IVPT Unplugged: From Challenges to Solutions in Topical Permeation Method Development.

Nahid Kamal, Ph.D.
Office of Pharmaceutical Quality Research
Office of Pharmaceutical Quality
FDA Center for Drug Evaluation and Research

Advancing Generic Drug Development: Modernizing Bioequivalence Approaches for Topical & Transdermal Products. September 10, 2026

DISCLAIMER
This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Everyone deserves confidence
in their *next* dose of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

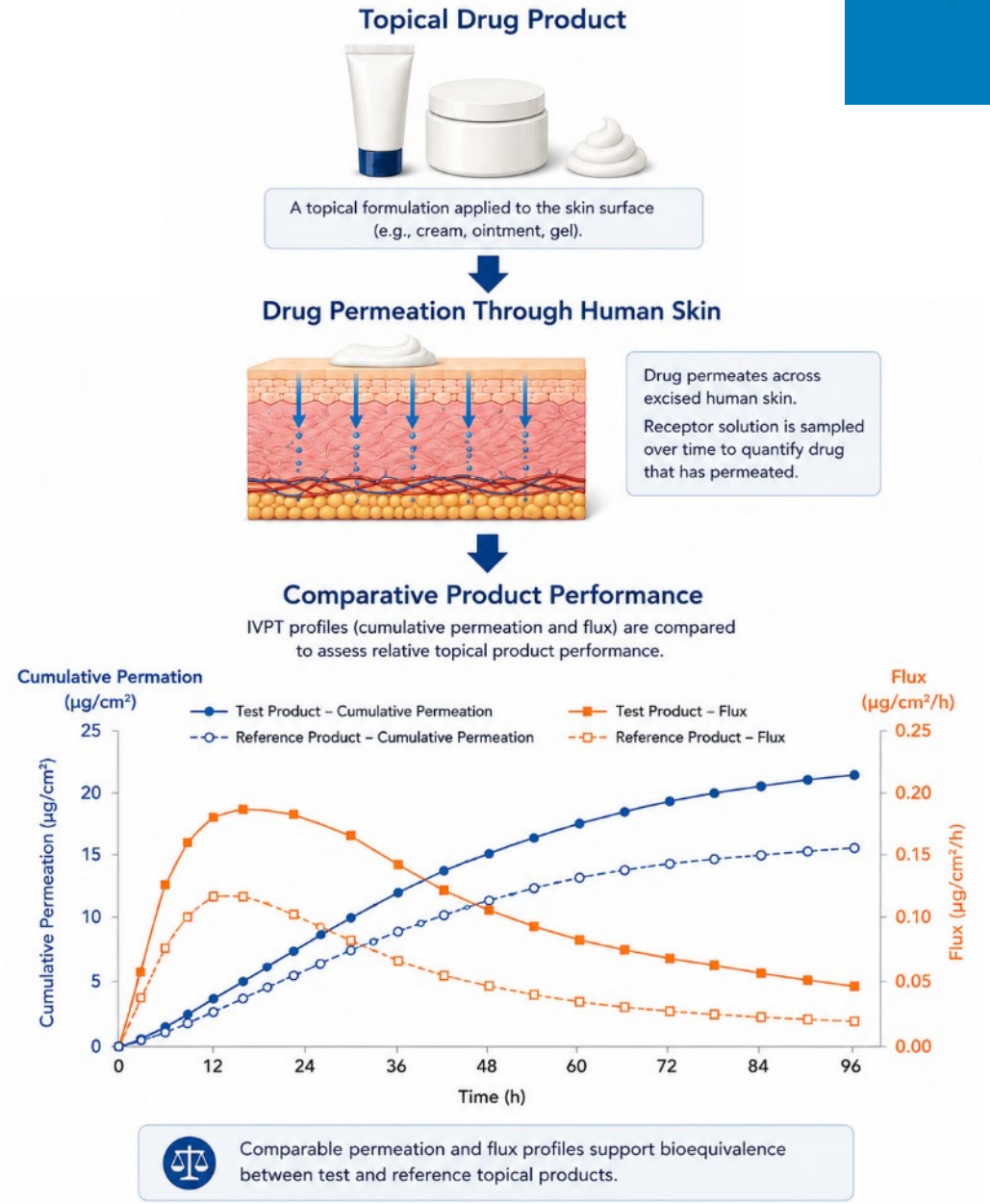
Objectives

- Illustrate key considerations and challenges in developing a fit-for-purpose IVPT method.
- Demonstrate a systematic, evidence-based approach to IVPT method development using ruxolitinib cream as a case study.
- Show how the development logic can inform method development for another topical product using roflumilast cream as an example.

IVPT: From Product Performance to Bioequivalence Assessment

- IVPT provides time-resolved information on drug permeation across excised human skin.
- Permeation and flux profiles can characterize topical drug-product performance at the skin barrier.
- For certain topical drug products, IVPT may be included as part of the recommended bioequivalence approach in a Product-Specific Guidance.

A fit-for-purpose IVPT method is essential for meaningful comparison of test and reference products.



Know Before You Go: Building an Informed IVPT Starting Point

KNOW THE DRUG
-Solubility
-Ionization
-Partition

Receptor solution, sink conditions & permeation

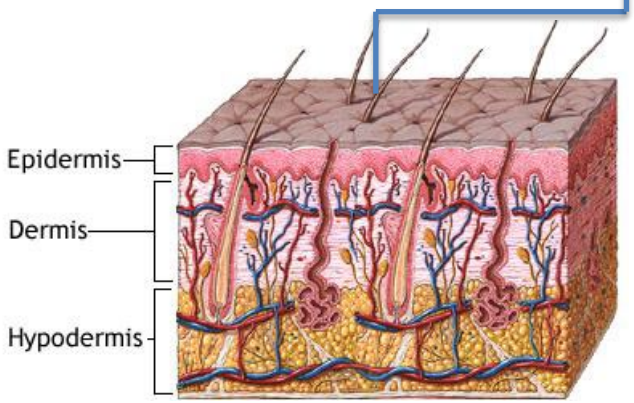
KNOW THE PRODUCT
-Formulation
-API state
--Distribution

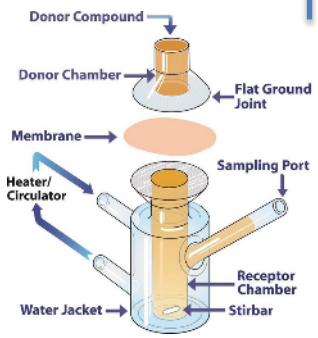
Drug availability & release

INFORMED IVPT
STARTING POINT

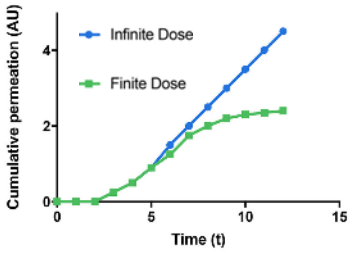
KNOW THE BARRIER
-Skin source
-Thickness
-Integrity
-Variability

Permeability & data variability





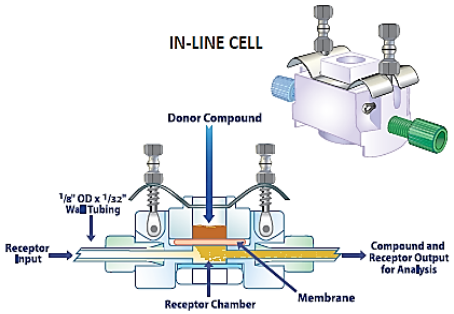
KNOW THE STUDY/ OBJECTIVE
-What to characterize
-Expected permeation levels
-Profile needed



Analytical sensitivity and study design

Risks to consider when buying topical creams made outside the US
API drying systems - GTI Industrial Dryers
Skin layers: MedlinePlus Medical Encyclopedia Image
https://doi.org/10.1016/j.ejps.2024.106873

From Product Understanding to a Fit-for-Purpose IVPT Method

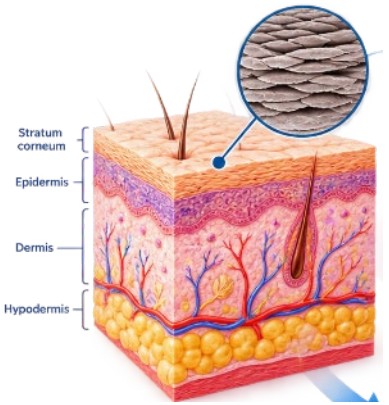


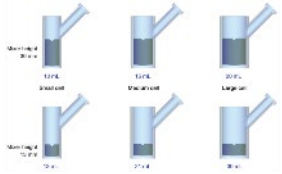
https://permegear.com/

https://kc-labtech.com/vision-microette-automated-test-system/

https://www.teledynelabs.com/products/diffusion/phoenix-db-6

https://www.loganinstruments.com/

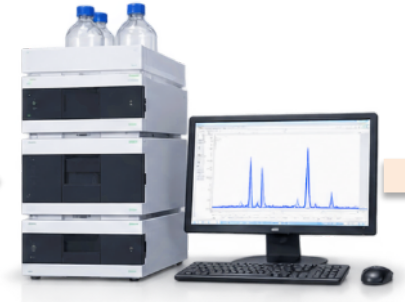


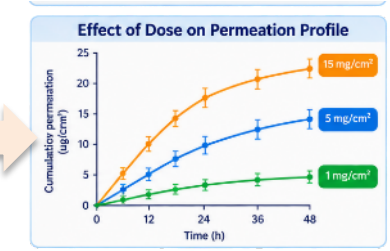


- **Skin Barrier**
  - Source • Integrity • Donor variability
- **Dose Optimization**
- Amount (consistency, reproducibility) and
- Application method (flux profile shape)
- **Temporal Design**
- Study duration (complete characterization)
- Sampling schedule (adequate resolution)

- **Apparatus & Sampling**
- Cell configuration • Automated/manual sampling
- **Receptor Solution**
- Composition • Volume • Receptor capacity

Receptor solution





Analytical Capability
Sensitivity • Quantitation

Informative Permeation & Flux Profiles

Ruxolitinib Topical Cream

Product
Opzelura (ruxolitinib phosphate) 1.5% cream is a Janus kinase (JAK) inhibitor

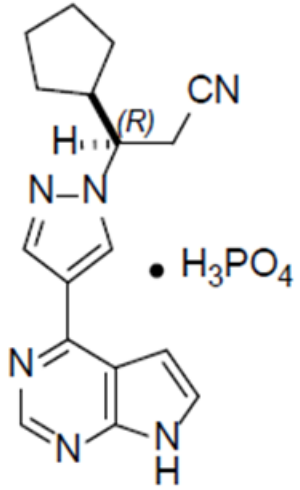
Indication
The topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older

Formulation
- Oil-in-water emulsion
- Complex multiphasic system

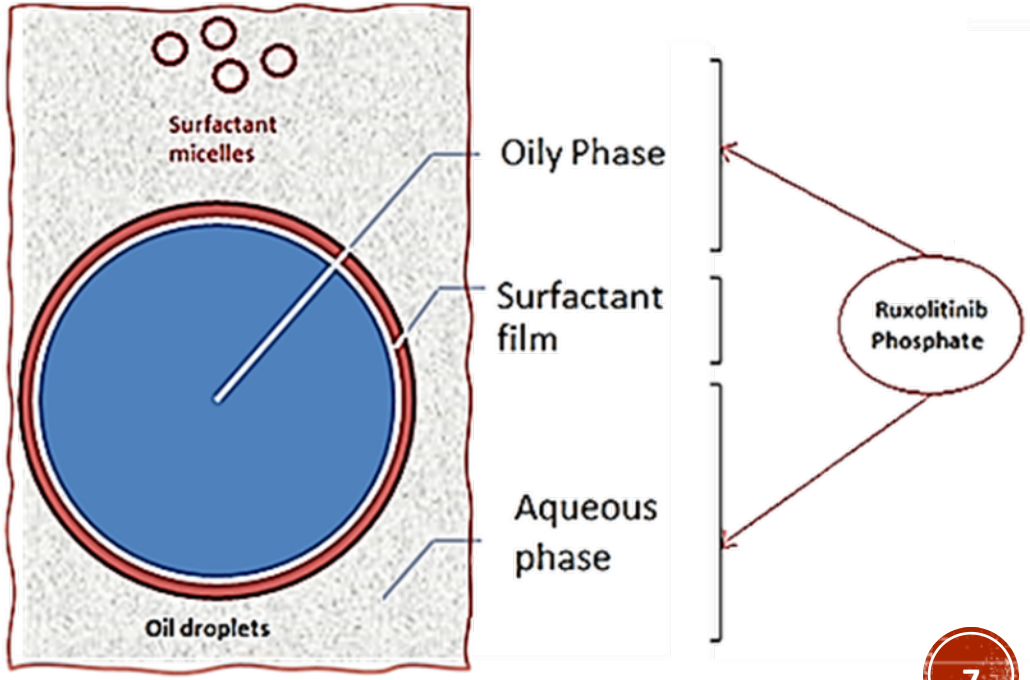
Drug Properties
- pKa 4.3, 11.8
- LogP 3.47
- pH-dependent solubility

Challenge
- Complex semisolid formulation
- pH-dependent drug solubility
- Need for measurable and interpretable IVPT profiles

https://www.skinsafeproducts.com/ruxolitinib-cream-1-5-rx-60-g-incyte-corporation



Ruxolitinib Phosphate



A Systematic Approach to Ruxolitinib IVPT Method Development

Start with an Initial IVPT Method

▼

Identify the Major Challenge

▼

Define the scientific question

▼

Design an experiment to address it

▼

Evaluate the IVPT Outcome

▼

Retain useful conditions / refine the method

▼

Identify the next limitation

▼

Repeat until the study objectives are met

Challenge	Scientific Question
Receptor solution	Which receptor solution is most suitable?
Analytical sensitivity	Can we improve detectability?
Study duration	Is the study duration sufficient?
Experimental artifacts	Are unexpected results biological or methodological?

One challenge → Focused experiment → Evidence-based decision

Challenge 1: Selecting the Receptor Solution

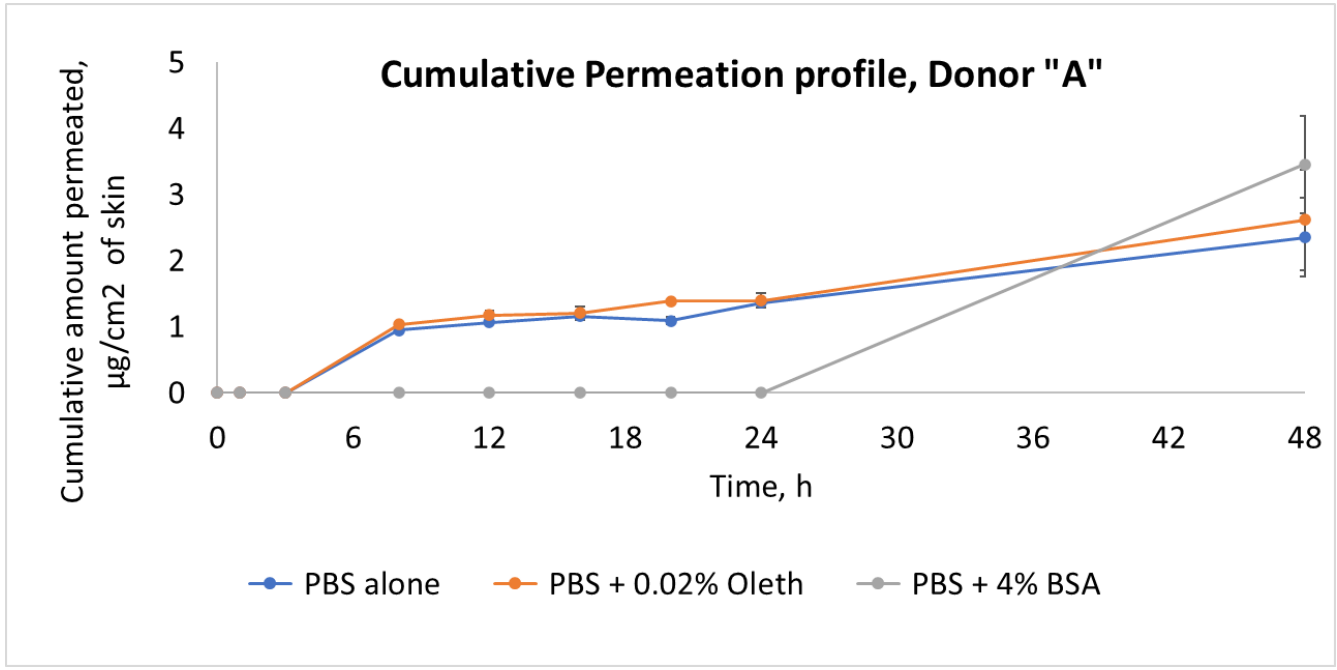
How do we choose a receptor medium that provides reliable IVPT data?

Scientific Question

Which receptor medium provides adequate receptor capacity and measurable permeation without unnecessary complexity?

Receptor media evaluated

Receptor Medium	Purpose
PBS (pH 7.4)	Physiological reference
PBS + 0.02% Oleth-20	Increase solubility
PBS + 4% BSA	Improve sink conditions



Key Findings of Exp. 1

- Similar permeation profiles observed
- No meaningful improvement with Oleth-20 or BSA

Decision: PBS alone was selected because it provided comparable permeation while minimizing experimental complexity.

Challenge #2: Improving Analytical Sensitivity

Can we improve analytical sensitivity without changing the analytical method?

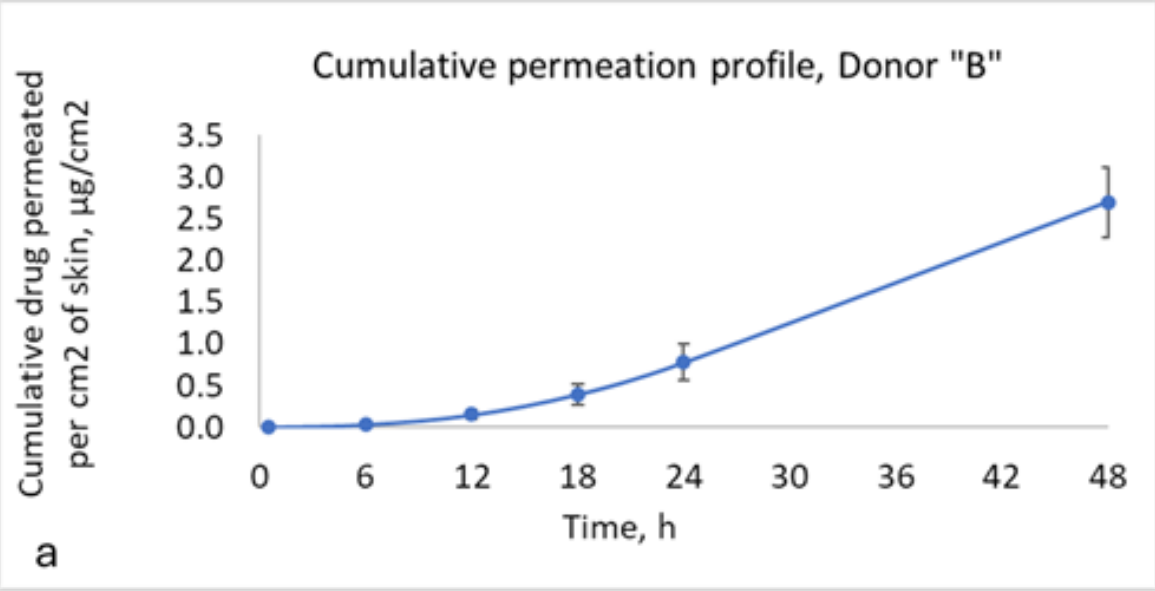
Observation from Exp. 1

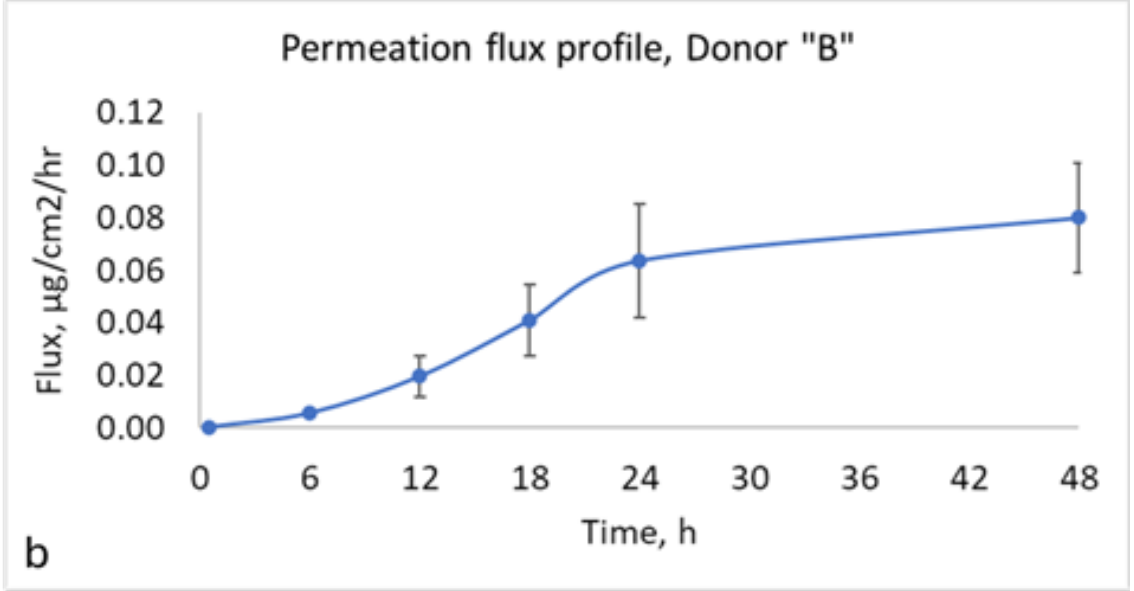
- Low receptor-phase concentrations
- Limited early-time-point detection

What changed in Exp. 2?

Parameter	Exp. 1	Exp. 2
Dose	11 mg/cm²	15 mg/cm²
Receptor Volume	15 mL	6.5 mL

Increase measurable receptor-phase concentrations and improve detectability. But the profile was still evolving at 48 h



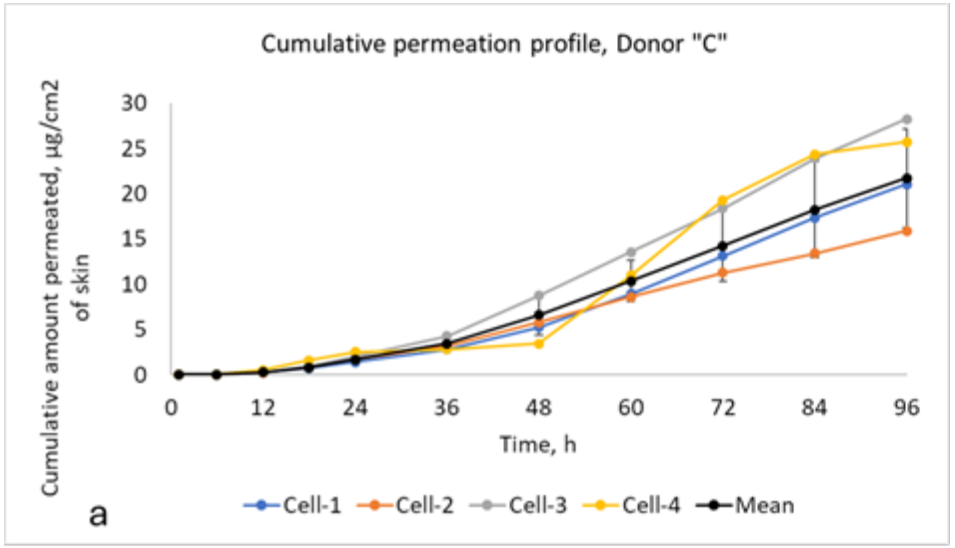


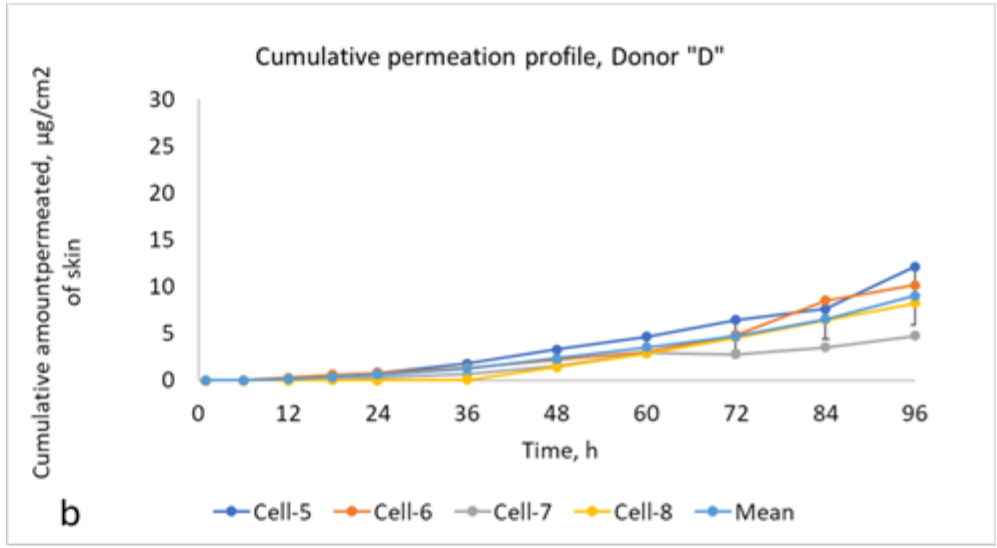
Challenge #3: Is 48 Hours Enough?-Permeation Profiles

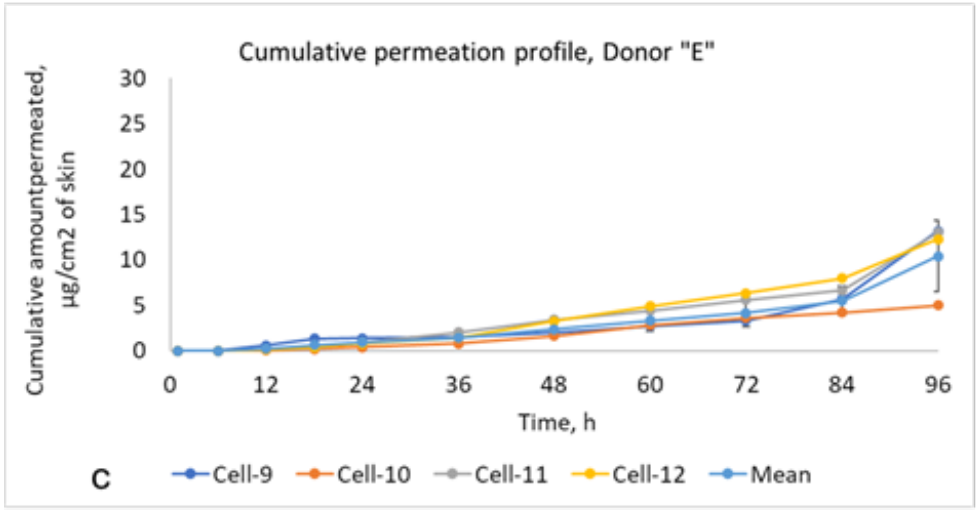
Capturing the Complete Permeation Profile

Observation from Exp. 2
48-hour study
↓
Flux still increasing
↓
Incomplete profile

What changed in Exp. 3?
- Study duration: 48 → 96 h
- More frequent sampling
- 15 mg/cm² retained
- 6.5 mL PBS retained
- 3 additional donors

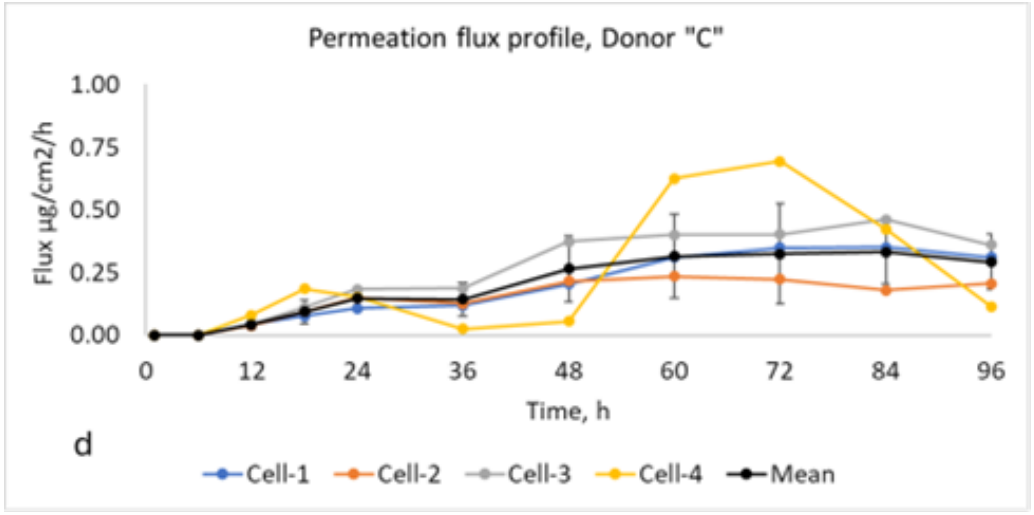


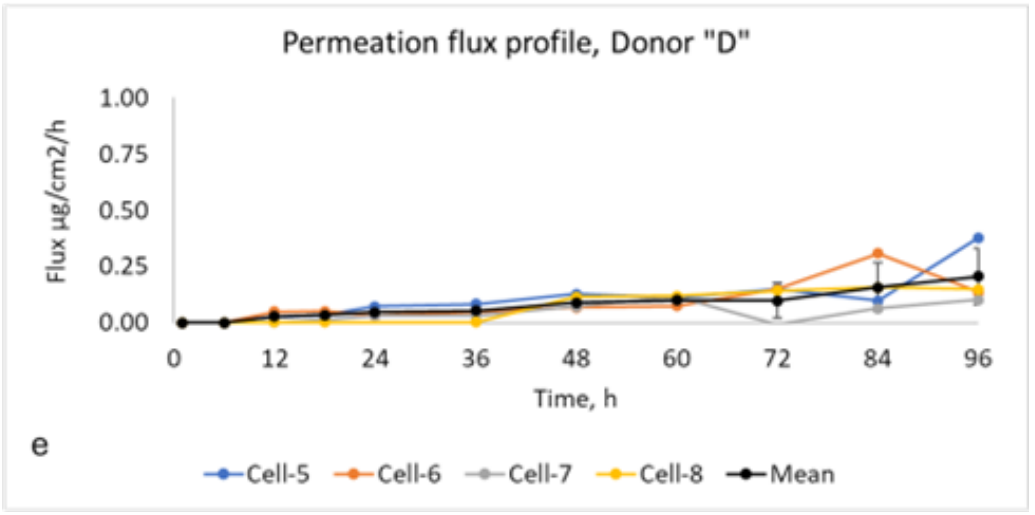


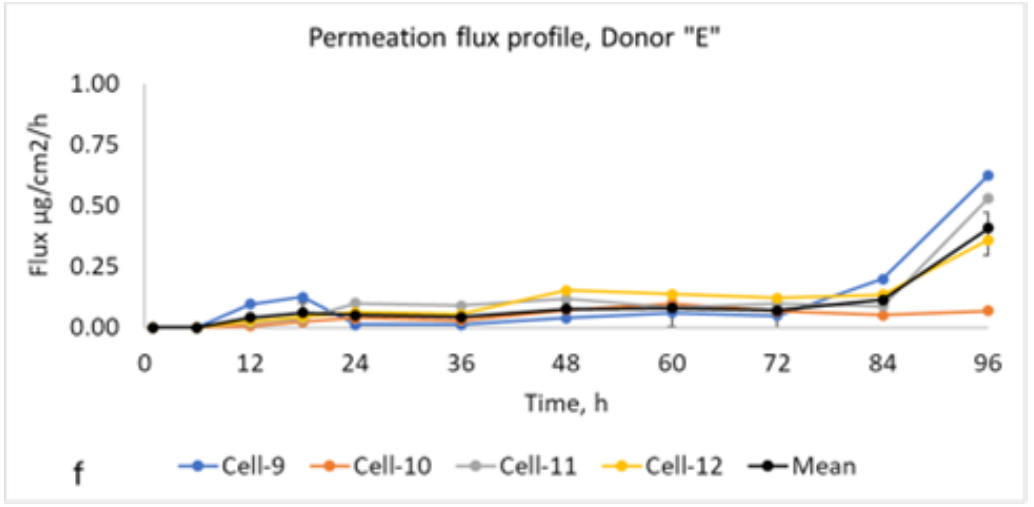


Challenge #3: Is 48 Hours Enough? –Flux Results

Capturing the Complete Flux Profile



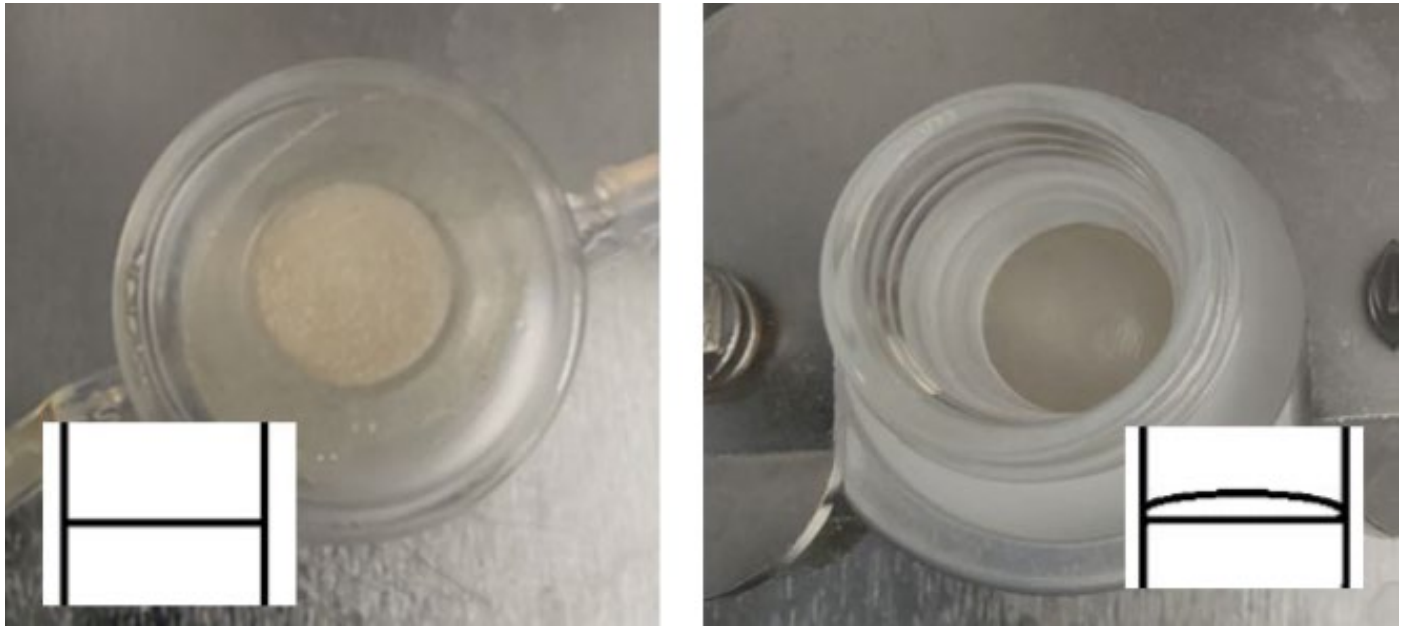




What we learned

- More complete permeation profiles
- Better characterization of flux over time
- Later decline observed in several replicates
- 96 h retained for subsequent optimization

An Unexpected Observation: Was It Biological or Experimental?



Photographic evidence suggested an experimental artifact rather than biological variability.

Observed in Experiment 2

- One replicate out of six developed visible skin doming
- Abnormal membrane geometry and data

Question: Could the automated sampling process be contributing to the deformation?

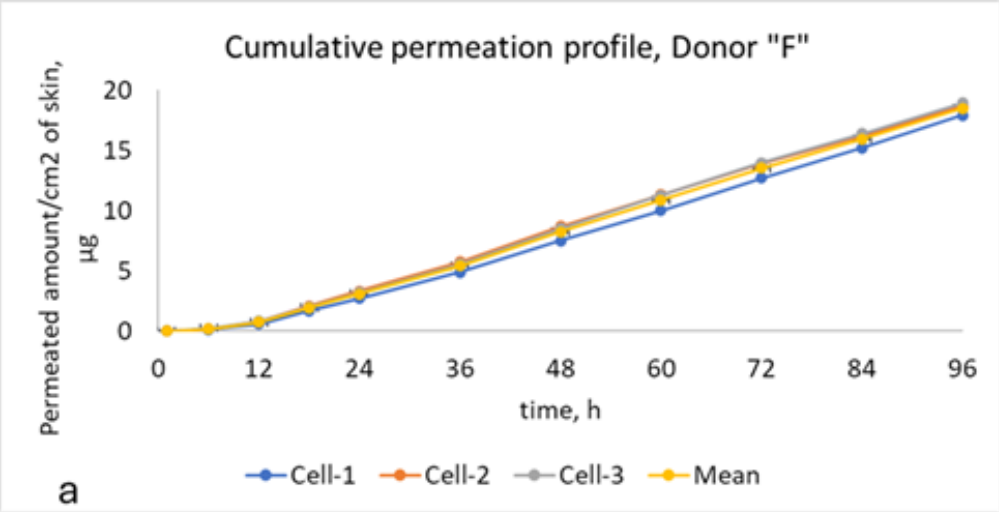
Challenge #4: Addressing the sampling artifact and final method optimization

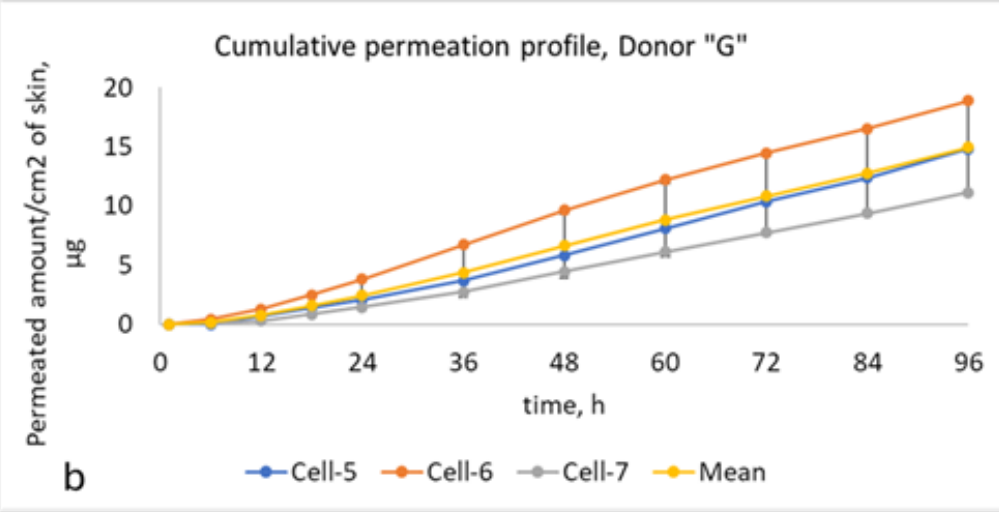
IVPT Conditions	Experiment 1	Experiment 2	Experiment 3	Experiment 4
Skin source	Dermatomed human cadaver skin			
Skin anatomical site	Thigh			
Skin thickness (µm)	~300 ± 100 (dermatomed)			
Skin integrity test and acceptance criterion	TEWL, ≤10 g/m2/h			
No. of donors	1, Donor A	1, Donor B	3, Donors C, D, and E	3, Donors F, G, and H
No. of replicates per treatment	3 (one additional non-dosed replicate)	6	4	3 (one additional non-dosed replicate)
Receptor solution	(1) PBS (pH 7.4) with 0.02% Oleth-20, 2) PBS (pH 7.4) with 4% BSA, and 3) PBS (pH 7.4) alone. Each also included 0.1% sodium azide.	PBS (pH 7.4) including 0.1% sodium azide		
Equipment evaluated	Phoenix dry heat diffusion cell system, automated sampling	Microette automated system		Phoenix dry heat diffusion cell system, manual sampling
Diffusion area of the orifice (cm2)	1.77			
Receptor solution volume (mL)	15	6.5		9
Dose amount (mg/cm2)	11 (unoccluded)	15 (unoccluded)		
Dose application method	The dose was applied with a positive displacement pipette, followed by gentle spreading using the closed end of a capillary rod.			
Skin surface temperature (°C)	32 ± 1			
Stirring rate (rpm)	600			
Sampling volume (mL)	0.7 (sample collection volume = 0.5 + prime volume = 0.2)	2 (sample collection volume= 1.5 + rinse volume = 0.5)		1
Sampling timepoints (h)	0.5, 1, 2, 4, 8, 12, 16, 20, 24, 48	0.083, 6, 12, 18, 24, and 48	1, 6, 12, 18, 24, 36, 48, 60, 72, 84, and 96	
Dose duration (h)	48		96	
Study duration (h)	48		96	

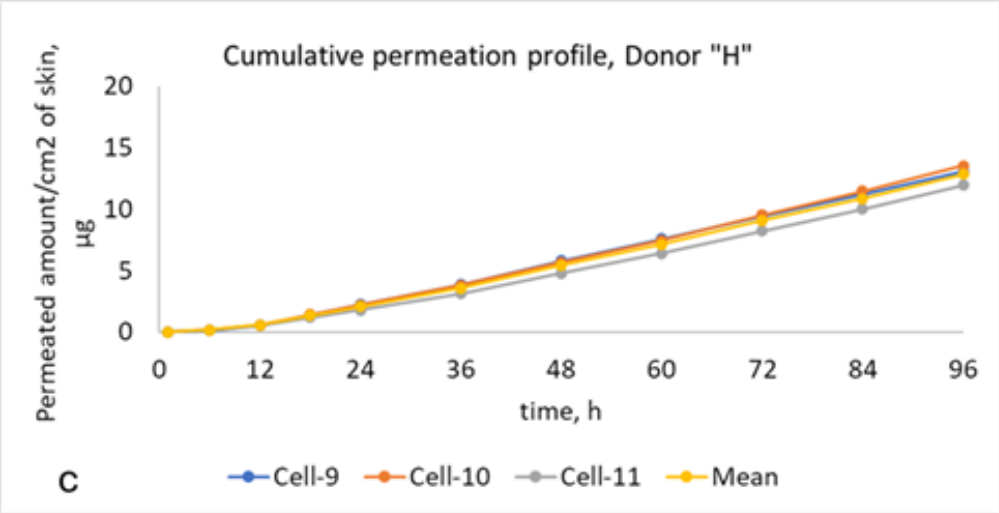
The final optimization addressed the experimental mechanics—not the drug, formulation, or skin.

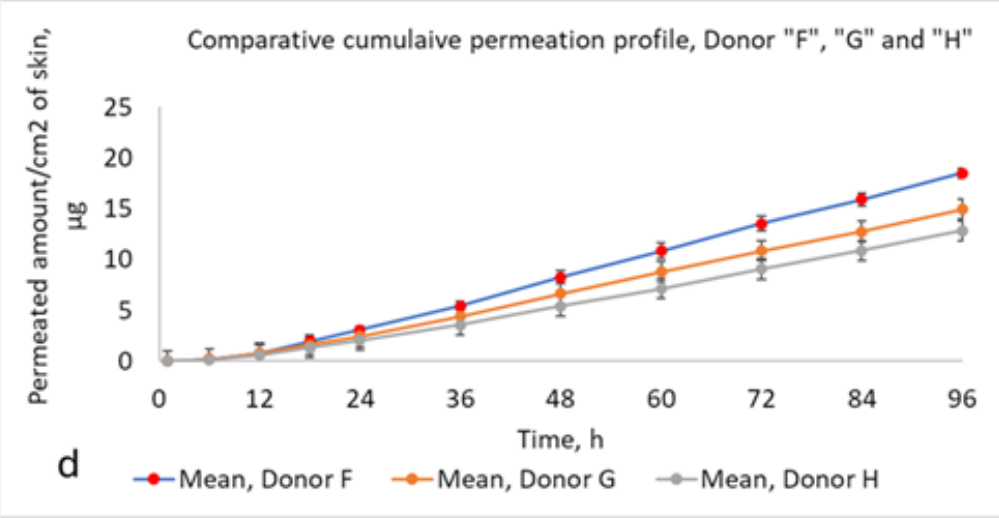
Final optimization: IVPT Permeation Profiles

Did the final modifications produce consistent and interpretable permeation profiles?









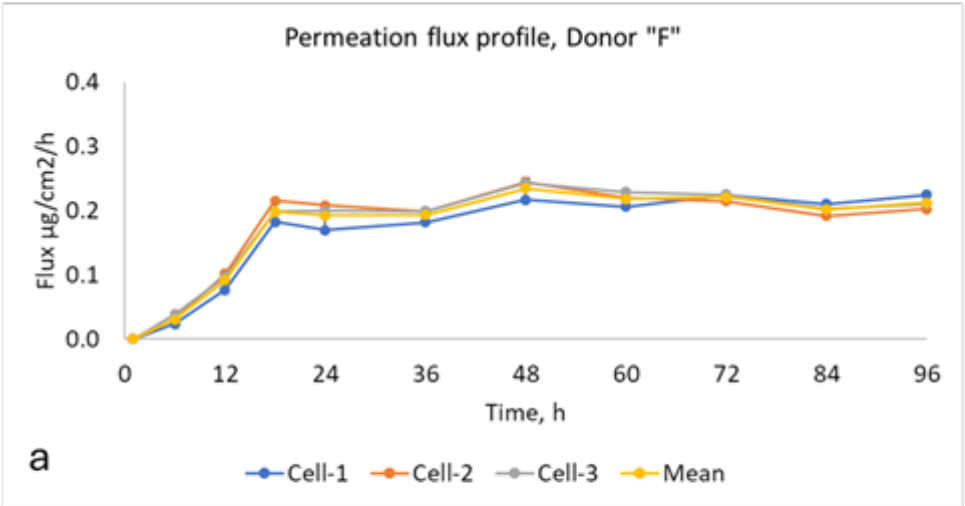
Key Observations

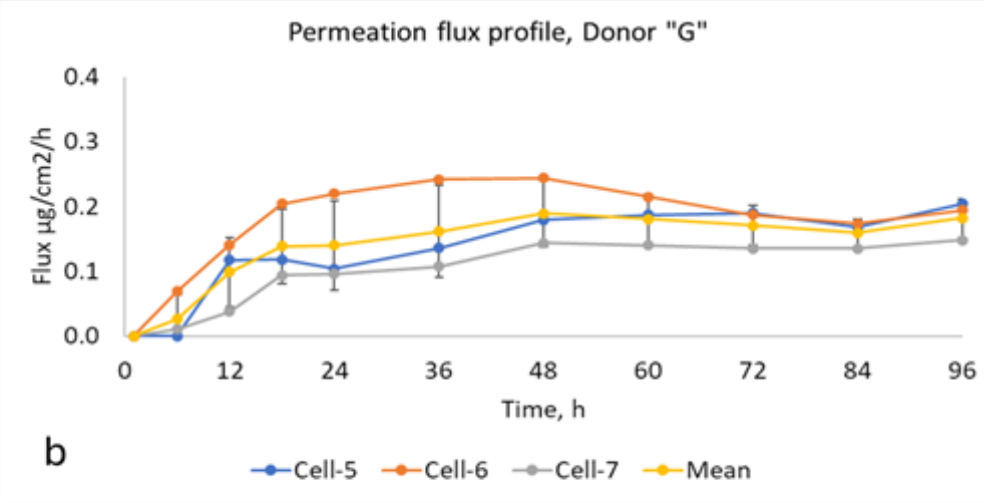
--Complete 96-h permeation profiles across all three donors

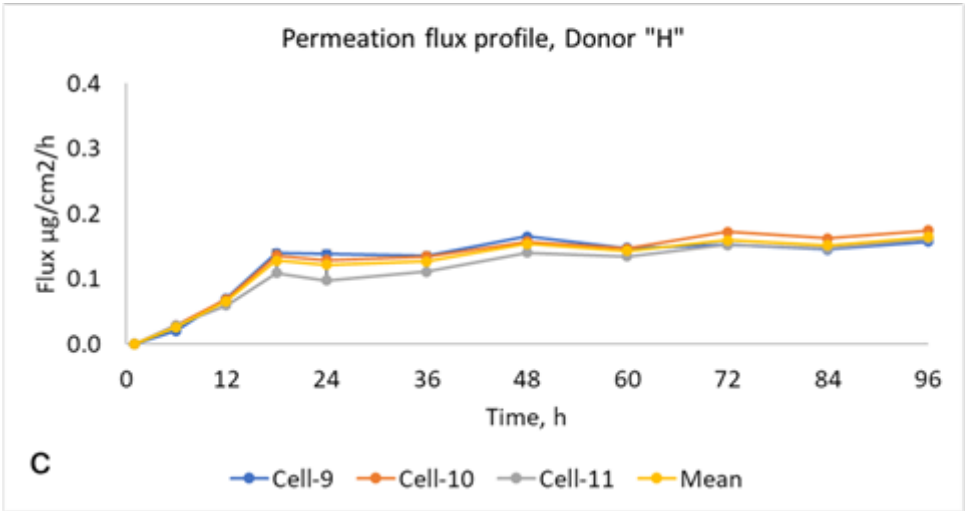
--Mean cumulative amounts at 96 h:18.48, 14.93, and 12.83 µg/cm²

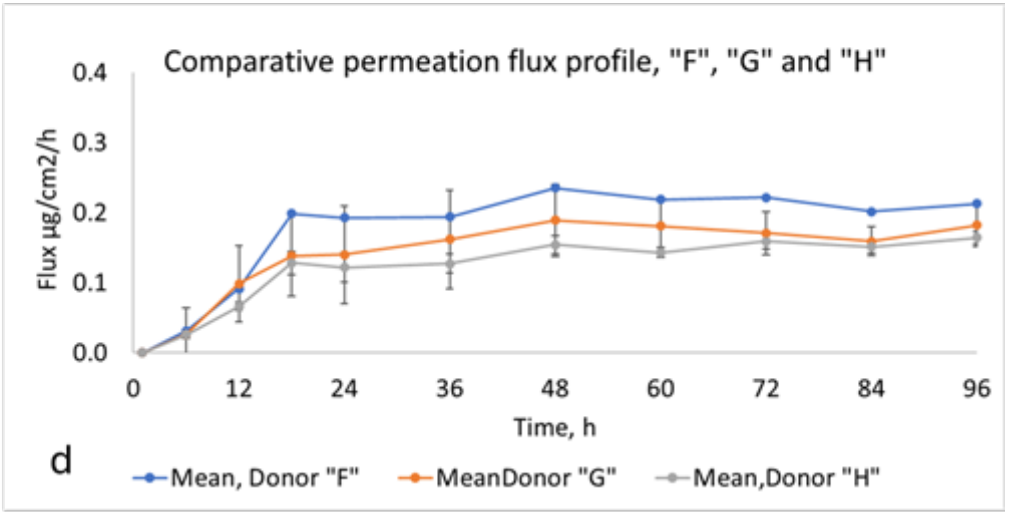
Final optimization: IVPT Flux Profiles

Did the final modifications produce consistent and interpretable flux profiles?









Key Observations

--Flux profiles showed the expected temporal evolution across donors

--Final conditions provided the most consistent and complete profiles observed during method development

The final optimization focused on the experimental mechanics of sampling while retaining key conditions established during earlier runs.

What This Study Taught Us

Development Is Progressive
Some limitations become apparent only after earlier challenges are addressed.

Parameters Are Interconnected
A change made for one purpose can influence other aspects of IVPT performance.

Unexpected Results Add Knowledge
Investigating unexpected observations improved understanding of the experimental system.

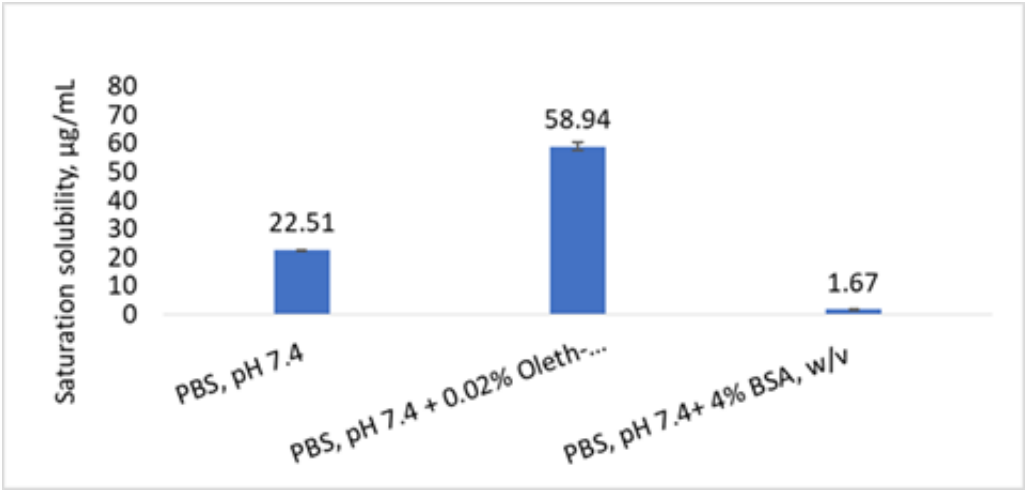
Rationale Matters
Final conditions are stronger when their selection can be traced to experimental evidence.

Key Message
The value of method development lies in understanding why a method works—not just what the final method is.

Applying the Same Thinking: Roflumilast Cream

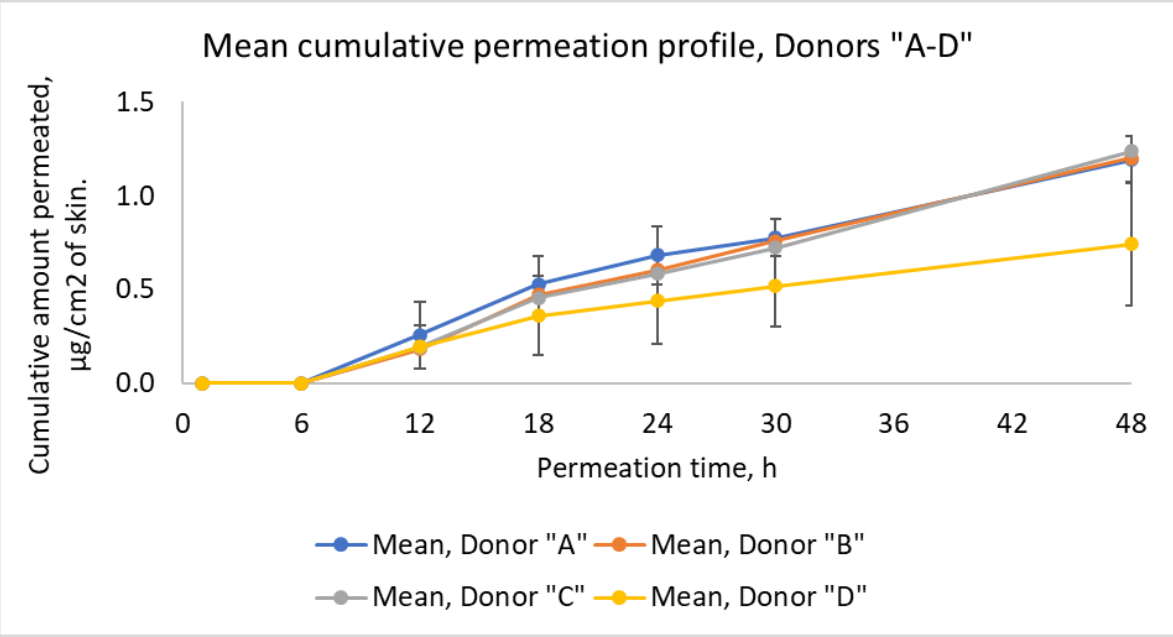
Different product. Different conditions.
Same development logic.

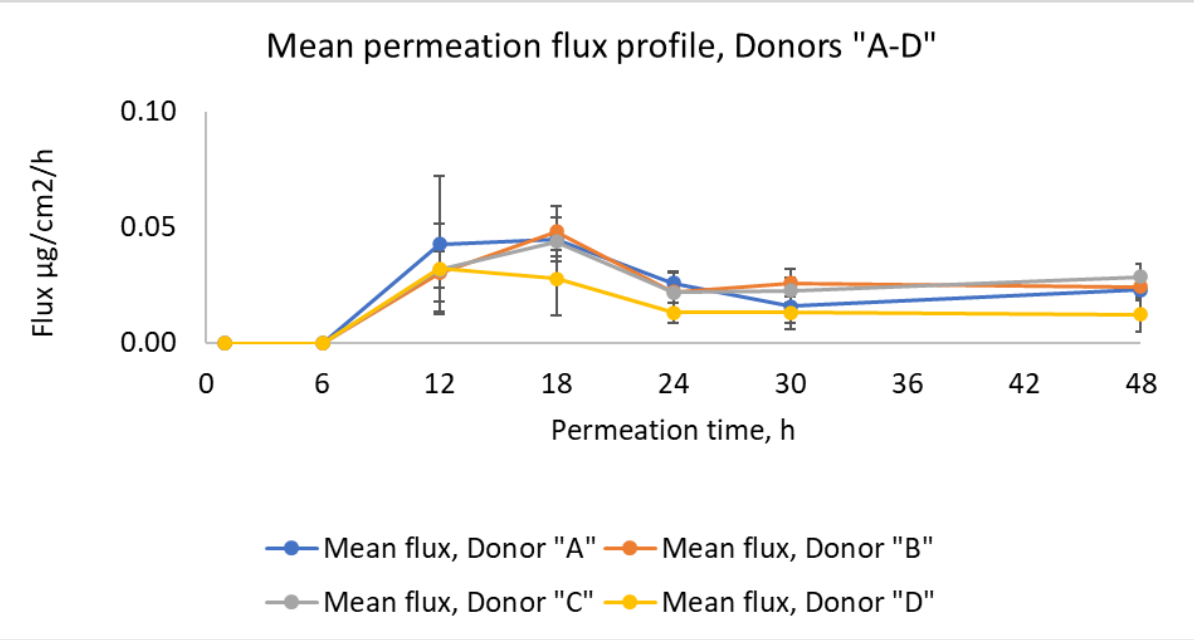
- ZORYVE (roflumilast, 0.3%) cream is a phosphodiesterase 4 inhibitor.
- Indicated for the topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older.
- Saturation Solubility



IVPT Conditions	
Skin source	Dermatomed human cadaver skin
Skin anatomical site	Thigh
Skin thickness (µm)	~500 ± 100 (dermatomed)
Skin integrity test and acceptance criterion	TEWL, ≤10 g/m²/h
No. of donors	4, Donors A-D
No. of replicates per treatment	4 (one additional non-dosed replicate)
Receptor solution	PBS (pH 7.4) with 0.02% Oleth-20, included 0.1% sodium azide.
Equipment evaluated	Phoenix dry heat diffusion cell system, automated sampling
Diffusion area of the orifice (cm²)	1.77
Receptor solution volume (mL)	15
Dose amount (mg/cm²)	15 (unoccluded)
Dose application method	The dose was applied with a positive displacement pipette, followed by gentle spreading using the closed end of a capillary rod.
Skin surface temperature (° C)	32 ± 1
Stirring rate (rpm)	600
Sampling volume (mL)	0.7 (sample collection volume = 0.5 + prime volume = 0.2)
Sampling timepoints (h)	0.5, 1, 6, 12, 18, 24, 30, 48
Dose duration (h)	48
Study duration (h)	48

Roflumilast: Permeation and Flux Profiles





Key Observations

--Roflumilast permeation was measurable across the evaluated skin donors

--Cumulative permeation increased over the study duration

--Flux profiles characterized the temporal permeation behavior across donors

--Automated sampling provided interpretable permeation and flux profiles under the evaluated conditions

Key Message

Product-specific IVPT conditions provided measurable and interpretable roflumilast permeation profiles, while the systematic development approach remained consistent across products.

Take-home Messages

1. The IVPT method evolved progressively.
Each experiment addressed a limitation identified during development.

2. Solving one challenge often revealed the next.
Improved detectability revealed the need for a longer study, while an unexpected observation led to refinement of the sampling approach.

3. The development approach—not the final conditions—was transferable.
Ruxolitinib and roflumilast required product-specific conditions, but the same systematic thinking guided method development.

The method was product-specific. The learning process was transferable.

References

1. *Kamal N, et al. Assessment of In Vitro Skin Permeation of Ruxolitinib from OPZELURA (Ruxolitinib Phosphate) Topical Cream, EQ 1.5% Base to Support a Demonstration of Bioequivalence. AAPS PharmSci 360; 2024; Salt Lake City, UT.*
2. *Kamal N, et al. Development of In Vitro Skin Permeation Testing Method to Assess the Bioequivalence of Topical Roflumilast Cream Formulations. AAPS PharmSci 360; 2024; Salt Lake City, UT.USP General Chapter <1724>. Semisolid Drug Products—Performance Tests.*
3. *Zidan A. Designing IVPT Methods: Practical Insights for Integrating the IVPT Guidance Recommendations. FDA–CRCG Workshop on Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration; Apr 29, 2025; Rockville, MD.*
4. *Yang Y, et al. Evaluation of In Vitro Skin Permeation of Clascoterone From Clascoterone Topical Cream, 1% (w/w). AAPS PharmSciTech. 2024;25(6):186. doi:10.1208/s12249-024-02887-7.*
5. *Yang Y, et al. Method Development for the Evaluation of In Vitro Skin Permeation of Tapinarof from VTAMA Topical Cream, 1%. ACS Fall 2025.*
6. *FDA Draft Guidance on Clascoterone, Topical Cream, 1%. Nov 2021; revised Aug 2023.*
7. *FDA Draft Guidance on Tapinarof, Topical Cream, 1%. Nov 2023; revised Dec 2025.*
8. *FDA Draft Guidance on Roflumilast, Topical Cream, 0.15% and 0.3%. May 2025.*
9. *FDA Draft Guidance on Tapinarof: Topical Cream, 1%. Recommended November 2023; revised December 2025.U.S.*
10. *FDA Draft Guidance on Clascoterone: Topical Cream, 1%. Recommended November 2021; revised August 2023.*

Acknowledgement

OPQR Collaborators
Muhammad Umer Ali, PhD.
Tasmin Ara Sultana, PhD.
Priyanka Srinivasan, PhD.
Ahmed Zidan , PhD
Muhammad Ashraf, PhD.

OGD Collaborators
Jackson Russo, PhD
Ying Jiang, PhD
Priyanka Ghosh , PhD

ORISE Research Participation Program, CDER/FDA

The authors acknowledge the use of Elsa, a generative AI tool developed for internal use at the FDA, which was used solely to assist with language editing and readability.