

# WHY DO WE CALL EXCIPIENTS IN TOPICAL PRODUCTS *INACTIVE* INGREDIENTS?

**FDA-USP Workshop on Standards for Pharmaceutical Products:**  
Critical Importance of Excipients in Product Development Why Excipients  
are Important Now and In the Future

**February 28<sup>th</sup>, 2017**

**Sam Raney, Ph.D.**

Scientific Lead for Topical and Transdermal Drug Products  
U.S. Food and Drug Administration, Office of Generic Drugs

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- I do not have any financial interest or conflict of interest with any pharmaceutical companies.

# The Roles of Topical Excipients

- Nominal functions of topical excipients
  - Penetration enhancers/modifiers
  - Emulsifiers/stabilizers
  - Viscosity modifiers
  - Gelling agents
  - Preservatives
  - Vehicle bases, Emollients
  - Colorants, Fragrances, Flavorants
  - pH adjusters
  - Solvents
  - Etc.

# Active vs. Inactive Ingredients

- An Active Ingredient (*per 21 CFR 210.3(b)(7)*)
  - Any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.
- An Inactive Ingredient (*per 21 CFR 210.3(b)(8)*)
  - Any component of a drug product other than the active ingredient



# Active vs. Inactive Ingredients

- An Active Ingredient
  - Directly responsible for therapeutic effect, frequently via activity in a molecular mechanism associated with the disease state.
- An Inactive Ingredient
  - Theoretically inert with respect to the disease state
  - Facilitates the formulation of the active ingredient in a dosage form appropriate for dose administration

# Active vs. Inactive Ingredients

- Do topical excipients act on the disease state?
  - Inactive ingredients in a placebo vehicle may account for 40% of the therapeutic effect; the active ingredient may only account for an additional 20% of therapeutic effect.
  - Inactive ingredients may modulate the delivery/bioavailability of the active ingredient, which then acts on the disease state. This is the most widely characterized.
  - Do changes in the quality of topical excipients impact therapeutic effect, either way?

- USP 39 – NF 34 Monograph

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## **Hydrocortisone Ointment**

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### **DEFINITION**

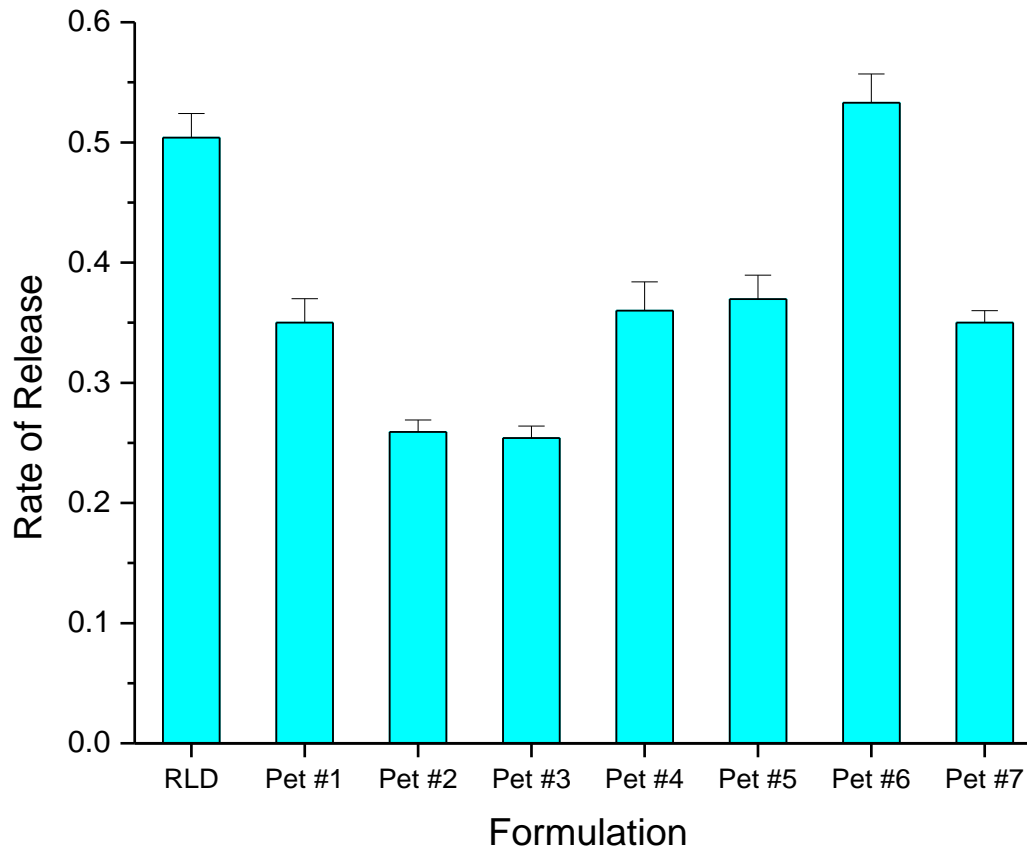
Hydrocortisone Ointment is Hydrocortisone in a suitable ointment base. It contains NLT 90.0% and NMT 110.0% of the labeled amount of hydrocortisone ( $C_{21}H_{30}O_5$ ).

- What is a suitable ointment base?
  - Would a PEG ointment base be suitable?
  - Is it suitable as long as it is Petrolatum, USP?

# Effects of Excipient Quality



- IVRT results of a drug product formulated with Petrolatum, USP from seven different sources

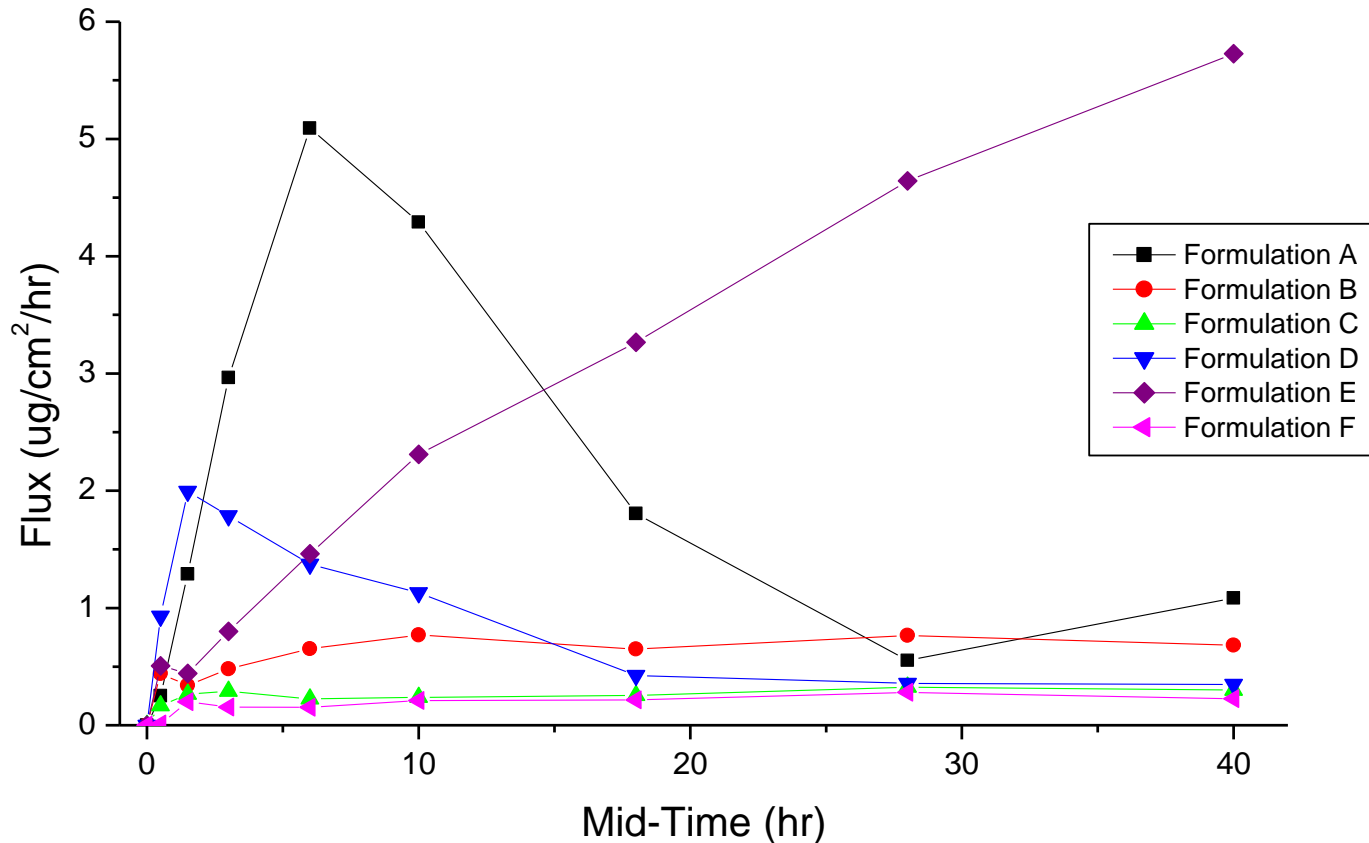




# Effects of Excipient Composition



- IVPT results of a drug product formulated with different excipients (inactive ingredients)



# Effects of Excipients on Bioavailability

- It is widely understood that the formulation of a topical semisolid dosage form matters greatly
- It is now increasingly clear how excipients 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

# Effects of Excipients on Bioavailability



- Excipient quality and composition can affect:
  - The phase states and the arrangement of matter
  - Drug diffusion within the dosage form
  - Drug partitioning from the dosage form into the SC
  - Alteration of skin structure and chemistry
  - Drug diffusion within the skin itself
  - Drug delivery & bioavailability at the target site
  - Skin (de)hydration, irritation or damage
  - Metamorphosis of the dosage form on the skin

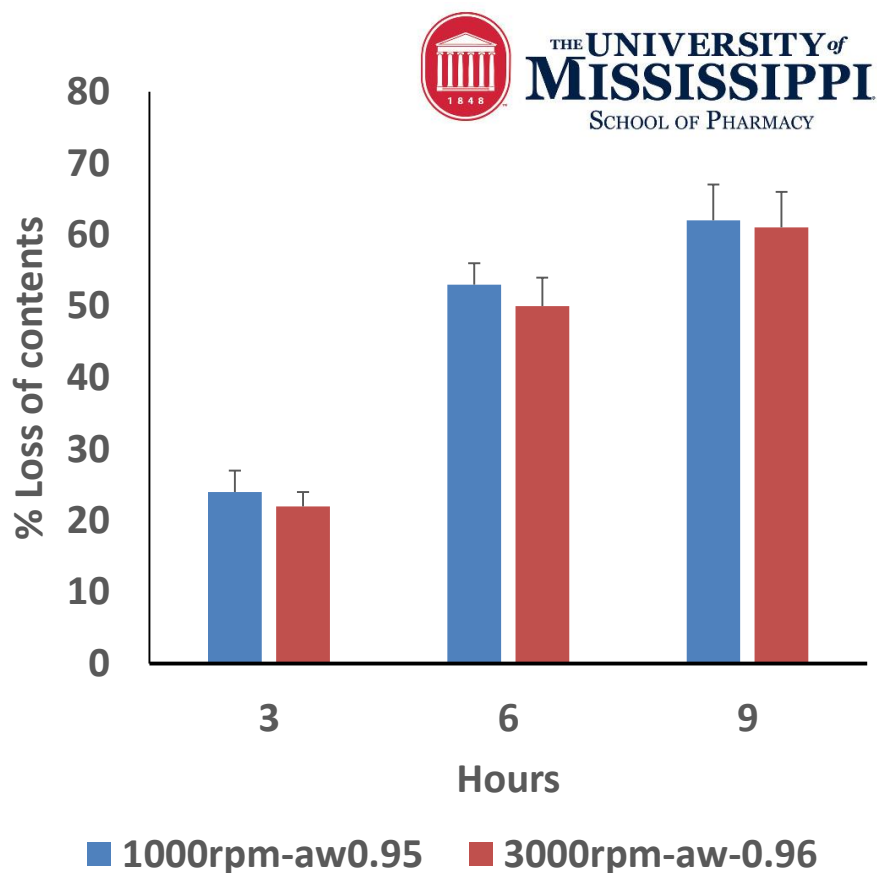
# Dosage Form Metamorphosis



- Solvent Activity of Q1/Q2 Identical Creams

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| Ingredients              | Quantity (%w/w)            |
|--------------------------|----------------------------|
| Drug                     | 1                          |
| Cetostearyl alcohol      | 7                          |
| Cremophor A6             | 1.5                        |
| Cremophor A25            | 1.5                        |
| Mineral Oil              | 12                         |
| Propylene Glycol         | 8                          |
| Water                    | 69                         |
| <b>Total</b>             | <b>100</b>                 |
| Manufacturing Conditions | Solvent Activity ( $a_w$ ) |
| 1000 RPM (20 min)        | 0.950 ± 0.004              |
| 3000 RPM (20 min)        | 0.961 ± 0.006              |



# Dosage Form Metamorphosis

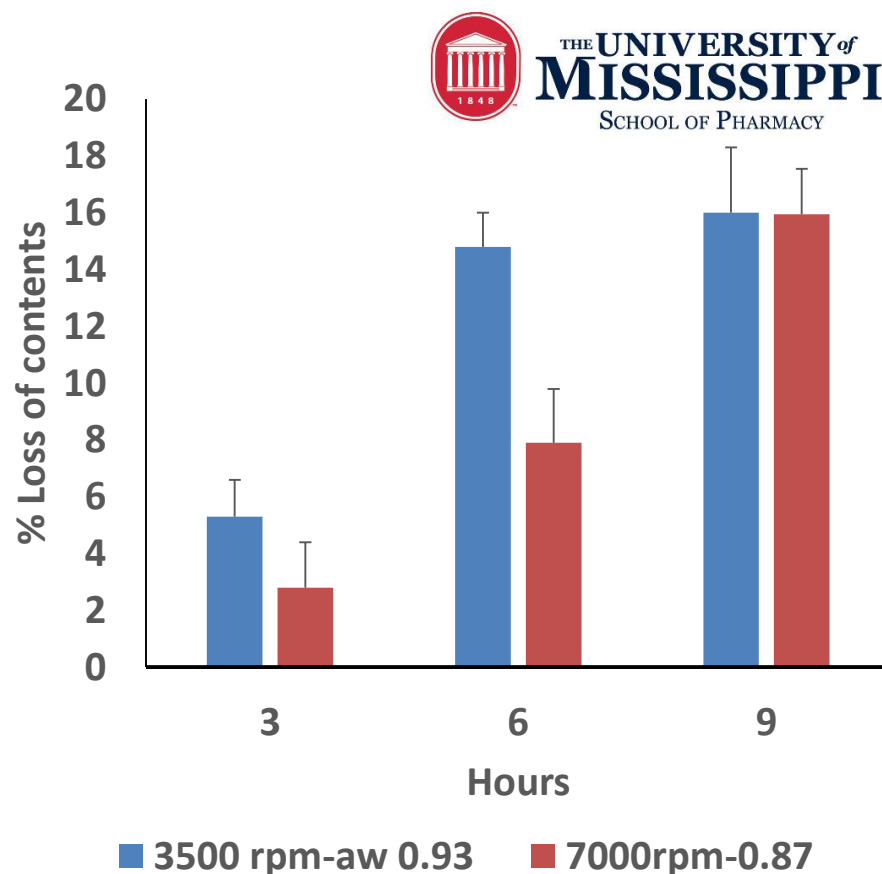


- Solvent Activity of Q1/Q2 Identical Creams

**Prof. Narasimha Murthy** FDA Award U01-FD005223

| 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              |



# Dosage Form Metamorphosis

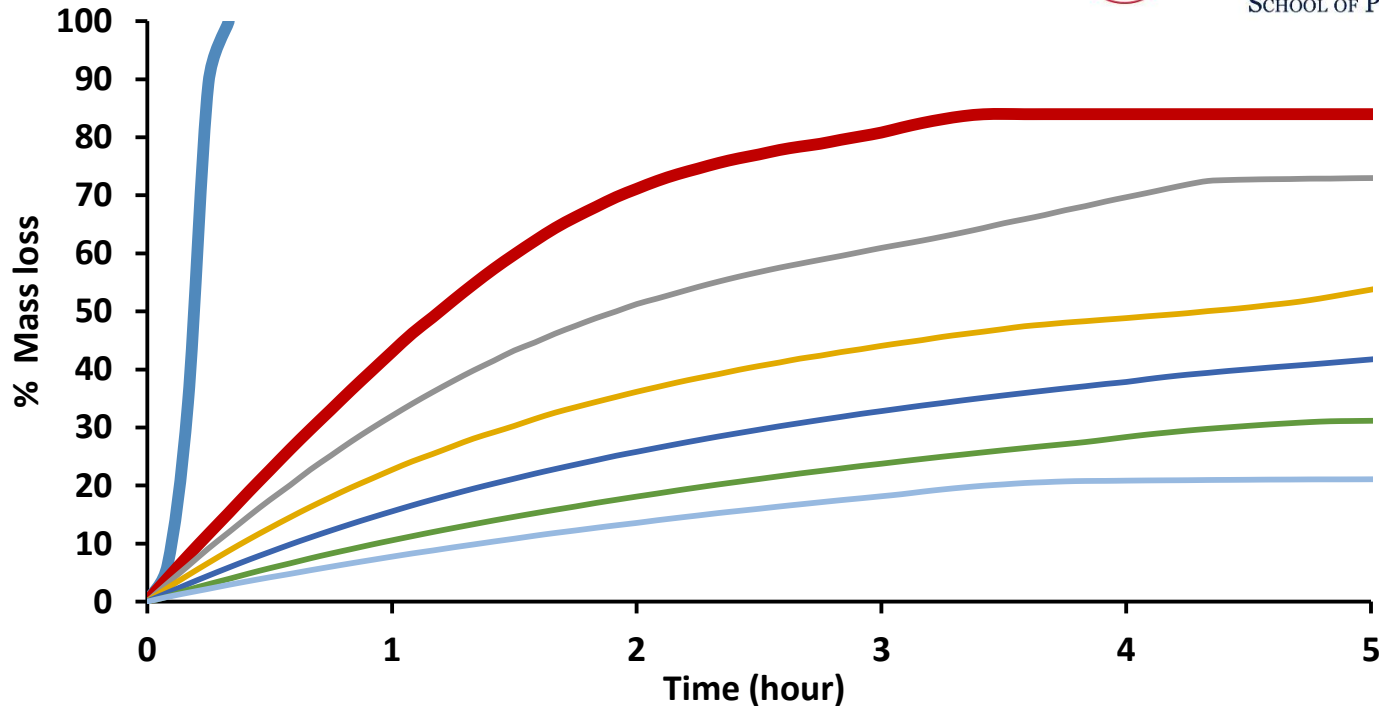
- Solvent Activity ( $a_s$ ) =  $\rho/\rho_0$

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- $\rho$  = partial vapor pressure of Solvents in the product
- $\rho_0$  = vapor pressure of pure Solvent system



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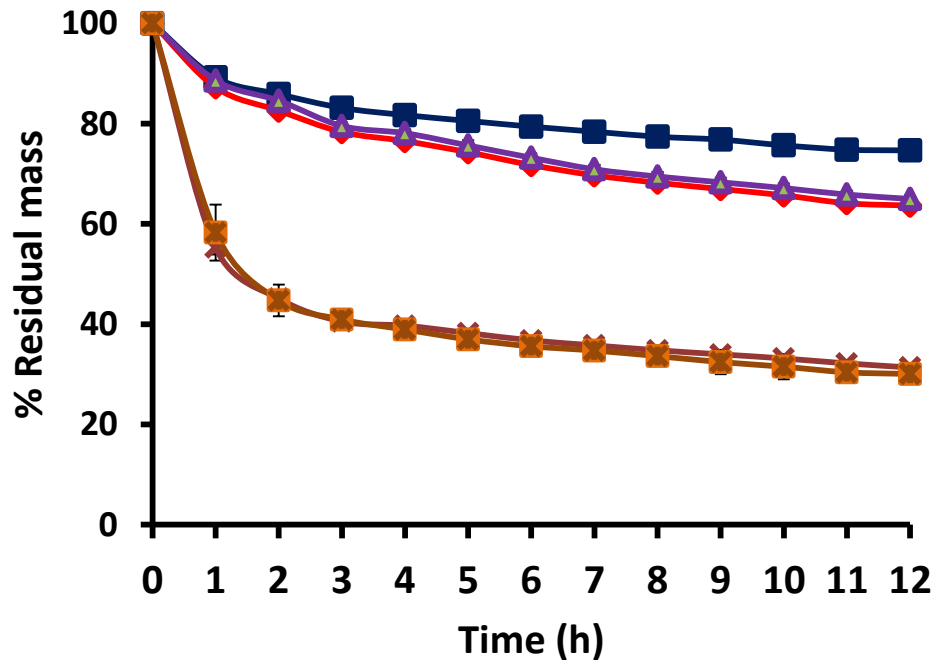


aw-0.98 aw-0.87 aw-0.78 aw-0.58 aw-0.42 aw-0.31 aw-0.22

# Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

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| Product       | Solvent Activity ( $a_w$ ) |
|---------------|----------------------------|
| Zovirax (US)  | $0.753 \pm 0.002$          |
| Zovirax (AUT) | $0.735 \pm 0.000$          |
| Zovirax (UK)  | $0.732 \pm 0.002$          |
| Aciclovir 1A  | $0.948 \pm 0.001$          |
| Aciclostad    | $0.948 \pm 0.003$          |

■ Zovirax (US)     ◆ Zovirax (AUT)     ▲ Zovirax (UK)  
✕ Aciclovir-1A     ■ Aciclostad

# Excipients Affect Product Quality



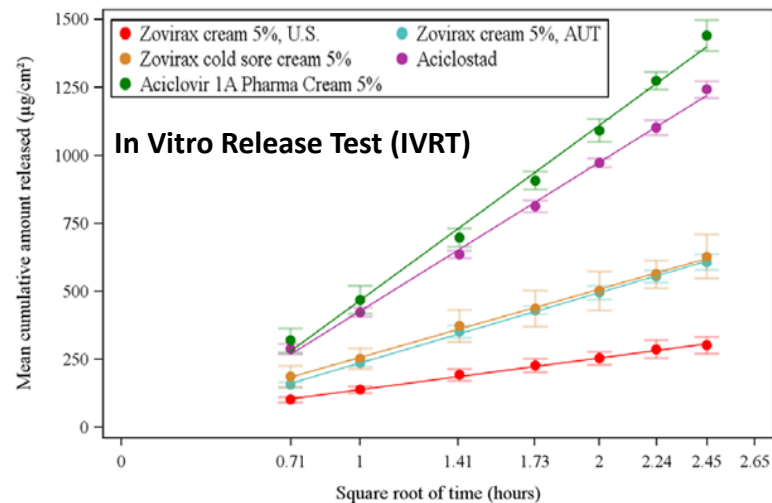
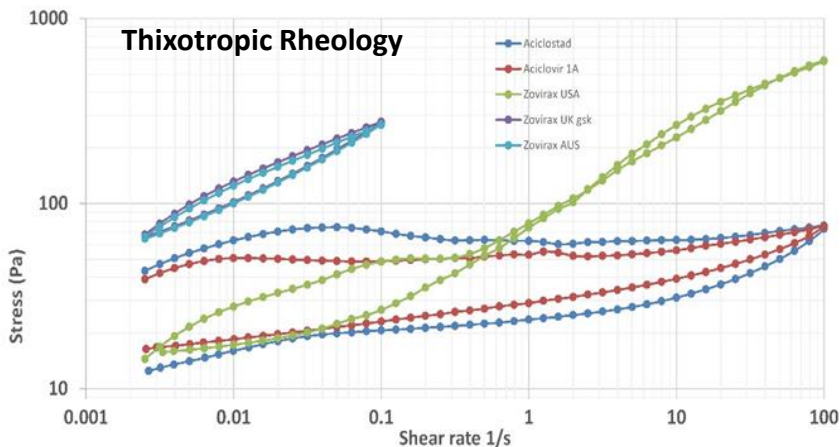
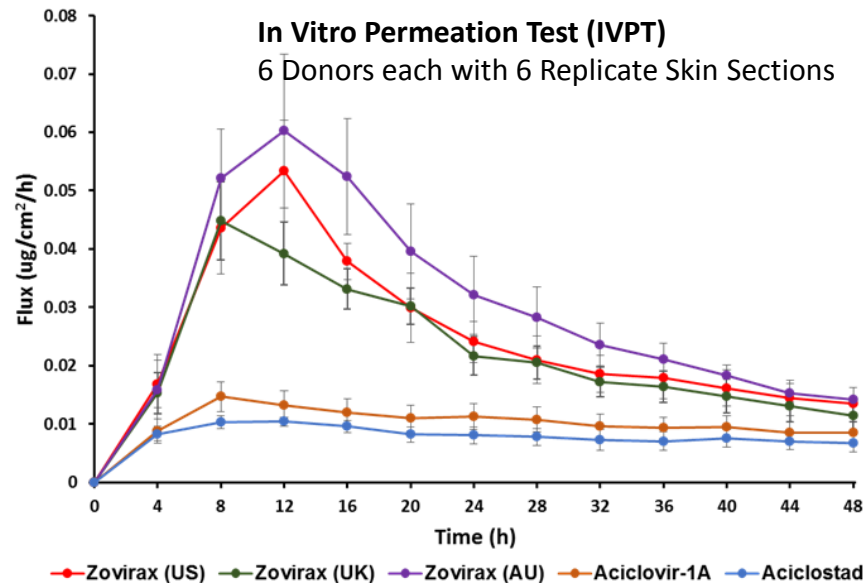
- 5 Pharmaceutically Equivalent Acyclovir Creams

| 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 |



# Excipients Affect Product Quality

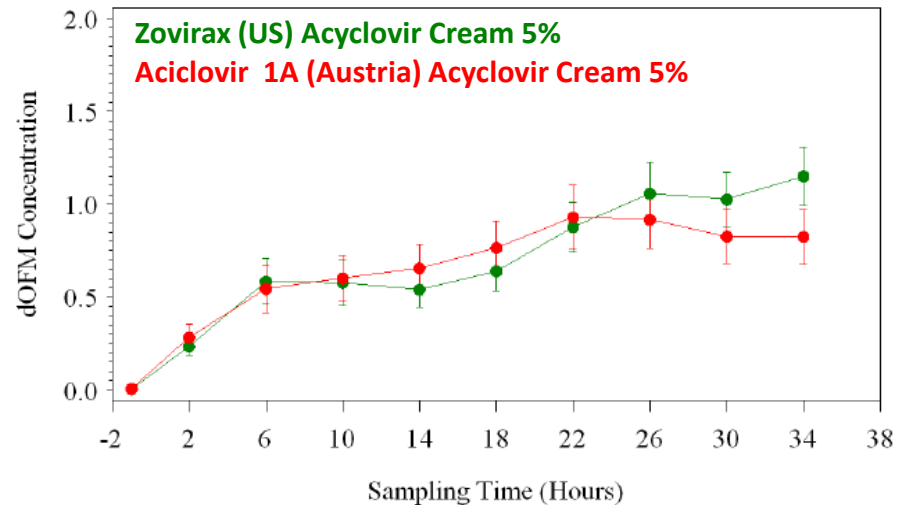
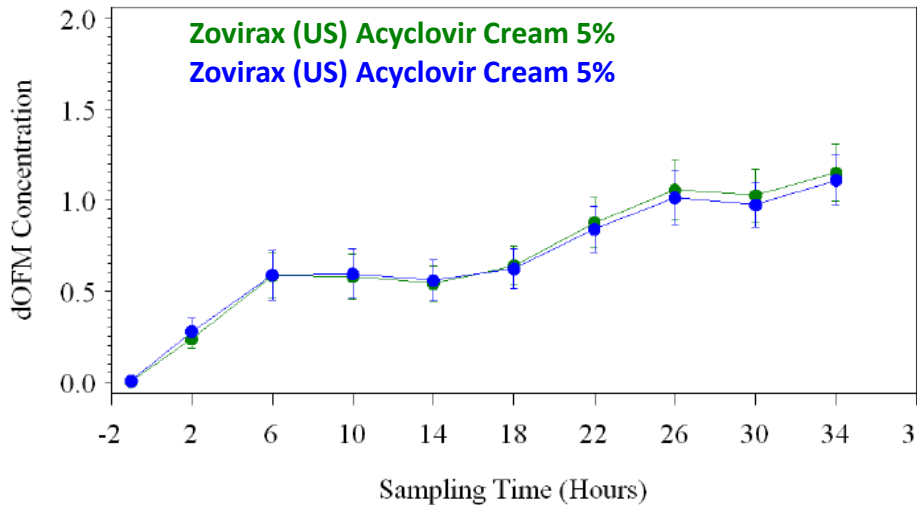
|                          | Zovirax (USA)       | Zovirax (UK)             | Zovirax (Austria)      | Aciclovir (Austria)      | Aciclovir-1A (Austria)   |
|--------------------------|---------------------|--------------------------|------------------------|--------------------------|--------------------------|
| Water                    | Water               | Purified water           | Water                  | Water                    | Water                    |
| Propylene glycol         | Propylene glycol    | Propylene glycol         | Propylene glycol       | Propylene glycol         | Propylene glycol         |
| Mineral oil              | Liquid Paraffin     | Liquid Paraffin          | Liquid Paraffin        | Viscous Paraffin         | Viscous Paraffin         |
| White petrolatum         | White soft paraffin | White Vaseline           | White Vaseline         | White Vaseline           | White Vaseline           |
| Cetostearyl alcohol      | Cetostearyl alcohol | Cetostearyl alcohol      | Cetyl alcohol          | Cetyl alcohol            | Cetyl alcohol            |
| SLS                      | SLS                 | SLS                      |                        |                          |                          |
| Poloxamer 407            | Poloxamer 407       | Poloxamer 407            |                        |                          |                          |
|                          | Dimethicone 20      | Dimethicone 20           | Dimethicone            | Dimethicone              | Dimethicone              |
|                          | Arlacel 165         | Glyceryl Mono Stearate   | Glyceryl Mono Stearate | Glyceryl Mono Stearate   | Glyceryl Mono Stearate   |
|                          | Arlacel 165         | Polyoxyethylene stearate | Macrogol stearate      | Polyoxyethylene 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              |
| Crystalline 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                     |



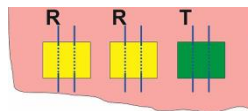
# Excipients Affect In Vivo BA/BE



- Dermal Pharmacokinetics by dOFM (20 subjects)



| Outcome variable           | CI <sub>90%</sub>                            |
|----------------------------|--|
| log(AUC <sub>0-36h</sub> ) | [-0.148 ; 0.162]<br>or<br>[86.2 % ; 117.5 %] |
| log(C <sub>max</sub> )     | [-0.155 ; 0.190]<br>or<br>[85.7 % ; 120.9%]  |



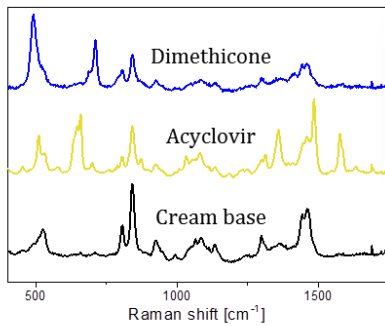
| Outcome variable           | CI <sub>90%</sub>                            |
|----------------------------|--|
| log(AUC <sub>0-36h</sub> ) | [-0.369 ; 0.050]<br>or<br>[69.1 % ; 105.2 %] |
| log(C <sub>max</sub> )     | [-0.498 ; 0.022]<br>or<br>[60.8 % ; 102.2%]  |

# Influence of Dispensing Stress on Q3

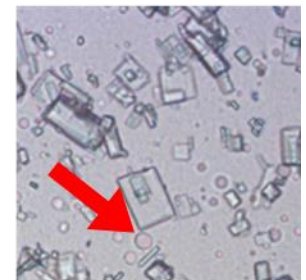
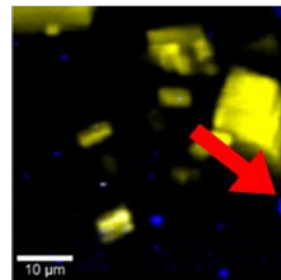
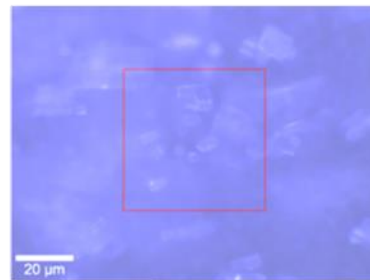
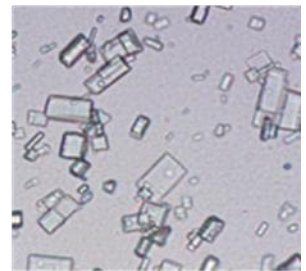
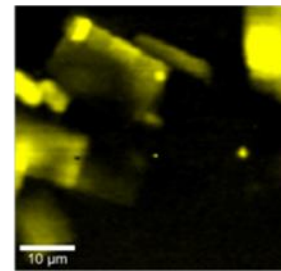
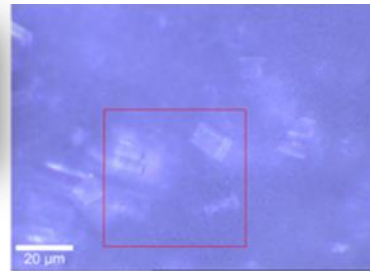


- Influence of Dose Dispensing on Product Quality

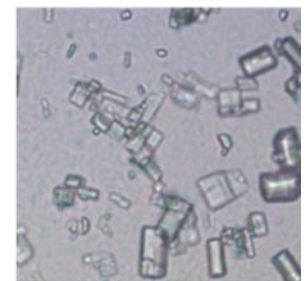
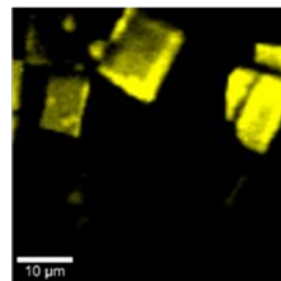
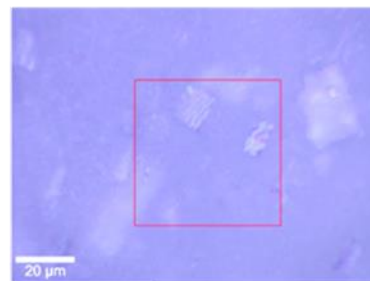
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Zovirax<sup>®</sup> UK  
**Tube**



Zovirax<sup>®</sup> UK  
**Pump**



Zovirax<sup>®</sup> UK  
**Pump**  
(from inside container)



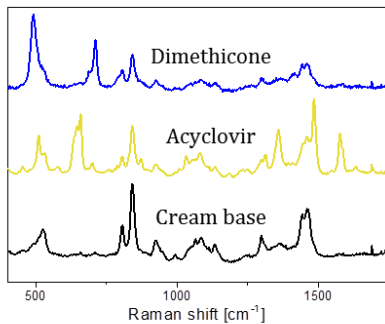
# Influence of Dispensing Stress on Q3



- Influence of Dose Dispensing on Product Quality

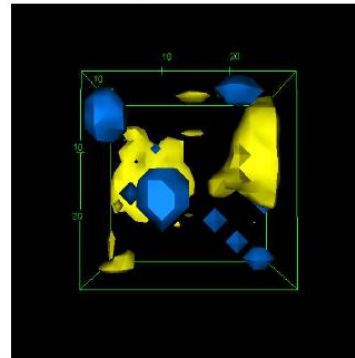
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## Comparison Zovirax UK pump and tube

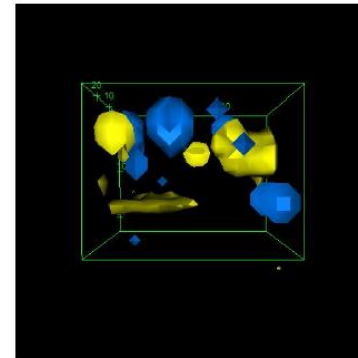


**pump**

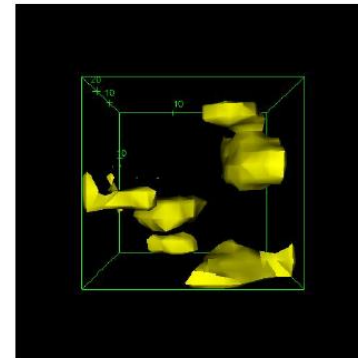
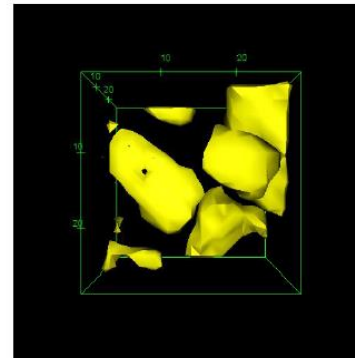
**top view**



**side view**



**tube**



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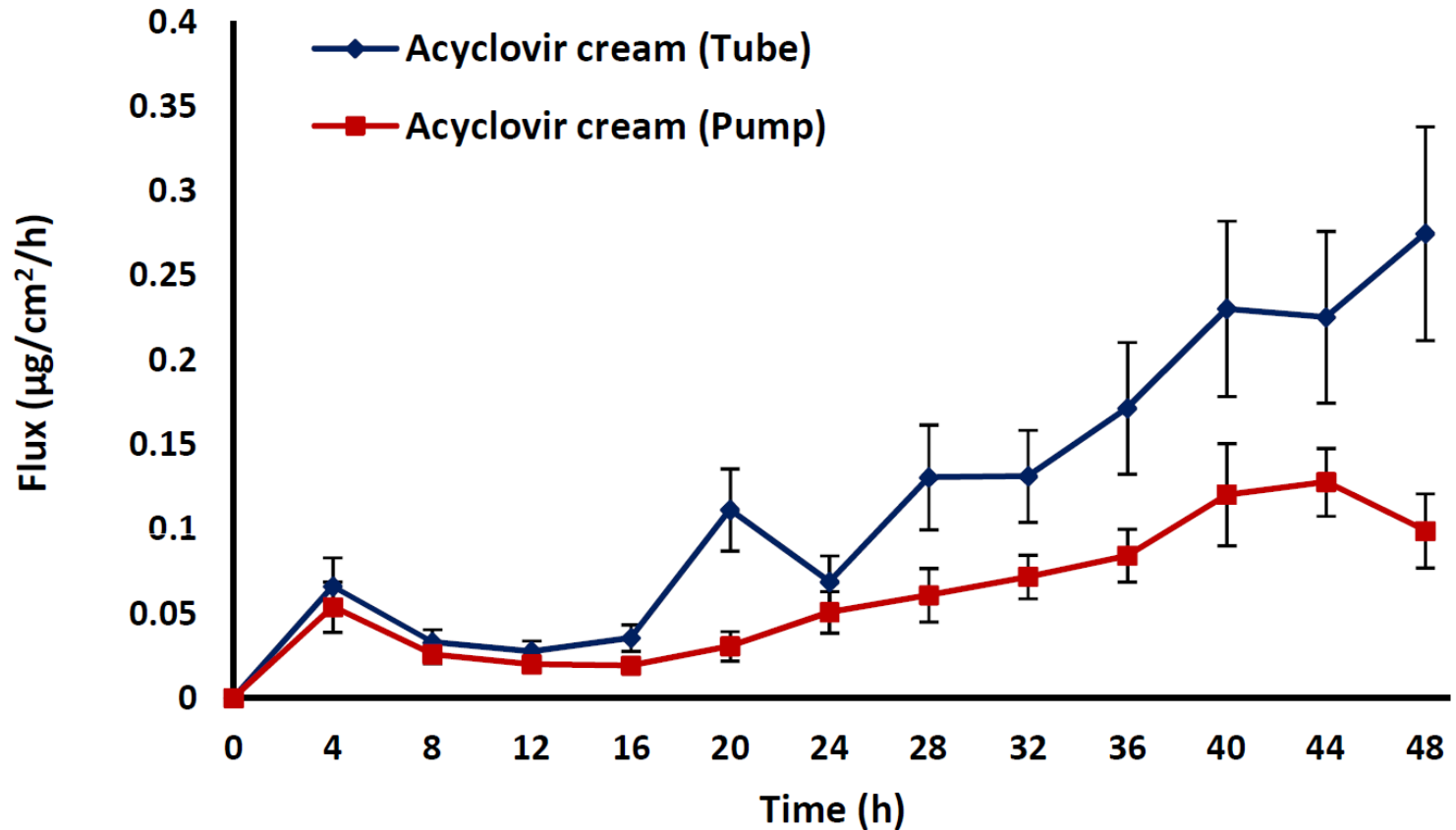
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# Influence of Dispensing Stress on Q3



- Influence of Dose Dispensing on Product Quality

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- Excipient-Related Effects on the Drug Product
  - How critical is the composition of inactive ingredients?
  - How critical is the grade of each inactive ingredient?
  - How consistent is the quality of each inactive ingredient?
  - How critical is the sequence of mixing?
  - How critical are mixing rates and durations?
  - How critical are temperatures and rates of change?
  - How critical are the orifice diameters, tube lengths? pressures, etc. during transfer, holding, packaging?
  - How critical is the inertness of the container closure system (e.g. are there adsorption/absorption issues)?
  - How critical are the product dispensing stresses/forces?

- **Excipient-Related Effects on the Patient**
  - Consider product quality attributes that relate to
    - Storage, dispensing and re-dispensing
    - Dose application, maintenance and removal
    - Patient perceptions of quality and acceptability
  - Consider how the product quality changes during dose application and during subsequent metamorphosis
  - Consider how the vehicle impacts the skin (hydrating or dehydrating effects, irritancy, burning sensation)
  - Consider how product quality attributes at the limits of stability specifications impact these factors
  - Consider how the control of excipient quality may impact patient perceptions and actual therapeutic performance



# Acknowledgements



## U.S. Food & Drug Administration

- Robert Lionberger, PhD
- Markham Luke, MD, PhD
- Yi Zhang, PhD
- Priyanka Ghosh, PhD

## Scientific Colleagues

- Paul Lehman, MSc
- Thomas Franz, MD

## Research Collaborators

Funding for research projects was made possible, in part, by the FDA through:

**GDUFA Award U01FD005223**

- Narasimha Murthy, PhD

**GDUFA Award U01FD005226**

- Michael Roberts, PhD

**GDUFA Award U01FD004946**

- Frank Sinner, PhD



