IN VITRO PERMEATION TEST (IVPT) FUNDAMENTALS: SCIENTIFIC AND PRACTICAL CONSIDERATIONS

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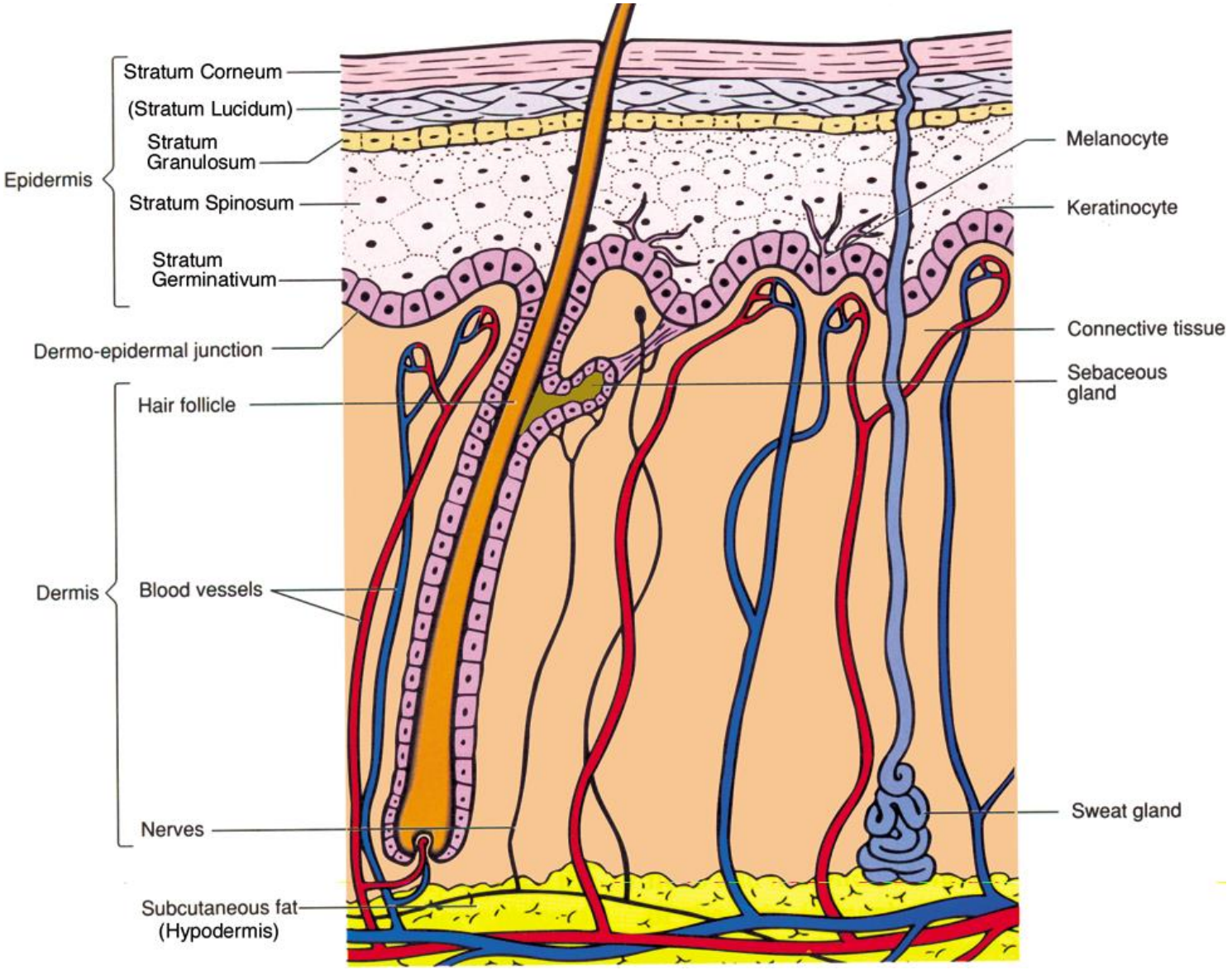
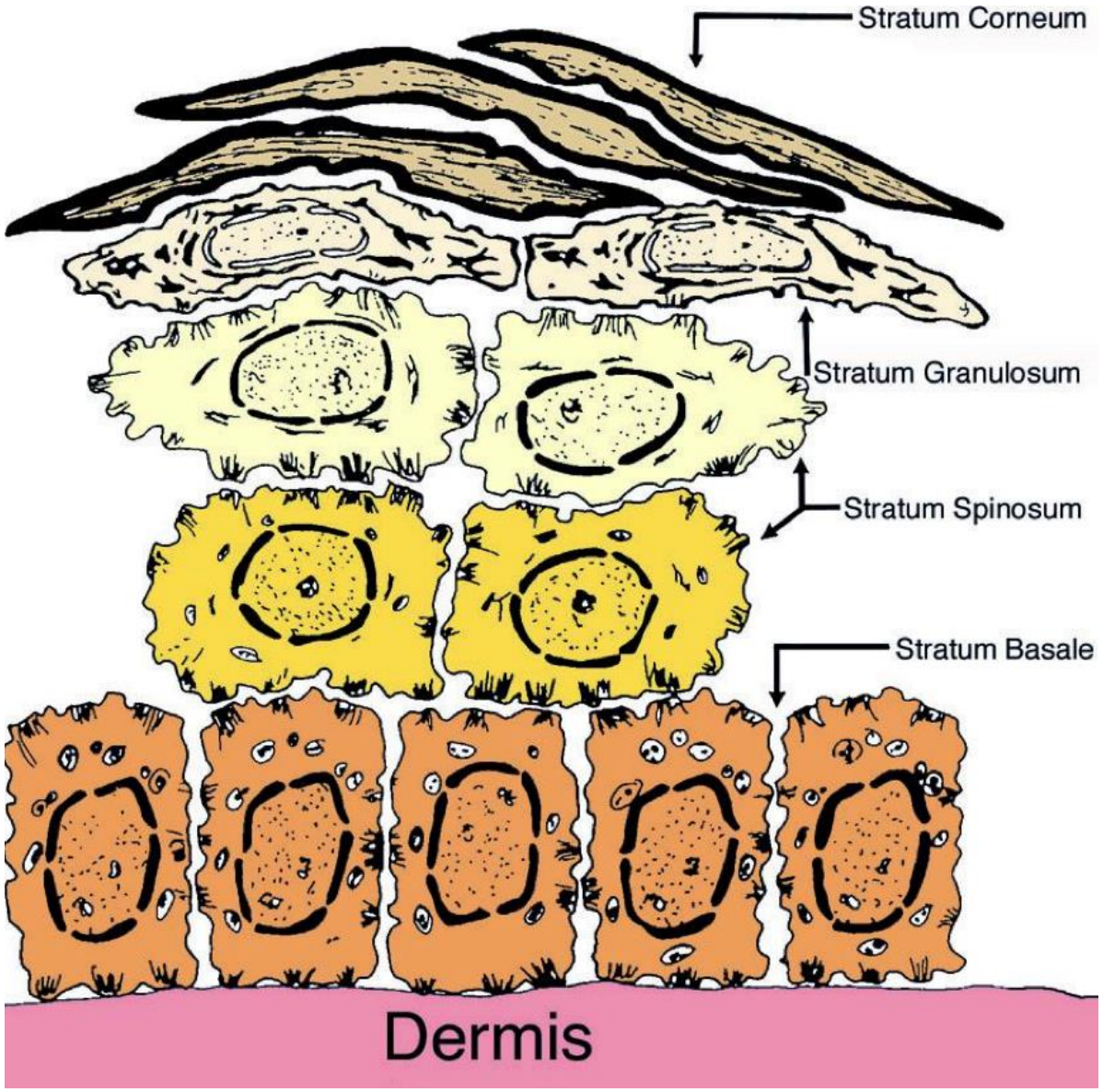
Human Skin Structure



Adapted from Cerio and Archer, 1998

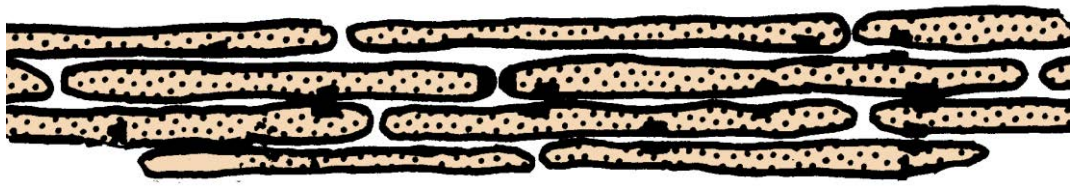
Human Skin Differentiation

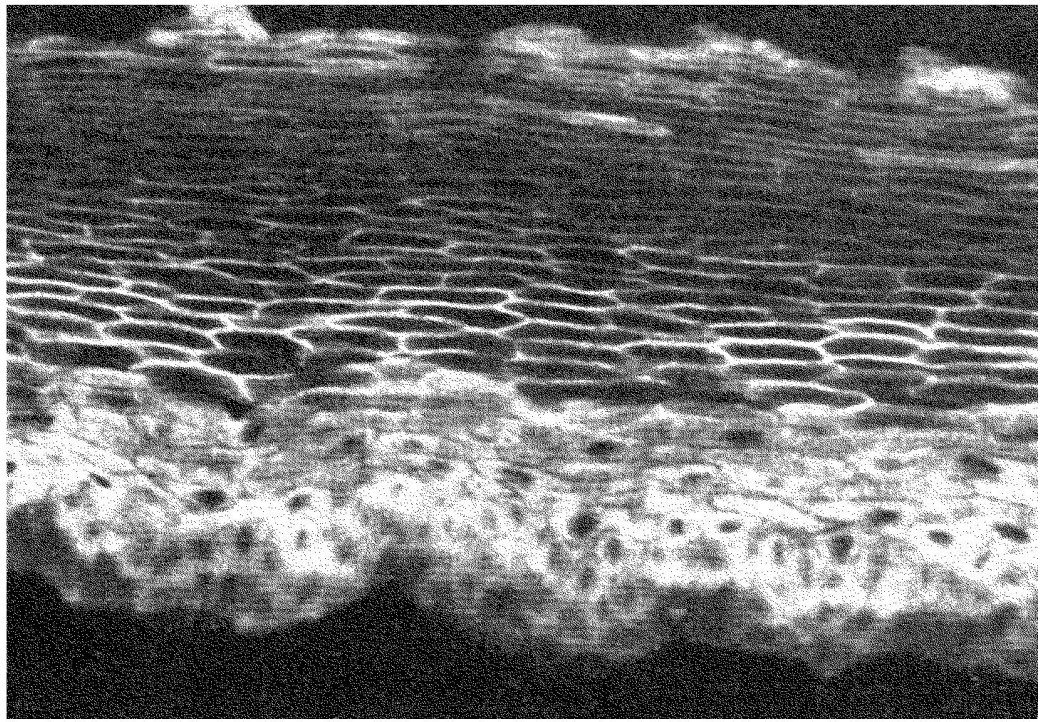


Adapted from Schaefer and Redelmeier, 1996

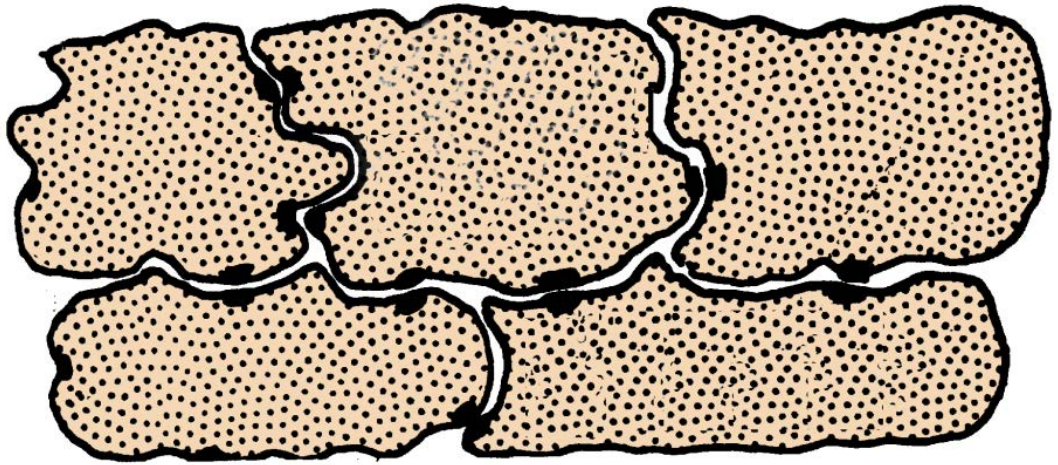
Skin Permeation Pathway

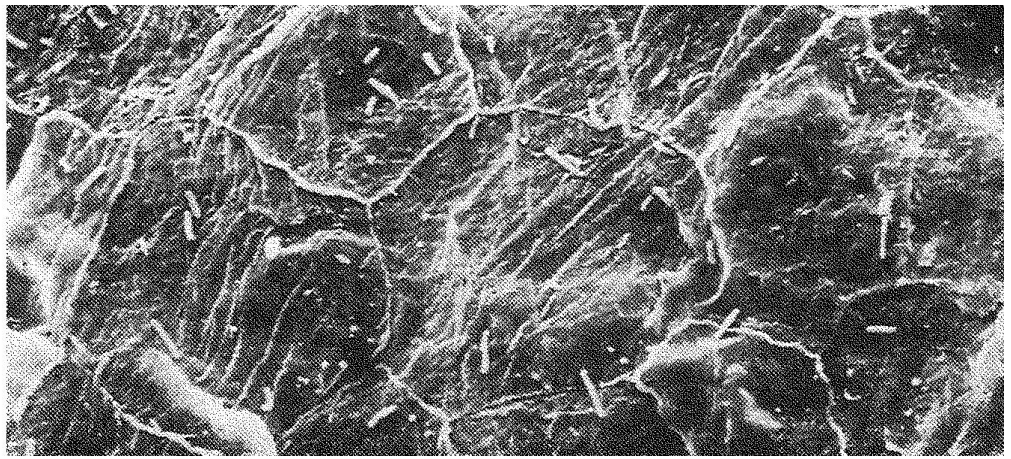
SIDE VIEW





TOP VIEW



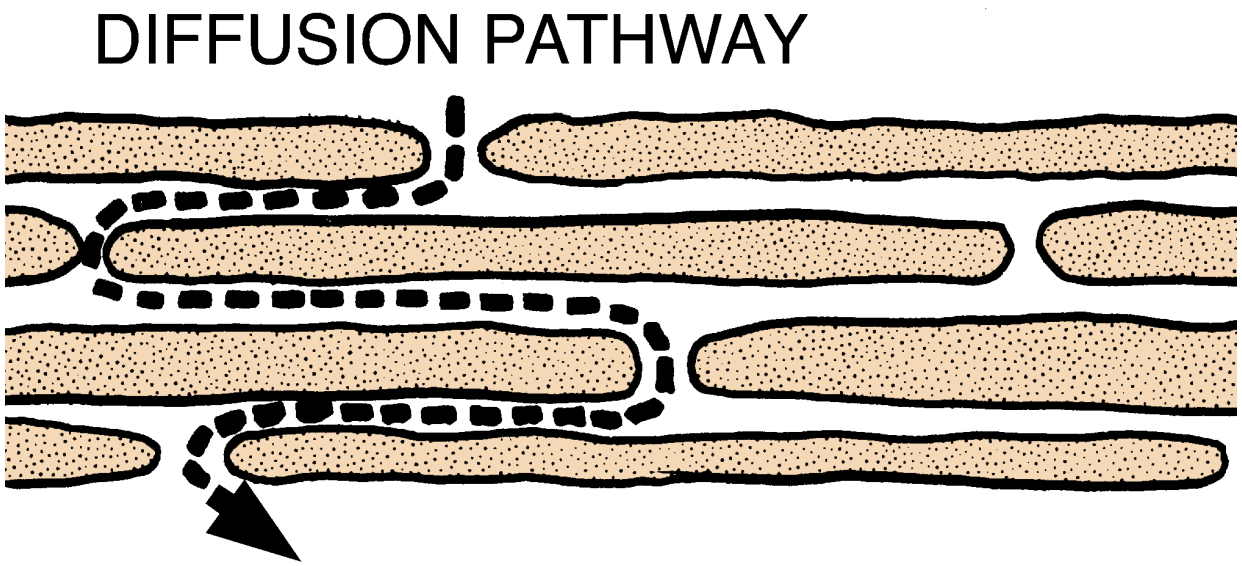


Drawings adapted from Odland, 1971.

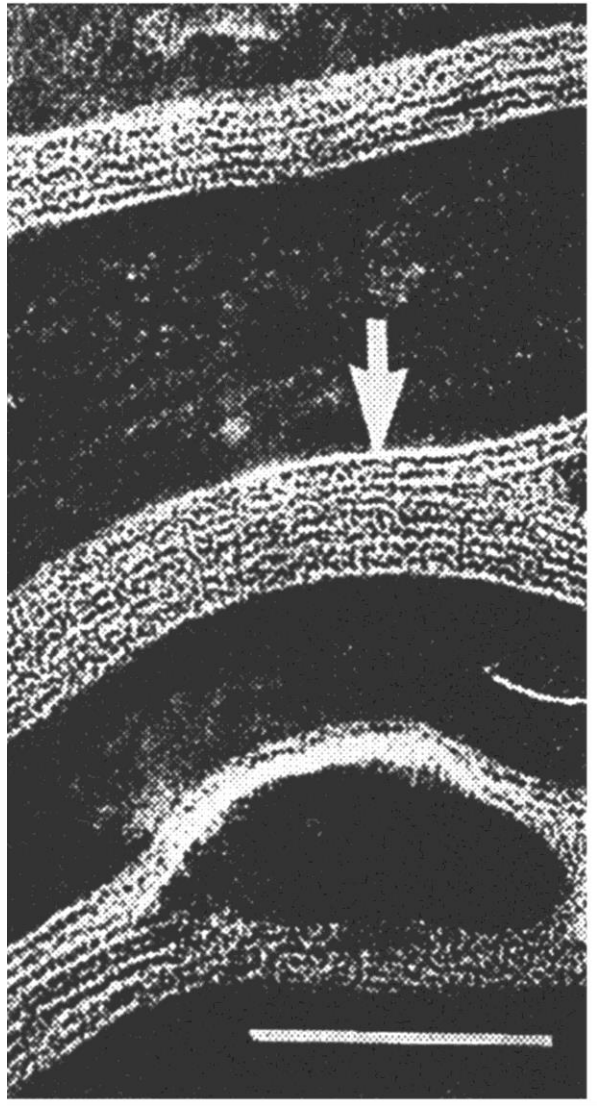
Micrograph accompanying “side view” from Christophers and Laurence, 1976.

Micrograph accompanying “top view” from Singh and Singh, 1995.

Diffusion of Topical Compounds



Drawing adapted from Odland, 1971.



Micrograph Fartasch et al., 1998.

Diffusion of Topical Compounds

- Katz & Poulsen, 1971 (Fick's Law of Diffusion)

$$J = \frac{P \times D \times \Delta C}{l}$$

- J = Flux (e.g. µg/cm^2/hour)
- C = Concentration
- P = Partition Coefficient
- D = Diffusion Coefficient
- *l* = Length of Travel

Diffusion of Topical Compounds

- Franz & Lehman, 1995 (Finite Dose Equation)

$$J = 2hpDC_0 \sum_{n=1}^{\infty} \frac{\alpha_n e^{-D\alpha_n^2 t}}{\sin \alpha_n l \left[l\left(\alpha_n^2 + h^2\right) + h \right]}$$

- Relevant to clinically applied thin film doses
- Accounts for the thickness of the applied dose as well as dose depletion over time

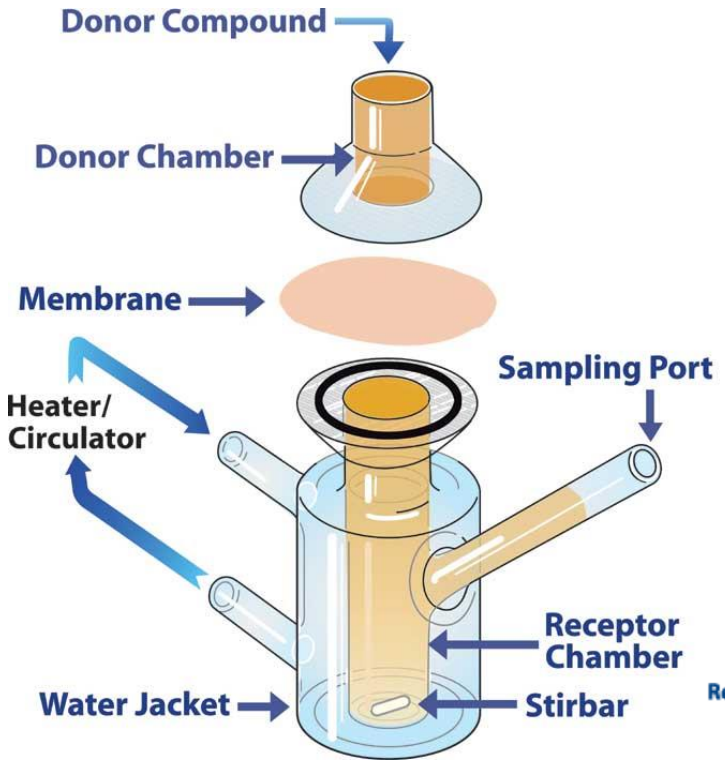
Qualities of Topical Dosage Forms

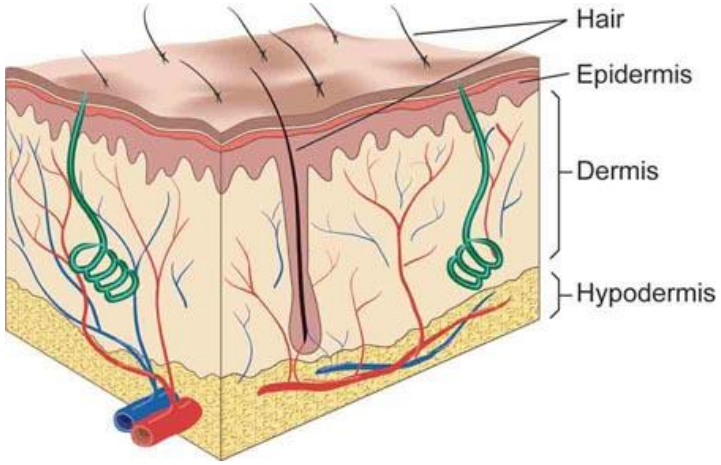
- Formulation Qualities
  - Once dosed, most formulations ‘dry’, stability and solubility change; only soluble drug is available for diffusion and partitioning to skin
  - The partitioning of the drug from a multi-phasic dosage form (e.g., an emulsion) into the stratum corneum (SC) may be different depending upon the phase(s) in the formulation from which the drug is partitioning (e.g., from a globule vs. from the continuous phase)
  - As formulations undergo metamorphosis, the thermodynamic activity of the drug in the dosage form changes; this can modulate the rate and extent of cutaneous bioavailability
  - The arrangement of matter in the dosage form can modulate its structural interface with the skin, its metamorphosis, and the rate and extent of cutaneous bioavailability

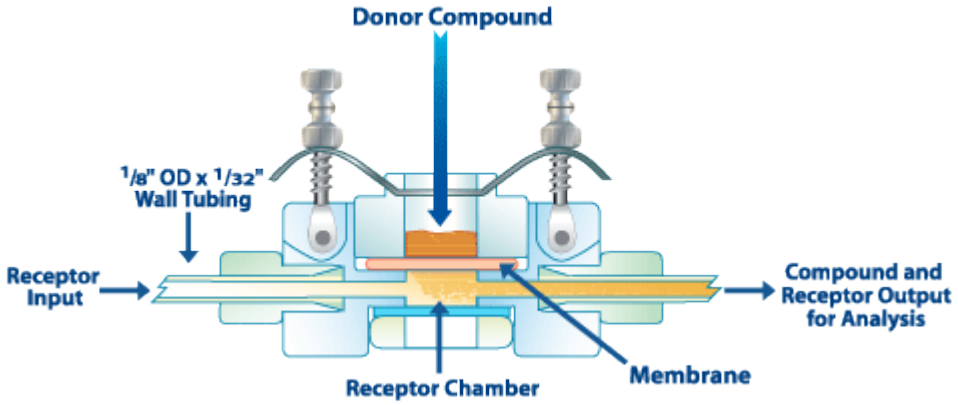
Qualities of Topical Dosage Forms

- Excipient Qualities
  - Excipients themselves can penetrate skin
    - Alter the drug solubility in SC intercellular lipids
    - Alter the ordered structure of SC intercellular lipids
    - Create domain phase separations
  - Excipients can impact the partitioning and diffusion of the drug

In Vitro Permeation Test (IVPT)







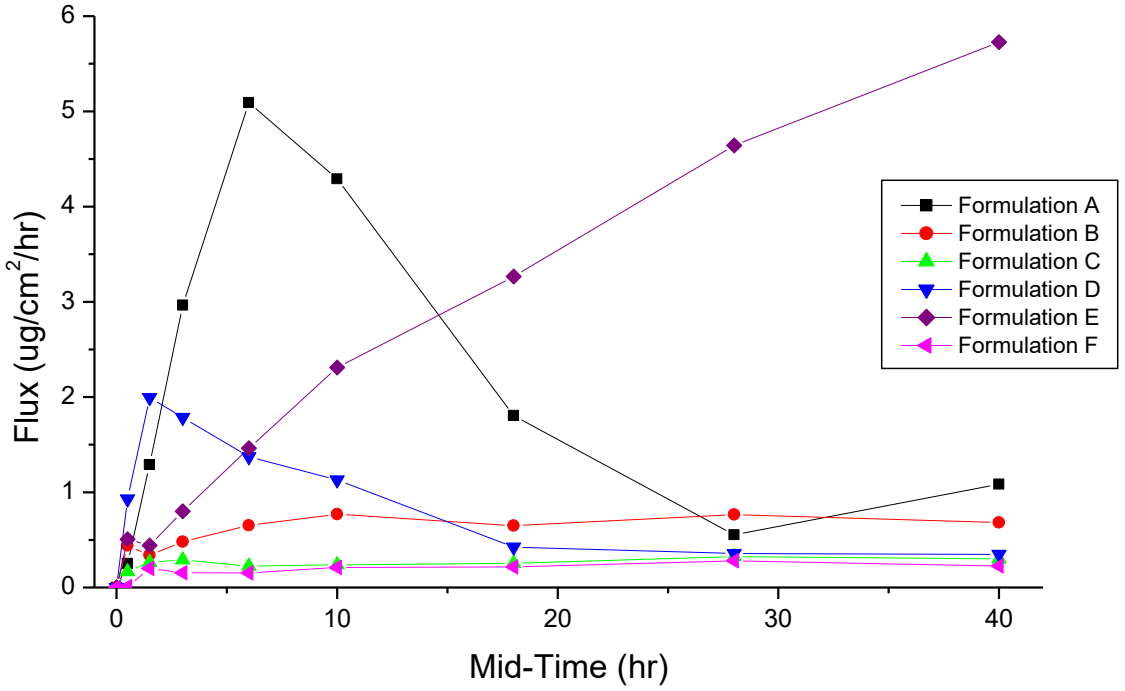
Cell images courtesy of PermeGear

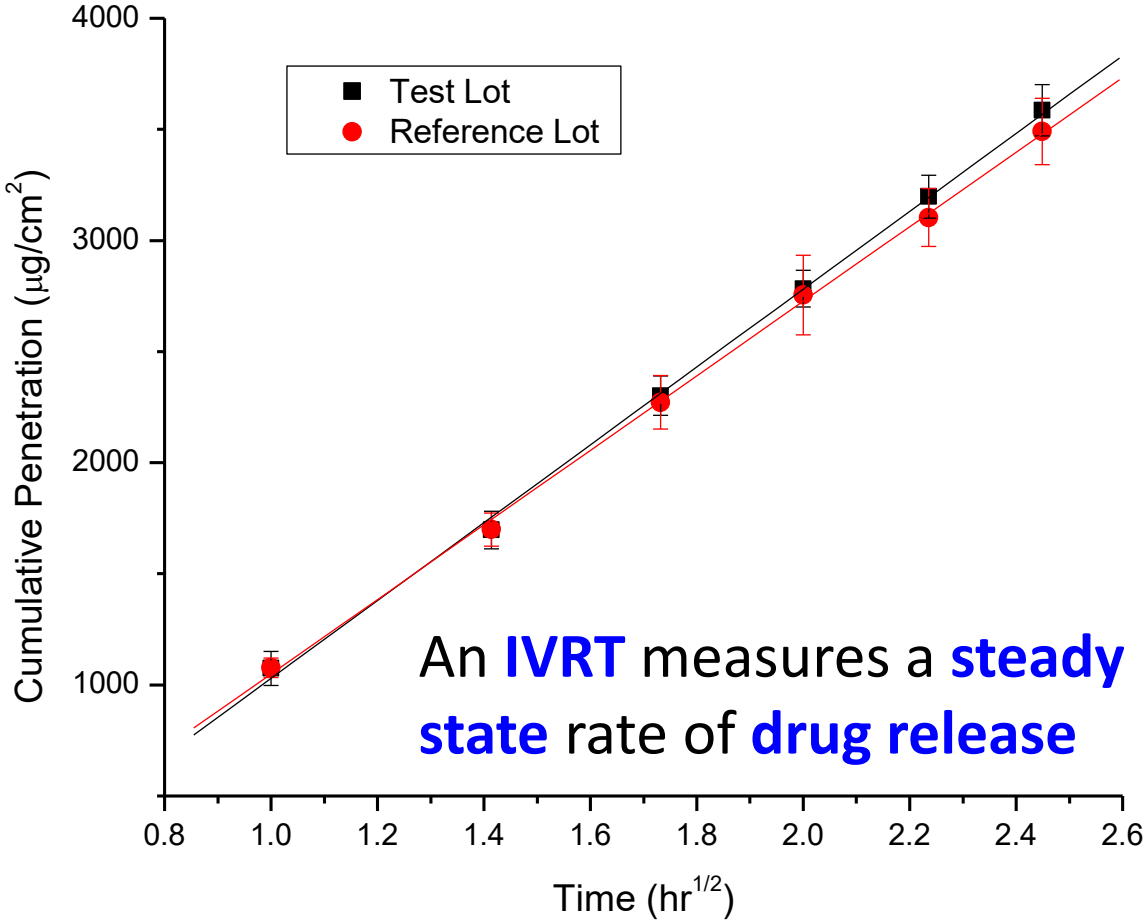
In Vitro Permeation Test (IVPT)

- IVPT Key Features
  - The IVPT membrane is typically excised human skin
  - The IVPT receptor solution/medium is typically a physiological buffer
  - The IVPT methodology maintains the skin at physiological conditions
  - The dose is typically a finite dose (thin-film) for non-steady-state kinetics
  - The dose is typically not occluded to allow drying/metamorphosis
  - The primary result is the dynamic rate and extent of permeation
  - Drug is often released into the receptor solution in the ng/mL range
  - The dosage form is maintained on the ‘dry’ surface of the skin
  - Validated IVPT methods can exhibit similar flux profiles within a donor
  - IVPT results can correlate with in vivo results under matched conditions
  - The rate and extent of permeation can be sensitive to changes in Q3 attributes

IVPT vs. IVRT Data (example)

An **IVPT** measures the **non-steady state** rate of **skin permeation**



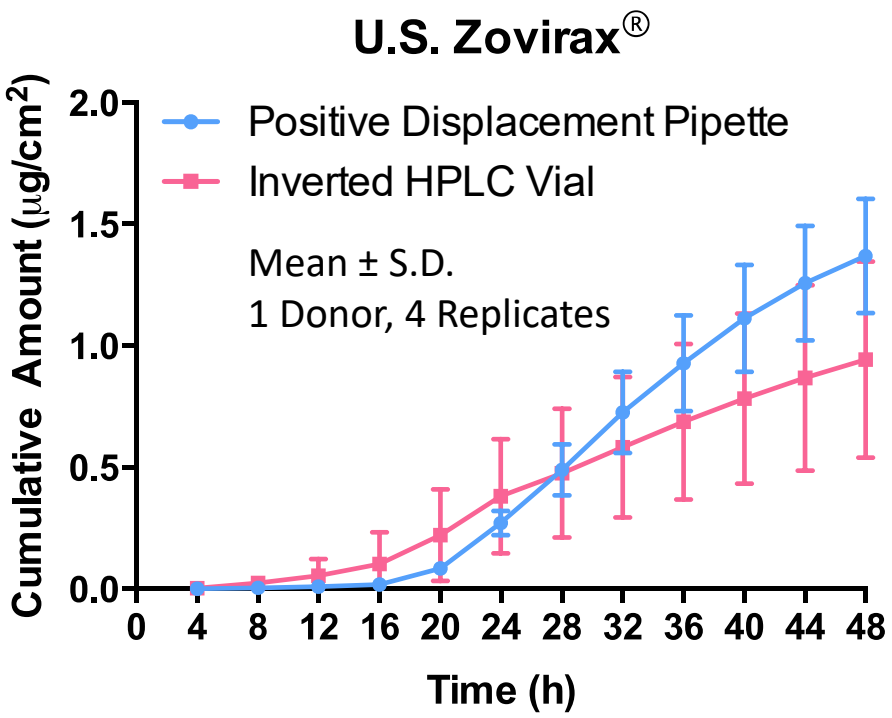


IVPT Data (example)

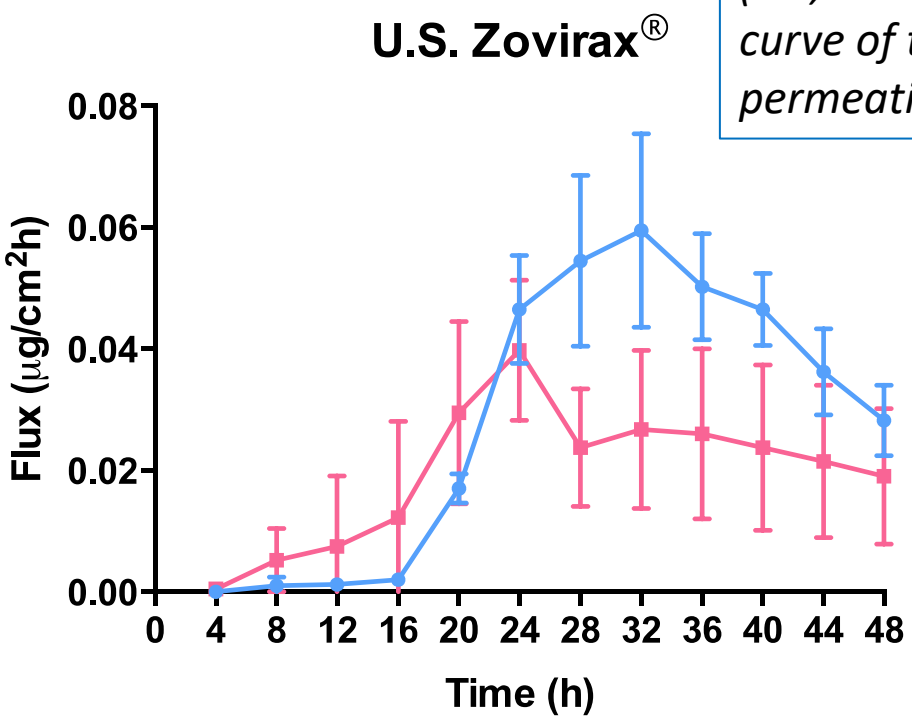
- Flux (J) Results vs. Cumulative Amount (AMT)* Permeated compared using different dosing techniques

***NOTE**: *The cumulative amount permeated was **previously called "AUC"** (i.e., the area under the curve of the incremental permeation profile)*

Cumulative Amount (AMT)



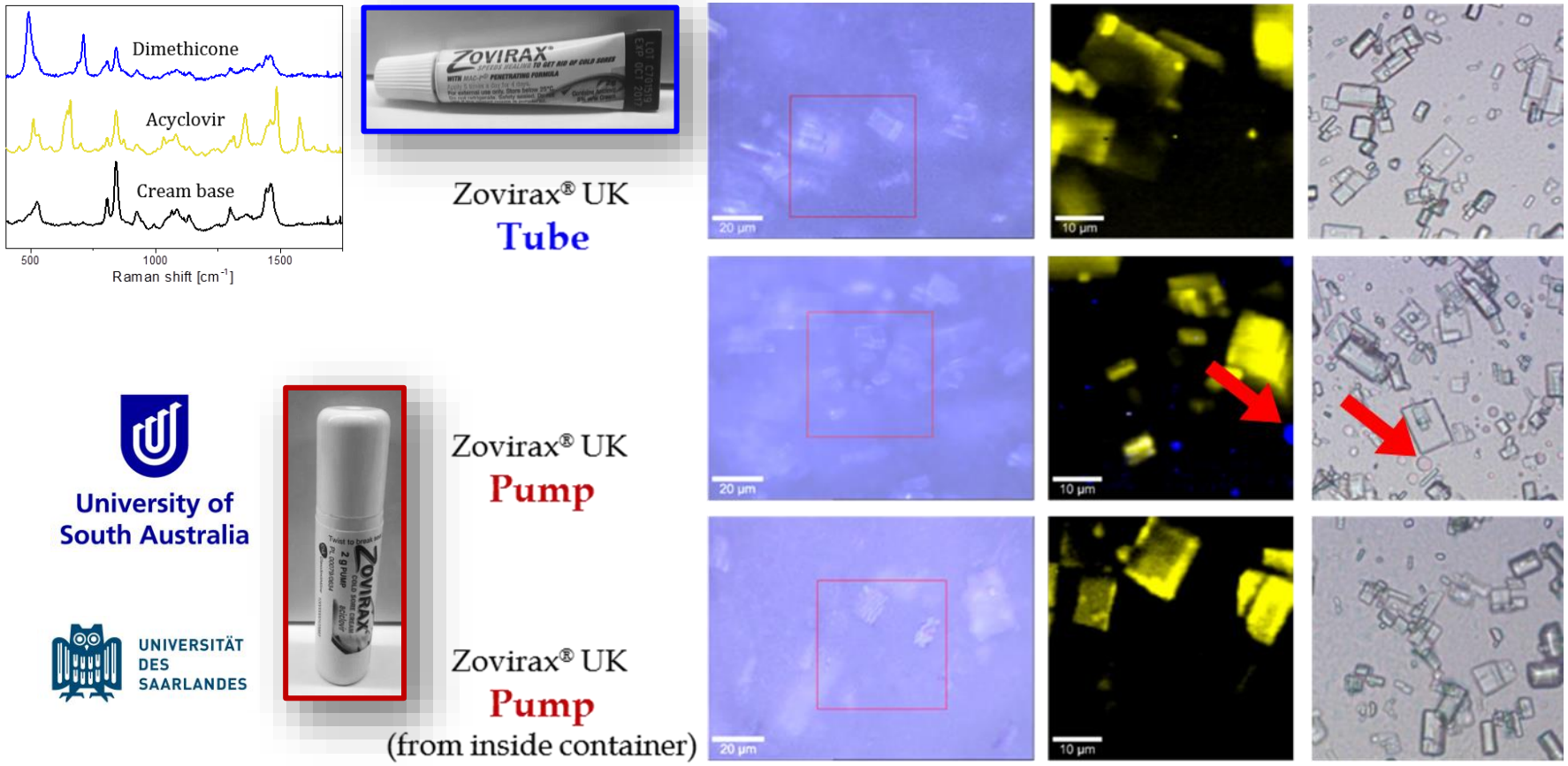
Flux (J)



Data provided courtesy of Drs. Audra Stinchcomb and Soo Shin associated with FDA funding for award U01FD0004947

Influence of Dispensing Stress on Q3

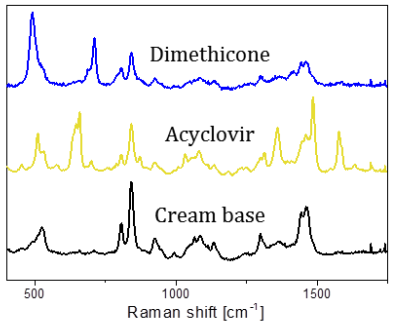
- Influence of Dose Dispensing on Product Quality



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



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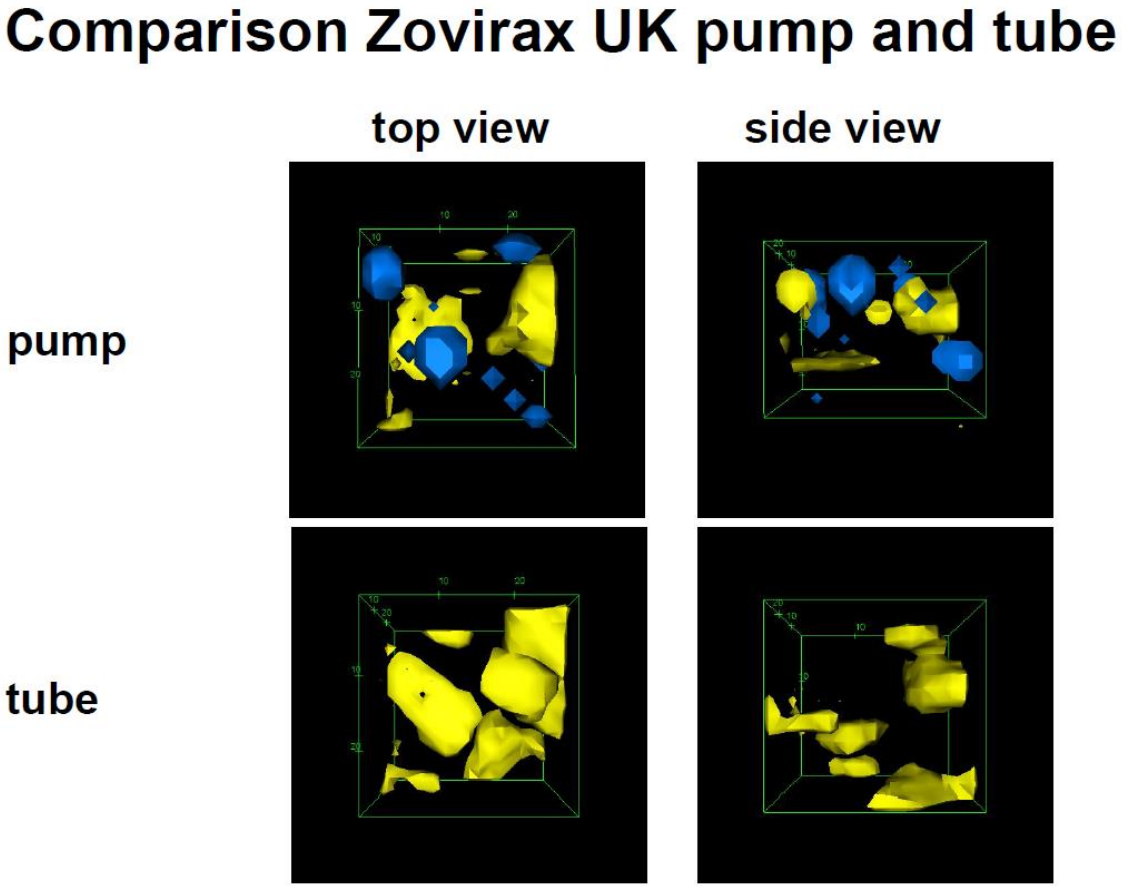
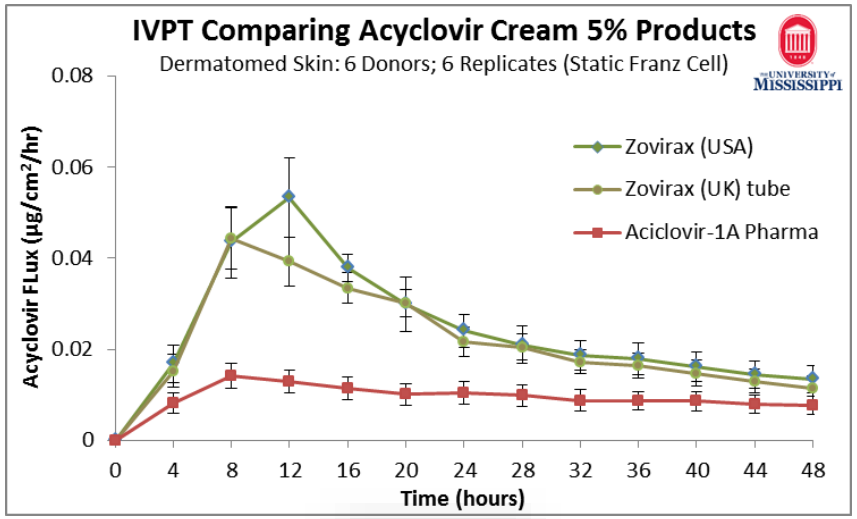
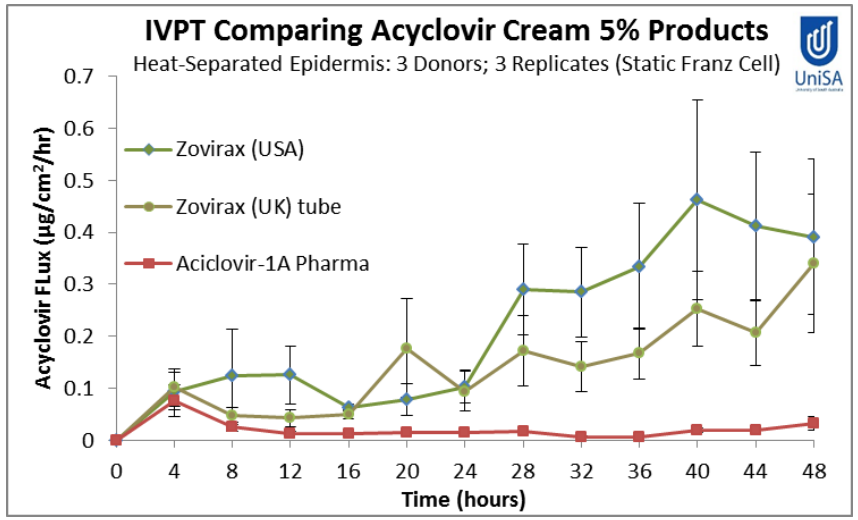
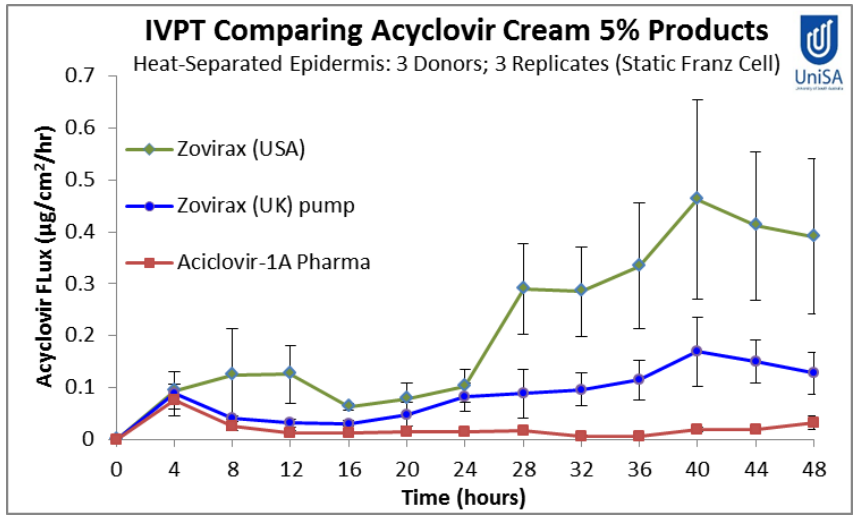


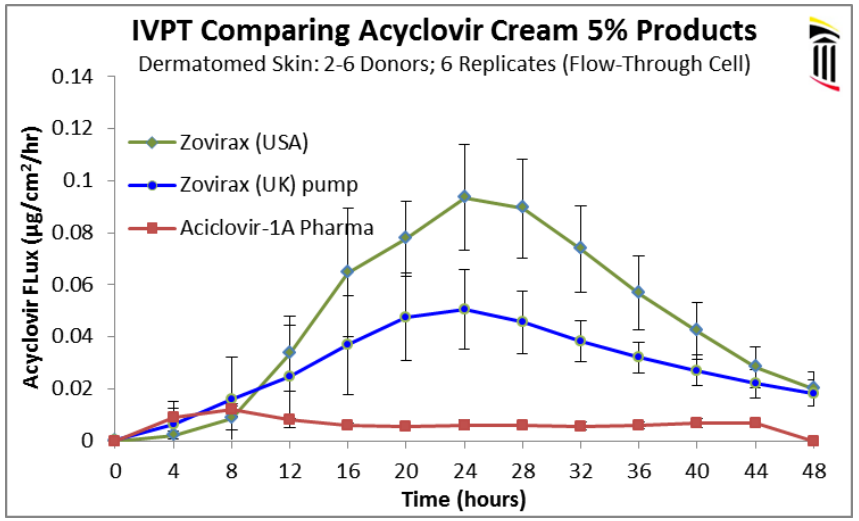
Data provided courtesy of Drs. Maike Windbergs and Mike Roberts associated with FDA funding for award U01FD0005226

IVPT Example Results







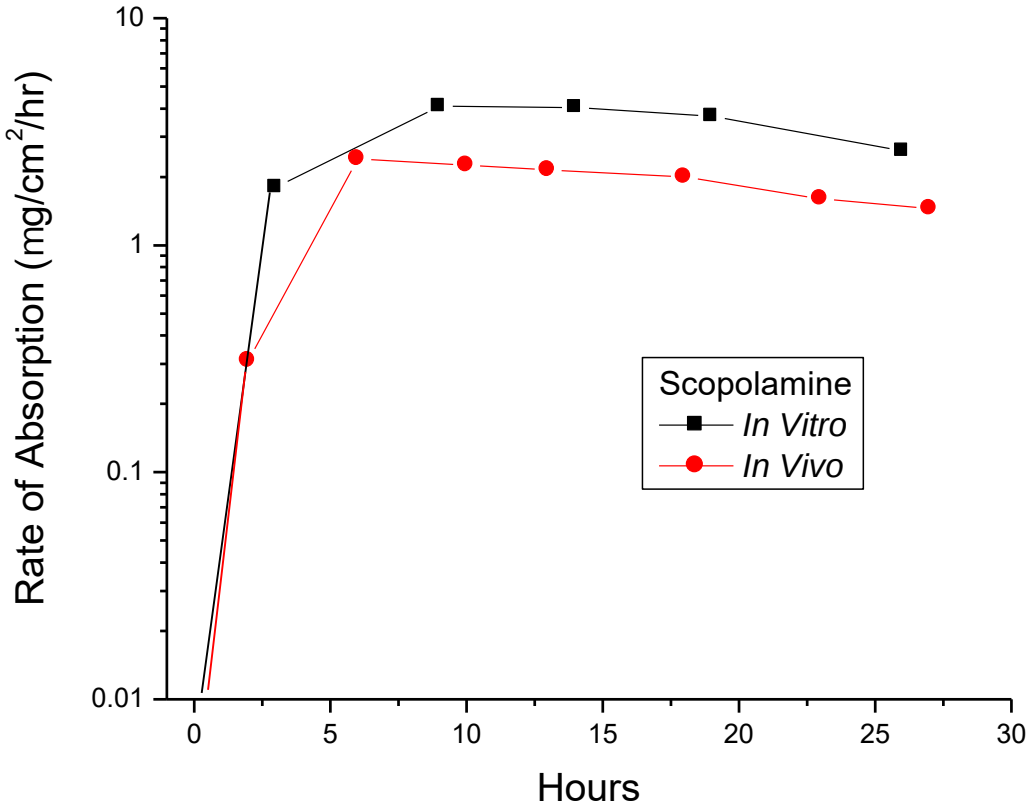


Data provided courtesy of Drs. Audra Stinchcomb, Mike Roberts, and Narasimha Murthy
associated with FDA funding for awards U01FD0004947, U01FD0005226,, U01FD0005233

IVPT: In Vitro In Vivo Correlation

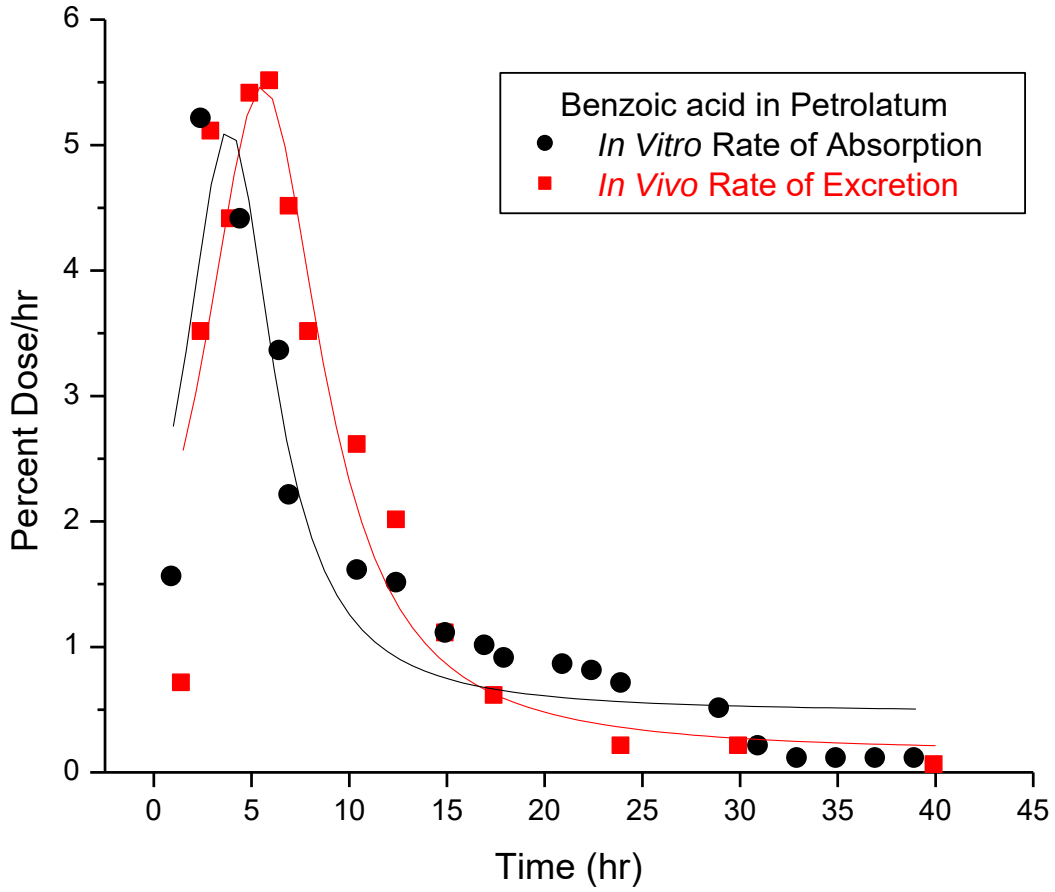
- Shaw et al., 1975

"… *in vitro* accurately predicted the situation which pertains *in vivo*."



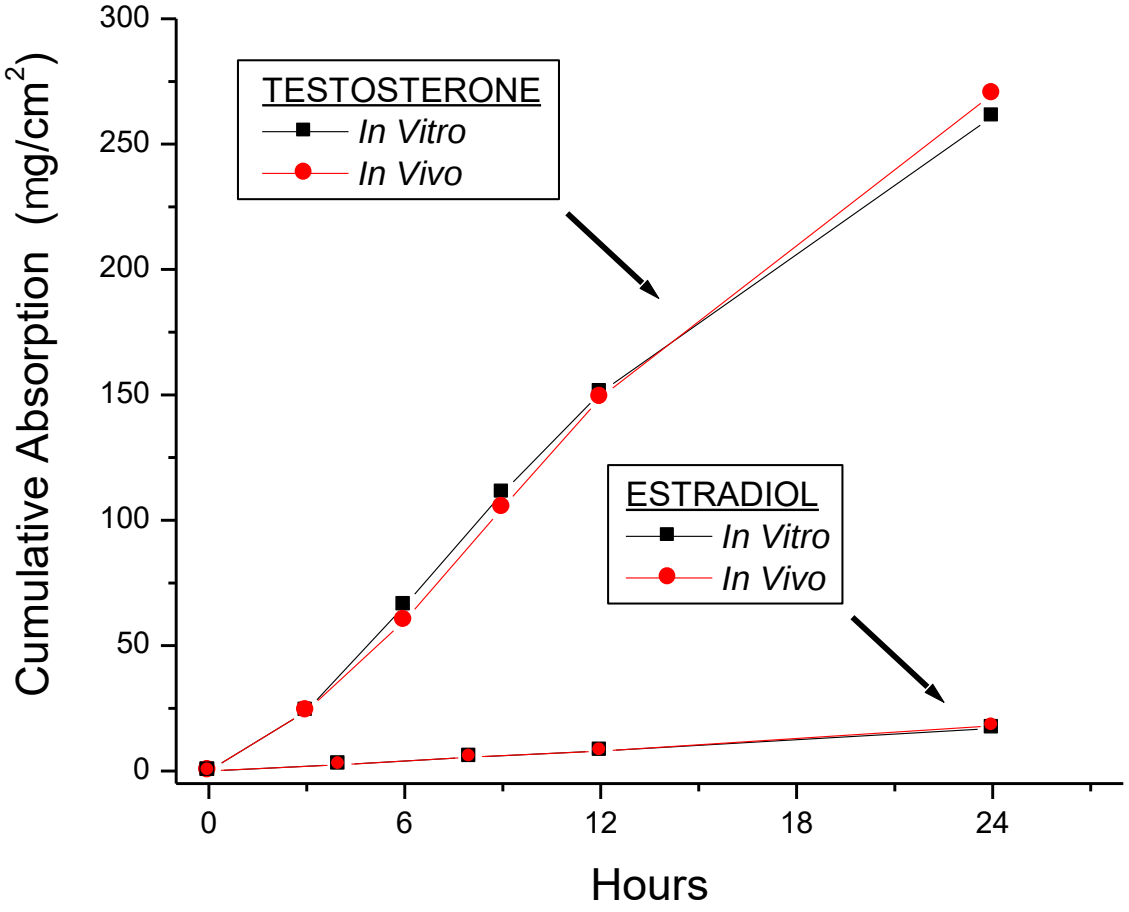
IVPT: In Vitro In Vivo Correlation

- Bronough & Franz, 1986



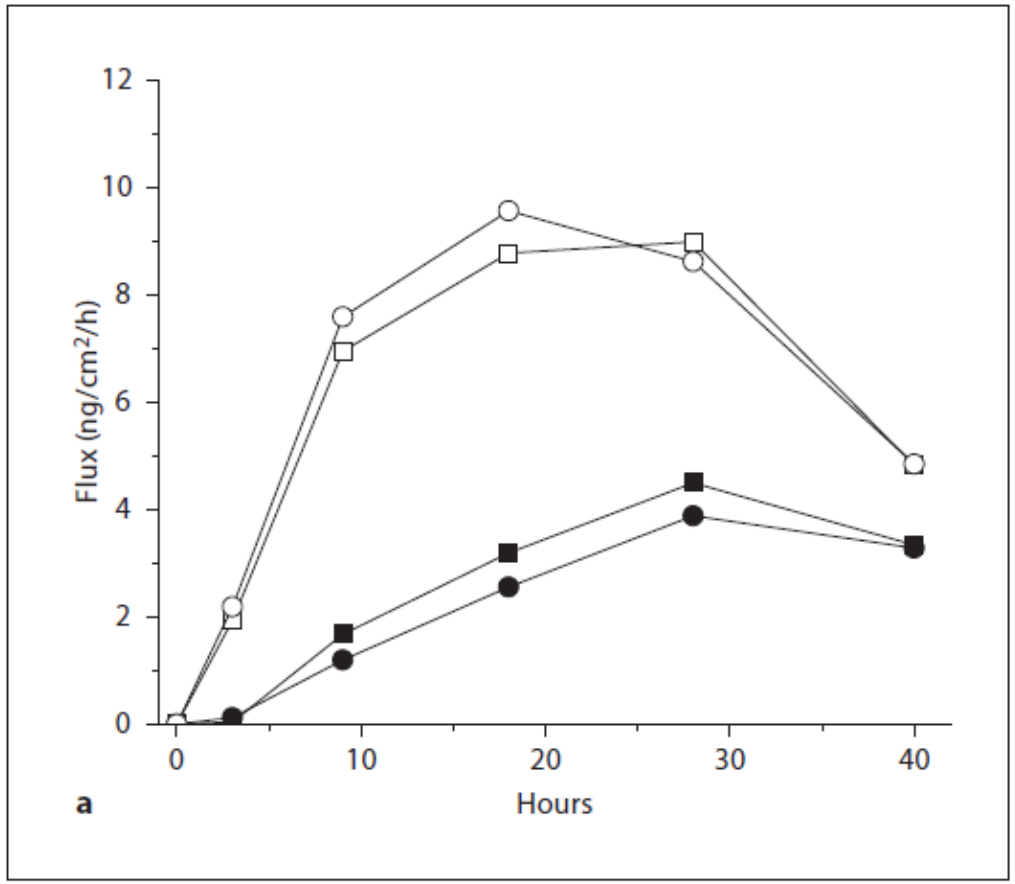
IVPT: In Vitro In Vivo Correlation

- Venkateshwaran S, 1997



IVPT: In Vitro In Vivo Correlation

- Franz et al., 2009



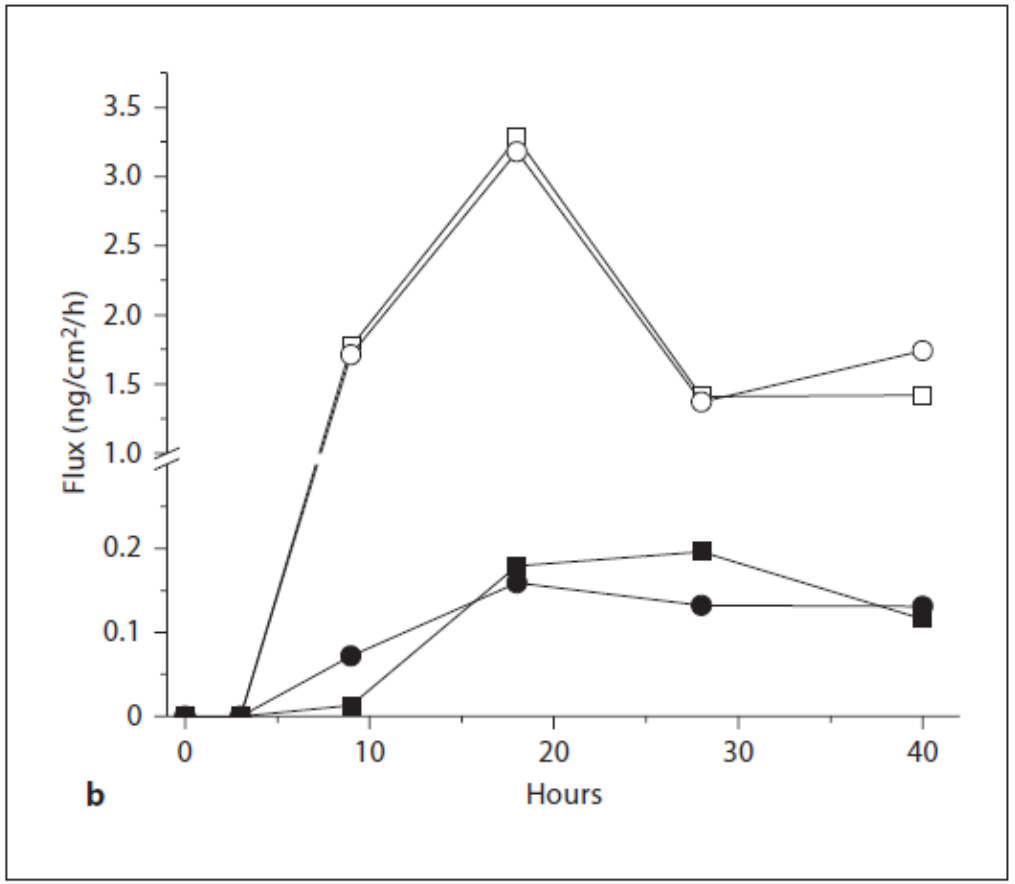


Fig. 4. In vitro percutaneous absorption of (**a**) Halobetasol propionate, and (**b**) alclometasone dipropionate. ■ = Test cream, ● = reference cream; □ = test ointment, ○ = reference ointment.

IVPT: In Vitro In Vivo Correlation

- Franz et al., 2009

	In vitro absorption[a], ng/cm^2/48 h			In vivo VC assay[a], negative $AUEC_{0-24\,h}$		
	test	reference	test/reference	test	reference	test/reference
Alclometasone cream	4.52	4.39	1.03	18.5	16.8	1.10
Alclometasone ointment	66.95	70.0	0.96	16.0	17.4	0.92
Halobetasol cream	110.4	96.9[b]	1.14	33.1	30.7	1.08
Halobetasol ointment	246.7	256.3	0.96	28.6	28.5	1.00
Mometasone ointment	213.4	338.7	0.63	13.7	12.3	1.11

[a] Listed numbers are mean values.

[b] Average of 3 reference lots, none of which were used in the VC study. In all other comparisons identical lots of test and reference products were used in both the in vivo and the in vitro studies.

IVPT: In Vitro In Vivo Correlation

- Lehman et al., 2011 (92 IVIVC Data Sets)

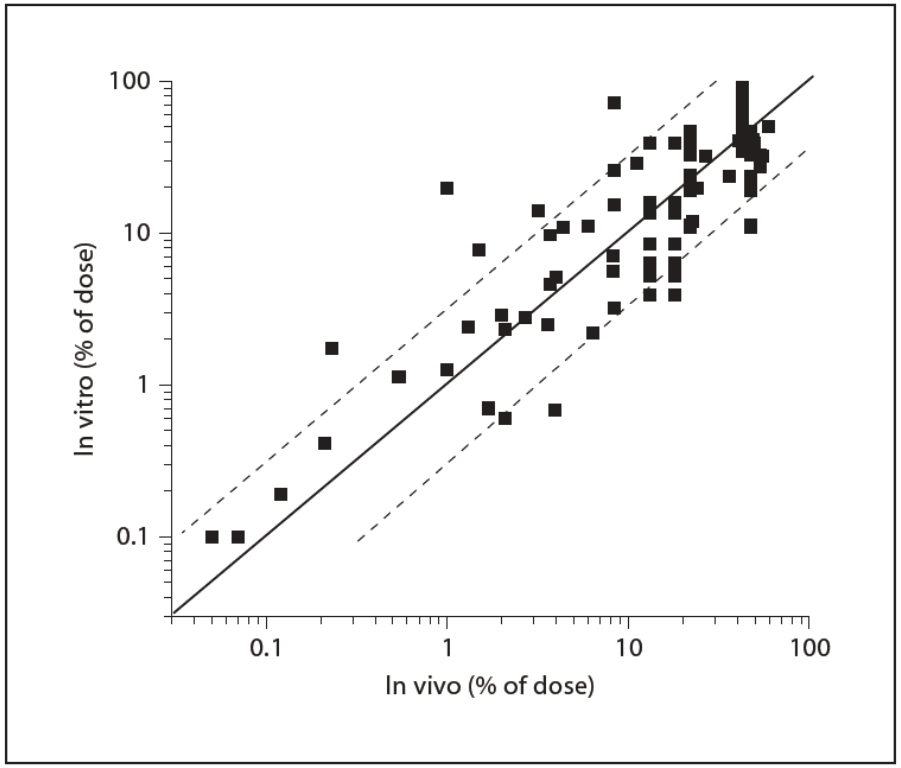


Fig. 1. IVIV ratios of total absorption for all 92 data sets plotted on log-log scale. The IVIV ratios ranged from 0.18 to 19.7, with an overall mean of 1.6. Solid line: ideal 1:1 correlation. Dashed lines: ±3-fold difference from ideal.

IVPT: In Vitro In Vivo Correlation

- Lehman et al., 2011 (92 IVIVC Data Sets)

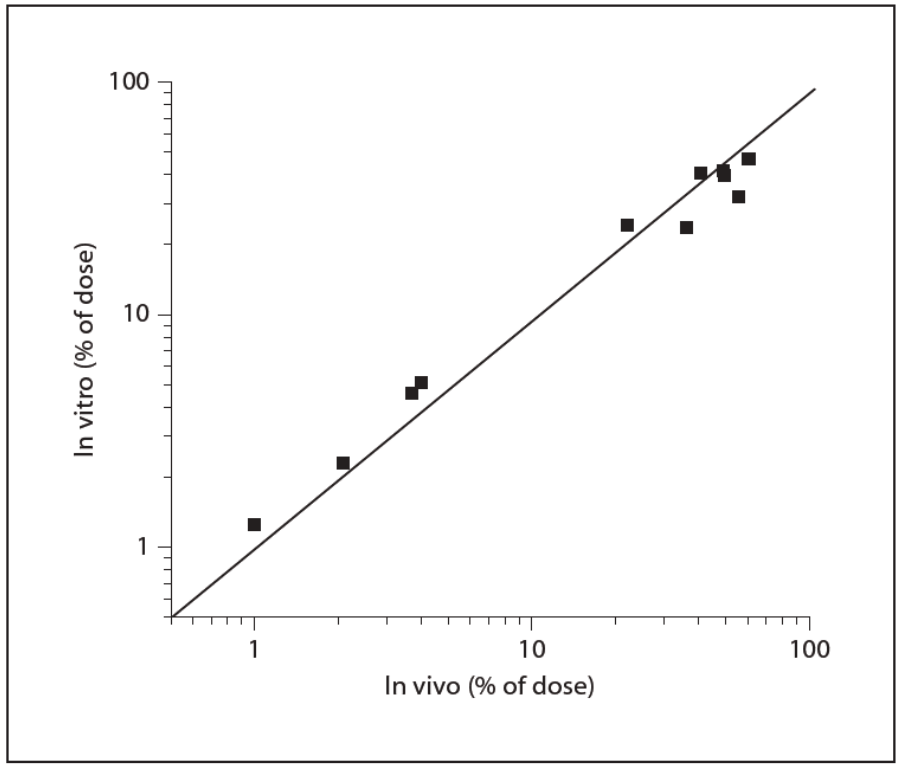
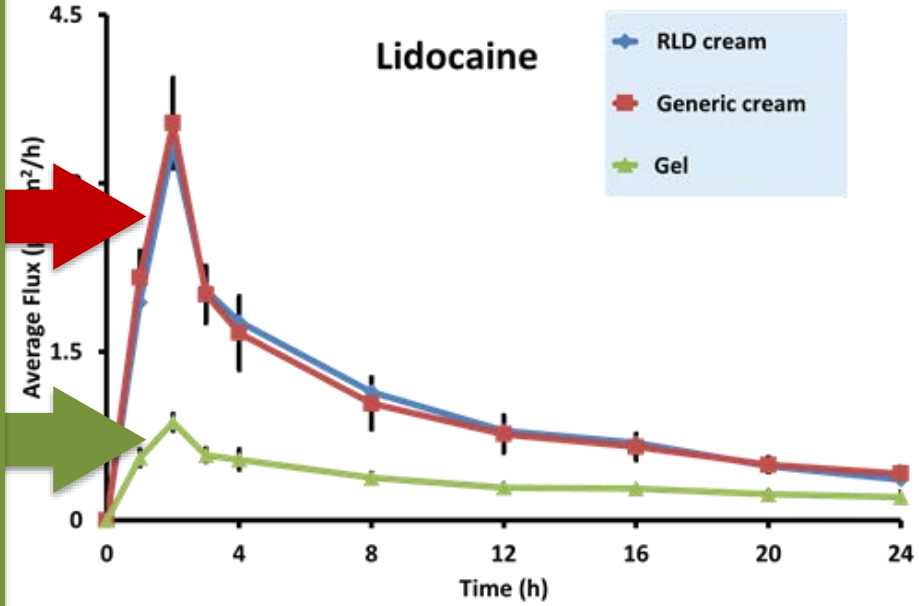


Fig. 2. IVIV ratios of total absorption for 11 fully harmonized data sets plotted on log-log scale. The IVIV ratios ranged from 0.58 to 1.28, with an overall mean of 0.96. Line: ideal 1:1 correlation.

In Vitro Cutaneous PK (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 ± 0.22	
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 Prof. Narasimha Murthy associated with FDA funding for award U01FD0005233

RLD = Reference Listed Drug

In Vivo Cutaneous PK (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
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Particle Size of API (µm)	Lidocaine and Prilocai		e completely dissolved i		n the formulation
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Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06			
	Prilocain e	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	---
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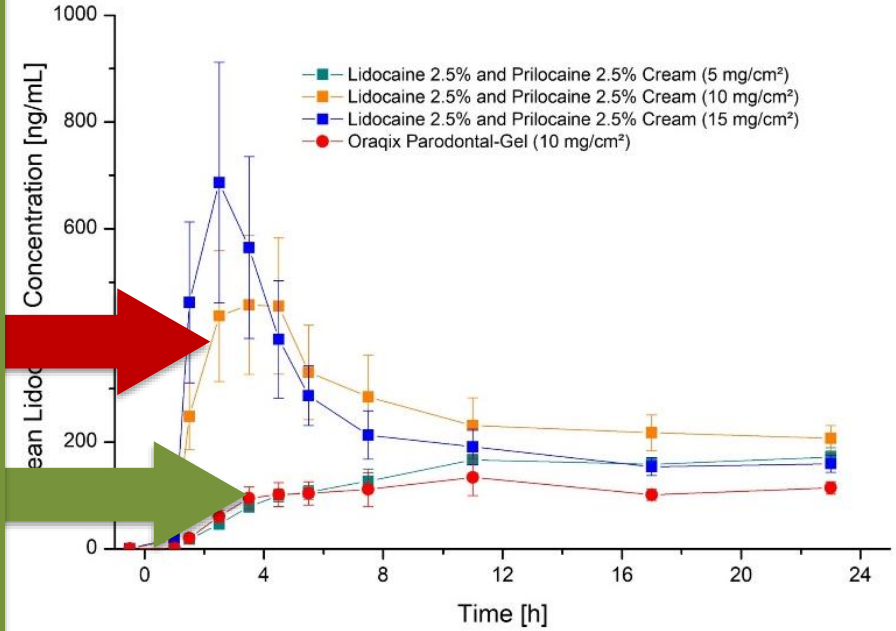
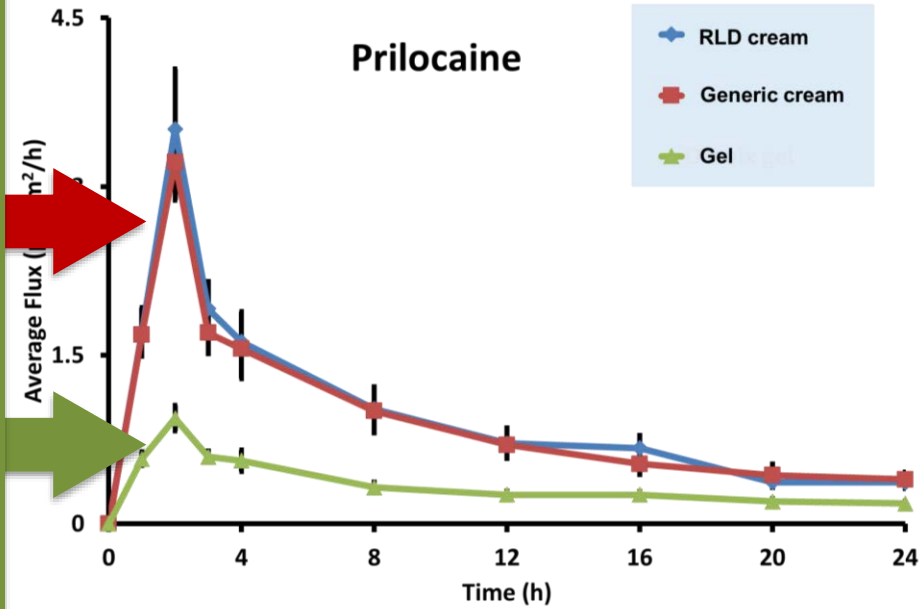


Data provided courtesy of Dr. Narasimha Murthy and Dr. Frank Sinner associated with FDA funding for awards U01FD0005233 and U01FD0005861

In Vitro Cutaneous PK (Prilocaine)

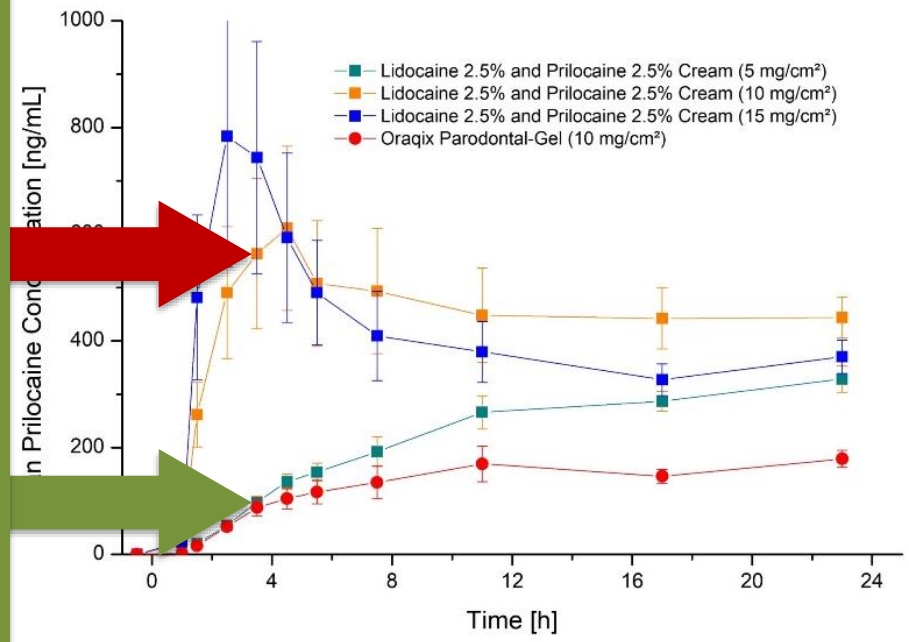
Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
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 ± 0.22	
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 associated with FDA funding for award U01FD0005233

In Vivo Cutaneous PK (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 i		n the formulation
Globule Size, d50 (µm)	3.30				
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 ± 0.22	
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



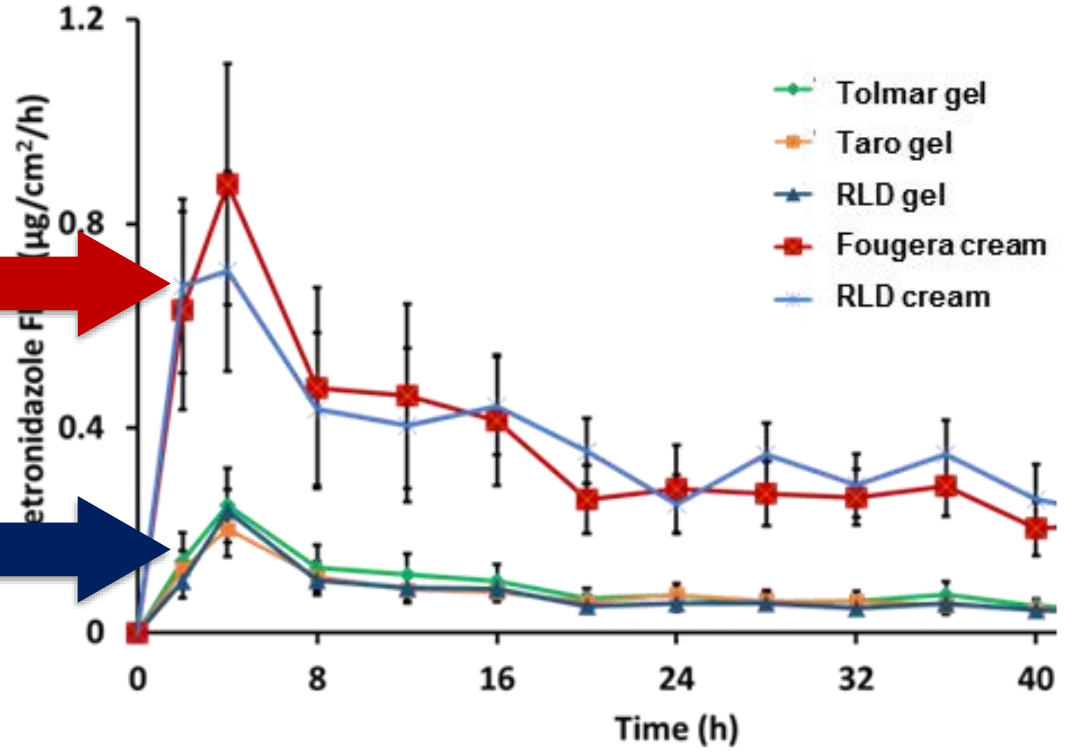
Data provided courtesy of Dr. Narasimha Murthy and Dr. Frank Sinner associated with FDA funding for awards U01FD0005233 and U01FD0005861

In Vitro / In Vivo (Metronidazole)

Quality Attribute	MetroCream® (RLD Cream)	Generic Crean (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

In Vitro Permeation Test

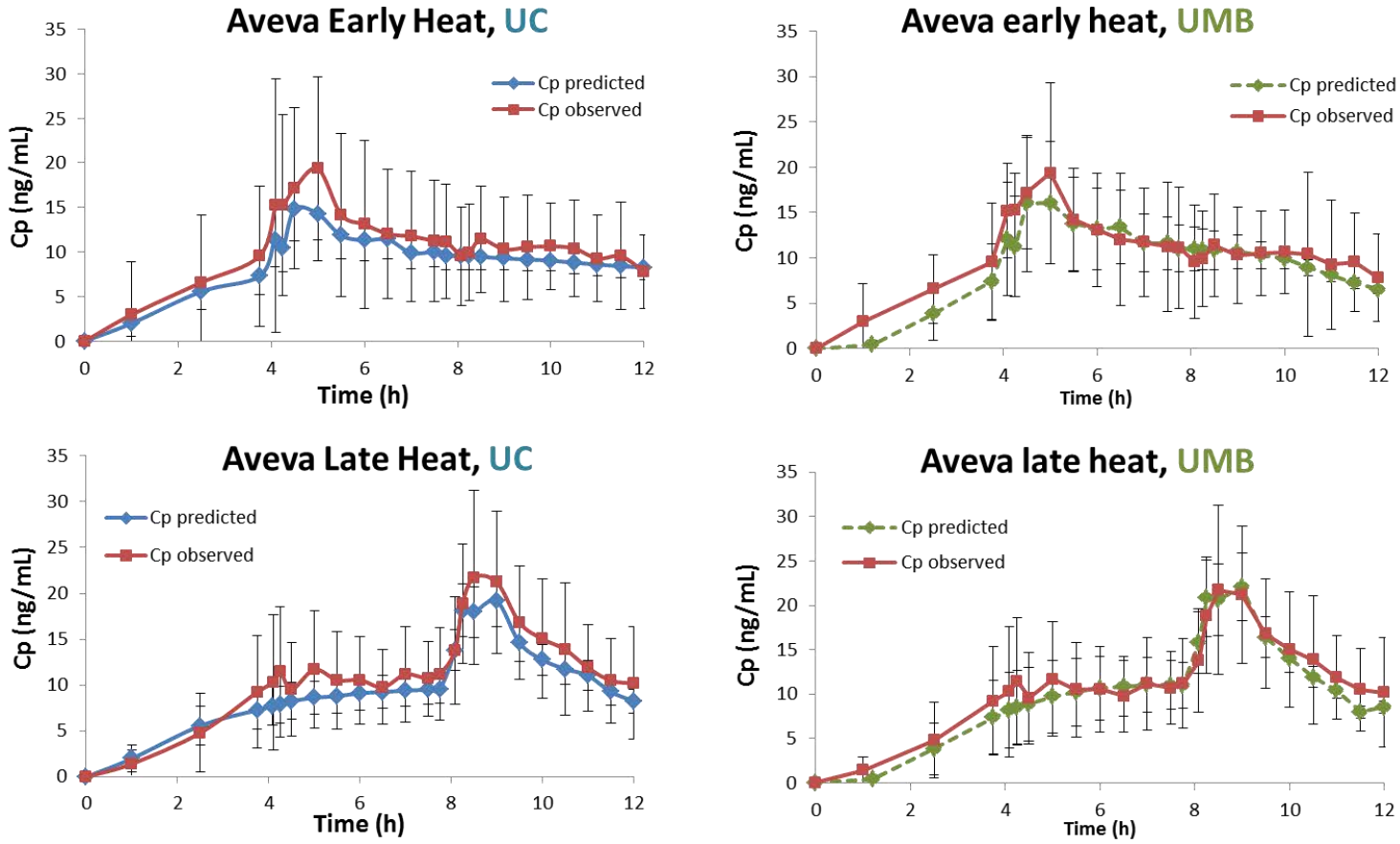
RLD = Reference Listed Drug



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

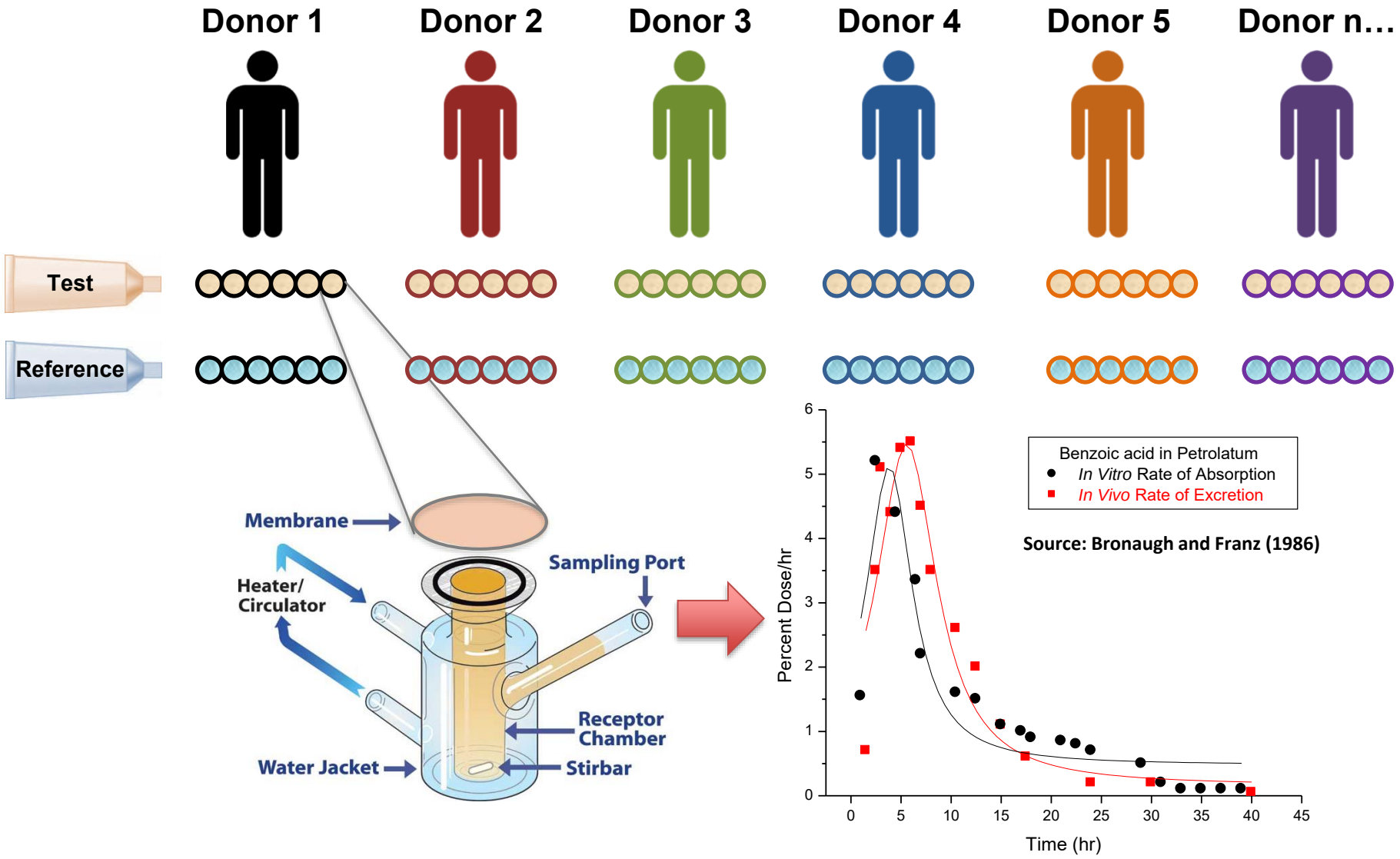
IVPT: In Vitro In Vivo Correlation

- Nicotine TDS: Level A In Vitro In Vivo Correlation



Refer to Shin et al. (2018) In vitro-in vivo correlations for nicotine transdermal delivery systems evaluated by both in vitro skin permeation (IVPT) and in vivo serum pharmacokinetics under the influence of transient heat application. J Control Release. 270: 76-88. (Funded, in part, by FDA through awards U01FD004955 (Dr. Audra Stinchcomb; University of Maryland, Baltimore) and U01FD004942 (Dr. Kevin Li; University of Cincinnati))

IVPT Study Design



IVPT Method Development Parameters

- Determination of suitable method parameters for:
  - Apparatus — Vertical Diffusion Cell (VDC) or Flow-Through Cell Types
  - Dose Amount — Finite Dose (e.g., 10 mg/cm^2)
  - Stirring Rate — Can often be standard
  - Sampling Amount — Larger sample volumes may reduce errors
  - Sampling Schedule — Suitable resolution for the flux profile
  - Receptor Solution — Suitable solubility for the drug without altering skin barrier
  - Skin Source — Typically cadaver or surgical skin
  - Skin Type — Anatomical location (e.g., posterior torso, abdomen, etc.)
  - Skin Preparation — Dermatomed, heat-separated epidermis, etc.
  - Barrier Integrity Test — Trans-Epidermal Water Loss (TEWL), electrical, radioisotope

IVPT Method Development Considerations

- Determination of suitable IVPT performance:
  - A sampling schedule and study duration sufficient to characterize the cutaneous pharmacokinetics of the drug.
  - A sampling frequency selected to provide a suitable resolution for the flux profile (e.g., a minimum of eight non-zero sampling time points across the study duration).
  - A sufficiently complete flux profile to identify the maximum (peak) flux and a decline in the flux thereafter across multiple subsequent time points.
  - A dose that can be applied in a consistent manner, provides reproducible flux profiles, provides a suitable shape for the flux profile (to identify peak flux), and results in sufficient drug permeation for analytical quantification.
    - A dose that remains on the skin for the duration of the study may undergo sufficient metamorphosis to produce a suitable flux profile.
    - Alternatively, wiping off the applied dose after a suitable duration on the skin and continuing to monitor the receptor solution for an extended period may be suitable.

IVPT Study Design

IVPT Method Development Considerations

- IVPT Skin Barrier Integrity Testing (for Membrane (Skin) Qualification):
  - Identifies (for exclusion) skin sections with compromised barrier integrity (intactness)
  - May not correlate with permeation of most topically applied drugs/compounds
  - The technical procedures do not irreversibly alter the skin barrier
    - If the test involves hydrating the stratum corneum, sufficient time is afforded for the stratum corneum to return to a normal state of hydration before dosing
    - If the test involves altering the temperature of the skin surface, sufficient time is afforded for the skin surface to return to 32°C ± 1°C before dosing
  - Acceptance criterion is a pre-defined inclusion/exclusion cutoff to pass/fail the test
    - Based upon the distribution of results (from multiple donors and replicates) when using the specific test procedures with the specific type and preparation of skin
  - Acceptance criterion discriminates skin sections with a normal barrier integrity from those with a compromised barrier integrity
    - Verified by assessing the ability of the barrier integrity test method to correctly identify skin sections with a deliberately compromised skin barrier

IVPT Method Validation Considerations

- The HPLC (MS) method used for IVPT validation is validated in a manner compatible with FDA or ICH guidelines
- IVPT validation characterizes critical method parameters
  - Apparatus Qualification (discussed separately with IVRT validation)
  - Membrane (Skin) Qualification
  - Receptor Solution Qualification
  - Receptor Solution Sampling Qualification
  - Environmental Control
  - Permeation Profile and Range
  - Precision and Reproducibility
  - Dose Depletion
  - Discrimination Sensitivity and Selectivity
  - Robustness

IVPT Method Validation Considerations

- IVPT Pilot Study:
  - Typically performed with four to six skin donors
  - Typically performed with at least four replicates per donor per treatment
  - Performed with three parallel treatments
    - Test product
    - Reference product
    - Other product with a differentiated flux profile
  - Supports a validation of IVPT method parameters like permeation profile, range, precision, reproducibility, and selectivity
  - May be useful to estimate the number of donors (and replicates) needed to power the pivotal IVPT study

IVPT Method Validation Considerations

- Membrane (Skin) Qualification
  - Skin thickness is measured and reported for each skin section to ensure that it is relatively consistent for test and reference treatments
    - The assignment of replicate skin sections from a donor to each treatment group is randomized
    - The distribution of skin thicknesses in each treatment group (test or reference) may be balanced by a procedure specified in the study protocol
  - The barrier integrity of each skin section dosed in the study is qualified
  - Barrier integrity tests may be based upon:
    - TEWL
    - Tritiated water permeation
    - Electrical impedance/conductance

IVPT Method Validation Considerations

- Receptor Solution Qualification
  - The composition and pH of the receptor solution is qualified in relation to:
    - Stability of the drug in the receptor solution samples (validated as part of the receptor sample analytical method validation)
    - Solubility of the drug in the receptor solution. 0.1% or 0.2% polyoxyethylene[20]oleyl ether (also known as Oleth-20, Volpo-20, or Brij-20; CAS number 9004-98-2) is commonly included for hydrophobic drugs
    - Solubility in the receptor solution is empirically determined (in triplicate) - sufficient to solubilize the highest drug concentration in the IVPT pilot and pivotal study samples, ideally by an order of magnitude
    - Compatibility with the skin (i.e., no alteration to skin barrier function). Inclusion of organic solvents and alcohols in the receptor solution may alter the skin barrier function
    - Skin stability to mitigate potential bacterial decomposition of the dermis and/or epidermis using and anti-microbial agent in the receptor solution (e.g., ~0.1% sodium azide or ~ 0.01% gentamicin sulfate)

IVPT Method Validation Considerations

- Receptor Solution Sampling Qualification
  - The accuracy and precision of receptor solution sample collection at each time point is appropriately qualified.
  - Evidence to qualify a sampling procedure typically illustrates that:
    - The sampling technique can reliably collect a consistent volume of the sample from the well-mixed volume of the receptor compartment at each sampling event.
      - The lengths of tubing, and their associated dead volumes are qualified to ensure a consistent lag time for flow through diffusion cells.
      - The sampling technique for VDC (e.g., the sampling volume) is demonstrated to not produce artifacts (e.g., apparent negative flux).
  - Available information describing the apparatus manufacturer's specification for the accuracy and precision of receptor solution sampling is included.

IVPT Method Validation Considerations

- Environmental Control
  - Ambient laboratory temperature and humidity during the study is monitored and reported.
  - A controlled environmental temperature is typically feasible (e.g., in the range of 21°C ± 2°C).
  - A humidity range of 50% ± 20% relative humidity is ideal, if feasible.

IVPT Method Validation Considerations

- Permeation Profile and Range
  - The flux profile and cumulative permeation profile for the IVPT pilot study results are plotted at each sampling time across the study duration.
  - The profiles validate that the selected study parameters adequately characterize the cutaneous pharmacokinetics across the range of sampling times.
  - A complete flux profile is one that identifies the maximum (peak) flux and a decline in the flux thereafter across multiple subsequent time points in the IVPT pilot study.
  - The results of the IVPT pilot study also validate that the sampling frequency provides suitable resolution to adequately characterize the permeation profile (particularly the flux profile).

IVPT Method Validation Considerations

- Precision and Reproducibility
  - The flux and cumulative permeation results from the IVPT pilot study are calculated, tabulated, and reported for each diffusion cell at each time point.
  - The tabulated IVPT pilot study data is clearly organized for each donor, replicate, treatment group, timepoint, etc.
  - Complete results for all data values utilized in the calculations are reported in a clear and organized manner, to facilitate the reconstruction of the flux and cumulative permeation results.
  - Summary statistics describe the:
    - Intra-donor average, standard deviation, and percent coefficient of variation (%CV) among replicates
    - Inter-donor average, standard error, and %CV

IVPT Method Validation Considerations

- Dose Depletion
  - The nominal amount of drug dosed on skin sections is estimated based on:
    - The nominal strength of the drug in the topical product and
    - The approximate mass of topical product dosed on the skin
  - The cumulative total permeation of the drug in the receptor solution is calculated for each skin section.
  - This is expressed as a percentage of the nominal amount of drug in the applied dose and represents the percentage dose depletion.

IVPT Method Validation Considerations

- Discrimination Sensitivity and Selectivity
  - **IVPT Sensitivity** is the ability of the IVPT method to detect changes in the cutaneous pharmacokinetics of the drug as a function of differences in drug delivery.

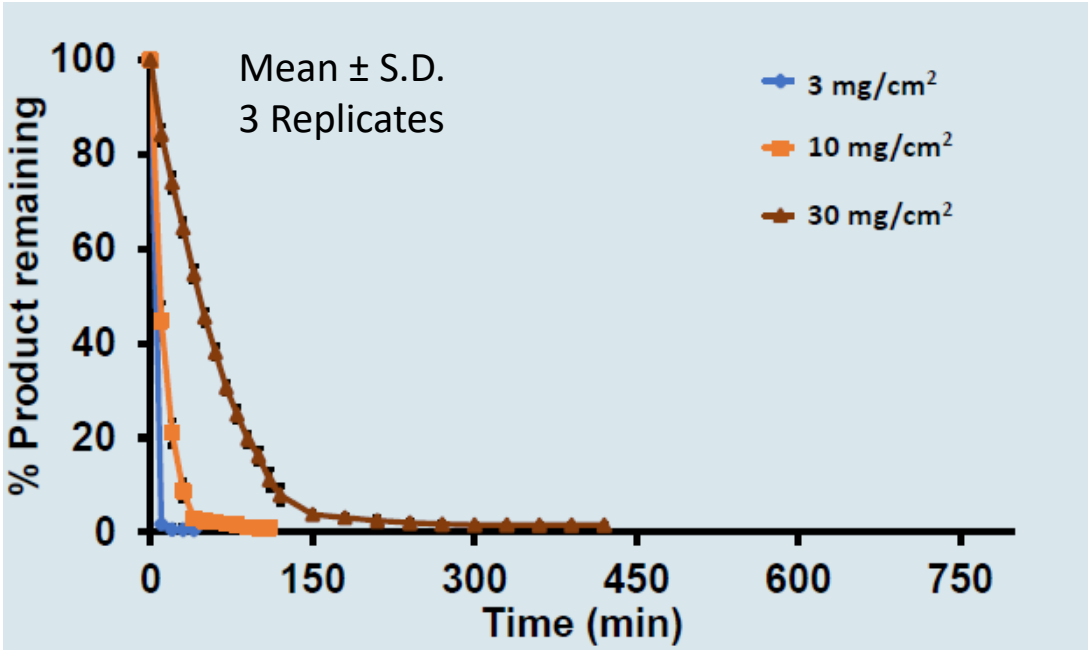


Fig 1: Rate of Drying of Metronidazole Gel, 0.75%

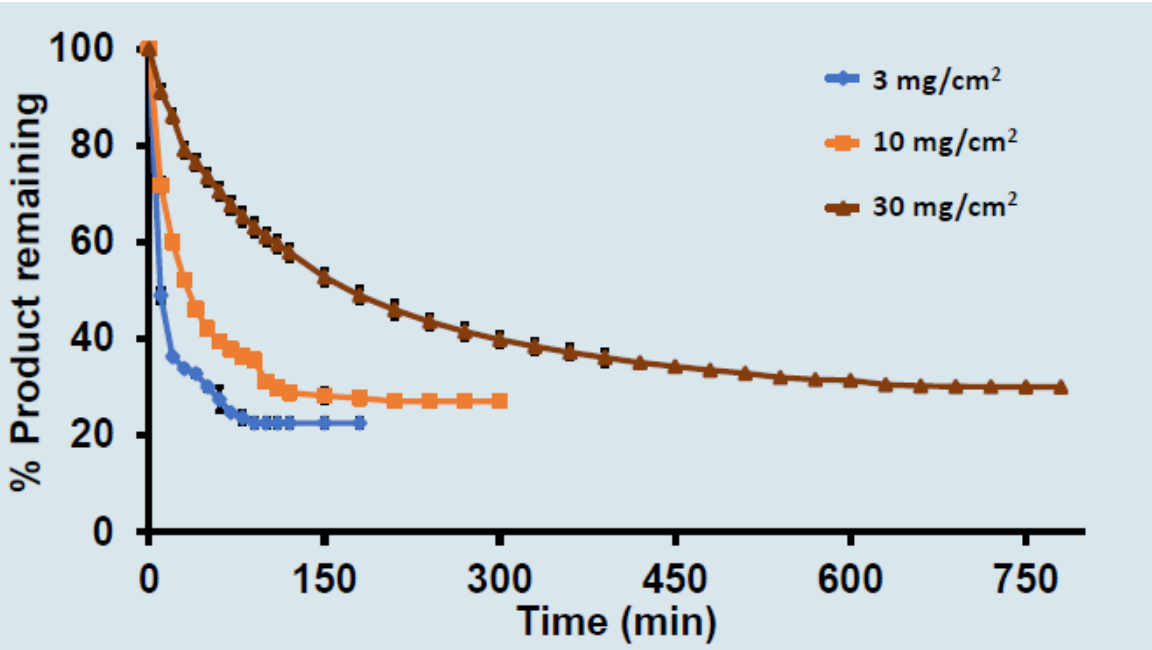


Fig 2: Rate of Drying of Metronidazole Cream, 0.75%

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

IVPT Method Validation Considerations

- Discrimination Sensitivity and Selectivity
  - **IVPT Sensitivity** is the ability of the IVPT method to detect changes in the cutaneous pharmacokinetics of the drug as a function of differences in drug delivery.

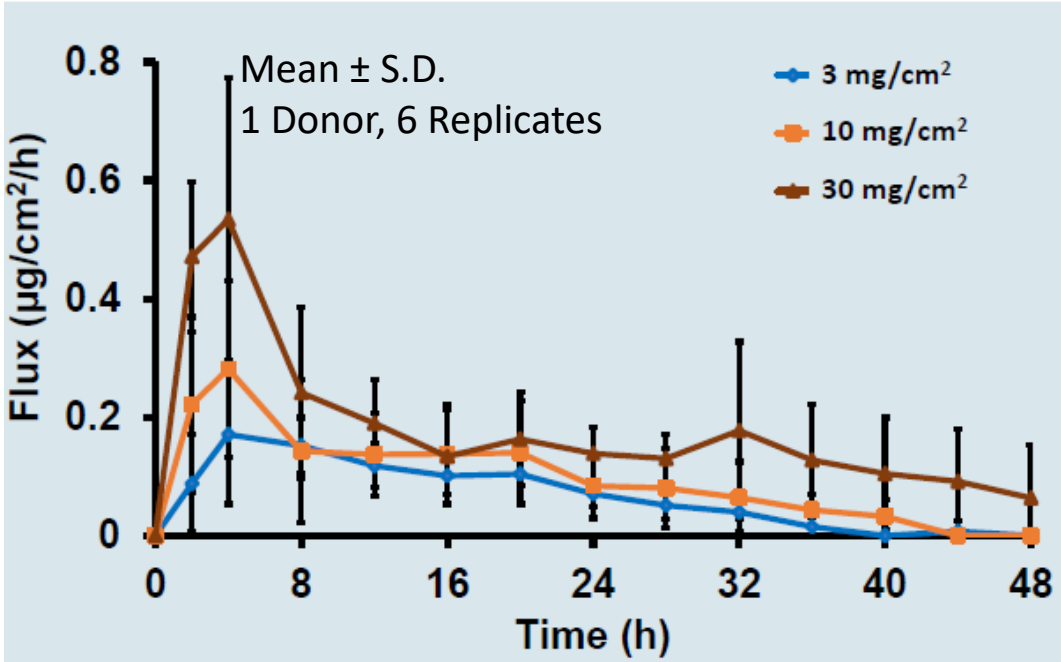


Fig 3: IVPT profile of Metronidazole Gel, 0.75%

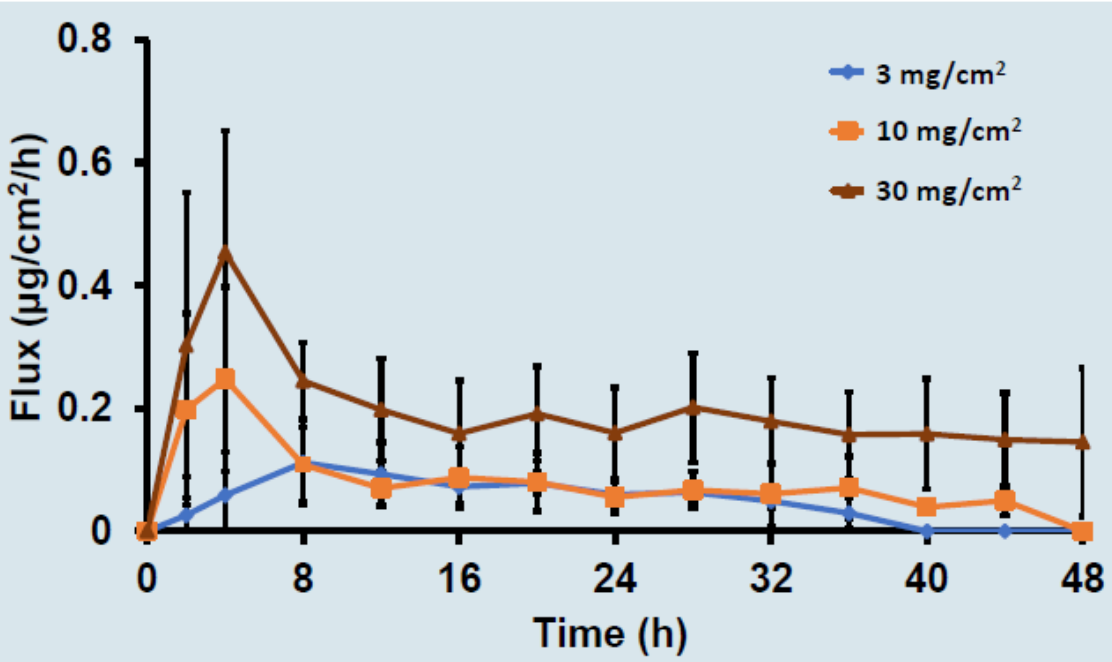


Fig 4: IVPT profile of Metronidazole Cream, 0.75%

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

IVPT Method Validation Considerations

- Discrimination Sensitivity and Selectivity
  - **IVPT Sensitivity** is the ability of the IVPT method to detect changes in the cutaneous pharmacokinetics of the drug as a function of differences in drug delivery.
  - Potential approaches to produce differences in drug delivery that can be differentiated by a suitably discriminating IVPT method are:
    - Modulation of Dose Amount
    - Modulation of Dose Duration
  - The differences in the IVPT permeation profiles are not expected to be specifically proportional to differences in the dose amount, dose duration, or product strength.
  - The IVPT sensitivity studies are typically **performed during IVPT method development** (to establish IVPT method parameters like the dose amount, dose duration, study duration, etc.).

IVPT Method Validation Considerations

- Discrimination Sensitivity and Selectivity
  - **IVPT Selectivity** is the ability of the IVPT method to discriminate the cutaneous pharmacokinetics of a drug between products (or formulations) that exhibit differences in drug delivery.
  - The parallel assessment in the IVPT pilot study of the reference topical product, the test topical product, and a third topical product or formulation (that is known or designed to be different from the reference topical product) provides supportive evidence that the IVPT methodology is selective.
  - This IVPT selectivity study is **performed as part of the IVPT pilot study**.

IVPT Method Validation Considerations

- Robustness
  - A primary assumption related to robustness testing is that the test system performs consistently when all system variables (e.g., temperature, stirring rate) are at nominal settings.
  - However, due to the variability inherent in the permeability of human skin, in vitro or in vivo, it may not perform consistently even when all system variables are at nominal settings.
  - Yet, an IVPT method may be robust to certain method parameters, like variations in the stirring rate of the receptor compartment.
  - So, results that support the robustness of an IVPT method may be reported.
  - Ultimately, since it may not always be feasible to validate the robustness of IVPT method parameters, IVPT study procedures are controlled as precisely as possible.

IVPT Quality Management System (QMS)

- IVPT validation and pivotal studies are conducted within a QMS that includes documented procedures for
  - Study personnel identification, training, qualification, and responsibilities
  - Study management and study management personnel responsibilities
  - Quality control (QC) and QC personnel responsibilities
  - Quality assurance (QA) and QA personnel responsibilities
  - Utilization of SOPs, study protocols, and study reports
  - Maintenance and control of the study facility environment and systems
  - Qualification and calibration of instruments and computerized systems
  - Good documentation practices
  - Maintaining suitable records that facilitate the reconstruction of study events
  - Archival of study records

IVPT BE Study Considerations

- Handling and Retention Product Samples
  - Refer to 21 CFR 320.38, 320.63 and the following Guidances for Industry, as applicable, regarding considerations for retention of study drug samples:
    - Handling and Retention of BA and BE Testing Samples (May 2004)
    - Guidances for Industry: Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c) (August 2020)
  - Refer to 21 CFR 320.36 for information on requirements for maintenance of records of BE testing.
  - Retention samples should be randomly selected from the drug supplies received prior to dispensing during the IVPT study in which the test and reference topical products are compared.
  - Experimental observations that may have the potential to influence the interpretation of the study results, as well as any protocol deviations, should be reported.

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