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IVPT Studies with Sunscreen Products: Experimental Parameters

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2021 IVRT and IVPT Methods Workshop: Best Practices and Scientific Considerations

August 18-20, 2021

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

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Sunscreens are no different.

People expect safe and effective sunscreens.

Outline

- Introduction
- UV filters in sunscreen
- Analytical method considerations
- IVPT device considerations
- Skin model and dosing methods
- References
- Acknowledgements

Introduction

- Sunscreens are OTC topical drug products indicated for the prevention of sunburn and skin damage following UV exposure.
- Sunscreen active ingredients - UV filters should act locally on the skin surface following dermal application.
- Absorption of UV filters may lead to safety and efficacy concern.
- IVPT method development to
  1) support sunscreen selection for maximal usage clinical trials (MUsT)
  2) support the evaluation of frequently reformulated sunscreens
  3) support the evaluation of generic *vs.* brand topical drug products

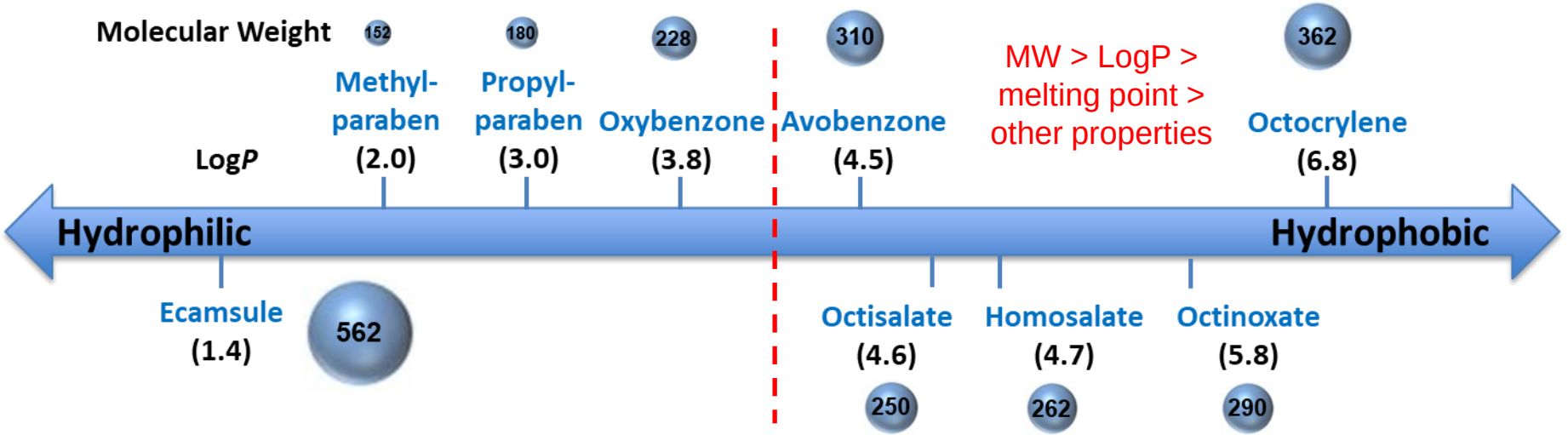
Active ingredients in commercial sunscreens

Product names in IVPT studies	UV Filters in Sunscreen Formulations	Product names in Clinical studies
Cream	*Avobenzone 2%, Octocrylene 10%, Ecamsule 2%*	Cream (Study I)
A-lotion	*Avobenzone 3%, Octocrylene 6%, Oxybenzone 4%*	Lotion (Study I & II)
B-lotion	*Avobenzone 3%, Octocrylene 6%, Oxybenzone 4%*	-
A-spray	*Avobenzone 3%, Octocrylene 8%, Oxybenzone 6%*	-
B-spray	*Avobenzone 3%, Octocrylene 10%, Oxybenzone 5%*	Spray-2 (Study I)
C-spray	*Avobenzone 3%, Octocrylene 10%, Oxybenzone 6%, Homosalate 15%, Octisalate 5%*	Spray-1 (Study II)
D-spray	*Avobenzone 3%, Octocrylene 10%, Homosalate 10%, Octisalate 5%, Octinoxate 7.5%*	Spray-2 (Study II)
D-oil spray	*Avobenzone 3%, Homosalate 10%, Octisalate 5%, Octinoxate 7.5%*	Spray-3 (Study II)

Physiochemical properties of UV filters affecting permeation

	Ecamsule	Oxybenzone	Avobenzone	Octisalate	Homosalate	Octinoxate	Octocrylene
Log*P*	1.4	3.8	4.5	4.6	4.7	5.8	6.8
Molecular Weight	562.7	228.2	310.4	250.3	262.3	290.4	361.5
Melting Point	255°C	62°C	83.5°C	<25°C	<20°C	-25°C	14°C
TPSA	160 Å^2	46.5 Å^2	43.4 Å^2	46.5 Å^2	46.5 Å^2	35.5 Å^2	50.1 Å^2
pKa	2.0	7.6	9.7	8.1	8.1	-4.8	-

LogP, octanol-water partition coefficient; TPSA, topological polar surface area in Å^2; pKa, acid dissociation constant at log scale.

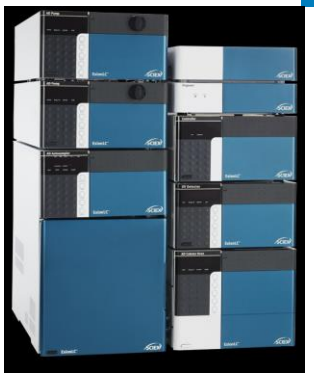


 SCCS "Scientific Advice on US FDA questions regarding the safety assessment of UV filters in the EU." 2015.

Considerations in Analytical Methods

Detection limit should be satisfied:

→ Aliquot sampling (500 µL) to ensure concentration of all active ingredients are above their LLOQ



***Avoid introducing errors during sample processing*:**

→ BSA crash out (protein precipitation)

→ Extraction of active ingredients

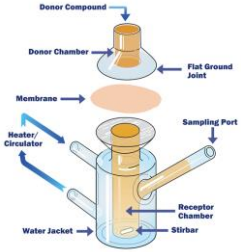
→ Sample dilution or concentration

→ Sample stability during storage and analysis

(SciEx UHPLC - Qtrap 6500 MS/MS)

Wet Heat Devices for IVPT

Franz Diffusion System

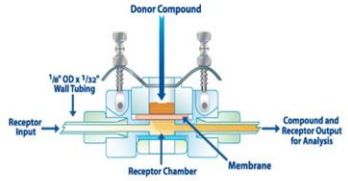


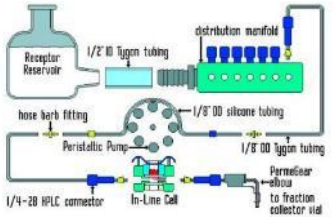
Pros:
- Low receiver volume
- No plastic tubing

Cons:
- Manual sampling is inconvenient at night

PermeGear, Inc.

Flow-Through Diffusion System





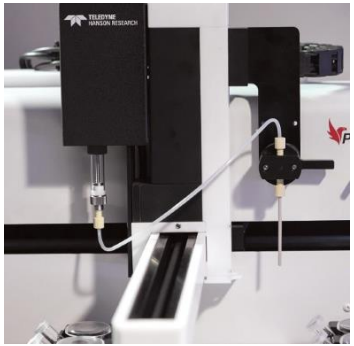
Pros:
- Auto-sampling
- Cell # 7
- Complete removal of receiver solution

Cons:
- Larger receiver volume → too much dilution
- Long plastic tubing

→ Temperature drop during solution transport

Dry Heat Devices for IVPT

Diffusion Master (Teledyne-Hanson)



Pros:
- Auto-sampling
- Low volume
- Heated resource block

Cons:
- Large plastic stirrers

→ Non-specific binding

→ Hard to remove bubbles

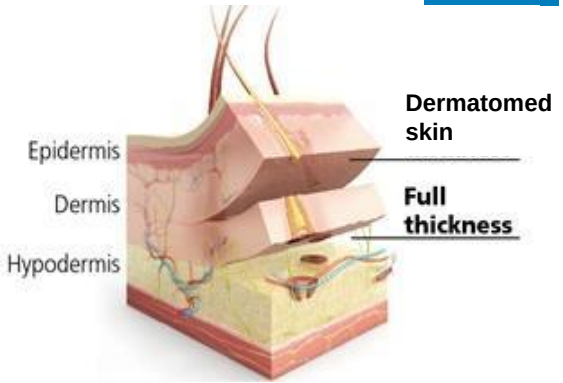
Automated Diffusion System (Logan Instruments)

Pros:
- Auto-sampling
- Air bubble removal (tilting) mechanism
- Maybe easier for complete receiver removal

Cons:
- Long plastic tubing → Non-specific binding

Selection of Skin Model and Dosing Method

Full thickness, partial thickness, dermatomed human skin



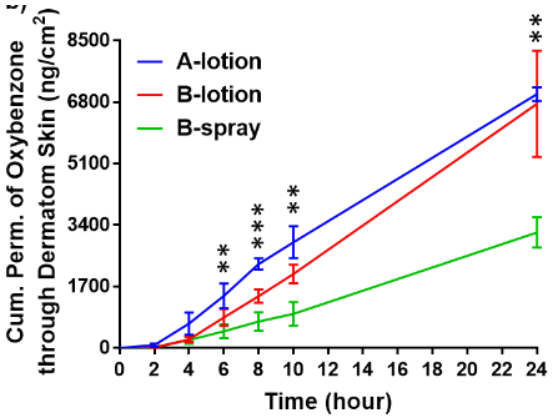
Pros:

- Good for long term tests (e.g., 24 - 96 hours)
- Good for infinite and finite dosing

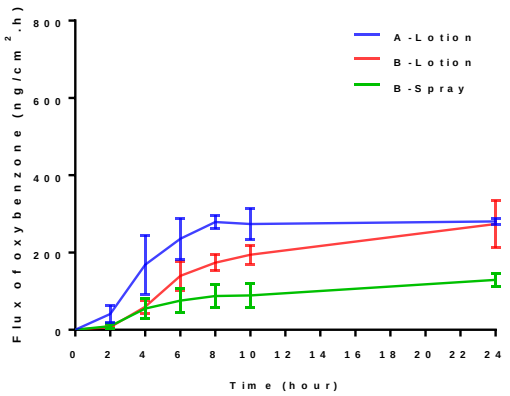
Cons:

- Manual collection → intra-donor variation in thickness
- Dermal layer inter-donor variation → data variation

Cumulative Permeation



Flux

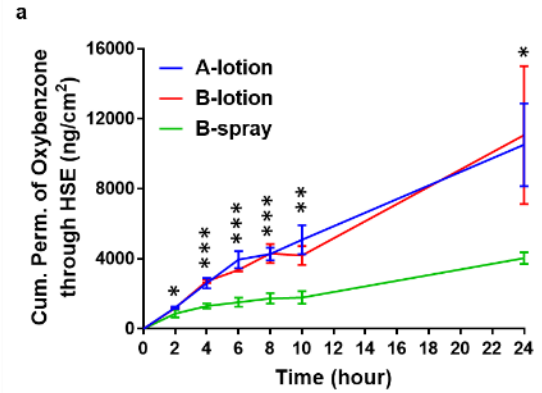


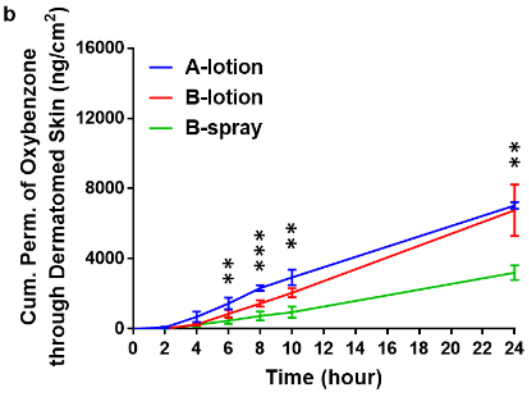
Selection of Skin Model and Dosing Method

Heat-separated epidermis (HSE) vs. dermatomed human skin (Infinite dose)

Cumulative Permeation

HSE

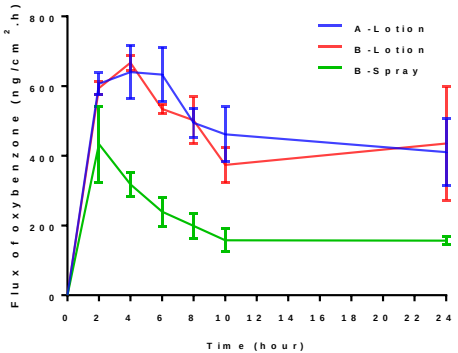


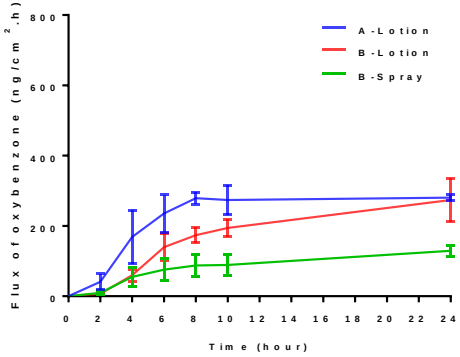


Cumulative Permeation

Dermatomed skin

Flux





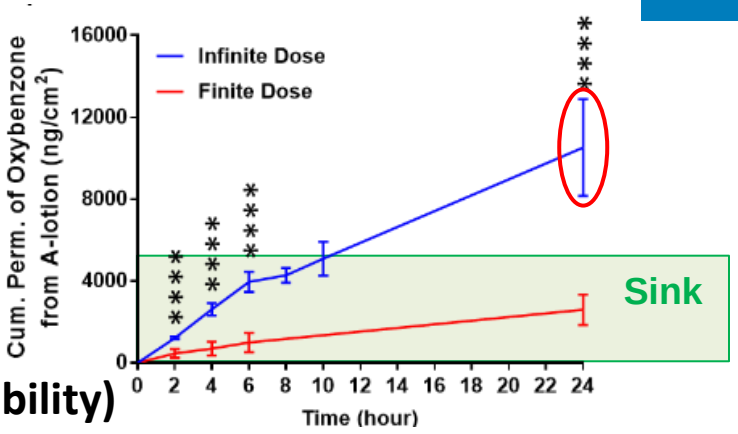
Flux

Selection of Skin Model and Dosing Method

Heat-separated human epidermis (HSE)

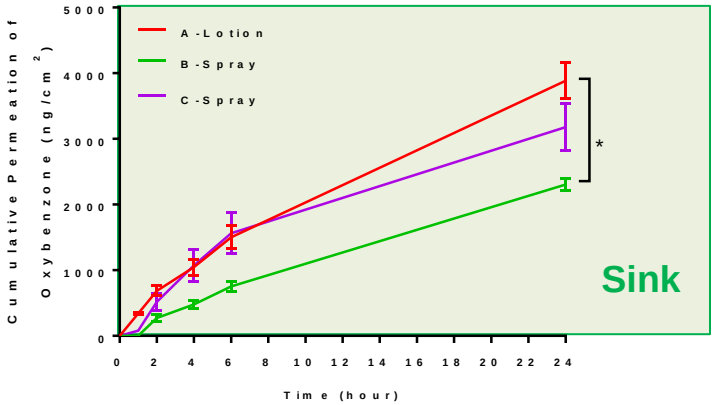
Pros:

- **Thickness less variable**
- **Good for short term tests (e.g., ≤ 24 hours)**
- **Good for finite dosing**
  → maintain sink condition (e.g., 5 time > solubility)



Cons:

- **Over hydration beyond 24 hrs.**
- **May not work well with infinite dosing**
- **May not work well with autosampler that introduces pressure in the receiver chamber**

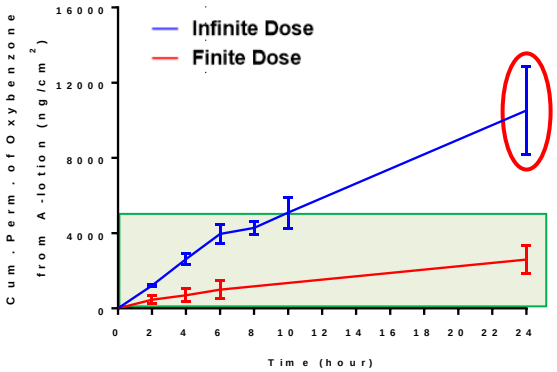


Selection of Skin Model and Dosing Method

Heat-separated human epidermis (HSE): Infinite vs. finite dose

Cumulative Permeation

A-lotion



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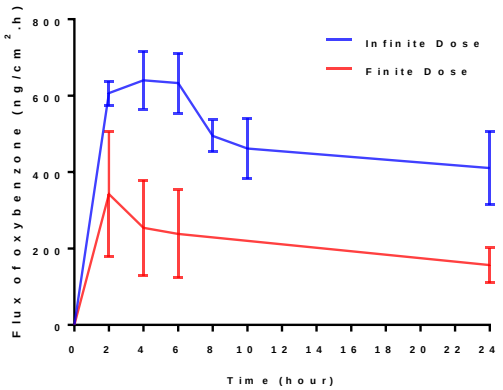
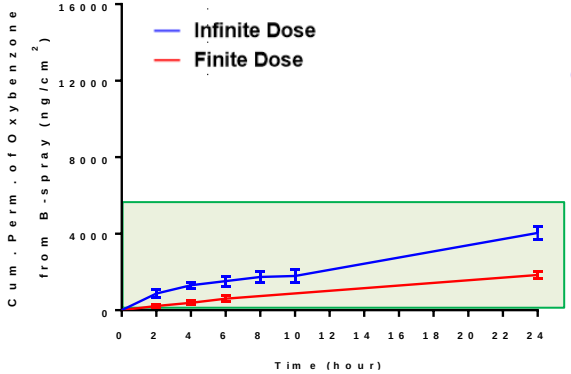


Cumulative Permeation

B-spray



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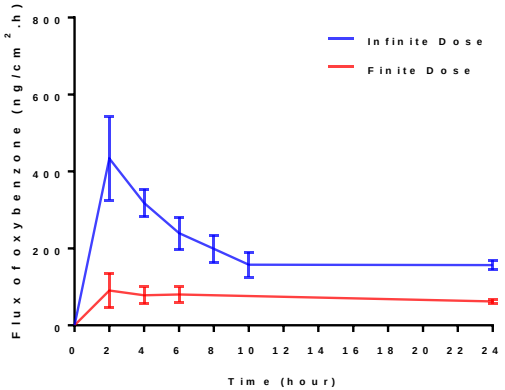

In vitro-in vivo rank order correlation

In vitro cumulative skin (HSE) permeation vs. clinical AUC at 24 hours:

Products	Permeation	AUC	Permeation	AUC	Permeation	AUC	Permeation	AUC
	Homosalate		Octisalate		Octinoxate		Oxybenzone	
A-lotion	-	-	-	-	-	-	1	1
C-spray	1	1	2	2	-	-	2	2
D-spray	2	2	1	1	1	1	-	-
D-oil spray	3	3	3	3	2	2	-	-

Products	Permeation	AUC	Permeation	AUC
	Octocrylene		Avobenzone	
A-lotion	2	1	3	1
C-spray	3	3	4	2
D-spray	1	2	2	3
D-oil spray	-	-	1	4

Not all UV filters demonstrated good correlation → IVPT method may need further optimization

Single finite dose (2 mg/cm²)

Summary

- **A fit-for-purpose IVPT method needs fine tuning of IVPT parameters.**
- **Both dermatomed cadaver skin and HSE may be employed in sunscreen IVPT studies to select products for MUsT studies.**
- **Rank order results of cumulative *in vitro* skin permeation may be correlated with the clinical AUC.**
- **Skin permeation of UV filters is influenced by their physicochemical properties. Absorption of UV filters also depends on the properties of sunscreen formulation. IVPT method may be extremely useful for comparing reformulated sunscreens against sunscreens with clinically proven safety.**

References

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Acknowledgements

- ❑ **FDA OND intramural funding support**
- ❑ **Participants:**

OPQ/OTR Research Team:

Ann-Marie Ako-Adounvo
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Huzeyfe Yilmaz
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