Theoretical Principles and Best Practices In Vitro Permeation Testing (IVPT)

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 3: (Topical Products Pt. 2)

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CDER | U.S. FDA

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Learning Objectives

- *Discuss how an IVPT can be utilized as a component of characterization-based bioequivalence (BE) approaches*
- *Discuss Challenges and Current Thinking Related to IVPT*
  - IVPT method development (MD) studies
  - IVPT method validation (MV) studies
  - IVPT pivotal study and data analysis

IVPT Studies

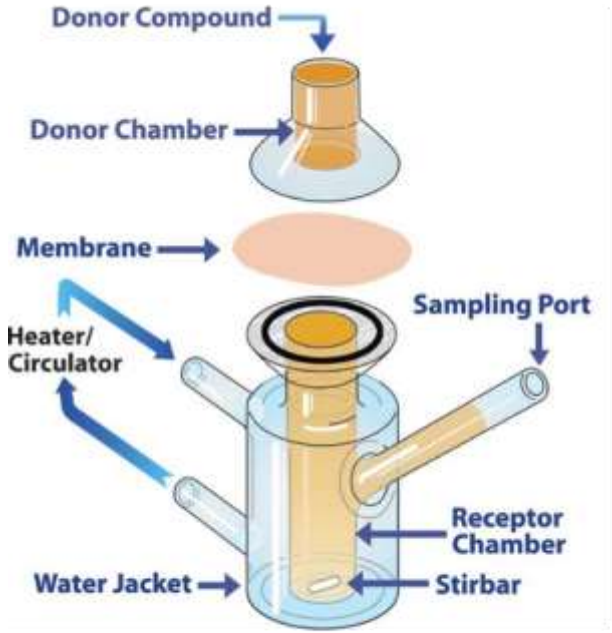
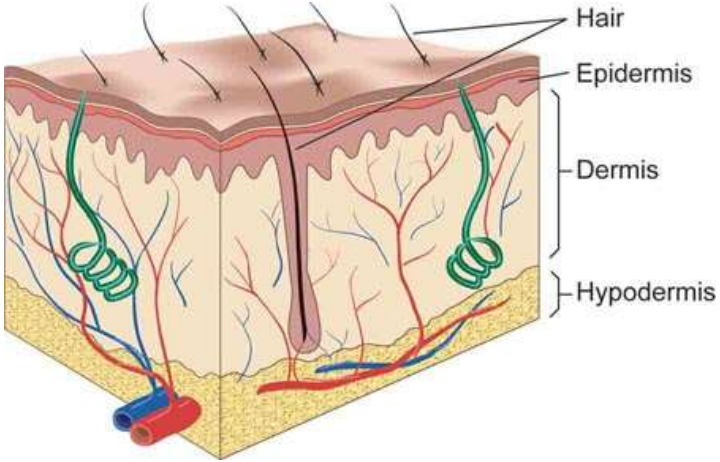
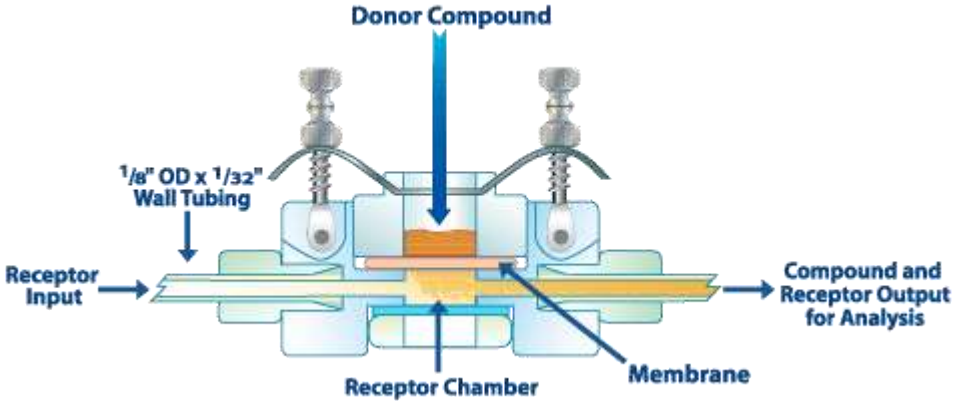
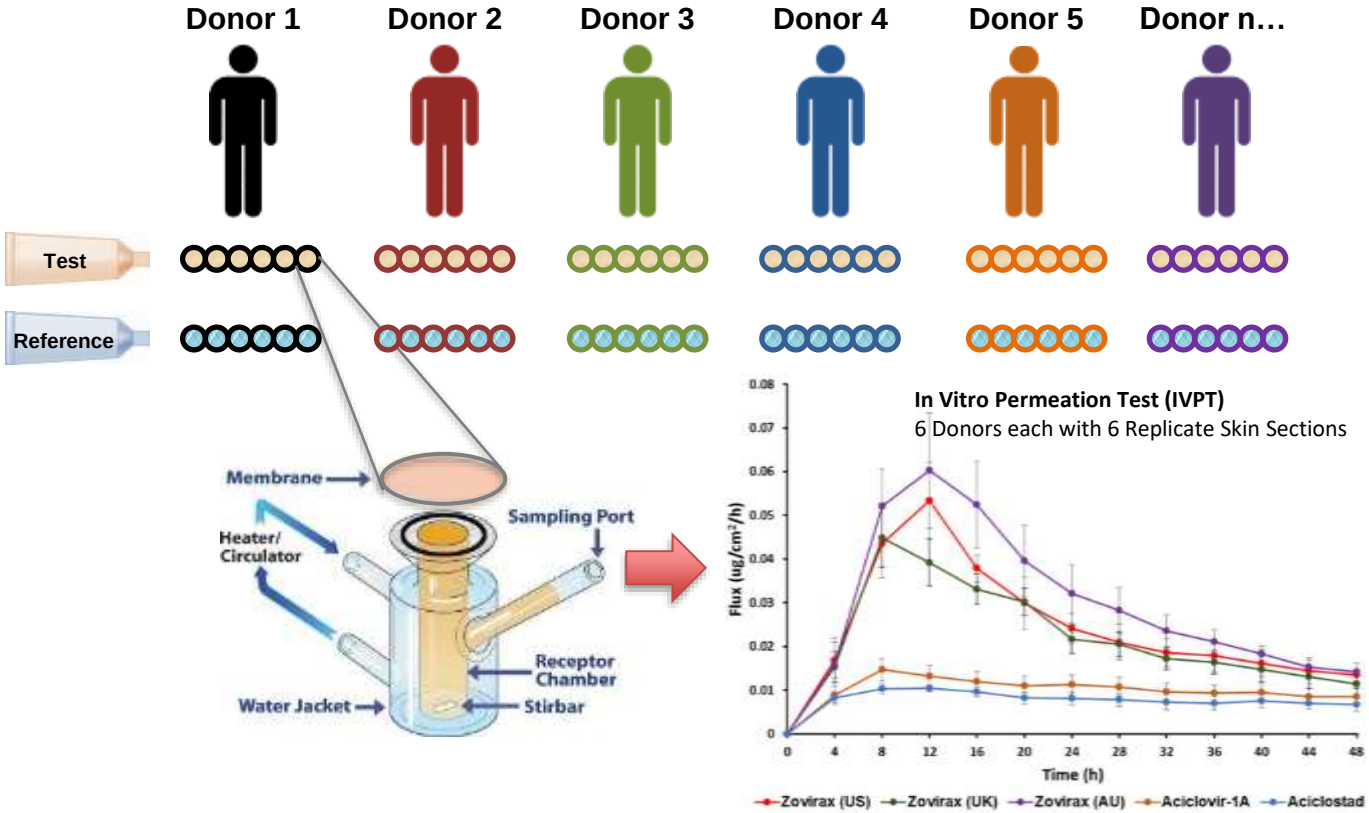


Image courtesy of PermeGear





IVPT STUDY DESIGN



Data courtesy Dr. Narasimha Murthy, U01FD005233

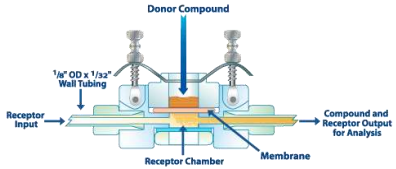
IVPT Method Development (MD)

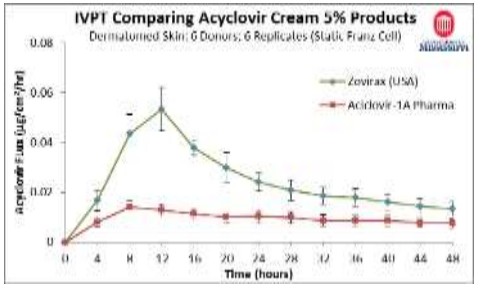
- *Apparatus Selection*
- *Selection of Skin Source*
- *Selection of Receptor Solution*
- *Assessment of the Barrier Integrity*
- *Selection of Dose Amount, Dosing Technique, and Dose Duration*
- *Selection of Study Duration, Sampling Schedule/ Methodology*

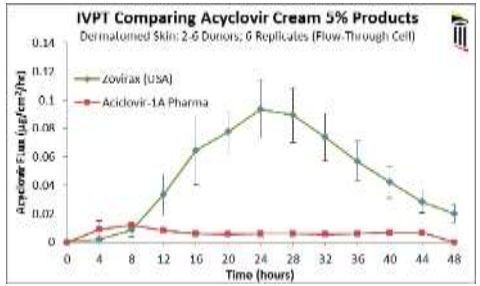
IVPT MD Challenges

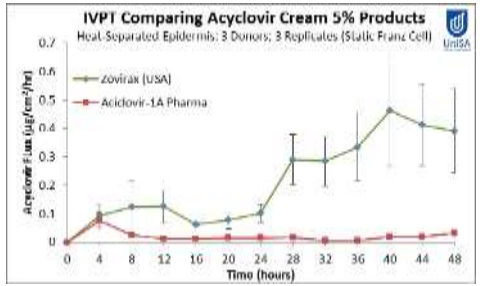
Apparatus Selection

	University of Mississippi	University of Maryland	University of South Australia
Dose	15 mg/cm^2		
Dosing technique	Dispensed-Spatula Dispersed-glass rod	Dispensed and dispersed- Positive displacement pipette	Dispensed- Pipette Dispersed- Syringe plunger
Skin type	Torso	Abdomen	Abdomen
Thickness	Dermatomed	Dermatomed	Heat separated epidermis
Instrument	Franz diffusion cell (2 cm^2)	In-Line Flow through cell (0.95 cm^2)	Franz diffusion cell (1.3 cm^2)
Skin Integrity	Electrical Resistance	Trans Epidermal Water Loss	Electrical resistance









Data courtesy Dr. Narasimha Murthy, U01FD005233, Dr. Audra Stinchcomb U01FD004947, Dr. Michael Roberts U01FD005226

IVPT MD Challenges

Skin Source and Anatomical Site *(Storage and Preparation)*

	University of Mississippi	University of Maryland	University of South Australia
Dose	15 mg/cm^2		
Dosing technique	Dispensed-Spatula Dispersed-glass rod	Dispensed and dispersed- Positive displacement pipette	Dispensed- Pipette Dispersed- Syringe plunger
Skin type	Torso	Abdomen	Abdomen
Thickness	Dermatomed	Dermatomed	Heat separated epidermis
Instrument	Franz diffusion cell (2 cm^2)	In-Line Flow through cell (0.95 cm^2)	Franz diffusion cell (1.3 cm^2)
Skin Integrity	Electrical Resistance	Trans Epidermal Water Loss	Electrical resistance

- *Control of skin harvesting and dermatoming*
- *Control of skin preparation protocols, prevent damage to the SC*
- *Control of skin setup prior to evaluation of barrier integrity*

IVPT MD Challenges

Selection of Receptor Solution

- *Adequate solubility and stability of active ingredient, based on apparatus of choice*
- *Physiologically relevant receptor solutions should be used, not appropriate to utilize "solubilizers" that may impact the barrier properties of the skin, e.g., ethanol*
- *Equilibrate skin in the presence of the receptor solution, on the apparatus of choice, prior to barrier integrity evaluation*

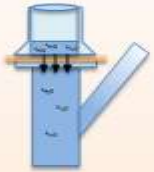
IVPT MD Challenges

Assessment of the Barrier Function

Trans-Epidermal Water Loss (TEWL) Skin Barrier Integrity Test

Test results reported as TEWL ($g/m^2/hr$)

Tritiated Water Skin Barrier Integrity Test



Test results reported as permeated amount of tritiated water per skin area (eq. $\mu L/cm^2$)

Trans-Epidermal Electrical Resistance (TEER) skin barrier integrity test

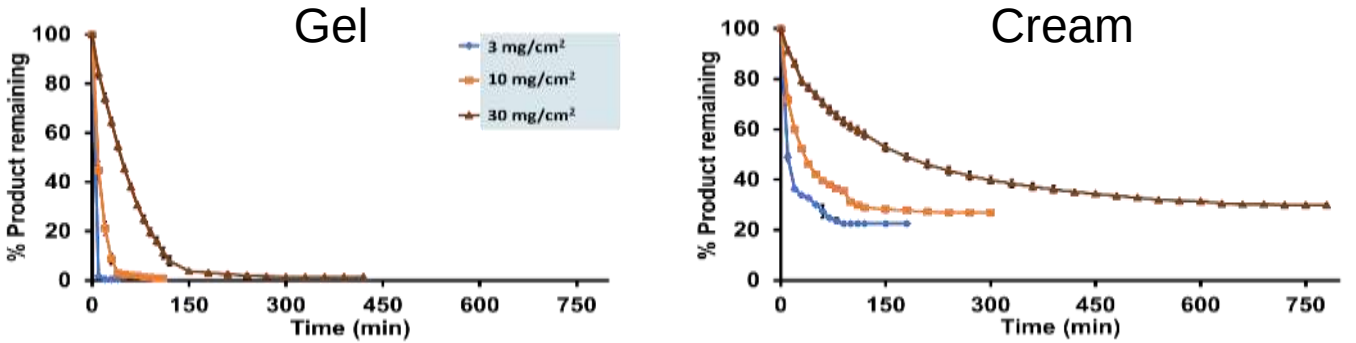
Test results reported as resistance ($k\Omega$) or conductance ($1/k\Omega$ or mS). Units may also involve normalization of skin area.

- Role of external factors (temperature & relative humidity)

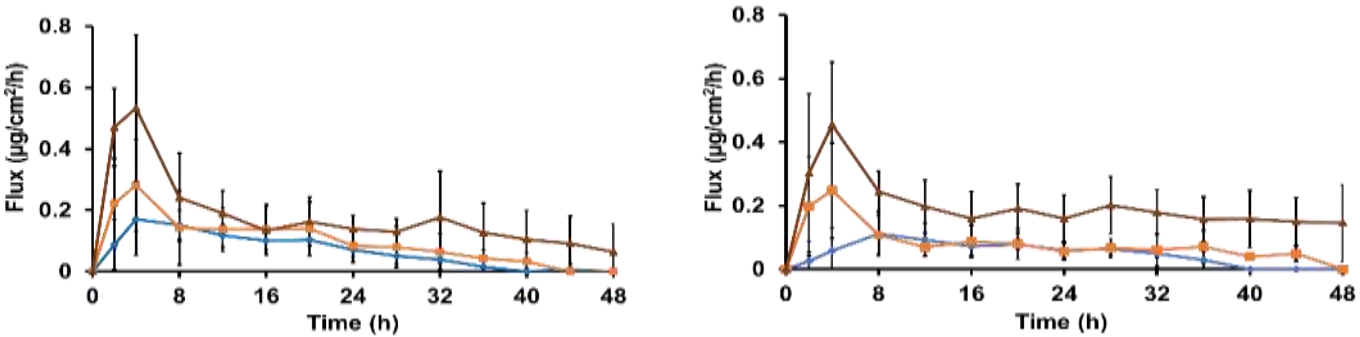
IVPT MD Challenges

Selection of Dose Amount

Drying Rate



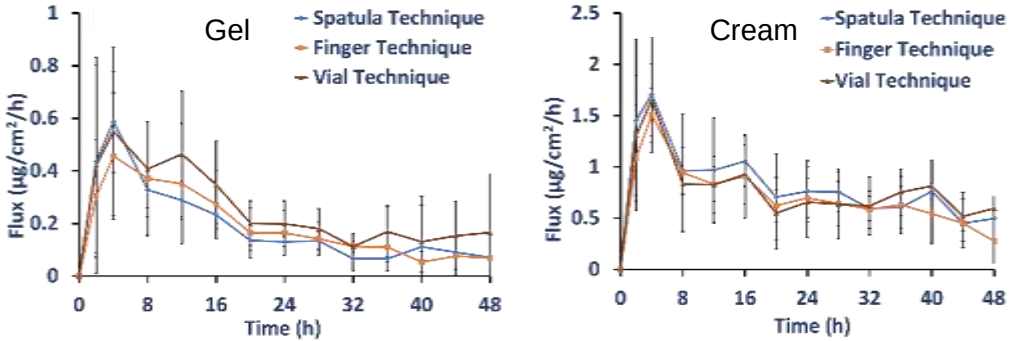
IVPT



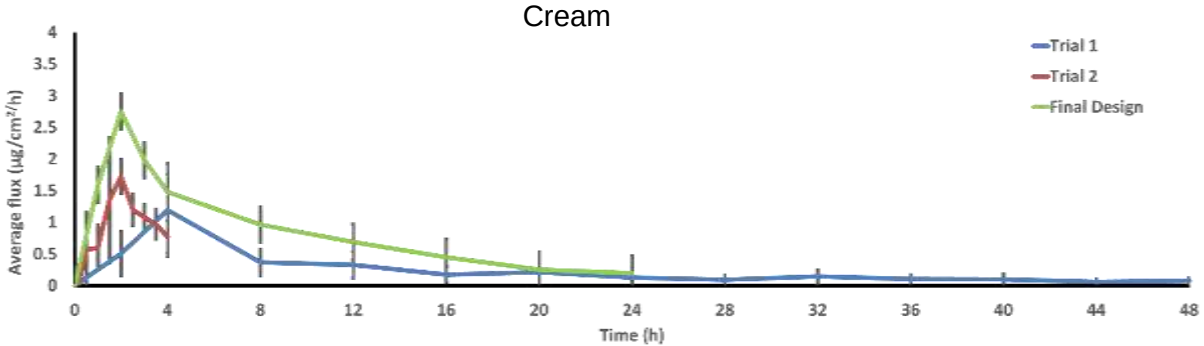
Data courtesy Dr. Narasimha Murthy, U01FD005233

IVPT MD Challenges

Selection of Dosing Technique and Dose Duration



Selection of Study Duration and Sampling Schedule/Method



Data courtesy Dr. Narasimha Murthy, U01FD005233

IVPT MD Report

- Include tabular information related to all studies conducted, chronologically, to demonstrate how the final study conditions/parameters were identified
- Specifically, if apparatus, methodologies or study conditions, that are different than those recommended in guidances are utilized consider documenting why such changes were necessary and scientifically justifiable

IVPT Method Validation (MV)

- *Apparatus Qualification*
- *Membrane (Skin) Qualification*
- *Receptor Solution Qualification*
- *Receptor Solution Sampling Qualification*
- *Discrimination Sensitivity and Selectivity*
  - *Sensitivity*
  - *Selectivity*

A validated analytical method should be used for the MV studies

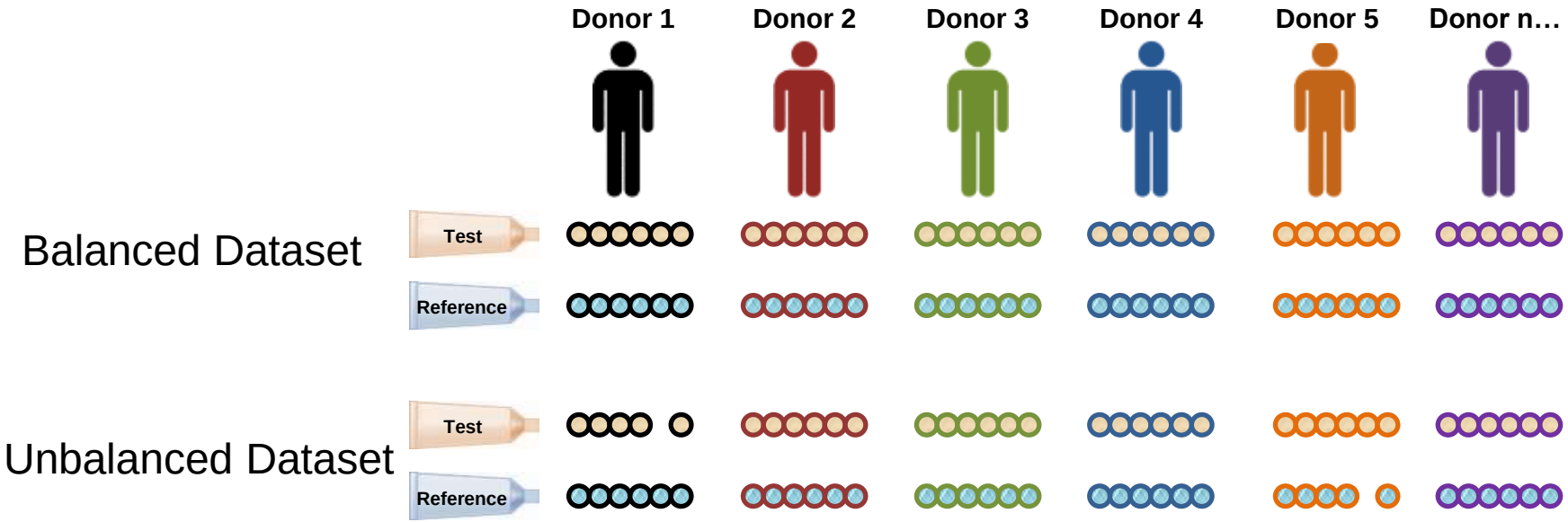
IVPT MV Challenges

Discrimination Sensitivity and Selectivity

- Sensitivity
  - Modulation of Dose Amount
  - Modulation of Dose Duration
- Selectivity
  - Test product, Reference Product, and Altered Product

Challenges with Data Analysis

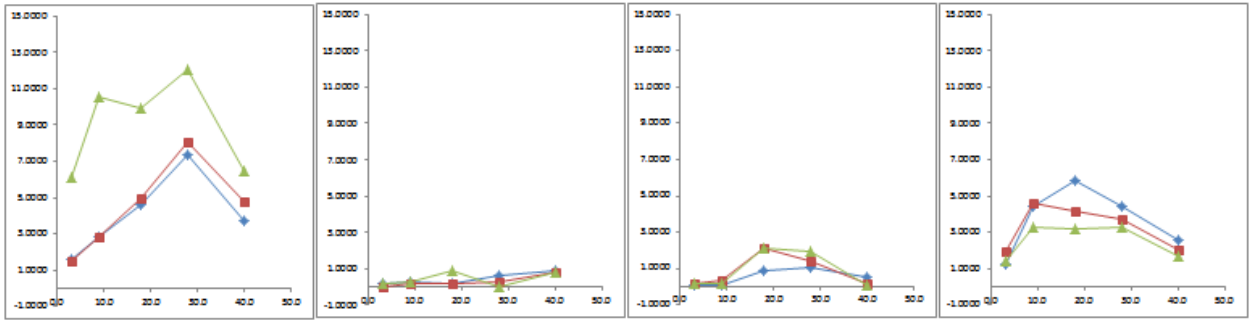
Balanced and Unbalanced Data



Presentation by Elena Rantou @ http://complexgenerics.org/IVRTIVPT/

Outstanding Challenges with IVPT

Challenges related "aberrant" data



- Documentation related to exclusion of data with documented protocol violations or experimental errors
- Handling of "aberrant" data without documented protocol violations or experimental errors

Challenge Question #1

What is the role of an IVPT study as a component of a characterization-based approach

A. An IVPT is used to deformulate the drug product

B. An IVPT is used to characterize the physical properties of a drug product

C. An IVPT is used to quantify the release of the active ingredient from the drug product

D. An IVPT characterizes the rate and extent to which the drug becomes available at or near the site of action

Summary

- An IVPT study is typically recommended to assess drug availability from multiphasic formulations by understanding the interaction of the drug product with the skin during metamorphosis
- For IVPT MD studies, it is important to systematically identify study conditions that are relevant for a given drug product, and to clearly outline the considerations/ data within the method development report
- For IVPT MV studies, it is important to validate the study conditions identified during MD, and establish the selectivity of the IVPT method
- For the IVPT pivotal study, it is important to implement controls to minimize variability and loss of data during the conduct of the study

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Research Collaborators

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Questions?

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