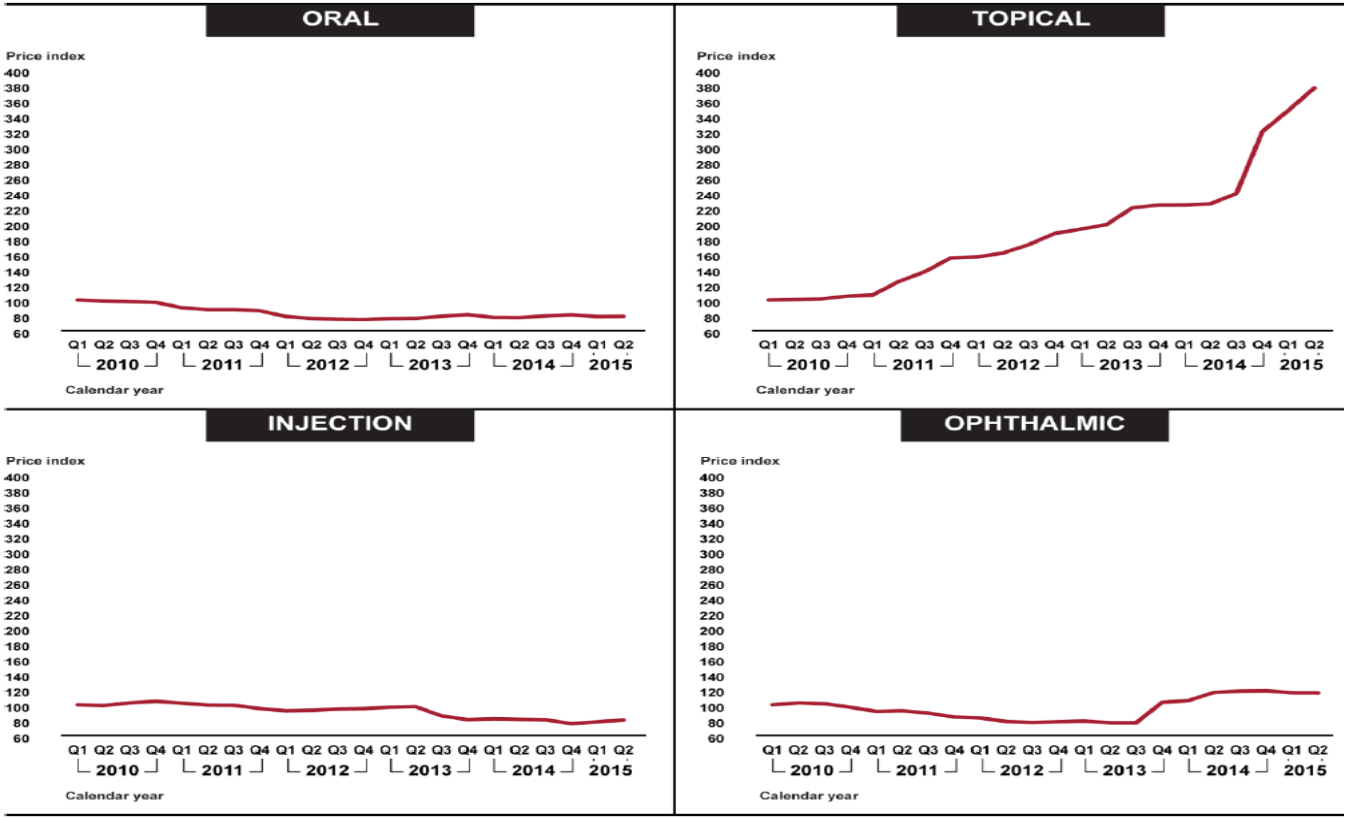
Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.
- The information discussed has not necessarily been evaluated by the relevant FDA centers or offices that regulate cosmetics or sunscreen products, and concepts discussed should not be misconstrued as representing policies currently under consideration by FDA centers or offices that regulate cosmetics or sunscreen products.

The GAO Report (GAO-16-706)

- The U.S. Government Accountability Office (GAO) Report in Aug 2016 analyzed a period spanning Quarter 1 of 2010 through Quarter 2 of 2015
- **57%** of the topical drug products experienced an extraordinary price increase in that period
- The average price of topical generic drugs was **276% higher** by the end of the period analyzed
- Manufacturers and other stakeholders reported that market **competition**, influenced by various factors, drives generic drug prices

The GAO Report (GAO-16-706)



Source: GAO analysis of Medicare Part D prescription drug event data. | GAO-16-706

Retail Prices for Dermatologic Drugs

Drug	Type	Price, US $ 2009	2011	2014	2015	Absolute Change, 2009-2015	% Change, 2009-2015
Altabax, 15 g	I	92.50	106.18	168.75	196.86	104.36	112.82
Benzaclin, 50 g	A	166.79	205.80	451.29	503.85	337.06	202.08
Carac cream, 30 g	N	159.40	227.16	2939.68	2864.70	2705.30	1697.18
Clobex spray, 4 oz	S	389.57	500.29	827.11	958.01	568.44	145.91
Cloderm cream, 30 g	S	96.47	132.92	220.75	360.02	263.55	273.19
Cutivate lotion 120 mL	S	305.00	493.92	918.63	1067.25	762.25	249.91
Derma-Smoothe FS oil, 4 oz	S	45.70	47.23	247.84	322.67	276.97	606.06
Finacea, 50 g	A	124.42	185.42	288.92	284.30	159.88	128.51
Olux-E foam, 100 g	S	307.58	382.79	750.79	841.76	534.18	173.67
Oracea, 40 mg (30 tablets)	A	439.01	416.09	632.80	702.46	263.45	60.01
Oxistat cream, 30 g	I	76.50	119.25	399.00	544.66	468.16	611.97
Oxsoralen-Ultra, 10 mg (50 capsules)	P	1227.32	2150.49	4568.54	5204.31	3976.99	324.04
Retin-A Micro, 0.1%, 50 g	A	178.05	335.73	791.47	914.52	736.47	413.64
Solaraze gel, 100 g	N	442.89	618.56	1738.91	1883.98	1441.09	325.38
Soriatane, 25 mg (30 capsules)	P	757.75	958.50	1452.50	1595.27	837.52	110.53
Taclonex, 60 g	P	465.99	522.58	848.21	962.90	496.91	106.64
Targretin gel, one 60-g tube	N	1686.78	1787.97	15 708.40	30 320.12	28 633.34	1697.51
Tazorac cream, 0.1%, 60 g	A	266.18	464.96	656.20	722.27	456.09	171.34
Xolegel, 30 g	I	212.50	278.00	389.25	641.96	429.46	202.10

Abbreviations: A, acne and rosacea; I, antiinfective; N, antineoplastic; P, psoriasis; S, corticosteroid.

Source: Miranda E. Rosenberg, BA and Steven P. Rosenberg, MD (2016) *Changes in Retail Prices of Prescription Dermatologic Drugs From 2009 to 2015*. JAMA Dermatology. 152(2):158-163. doi:10.1001/jamadermatol.2015.3897

Patient Access to Topical Products

- The majority of topical dermatological drug products have fewer than three generic competitors; for many products no generics are available at all.
- This may have been attributable to the historical barriers to the development of topical dermatological drug products, possibly including
  - Difficulty/issues with comparative clinical endpoint bioequivalence (BE) studies
  - The complex nature of topical formulations

Formulations Can Alter Bioavailability

- It is widely understood that the formulation of a topical semisolid dosage form can influence its performance
- It is now increasingly clear how excipients may exert their influence, by modulating the physicochemical and microstructural arrangement of matter in the dosage form
- The resulting physical and structural characteristics of topical dosage forms, and their metamorphic properties on the skin, can directly influence topical bioavailability

Topical Dermatological Formulations

- Components, composition, physicochemical, and structural properties of a topical product can influence:
  - The drug state(s) and phase(s) of the dosage form
  - The distribution of the drug in the dosage form
  - Drug diffusion within the dosage form
  - Drug partitioning from the dosage form into the skin barrier
  - The structure and chemistry of the skin barrier
  - Drug diffusion within the skin itself
  - Drug delivery and bioavailability at the target site
  - Skin (de)hydration, irritation, or damage
  - The metamorphosis of the dosage form on the skin

The Concepts of Q1, Q2, Q3

- Q1: Components in a product
  - Q1 characterization of a reference product provides a profile of the qualitative components (ingredients) in that reference product
- Q2: Composition of a product
  - Q2 characterization of a reference product provides a profile of the quantitative formulation composition of that reference product
- Q3: Arrangement of matter in a product
  - Q3 characterization of a reference product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that reference product

Q3 Characterization

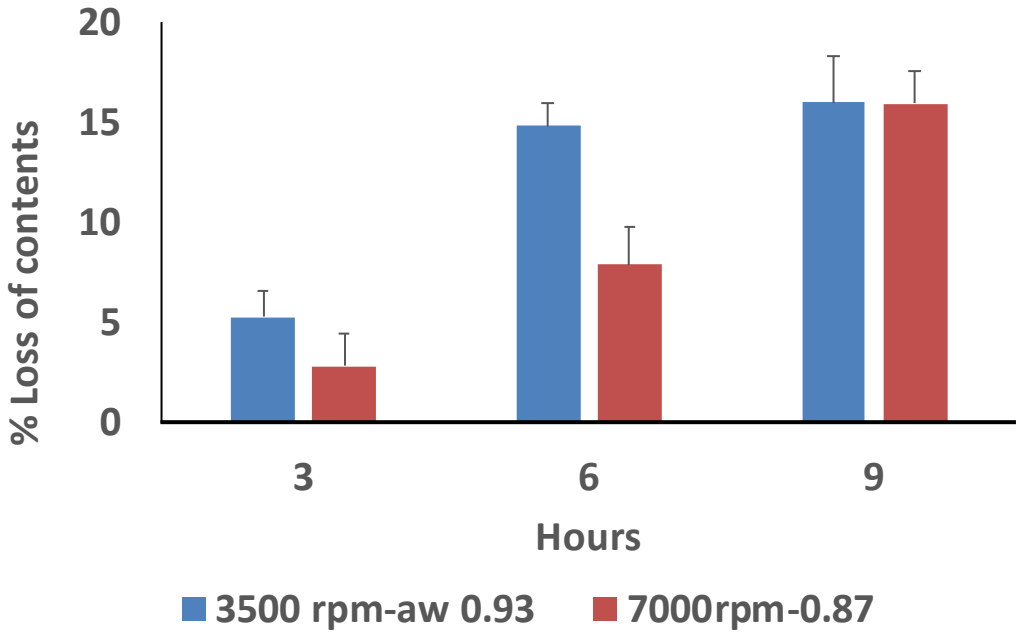
1. Characterization of appearance and texture
2. Characterization of phase states
3. Characterization of structural organization of matter
4. Characterization of polymorphic form of the active ingredient
5. Characterization of rheological behavior
6. Characterization of water activity and/or drying rate
7. Characterization of pH and buffering
8. Characterization of oleaginous components
9. Characterization of specific gravity
10. Characterization of metamorphosis-related changes

Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

Ingredients	Quantity (%w/w)
Cetostearyl Alcohol	12.5
White Wax	12
Mineral Oil	56
Sodium Borate	0.5
Water	19
Total	100

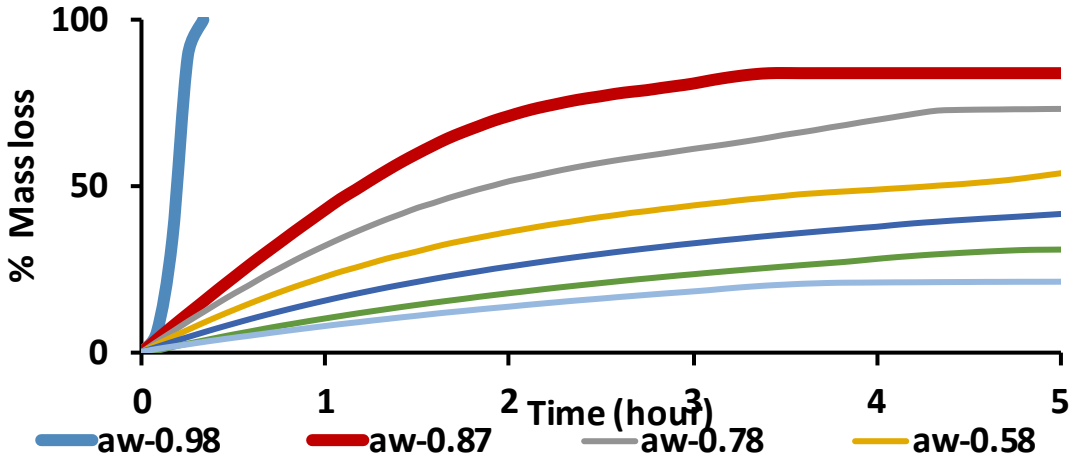
Manufacturing Conditions	Solvent Activity (a_w)
3500 RPM (15 min)	**0.931 ± 0.002**
7000 RPM (45 min)	**0.875 ± 0.006**



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

Dosage Form Metamorphosis

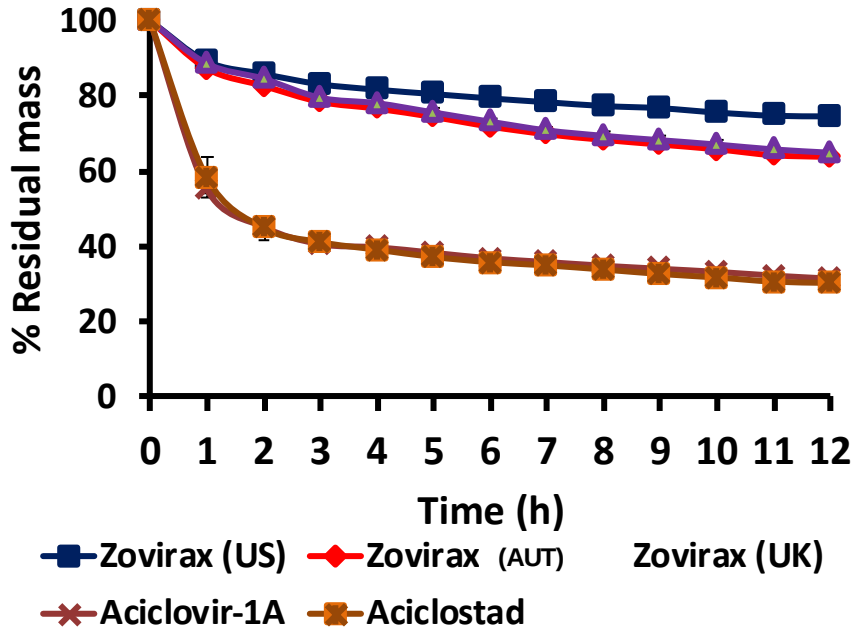
- Solvent Activity (a_s) = ρ/ρ_0
  - ρ = partial vapor pressure of Solvents in the product
  - ρ_0 = vapor pressure of pure Solvent system



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

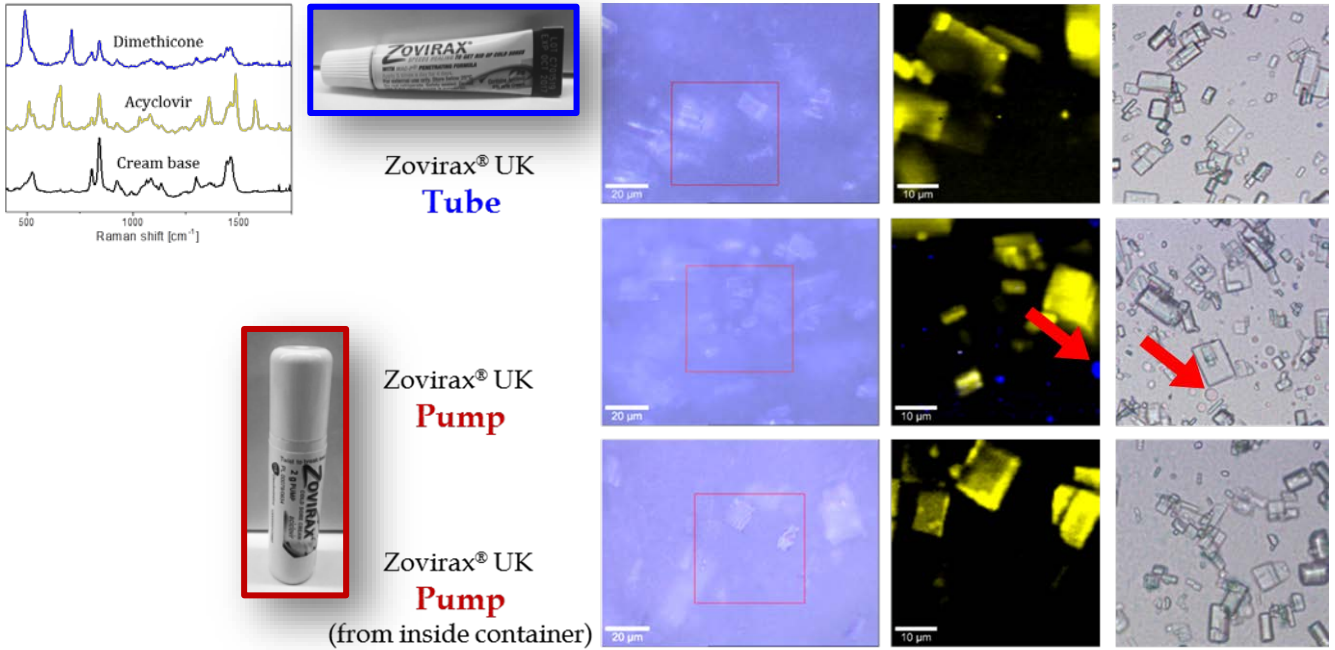


Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732± 0.002
Aciclovir 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

Influence of Dispensing Stress on Q3

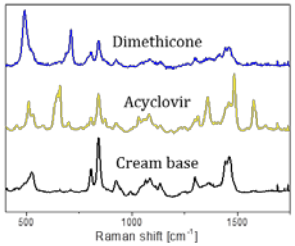
- Influence of Dose Dispensing on Product Quality

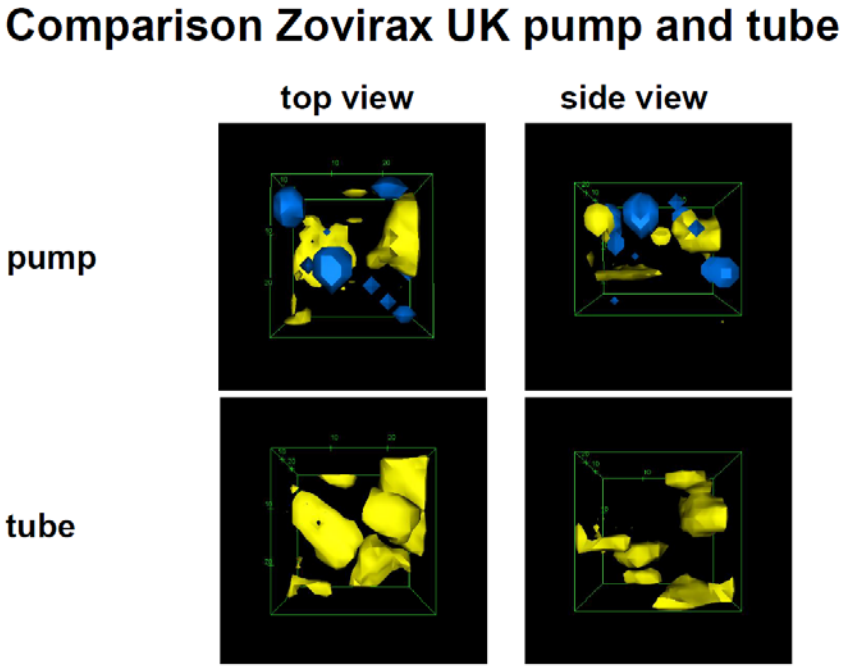


Data provided courtesy of Drs. Maike Windbergs and Mike Roberts associated with FDA funding for award U01FD0005226

Influence of Dispensing Stress on Q3

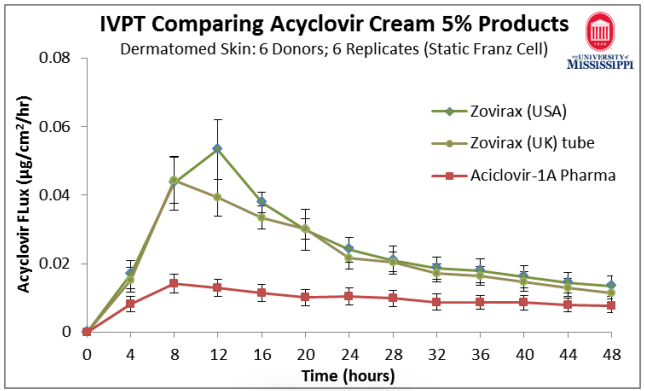
- Influence of Dose Dispensing on Product Quality

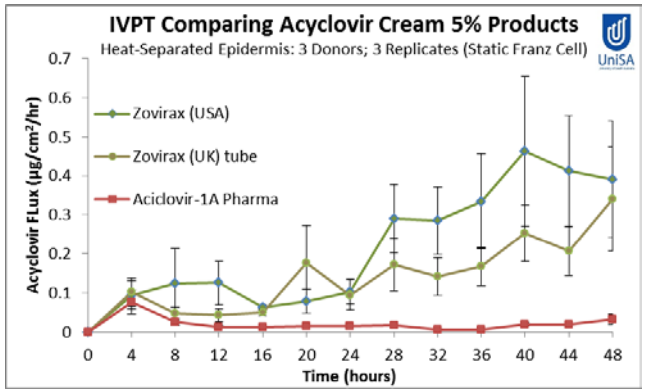


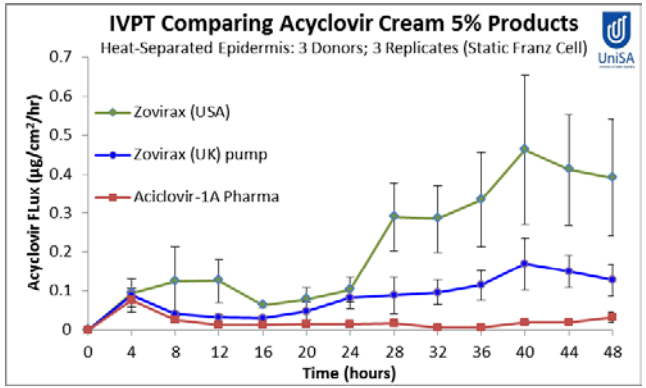


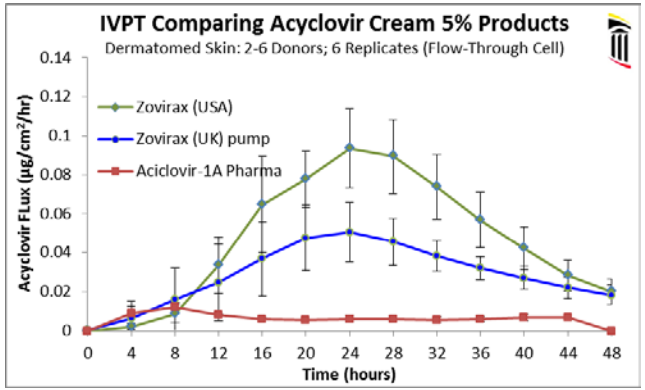
Data provided courtesy of Drs. Maike Windbergs and Mike Roberts associated with FDA funding for award U01FD0005226

Influence of Dispensing Stress on IVPT





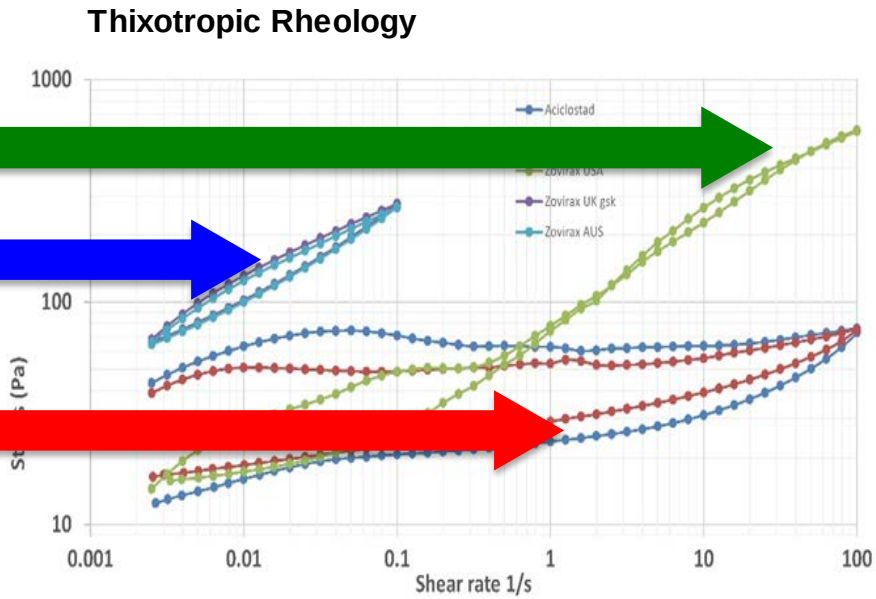




Data provided courtesy of Drs. Audra Stinchcomb, Mike Roberts, and Narasimha Murthy associated with FDA funding for awards U01FD0004947, U01FD0005226,, U01FD0005233

In Vitro Characterization (Acyclovir)

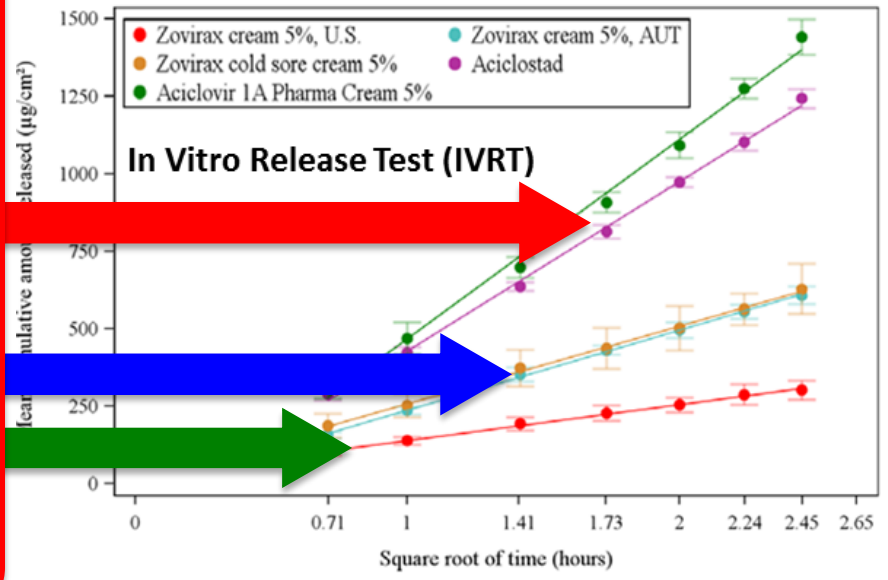
	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum				
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20		
		Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Polyoxyethylene stearate	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

In Vitro Characterization (Acyclovir)

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2		
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate		
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8				
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95

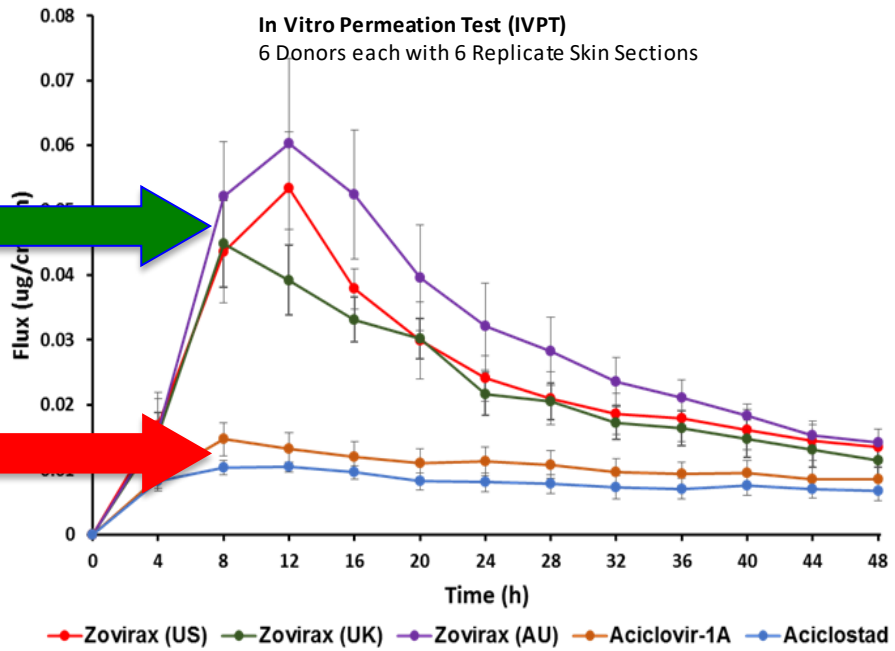


Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

In Vitro Characterization (Acyclovir)

In Vivo Cutaneous PK Study

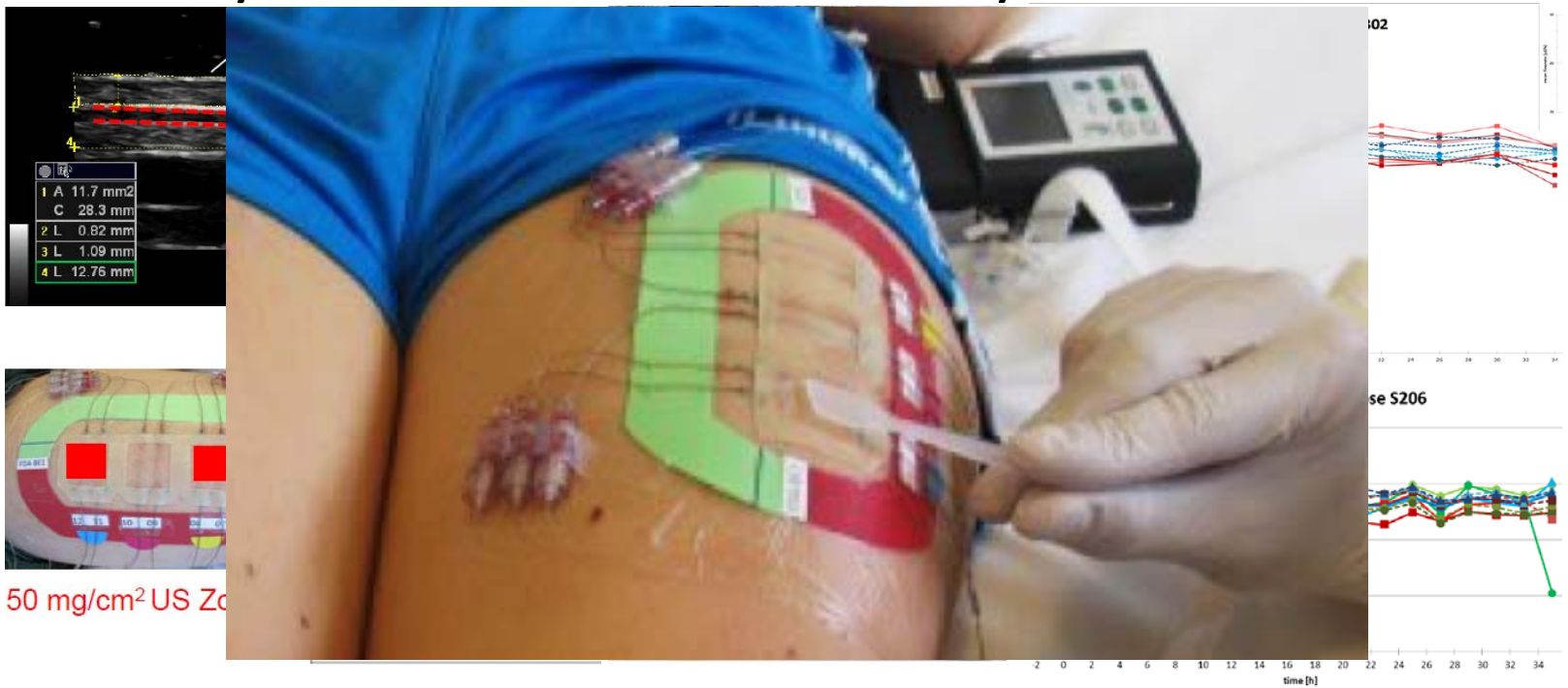
	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcoh	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol Stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

In Vivo Characterization (Acyclovir)

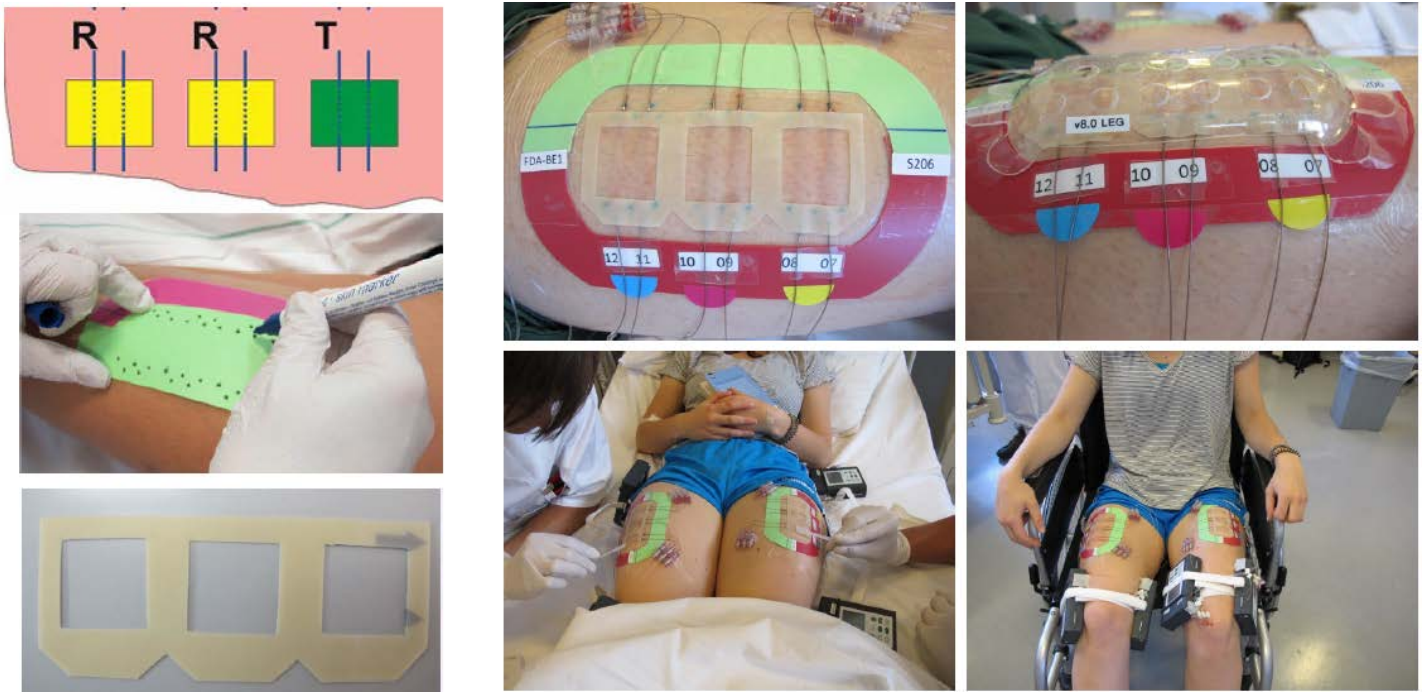
- dOFM System Validation and Study Controls



Data/Images provided courtesy of Dr. Frank Sinner (Joanneum Research) ***FDA Award U01-FD004946***

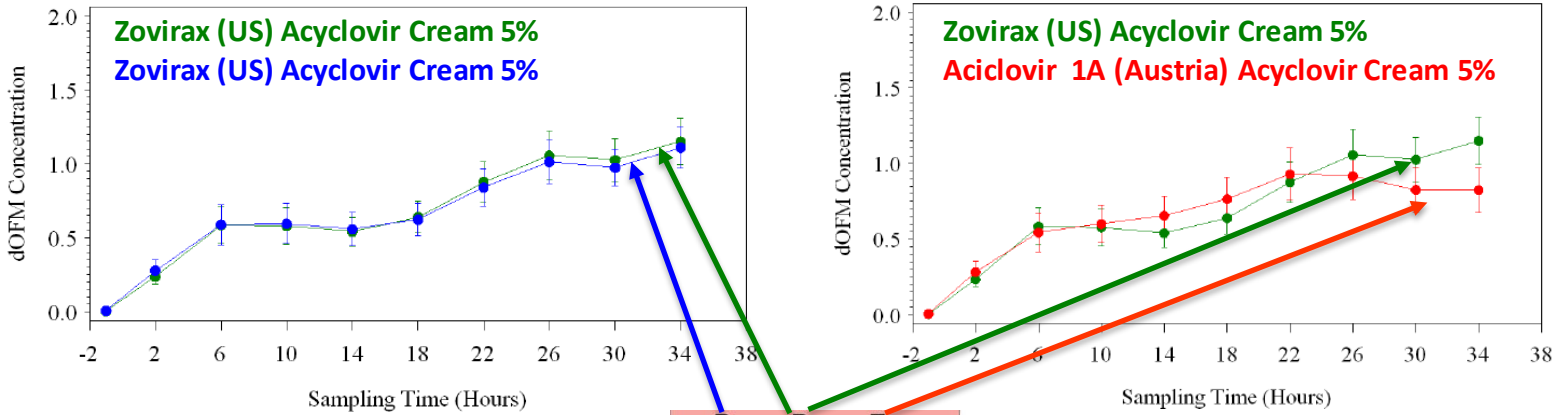
In Vivo Characterization (Acyclovir)

- dOFM: Testing Positive and Negative Controls for BE



Images provided courtesy of Dr. Frank Sinner (Joanneum Research) ***FDA Award U01-FD004946***

In Vivo Characterization (Acyclovir)



Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]
log(C_{max})	[-0.155 ; 0.190] or [85.7 % ; 120.9%]

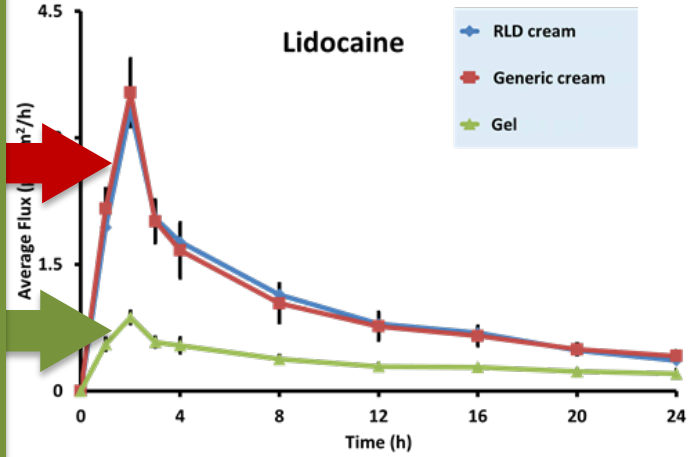
Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
log(C_{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

Data provided courtesy of Dr. Frank Sinner (Joanneum Research) ***FDA Award U01-FD004946***

Bodenlenz et al. (2017) Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence. Clin Pharmacokinet. 2017 Jan;56(1):91-98. doi: 10.1007/s40262-016-0442-z (FREE Full Text Article)

In Vitro Characterization (Lidocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved				the formulation
Globule Size, d50 (µm)	3.30		3.00		
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.2	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3

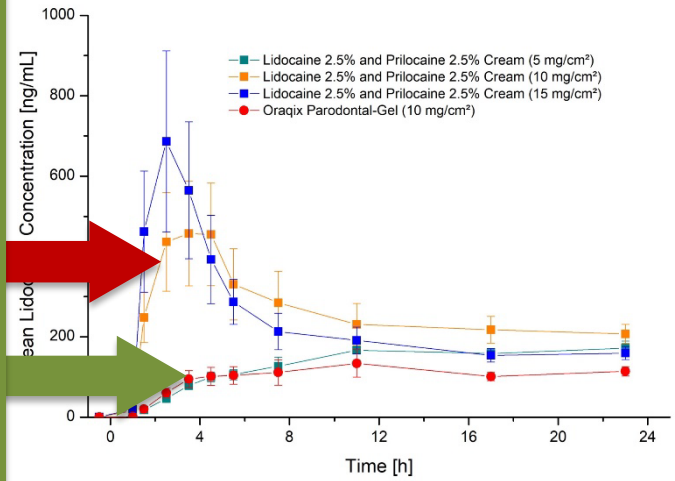


Data provided courtesy of Prof. Narasimha Murthy associated with FDA funding for award U01FD0005233

RLD = Reference Listed Drug

In Vivo Characterization (Lidocaine)

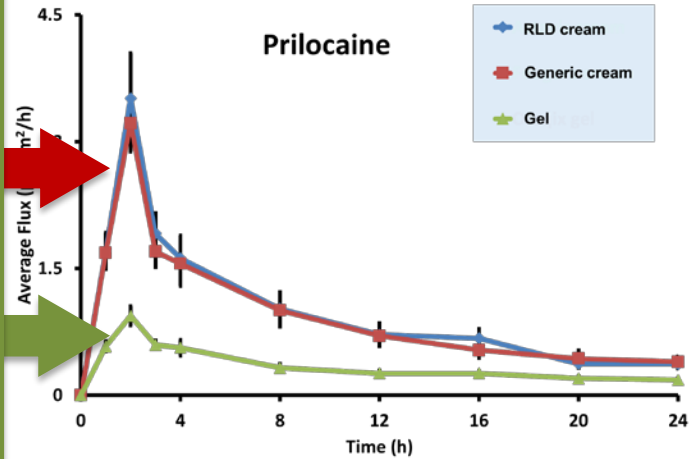
Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocai		e completely dissolved		the formulation
Globule Size, d50 (µm)	3.30		3.00		---
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06			---
	Prilocain e	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.22	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3



Data provided courtesy of Dr. Narasimha Murthy and Dr. Frank Sinner associated with FDA funding for awards U01FD0005233 and U01FD0005861

In Vitro Characterization (Prilocaine)

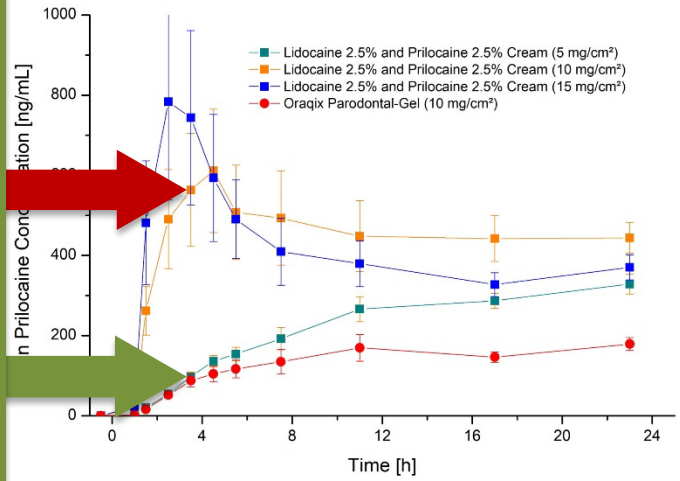
Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved				the formulation
Globule Size, d50 (µm)	3.30		3.00		
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.2	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3



Data provided courtesy of Dr. Narasimha Murthy associated with FDA funding for award U01FD0005233

In Vivo Characterization (Prilocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocai		e completely dissolved		the formulation
Globule Size, d50 (µm)	3.30				
Drug in Aqueous Phase (µg/g)	idocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocain e	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	idocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	rilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.22	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3

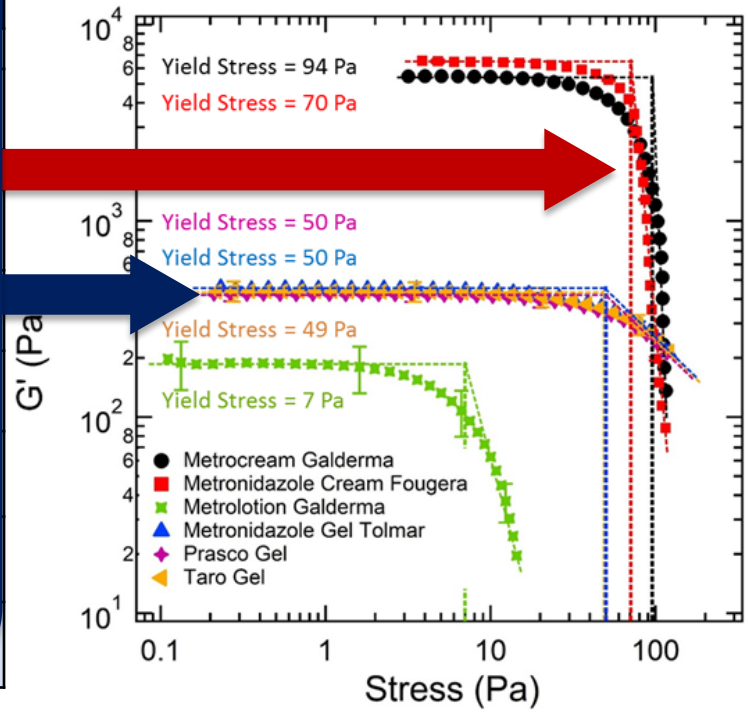


Data provided courtesy of Dr. Narasimha Murthy and Dr. Frank Sinner associated with FDA funding for awards U01FD0005233 and U01FD0005861

In Vitro / In Vivo (Metronidazole)

Quality Attribute	MetroCream®	Generic Cream (Fougera)	MetroGel®	Generic Gel (Tolmar)	Generic Gel (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			
Particle size (µm)	Active ingredient is completely dissolved				
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

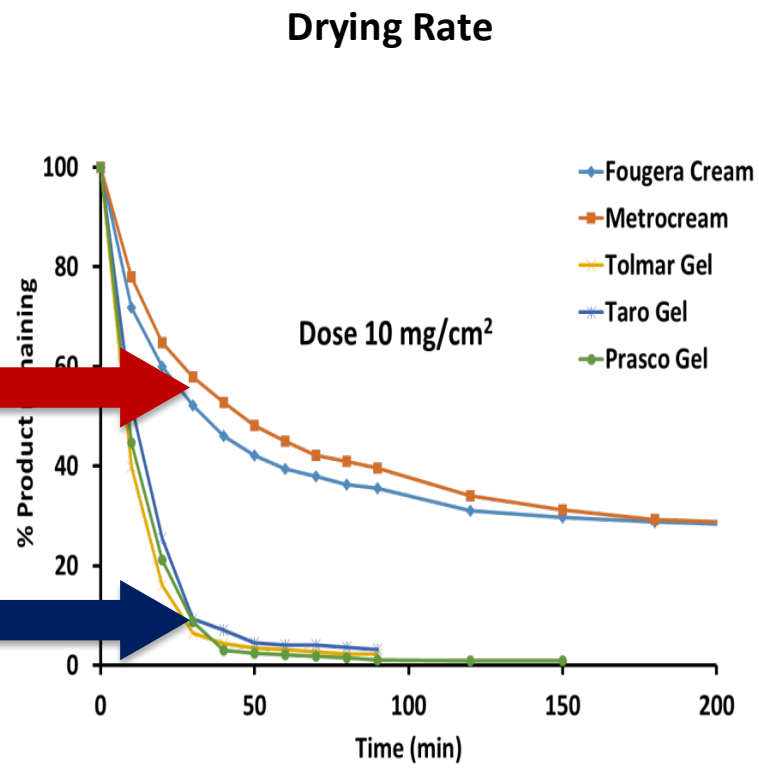
Rheology



Data provided courtesy of Dr. Narasimha Murthy associated with FDA funding for award U01FD0005233

In Vitro / In Vivo (Metronidazole)

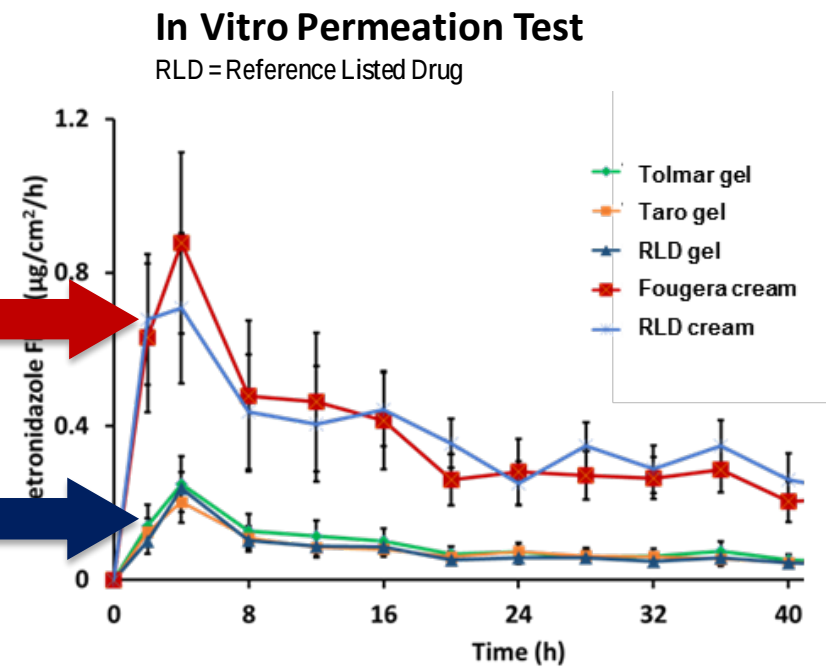
Quality Attribute	MetroCream®	Generic Cream (Fougera)	MetroGel®	Generic Gel (Tolmar)	Generic Gel (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingredient is completely dissolved				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
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 associated with FDA funding for award U01FD0005233

In Vitro / In Vivo (Metronidazole)

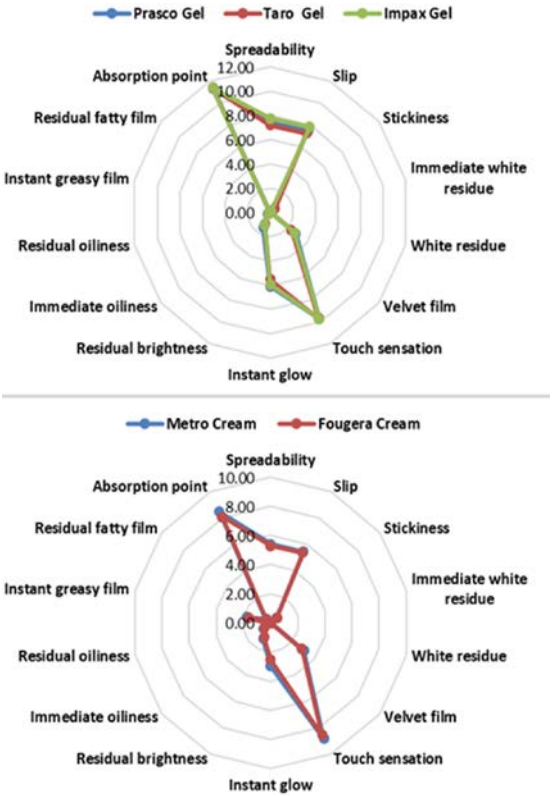
Quality Attribute	MetroCream® (RLD Cream)	Generic Cream (Fougera)	Metrogel® (RLD Gel)	Generic Gel (Tolmar)	Generic Gel (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingred				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
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 associated with FDA funding for award U01FD0005233

In Vitro / In Vivo (Metronidazole)

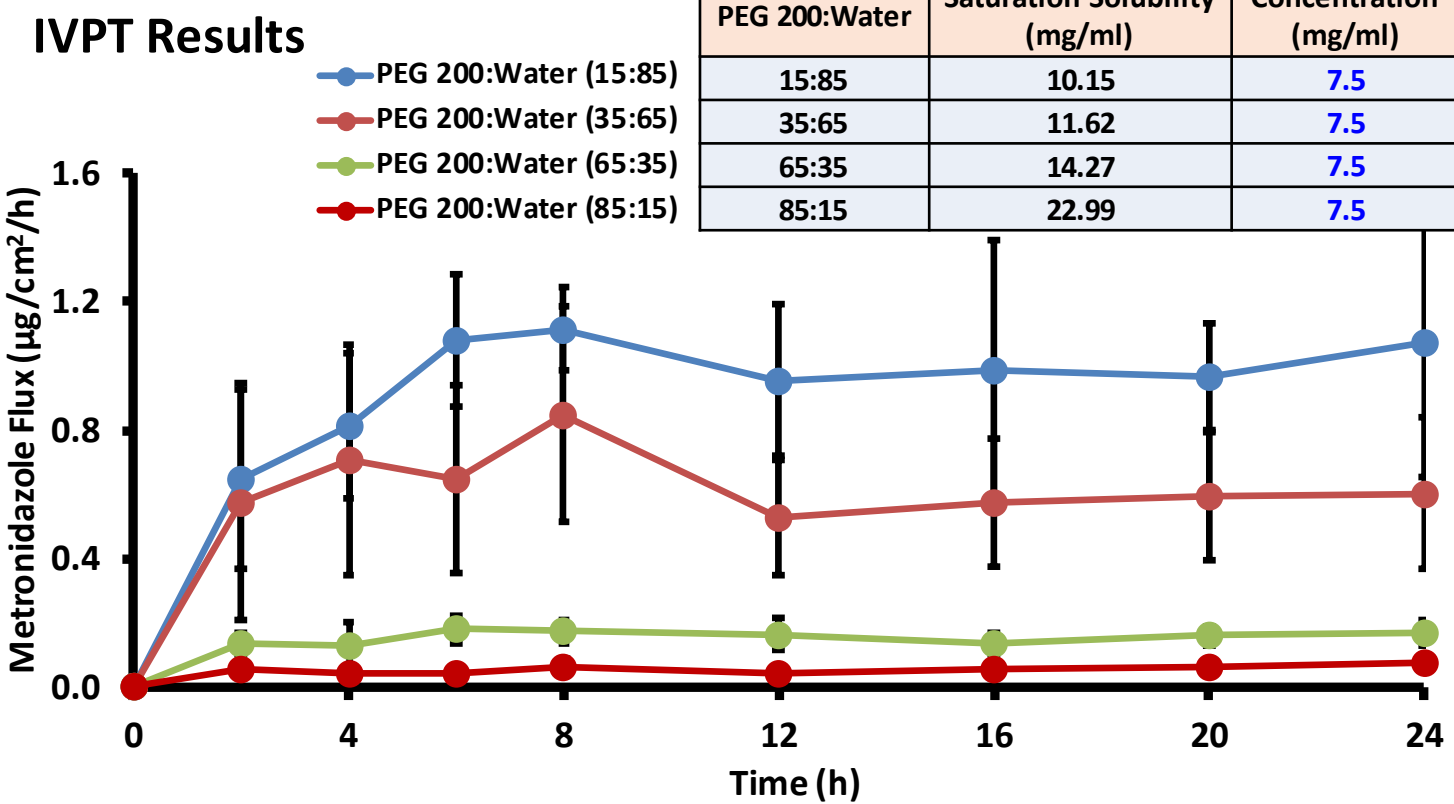
Quality Attribute	MetroCream® (RLD Cream)	Generic Cream (Fougera)	Metrogel® (RLD Gel)	Generic Gel (Tolmar)	Generic Gel (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingredient is completely dissolved				
Drug in Aq (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. Mike Roberts and Dr. Yousuf Mohammed associated with FDA funding for award U01FD0005226

Thermodynamics (Metronidazole)

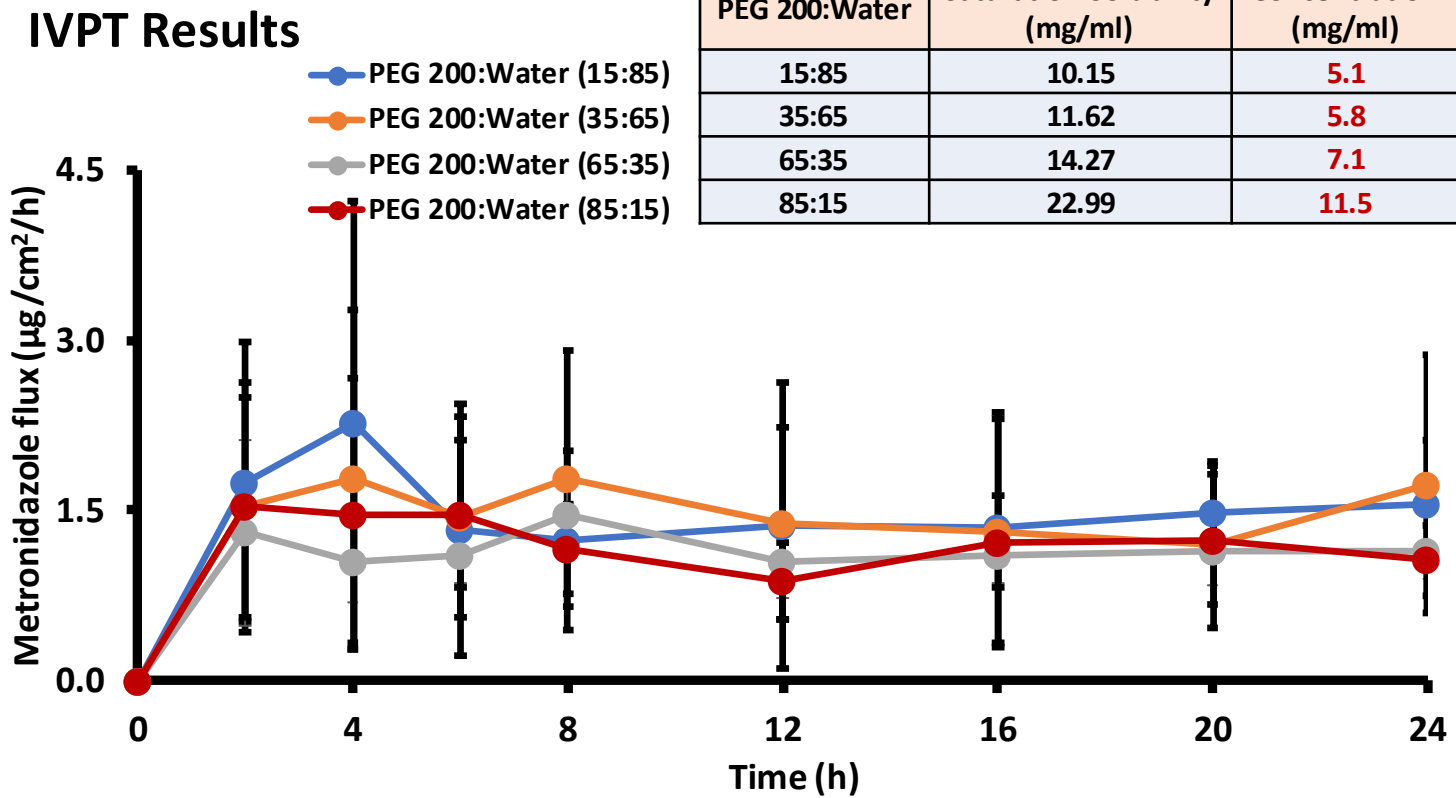
PEG 200:Water	Saturation Solubility (mg/ml)	Concentration (mg/ml)	α
15:85	10.15	7.5	0.74
35:65	11.62	7.5	0.65
65:35	14.27	7.5	0.53
85:15	22.99	7.5	0.33



Data provided courtesy of Dr. Narasimha Murthy associated with FDA funding for award U01FD0006507

Thermodynamics (Metronidazole)

PEG 200:Water	Saturation Solubility (mg/ml)	Concentration (mg/ml)	α
15:85	10.15	5.1	0.5
35:65	11.62	5.8	0.5
65:35	14.27	7.1	0.5
85:15	22.99	11.5	0.5



Data provided courtesy of Dr. Narasimha Murthy associated with FDA funding for award U01FD0006507

Topical Dermatological Formulations

- Clinical evidence has demonstrated the bioequivalence (BE) of several topical generics that are not necessarily Q1, Q2, or Q3 the same as the reference product
- An expanding body of evidence has demonstrated that these topical generics exhibit comparable cutaneous pharmacokinetics (PK) …not only comparable clinical efficacy

➲ ***When do Q1, Q2, or Q3 differences impact the BE of topical products, and what may be acceptable differences between a test and reference product formulation?***

Acknowledgements

U.S. Food & Drug Administration

- Priyanka Ghosh, PhD
- Tannaz Ramezanli, PharmD, PhD
- Megan Kelchen, PhD
- Bing Cai, PhD
- Pahala Simamora, PhD
- Richard Chang, PhD
- Markham C. Luke, MD, PhD
- Robert Lionberger, PhD

Research Collaborators

Funding for studies for which results were shown was made possible, in part, by U.S. FDA through:

GDUFA Award U01FD00**4946/5861**
- Frank Sinner, PhD

GDUFA Awards U01FD00**4947/4955**
- Audra Stinchcomb, PhD

GDUFA Award U01FD00**5223/6507**
- Narasimha Murthy, PhD

GDUFA Award U01FD00**5226**
- Michael Roberts, PhD


FDA
U.S. FOOD & DRUG
ADMINISTRATION