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IVRT as a Tool for BA/BE Waiver

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Co-Founder Emeritus
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CRO Perspective for IVRT

Release Test to support development of new as well as generic dosage forms

Release Test to characterize clinical formulation/assess manufacturing and storage variables

Validated Release Test to compare new and old formulations post marketing per SUPAC-SS

Validated Release Test as part of in vitro option for BA/BE Waiver for products where guidance exists

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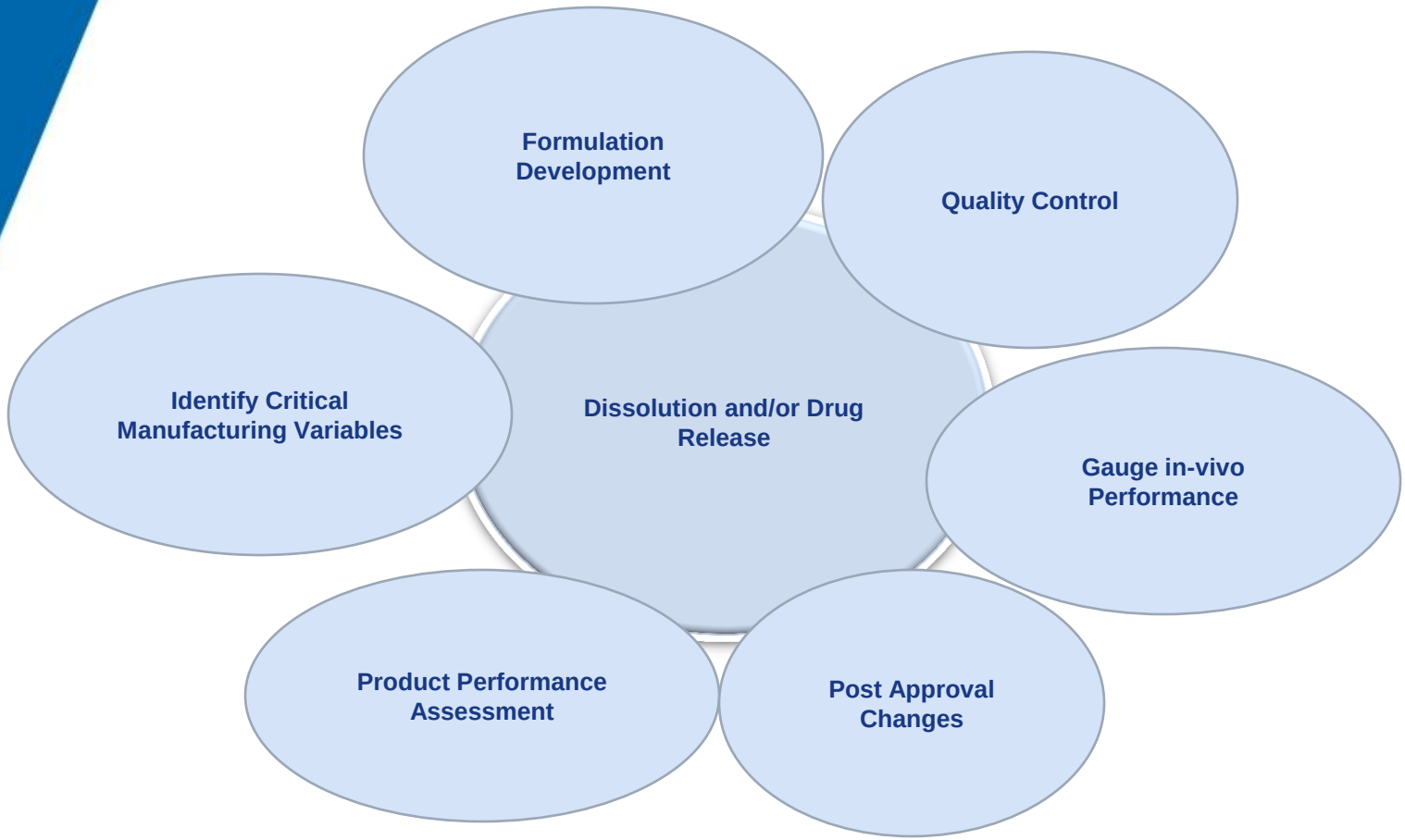

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Regulatory Definitions bioavailability and bioequivalence according to 21CFR 320.1

- Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drugs that are not intended to be absorbed into the blood stream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

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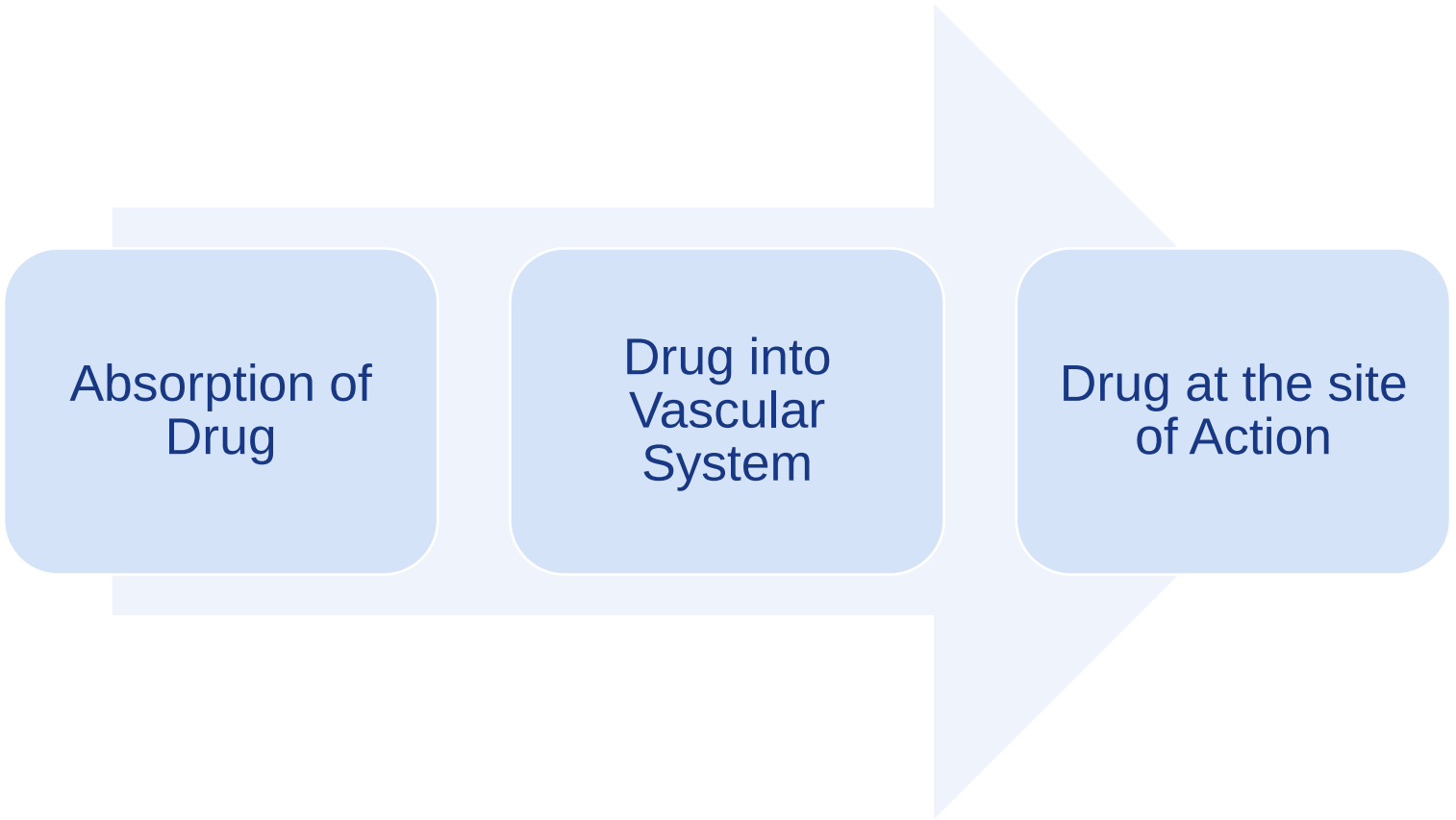
Regulatory Definitions bioavailability and bioequivalence according to 21CFR 320.1

- Bioequivalence means the absence of significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutically equivalent or pharmaceutically alternative becomes available at the site of action when administered at the same molar dose under similar conditions in an appropriately designed study.

For Systemically Active Drugs



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For Locally Acting Drugs: Topicals

Site of Drug Absorption

Drug at the site of action

Drug in Vascular System??

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Strategies to Establish Bioequivalence for Topical Products

1. Clinical Endpoint BA/BE Studies
   - Patient response measured – Test vs reference vs placebo
   - Highly variable, not sufficiently conclusive
   - Least accurate but most commonly used for topicals today
2. Pharmacodynamic Studies
   - Used mostly for Corticosteroids
3. Systemic PK Studies
   - Limited application mainly to ensure safe systemic exposure of active
4. In Vitro Studies/Combination Studies
   - Getting more popularity with several guidance documents published
   - Applicable on case by case basis and must be properly justified

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Regulatory Rationale and Justification to allowing In Vitro Biowaiver

- For some of the complex topicals, the cost of developing a generic dosage form is very high, precluding small players from developing generics
- BE clinical trials are often either not sensitive enough and/or highly variable to differentiate between different formulations, and are not conclusive to allow generics to demonstrate equivalence.
- BE trials are sometimes bigger than the original clinical trials requiring lot of testing that can be avoided

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For any generic to substitute a brand product, it must have several levels of similarities between the two.

- Pharmaceutical equivalence
  - Where the active ingredients, strength, route and dosage form are the same as the marketed product
- Bioequivalence
  - Where the rate and extent of the active at the site of action are the same
- Therapeutic equivalence
  - Generic dosage form must demonstrate both pharmaceutical and bioequivalence when compared to the marketed product while relying on the marketed product for safety and efficacy

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Q1/Q2/Q3 Concept

- Q1 - Specific components of a dosage form
- Q2 - Specific Ratios of the components in a dosage form
- Q3 - Specific arrangement of components in a dosage form that impact the physico-chemical properties of a dosage form. Also the micro structure of the dosage form can completely determine the success of the dosage form for it's therapeutic equivalence to the RLD.

- Q1/Q2 similarity between RLD and generic dosage form does not guarantee Q3 similarity. Differences in microstructure, Q3, can impact the performance of a product.

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IVRT used for Biowaiver

- Allows generic manufacturers to use IVRT as a bioequivalence tool to compare their formulations with RLD.
- Allows de-risking of clinical trials. By selecting a formulation with the comparable release rate, the outcome of BE clinical study is more accurately predictable.
- Provides strategic advantage and scientific basis for a better generic dosage form.
- Properly developed IVRT method can aid in demonstrating the similarities in microstructure of the dosage form.
  - While Q1/Q2 criteria can be met by formulation development and/or deformulation, i.e. same excipients in the same ratio as the RLD, attaining Q3 criteria requires understanding of microstructure of the dosage form.

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Several Draft Guidance documents have been published on topical products with different complexities.

For simpler, solution based topicals, the comparison of physico-chemical properties between the generic and brand product allow development of appropriately safe products.

- Examples are:
  - Draft Guidance on Ciclopirox Topical Solution
    - Polymeric resin imparts important characteristics that have significant effect on the efficacy of the product. It is important to have resin with similar properties in a generic product.
  - Draft Guidance on Erythromycin Swab
    - Performance of the generic product must show similarity to the marketed product.

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For Complex topicals, Product Specific Guidelines are provided:

- Draft Guidance on Mesalamine Rectal Suppository
  - Sponsors are required to demonstrate same physico-chemical characteristics of their generic dosage form as the RLD, including but not limited to viscosity, density, melting point and DSC.
  - Additionally, in vivo BE study is also required

- Draft Guidance on Acyclovir Ointment
  - Sponsors are required to demonstrate that Generic formulation (test) meets Q1/Q2 criteria (the generic and RLD formulations are Qualitatively and Quantitatively the same
  - The test and RLD formulation must have same physicochemical characteristics
  - Test and RLD show the same rate of release when using an appropriately validated IVRT method

- **Active ingredient:** Acyclovir
- **Form/Route:** Ointment; Topical

- **Recommended study: 2 Options: *In Vitro* or *In Vivo* Study**
- **I. In Vitro option:**
- To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which
- “any other approach deemed adequate by FDA to measure bioavailability or establish
- bioequivalence” may be acceptable for determining the bioavailability or bioequivalence (BE) of a
- drug product, all of the following criteria must be met:
  - i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively
  - the same (Q1/Q2).
  - ii. Acceptable comparative physicochemical characterization of the test and RLD formulations.
  - iii. Acceptable comparative in vitro drug release rate tests of acyclovir from the test and RLD

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- Not all Q1/Q2 formulations have same microstructure.
- Several single phase ointment products, all Q1/Q2 needed to have IVRT method developed to qualify for BA/BE waiver.
- Examples of differences in IVRT parameters to satisfy requirements of IVRT method are described next.
- All products showed equivalent release rate when compared to RLD

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Parameters	Product 1	Product 2	Product 3	Product 4	Product 5
Receiving Medium	0.1 N HCl	pH 7 Phosphate Buffer	70:30 1N HCL: IPA	80:20 1N HCL:IPA	75:25 1N HCl:IPA
Membrane	Supor-450 Pall	PVDF Sterlitech	PVDF Sterlitech	Tuffryn	Strelitech Nylon
Nominal Cell Volume	8 ml	12 ml	8 ml	8 ml	8 ml
Surface area of Exposure	0.999 cm^2	1.767 cm^2	1.00 cm^2	1.00 cm^2	1.00 cm^2
Method of Dosing	Syringe Application	By spreading on membrane	Syringe Application	Syringe Application	Syringe Application
Amount Dosed	1 G	400 mg	1.5 G	1.5 G	1.5 G

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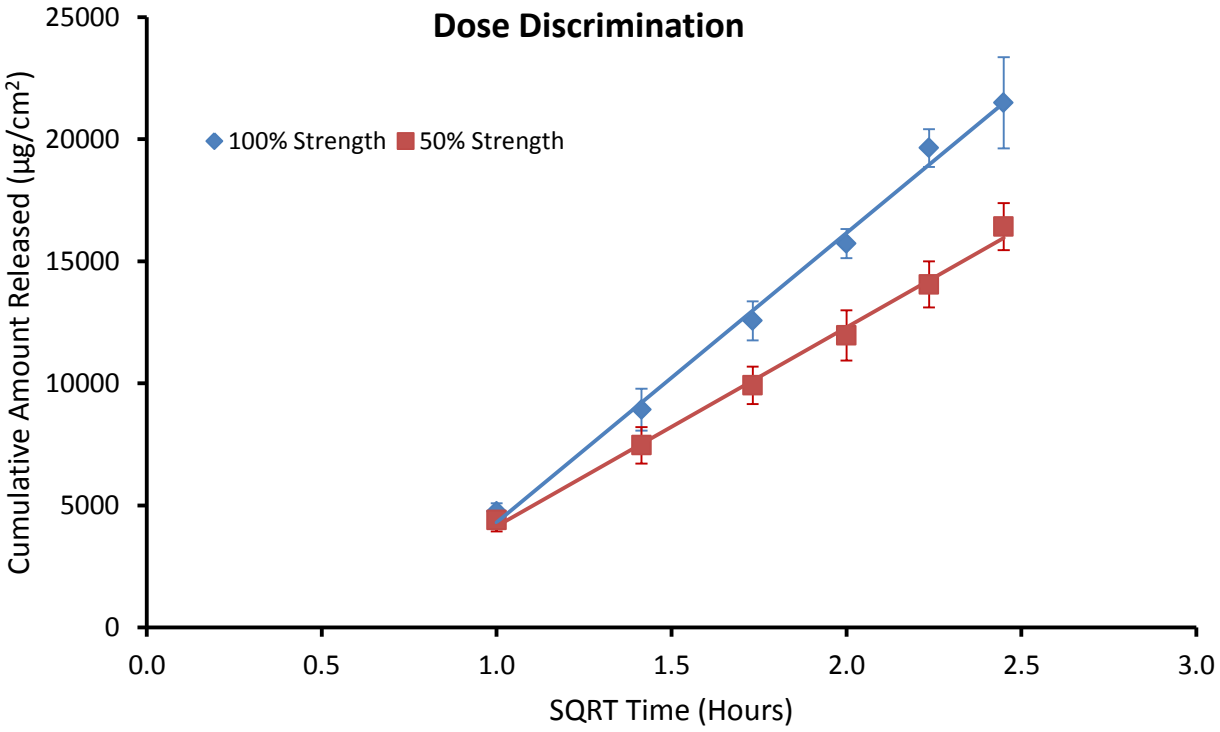
Ointment #1 Dose Discrimination



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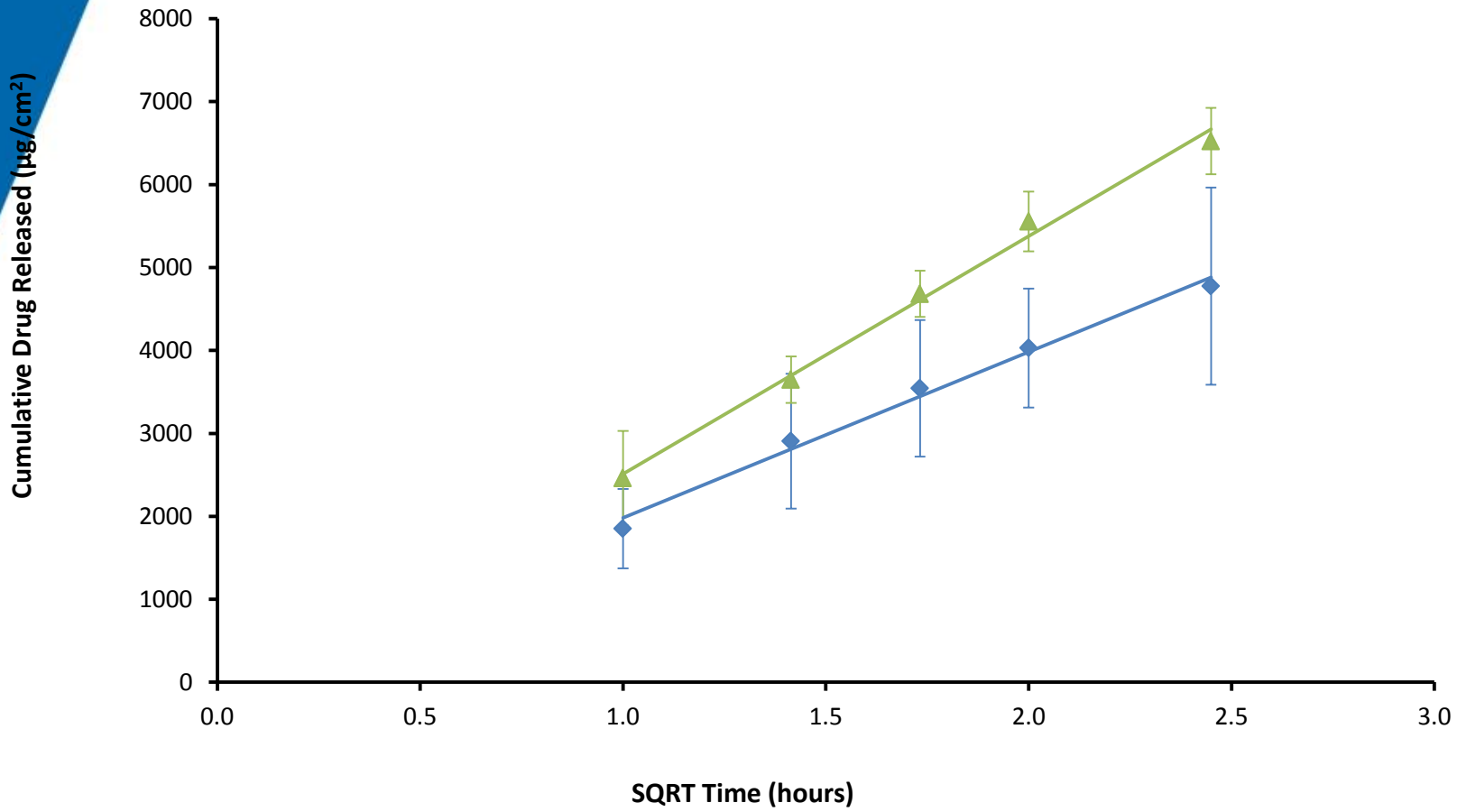
Ointment #2 Dose Discrimination



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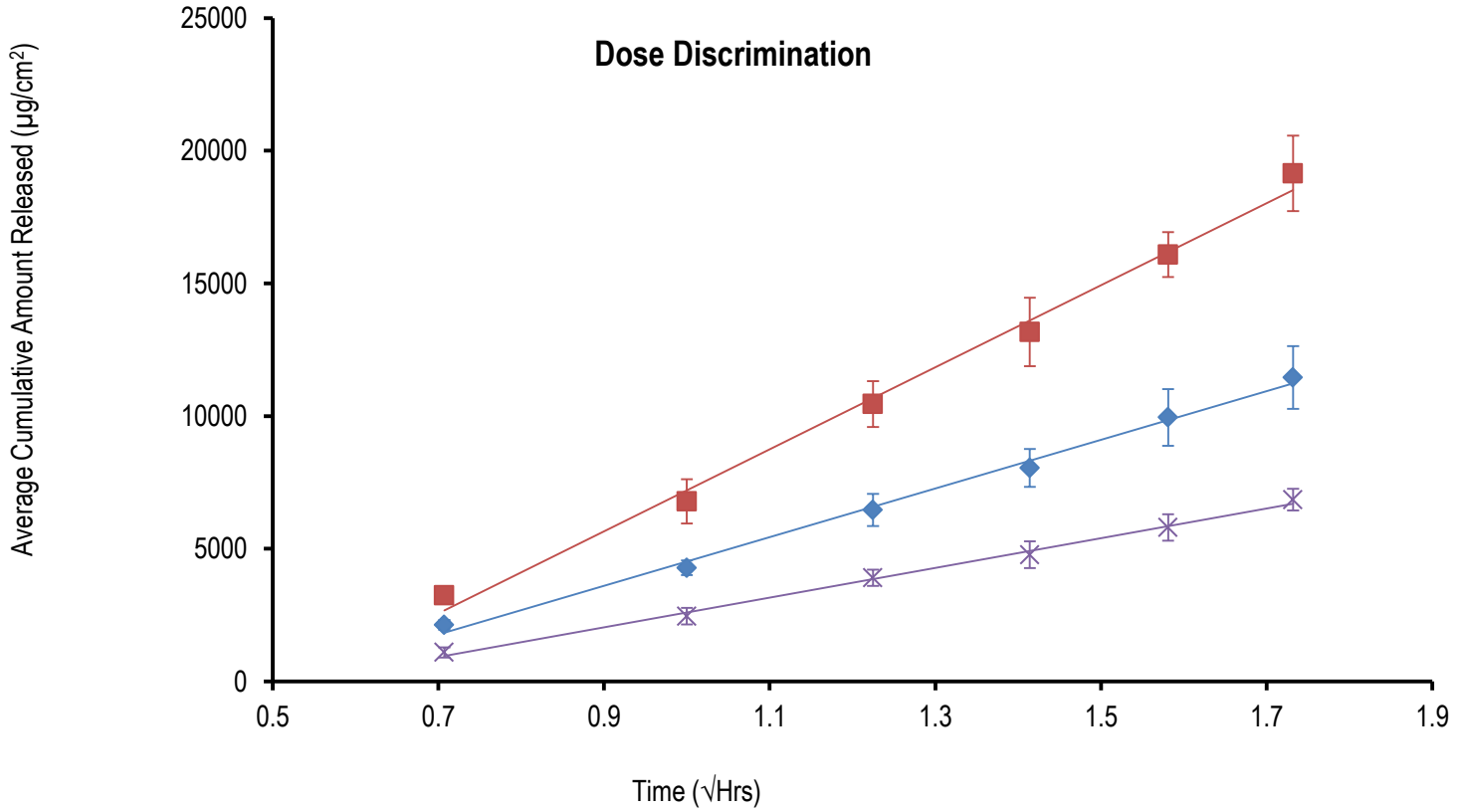
Ointment #3



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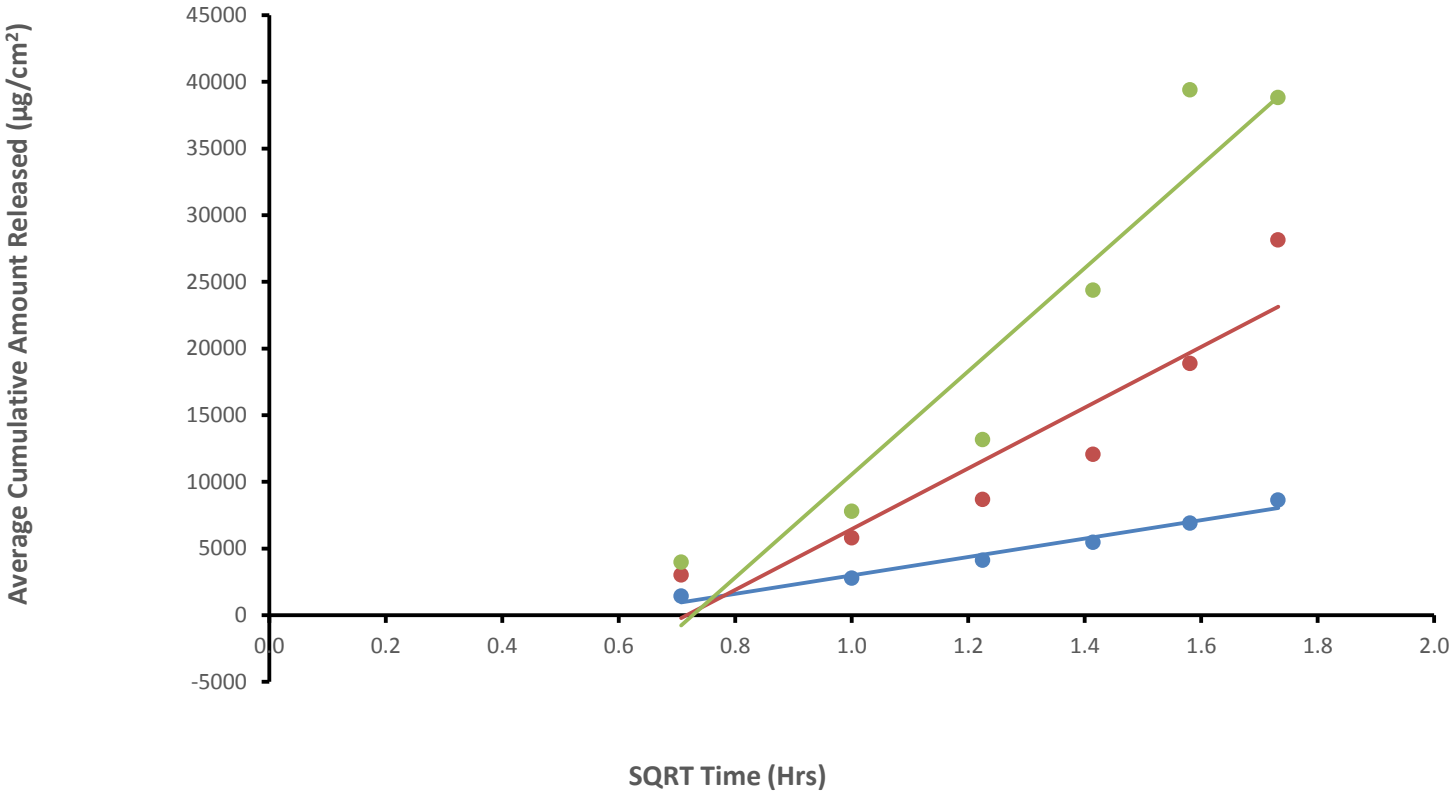
Ointment Product # 4



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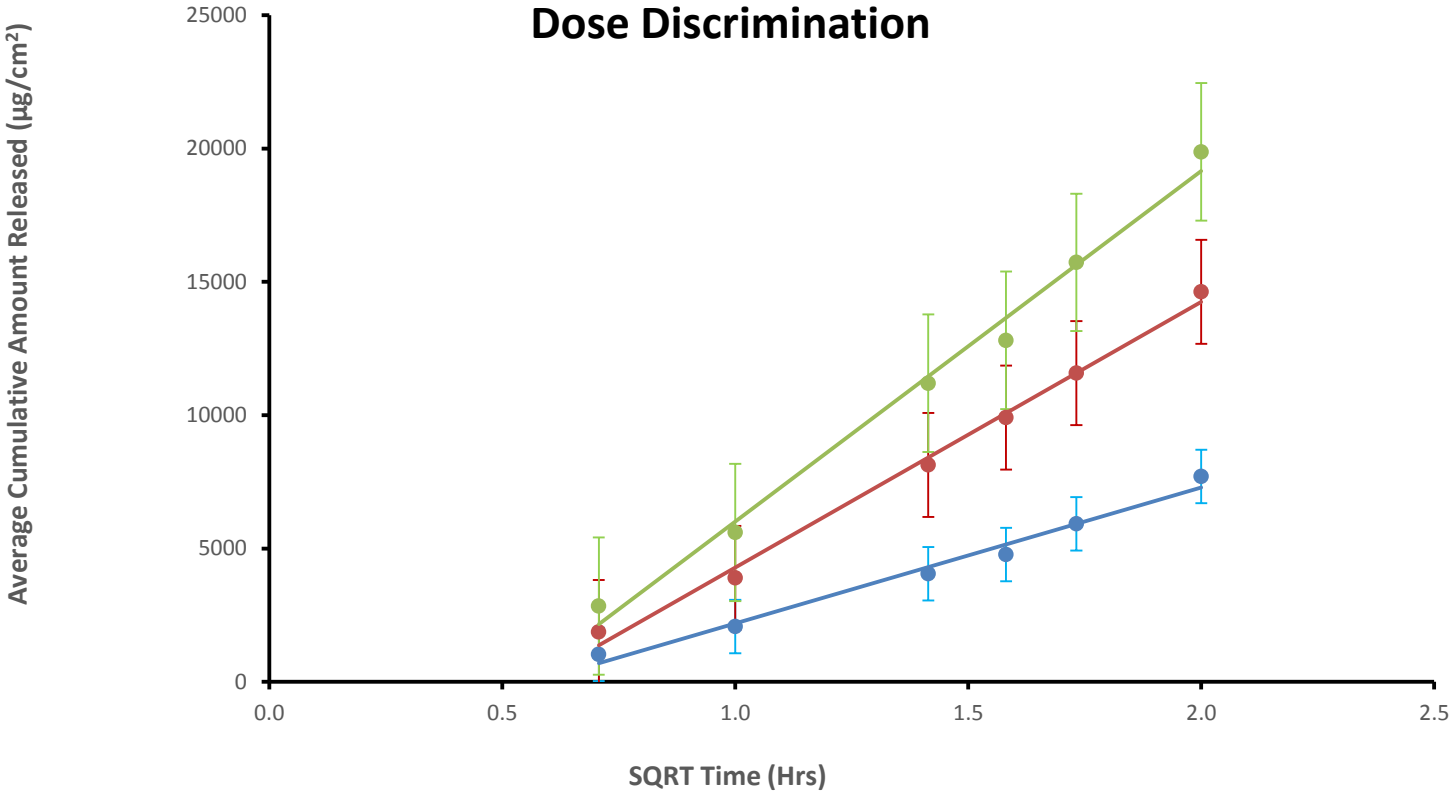
Ointment product #5



Examples of properties that can affect micro structure and therefore equivalence:

1. pH of a dosage form
2. Polymorphic form of the active ingredient
3. Particle size and its distribution of the active ingredient and structure forming excipient
4. Rheological properties of the formulation
5. Release characteristics of the formulation
6. The interaction of formulation and skin upon application and the effect of mode of application of the dosage form

- Some examples of differences in release and/or permeation rates with differences in some of the physical properties listed earlier.
- **The work presented in next eight slides was carried out by Dr. Murthy of University of Mississippi (Murthygroup@gmail.com 662-202-4929) and was funded by a grant from US FDA** Grant # 1U01FD005223-01

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Effect of stirring rate/cooling times on the globule size and flux of an O/W Cream

O/W Cream prepared with Cetostearyl alcohol, Cremophor A6 and A25, mineral oil, propylene glycol and water. The API concentration was 1%.

Acknowledgment: Work carried out by Dr. Murthy, funded by a grant from US FDA Grant # 1U01FD005223-01

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Formulation	Variable	Globule Size(um)
F1	500 rpm-20 minutes	11.37 ± 7.03
F2	1000 rpm 20 minutes	7.41 ± 2.19
F3	3000 rpm 20 minutes	2.98 ± 1.25
F4	5000 rpm 20 minutes	1.71 ± 0.41
F5	3000 rpm 10 minutes	4.30 ± 1.33
F6	3000 rpm 40 minutes	4.36 ± 0.88
F7	3000 rpm 20 minutes Gradual cooling	4.25 ± 0.99

Acknowledgment: Work carried out by Dr. Murthy, funded by a grant from US FDA Grant # 1U01FD005223-01

Globule Size

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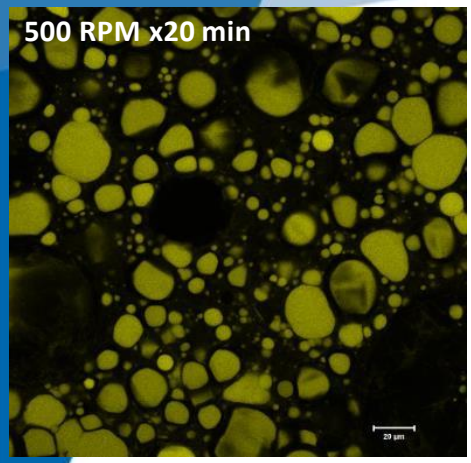

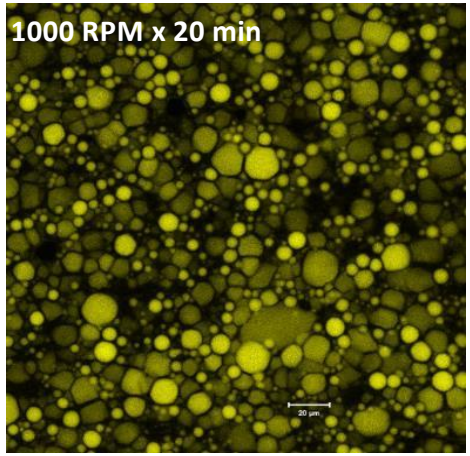

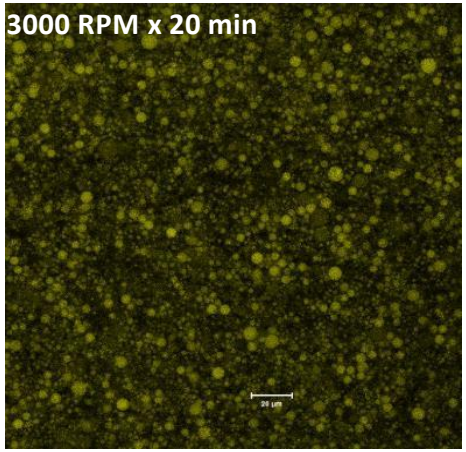

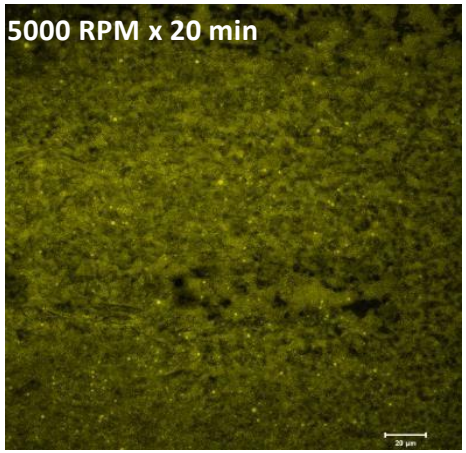

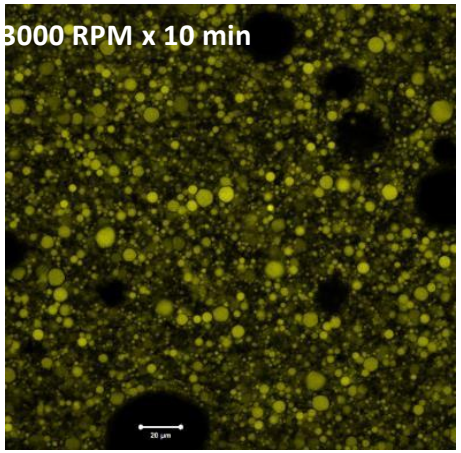

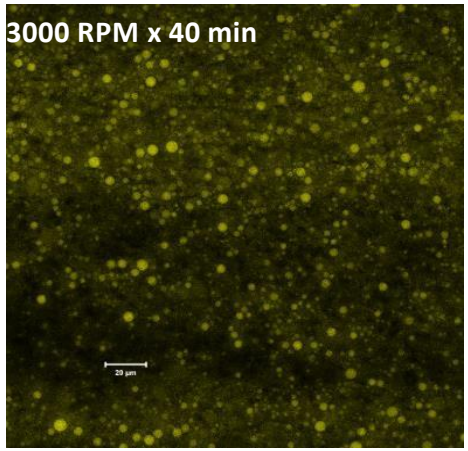

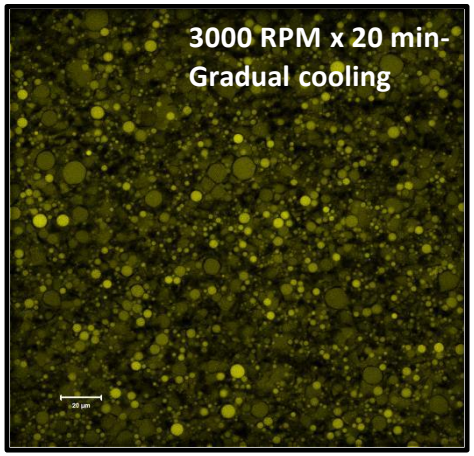

Acknowledgment: Work carried out by Dr. Murthy, funded by a grant from US FDA 1U01FD005223-01

In Vitro Permeation Testing (IVPT)

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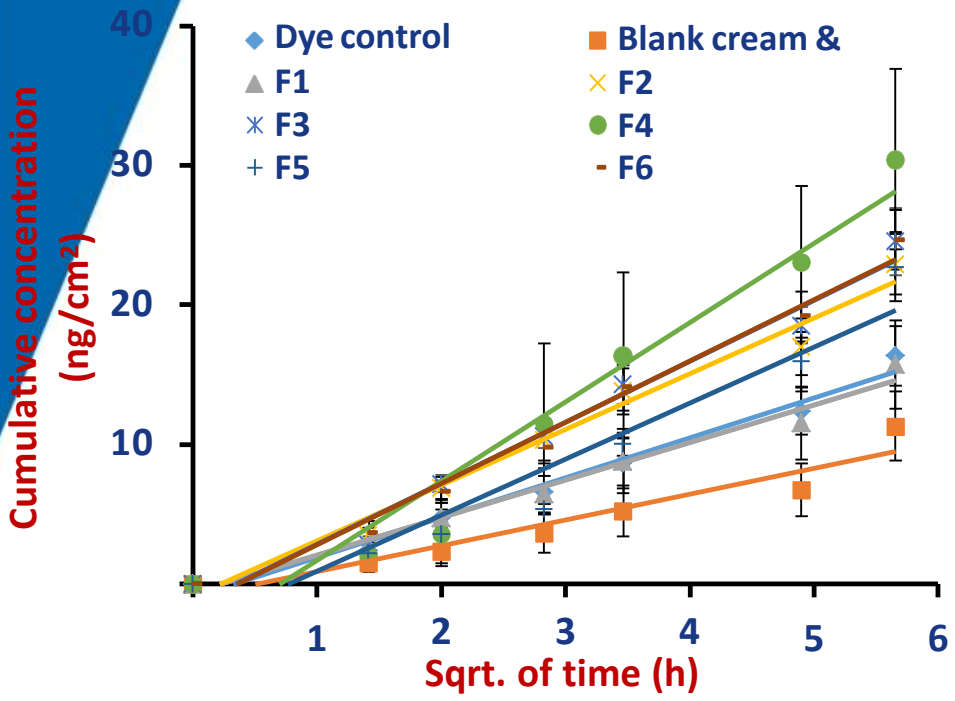
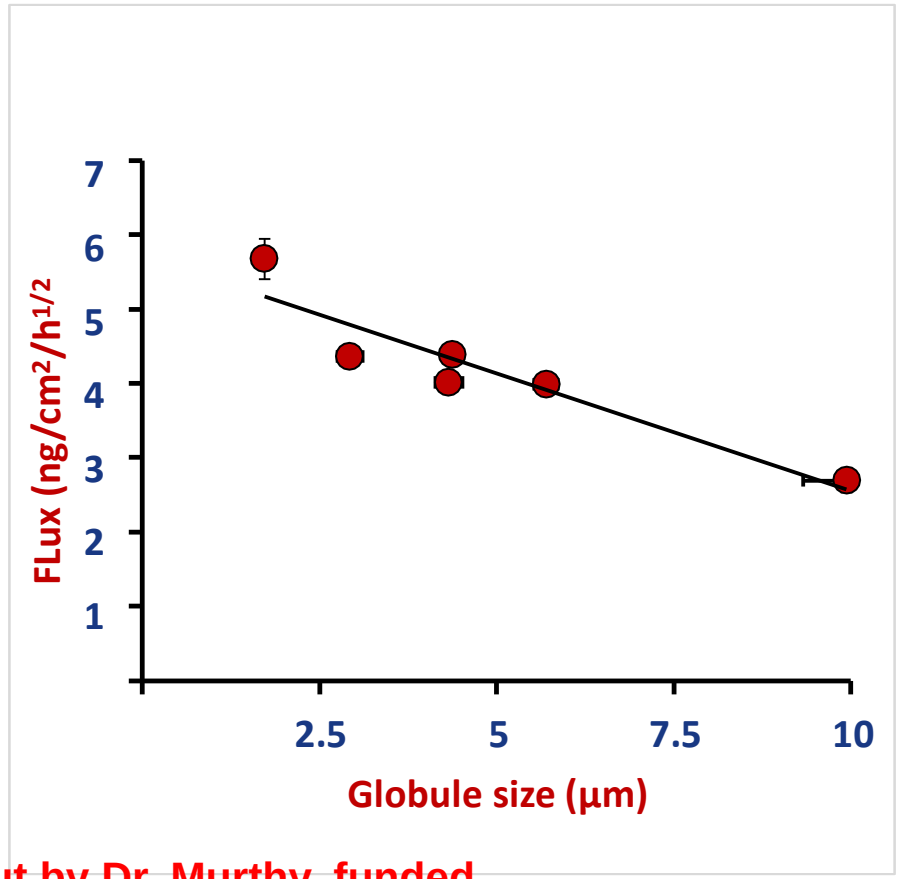
Cumulative permeation of NR across the porcine epidermis



Permeation flux Vs Globule size of dispersed phase



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Properties that affect Permeation of Drugs from Topical Products

- Drug may be dissolved state or partially dissolved state
- When partially dissolved, the diffusion of drug across a barrier takes place in two steps
- Diffusion of dissolved drug across barrier(K_d)
- Diffusion of dissolved drug triggers dissolution of undissolved drug in matrix (K_{und})
- Followed by diffusion of newly dissolved drug across the barrier
- Properties of drug that can affect K_{und} are, among others:
  - Polymorphic form of API
  - Morphology
  - Particle size

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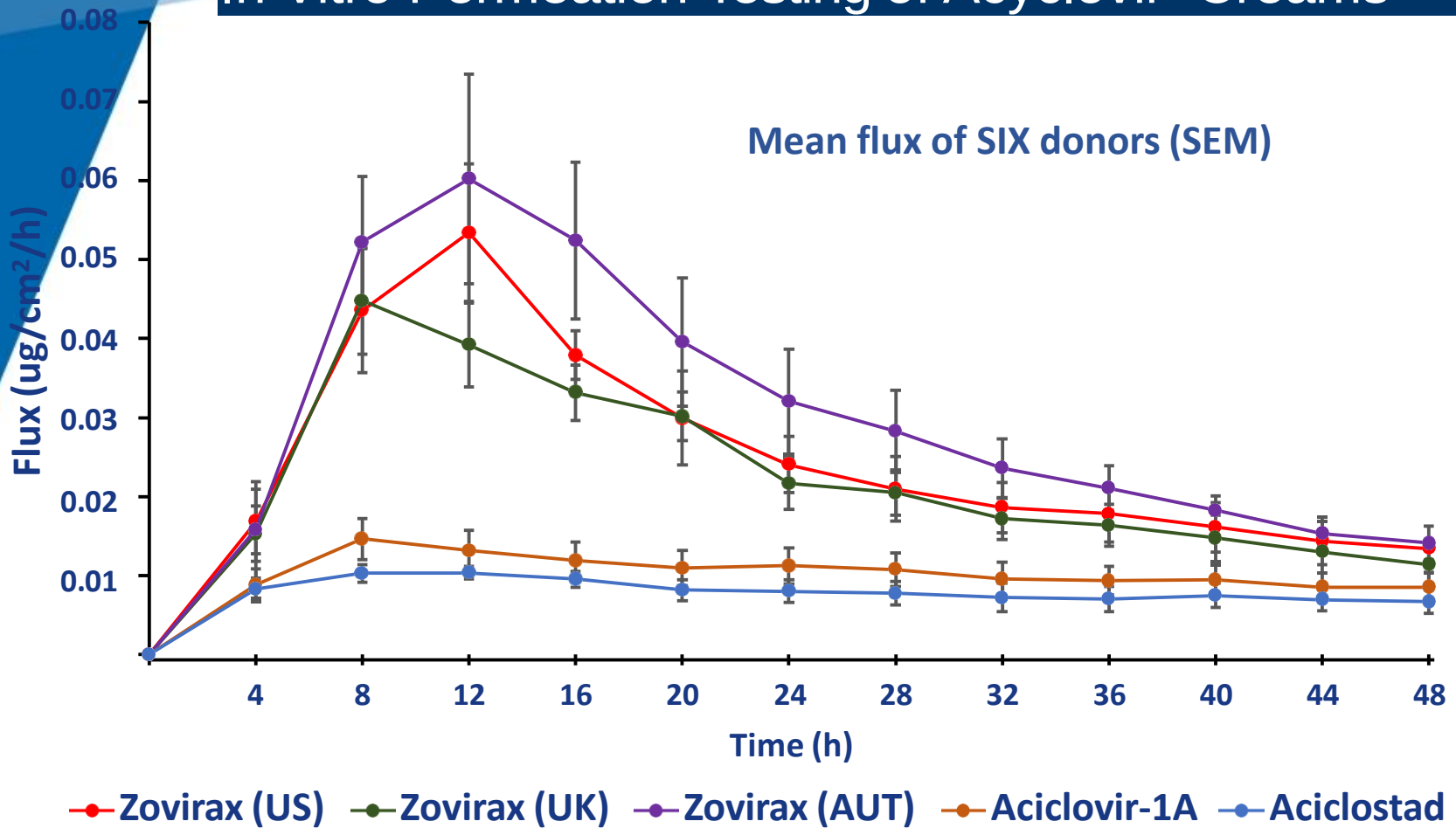
In Vitro Permeation Testing of Acyclovir Creams



Acknowledgment: Work carried out by Dr. Murthy, funded by a grant from US FDA 1U01FD005223-01

Polymorphic form

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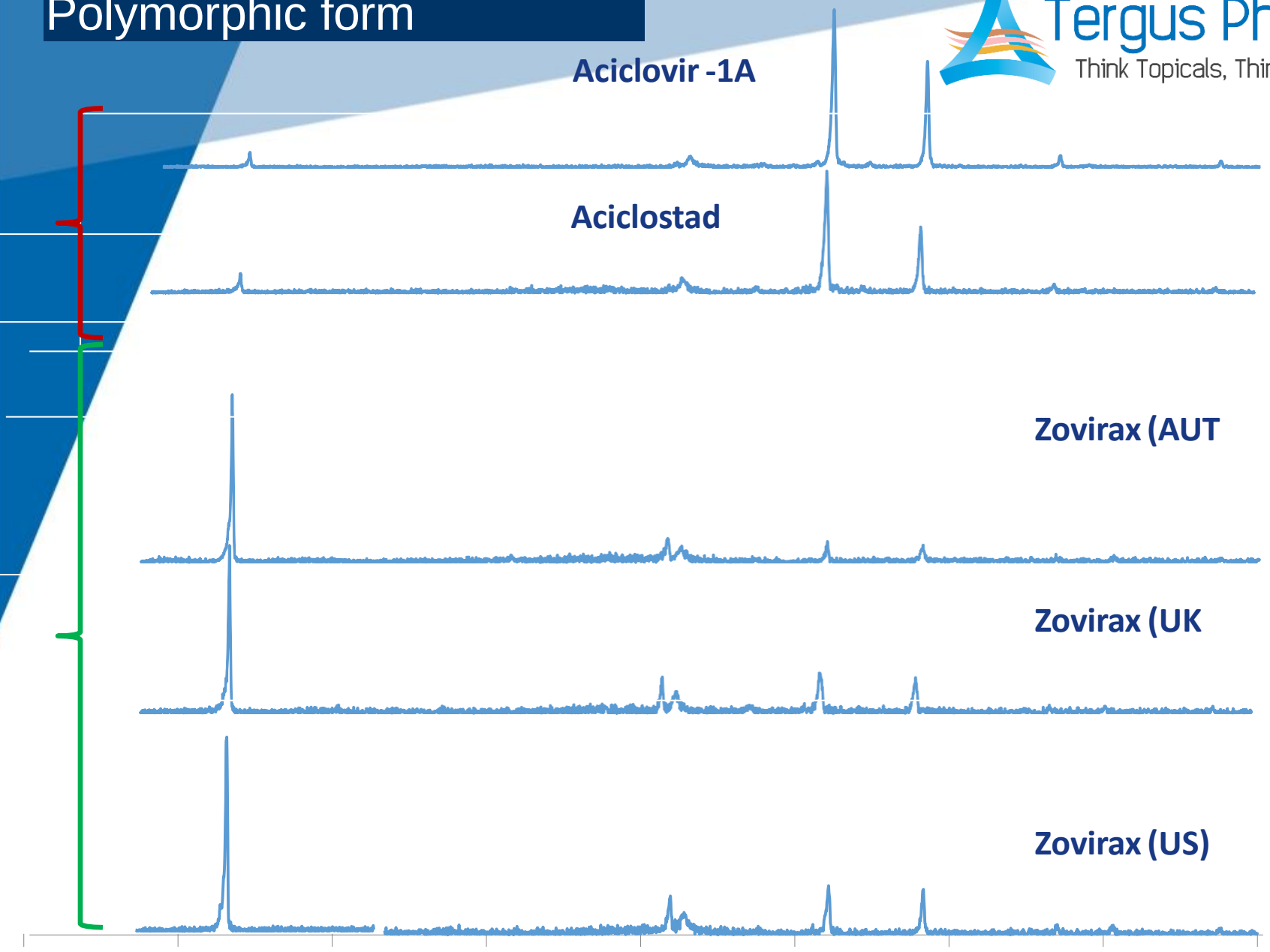

Particle Size and Morphology

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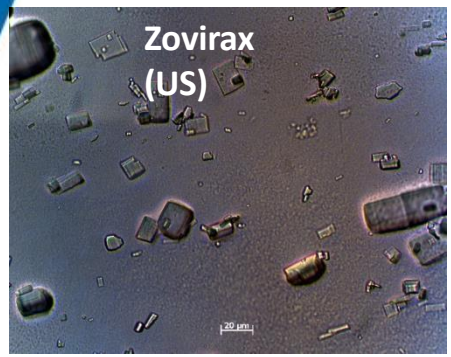
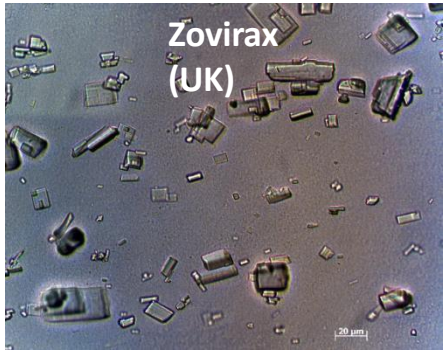
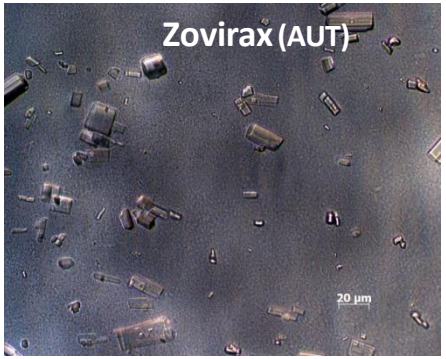
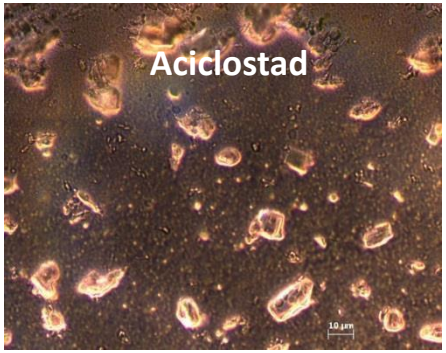
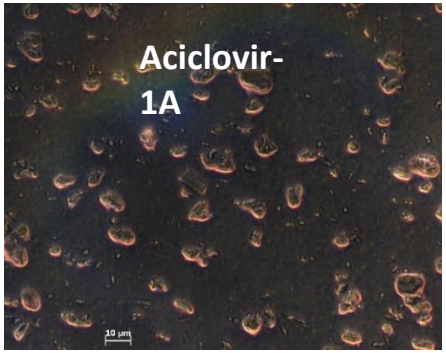
Product	d_{10}	d_{50}	d_{90}
Zovirax (US)	2.07	3.77	19.05
Zovirax (AUT)	1.76	3.43	20.76
Zovirax (UK)	1.36	2.50	24.18
Aciclovir -1A	4.0	5.95	10.94
Aciclostad	3.67	6.75	11.40











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More Examples of Properties that affect Microstructure

- Rheological differences due to differences in spreading and sample application technique, differences in rate of evaporation of solvents from the dosage form are reflective of differences in microstructure of the dosage forms.
- Differences in solvent evaporation rates, differences in change in skin pH also show as differences in release characteristics.
- Small process changes in formulations with identical composition have different microstructure as they show different permeation rates.

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- These and many other differences in properties that dictate the microstructure of dosage form and hence the release of active from the matrix result in non-equivalence.
- Some of these findings have resulted in developing better, more detailed guidance documents that assist sponsors to carry out BA/BE studies with greater confidence.

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- Guidance for Acyclovir Cream
  - New Guidance
  - In Vitro and In Vivo options are required
  - Test formulation must meet Q1/Q2 criteria
  - Test formulation must have similar physico-chemical characteristics as the RLD
  - Test formulation must demonstrate equivalent rate of release by a validated IVRT method compared to RLD
  - Test formulation must be bioequivalent to RLD using an acceptable in vitro permeation test(IVPT).

Guidance is very specific for

1. Physico –chemical tests that should be conducted to compare test and RLD
2. IVRT method development, validation and comparison of test and RLD
3. IVPT method development, validation and protocol for comparing skin permeation rate of test with RLD.

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1. Guidance document provides detailed, specific instructions for calculation of flux and other cutaneous pharmacokinetic parameters.
2. Guidance also provides instructions for the use of SAS statistical analysis to compare flux and other parameters between test and RLD formulations.
3. Other control procedures described in IVRT pivotal comparison such as packaging and blinding of test and RLD also apply.
4. Compliance to Good laboratory practice as described in 21 CFR part 58 is expected.
5. According to 21 CFR part 320.38 and 320.58, and Guidance to Industry “Handling and retention of BA and BE samples” must be adhered to.

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- Evolution of Guidance documents shows a much greater input from agency on developing higher quality generic dosage forms. It is the mission of OGD to make high quality Generics available to public;

- Key initiatives to support the mission are:
  - High Quality generics(product quality characterization)
  - Availability of Generics(Efficient bioequivalence standards)

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Taking Your Topical Programs to a Higher Level

THANK YOU

Questions???

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