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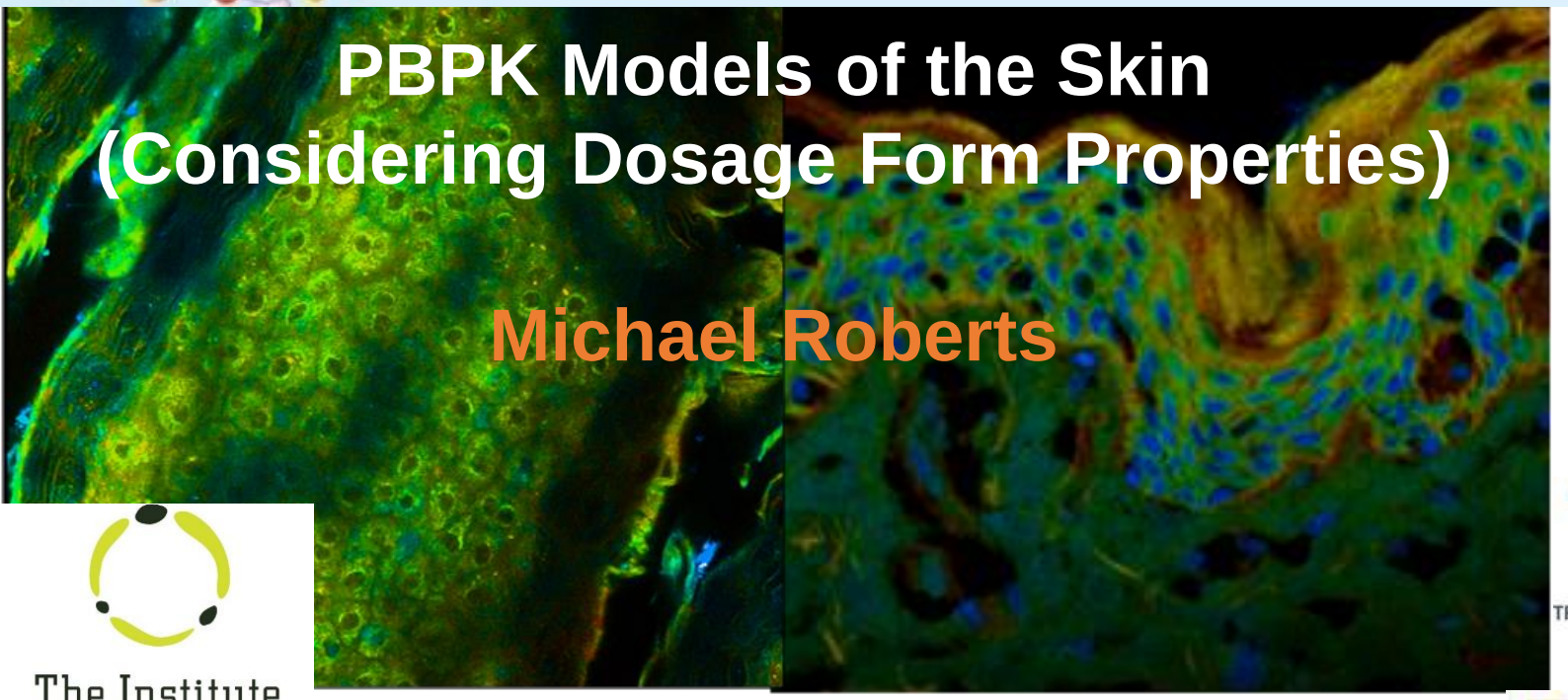
MARCH 13-16 • WASHINGTON MARRIOTT WARDMAN PARK • WASHINGTON, DC

PBPK Models of the Skin (Considering Dosage Form Properties)



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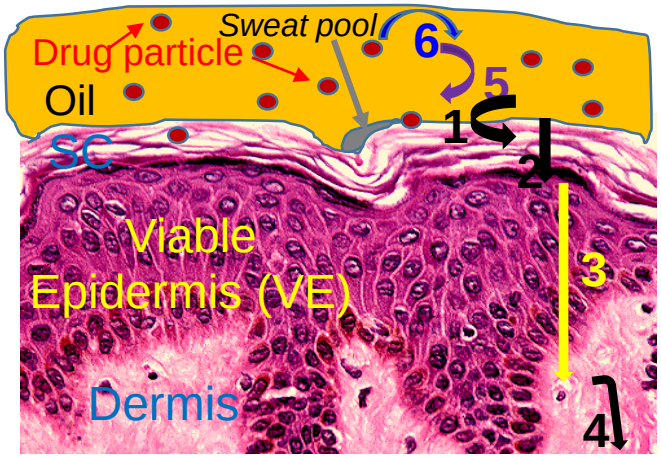
The views expressed in this presentation do not reflect the official policies of the Food and Drug Administration, or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

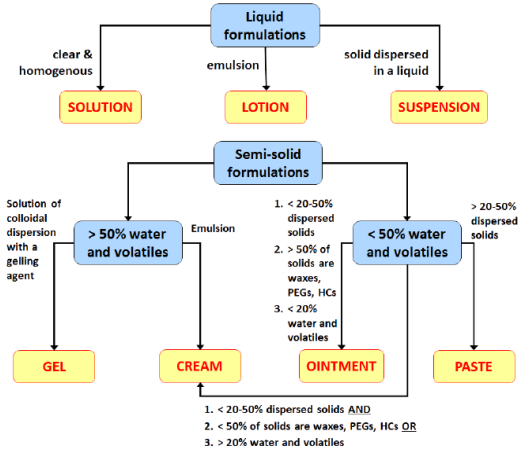
Physiological based pharmacokinetic (*PBPK*) models of the skin

Considering Dosage Form Properties - Scope of presentation

- Types of products approved by FDA
- Key *PBPK* determinants of *in vitro – in vivo* relationships (*IVIVR*)
- Application of *IVIVR* for *in vivo* data for various dose forms
- Role of drug properties & nature of drug applied with *in use conditions* (finite dose) epidermal *in vitro* permeation test (*IVPT)*
- PBPK analysis of *IVPT* behaviour of acyclovir products
- *IVPT* of metronidazole products



Transdermal Formulations



Adapted from SR Chaudhuri, AAPS Workshop 2017 San Diego

FDA approved topical products

TOPICAL PRODUCTS

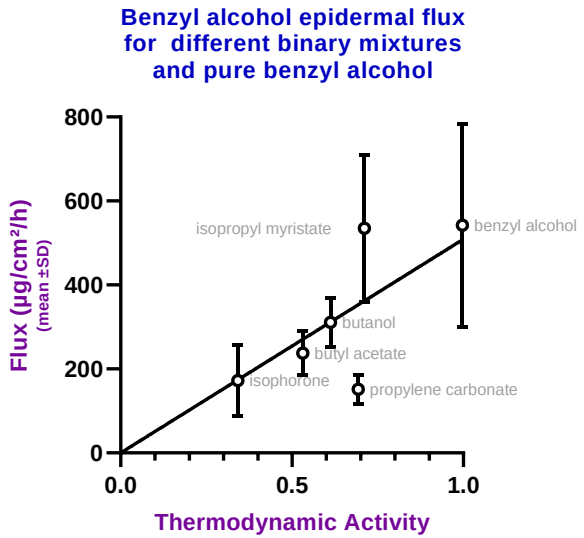
Active Ingredient	**Formulation**
Acyclovir (Zovirax etc.)	ointment, cream
adapalene (Differin)	gel, cream, lotion
azelaic acid	gel, cream, foam
becapermin (Regranex)	gel
brimonidine tartrate	gel
butenafine hydrochloride	cream
capsaicin	patch
chlorhexidine gluconate	solution, sponge
clindamycin phosphate	gel, solution, foam
condylox (Podofilox)	solution, gel
crisaborole (Eucrisa)	ointment
desonide	gel, cream, ointment, lotion
diclofenac sodium	solution, gel
efinaconazole (Jublia)	solution
fluocinolone acetonide	ointment, cream, solution, oil, oil/drops
hydrocortisone	lotion, cream, ointment
hydrocortisone butyrate	solution, cream, ointment, lotion
hydrocortisone valerate	cream, ointment
imiquimod	cream

TOPICAL PRODUCTS *ctd*.

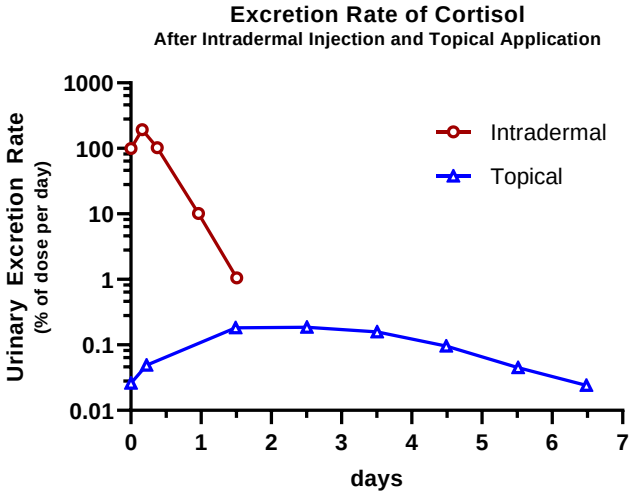
Active Ingredient	**Formulation**
ingenol mebutate	gel
ivermectin	lotion, cream
ketoconazole	foam, cream, shampoo, gel
lidocaine	ointment, patch
lidocaine / prilocaine	cream
lidocaine hydrochloride	solution, jelly
luliconazole (Luzu)	cream
mafenide acetate	cream, solution
mechlorethamine hydrochloride (Valchlor)	gel
metronidazole	cream, gel, lotion
minoxidil	solution, foam
mupirocin	ointment, cream
pimecrolimus (Elidel)	cream
retapamulin (Altabax)	ointment
sulfacetamide sodium (Klaron)	lotion
tacrolimus	ointment
tazarotene (Tazorac)	gel, cream
terbinafine hydrochloride	cream
tretinoin	cream, gel

Key determinants of dose form kinetics on skin transport

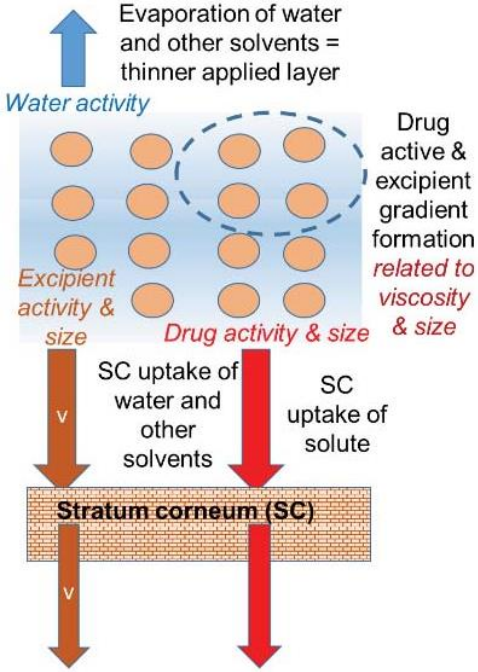
- A key concept defining all skin permeation studies comes from Takeru and asserts As a solute's flux is related to its thermodynamic activity in an applied product (Higuchi ,J Soc Cosmet Sci 1960), skin flux should then be the same for a saturated solutions of the solute in various vehicles - providing the vehicle does not modulate solute transport in the vehicle or skin permeability.
- In most cases, the stratum corneum is the main resistance to skin transport. So much so, as Sid Riegelman (*Clin Pharm Ther* 16(5) 873- 883, 1974) points out, percutaneous absorption of an active is often slower than its elimination from the body, leading to a so-called "flip-flop" effect.
- In practice, supersaturation, vehicle diffusion limitations, coalescence, vehicle evaporation, penetration enhancement & other effects can impact on skin *PBPK*, as we will explore in this talk. Supersaturation may accompany solvent evaporation. So, a drug particle dissolution may be slower than its diffusion in a vehicle and subsequent absorption. Further, after evaporation of volatiles an o/w product may become w/o, with an oily diffusion barrier; drug may have a higher solubility in the oily residue and a lower thermodynamic activity; Drug precipitation may occur in the residue as well as in the stratum corneum (SC).



Barry BW et al. J Pharm Pharmacol. 1985 Apr;37(4):226-36.



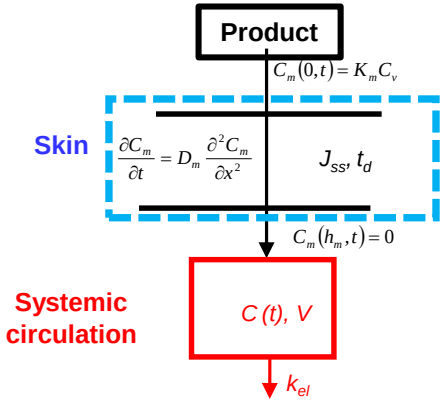
Riegelman, S; Clinical Pharmacol. & Therapeutics;16(5) p873, Fig 7



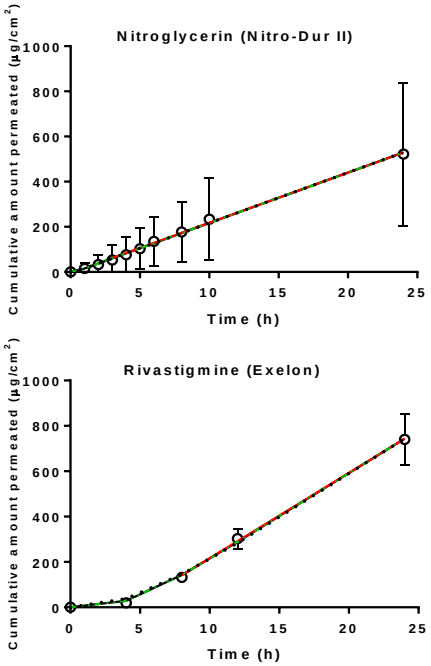
One of our key interests is in *in vitro* – *in vivo* relationships (*IVIVR*) for a drug using *in vitro* permeation test (*IVPT*) data for human skin and blood /urine for that drug

Shown below are our results for transdermal patches using a diffusion model representation of the skin barrier

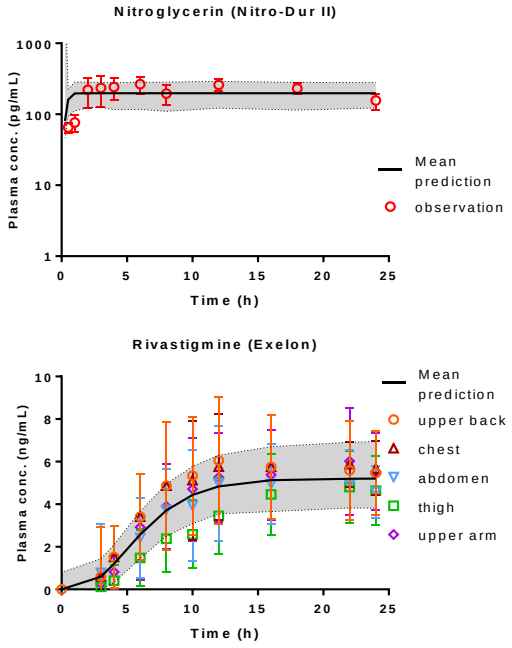
Diffusion model for skin transport



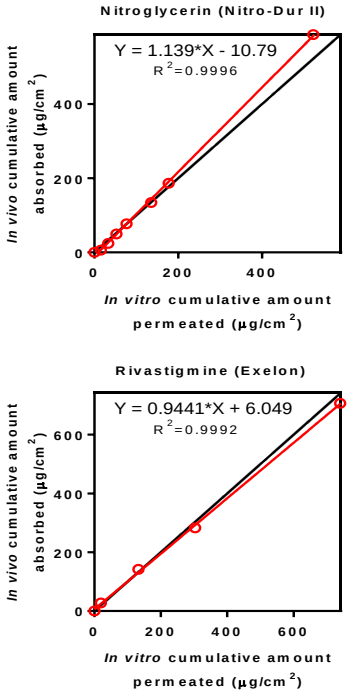
A. *In vitro* skin permeation test (*IVPT*)



B. 1 stage *IVIVR*, *where IVPT* and convoluted with intravenous pharmacokinetics to predict plasma levels for dose form.

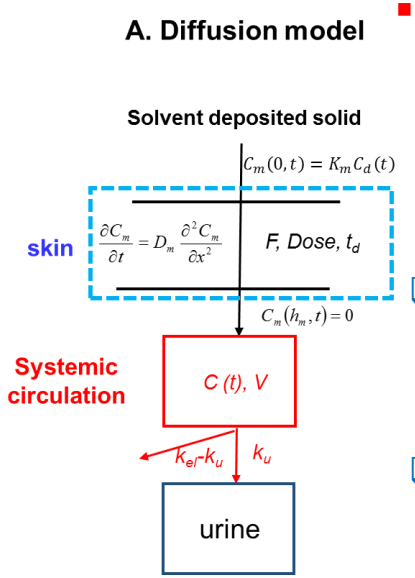


B. 2 stage *IVIVR*, 1. Deconvolution of plasma data to estimate absorption profiles that are 2. Compared with IVPT data.



We then look at a different dose form, solvent deposition on the skin, and modelled *IVPT & in vivo* urinary excretion data from Tom Franz.

- Radiolabelled compounds (^{14}C-benzoic acid, ^{14}C-caffeine, ^{14}C-testosterone) were formulated in vehicles: petrolatum, ethylene glycol gel, and water gel
- Formulations were applied to an area of 20-60 cm2 using flat metal spatula to spread a layer of uniform thickness on abdomen.
- Urine was collected throughout the course of experiment until background levels of radioactivity were approached



- 2-stage analysis using diffusion model (analysing individual subject data first)

$$\widehat{M_u}(s) = \frac{k_u}{s(s+k_{el})} \frac{F \times dose}{\cosh\sqrt{st_d}}$$

- k_{el} – elimination rate constant (2.37, 0.075, 0.314 h^{-1} for benzoic acid, caffeine and testosterone, respectively) – obtained from IV data
- k_u – urinary elimination rate constant (2.27, 0.055, 0.27 h^{-1} for benzoic acid, caffeine and testosterone, respectively) – obtained from IV data
- F – bioavailability (%) (model parameter)
- t_d – diffusion time (h) (model parameter)

Solvent evaporation

Although not addressed explicitly here, we recognise that mosquito repellents are lost by evaporation at a rate comparable to their percutaneous absorption (Reifenrath & Robinson J Pharm Sci, 1982. 71: 1014-1018). Anissimov (2008) has reported the Laplace expression for an IVPT cumulative amount permeated with evaporation as a kinetic process $\kappa_{ev} = k_{ev} / \left(A k_p \right)$ as:

$$\hat{Q}(s) = \frac{k_p A C_{v0} V_{vN} t_d}{s\left(\cosh\sqrt{st_d} + \frac{V_{vN} st_d + \kappa_{ev}}{\sqrt{st_d}} \sinh\sqrt{st_d} \right)}$$

Anissimov, Y.G. in *Dermal Absorption and Toxicity Assessment* (M.S. Roberts & K.A. Walters, Eds.) 2008, Informa New York. p. 271-286.

Urinary excretion of benzoic acid, caffeine & testosterone after application in different dose forms

First part of 2- stage analysis using diffusion model

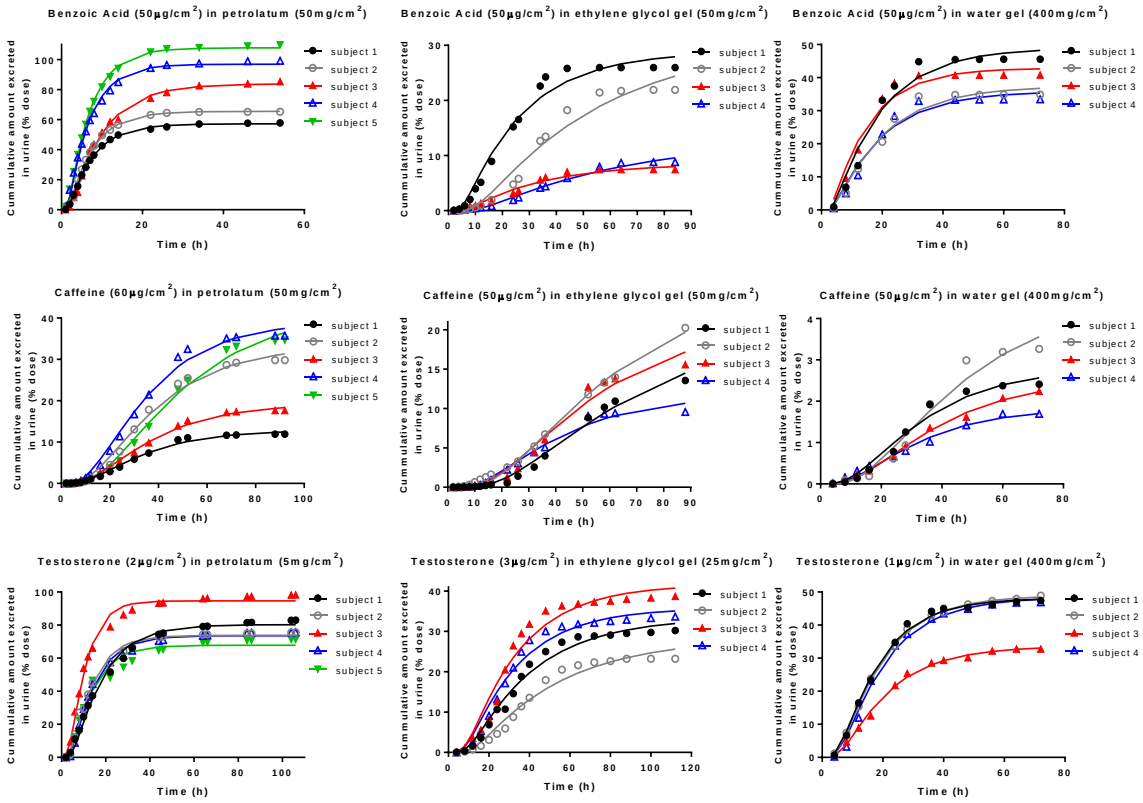


Fig 1. Individual fitting curves of cumulative amount excreted into urine versus time profiles. Symbols represent experimental data and lines represent fitting curves.

Compound	Vehicle	*t_d (h)	*F(%)
Benzoic acid	petrolatum	15.4± 2.75	85.8± 22
	ethylene glycol gel	93.8± 36.8	21.3± 11.8
	water gel	38.0± 4.51	43.1± 6.18
Caffeine	petrolatum	59.5± 16.0	40.1± 17.6
	ethylene glycol gel	102± 29.7	27.8± 8.63
	water gel	55.4± 15.6	3.98± 1.56
Testosterone	petrolatum	23.3± 5.61	91.3± 12.0
	ethylene glycol gel	79.1± 19.0	40.8± 6.40
	water gel	36.0± 3.07	52.4± 9.68

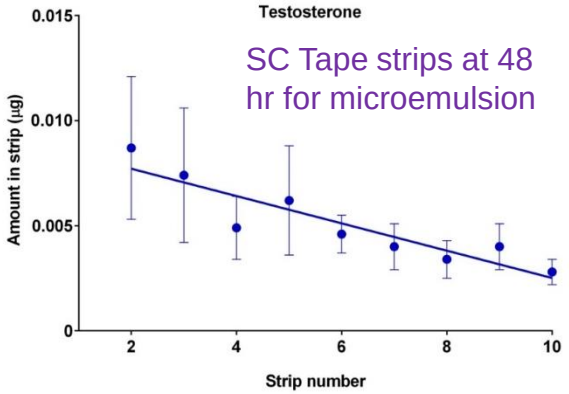
*data were expressed as mean ± SD

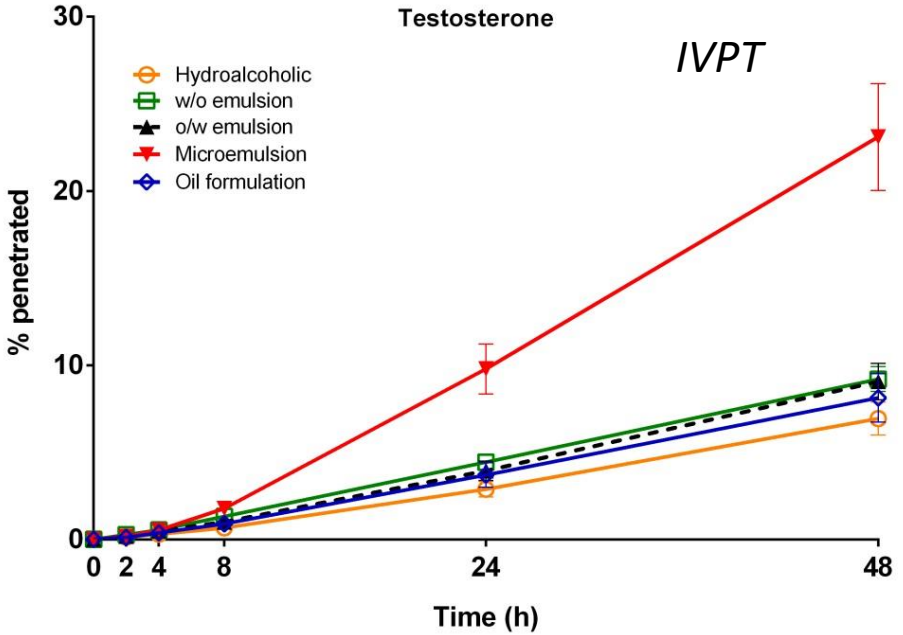
Conclusions: Faster diffusion (shorter diffusion *time, td*, for petrolatum<water gel<ethylene glycol gel; Petrolatum higher bioavailability than other products

Case study in dose form effects for various drugs studied by *in use IVPT*

- Four different Radiolabelled (^{3}H) + cold solutes Five formulations:
  - Hydro-alcoholic gel
  - W/O emulsion
  - O/W emulsion
  - Micro-emulsion
  - Oil
- 2mg/cm^{2}each formulation to human epidermal membrane surface in Franz-type skin under non-occlusive conditions (n=12-18 for each formulation/solute combination).
- Receptor chambers (approx 2.5-3.5mL)
  - pH 7.4 phosphate buffered saline (PBS) for 5FU & hydrocortisone studies
  - PBS + 25% ethanol for testosterone & ketoconazole.

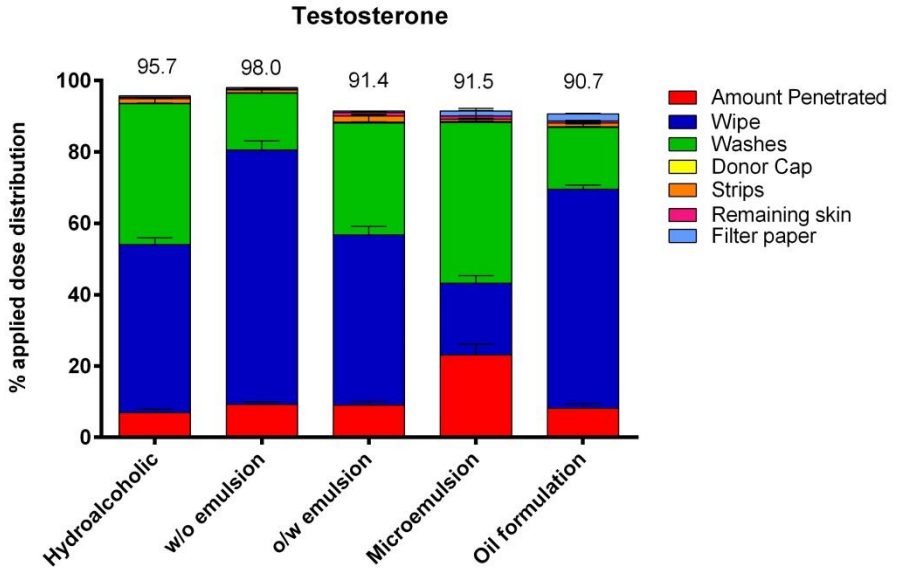
Solutes	MW	LogP	Polarity index
5-FU	130.1	-0.97	Polar
Hydrocortisone	362.5	0.54	Relatively polar
Testosterone	288.4	3.22	Relatively lipophilic
Ketoconazole	532.0	4.34	Lipophilic

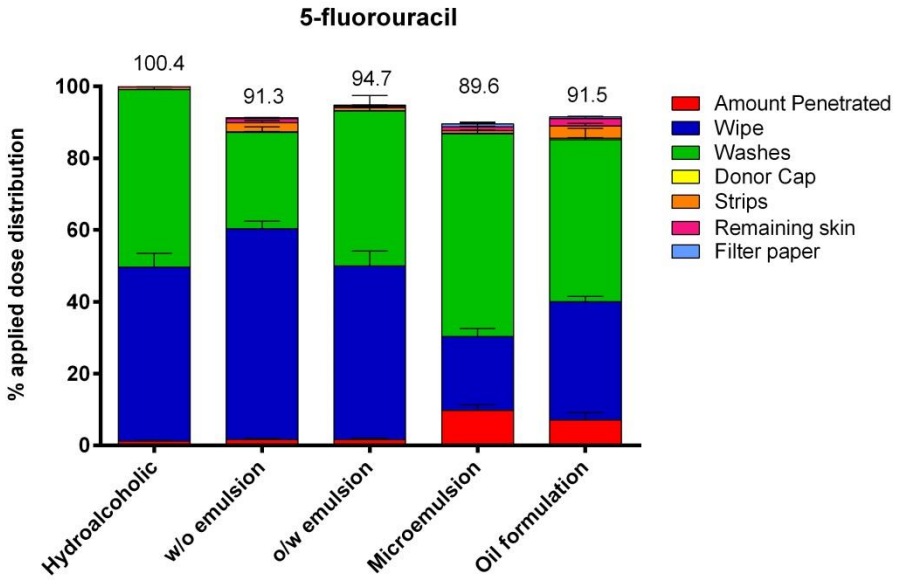


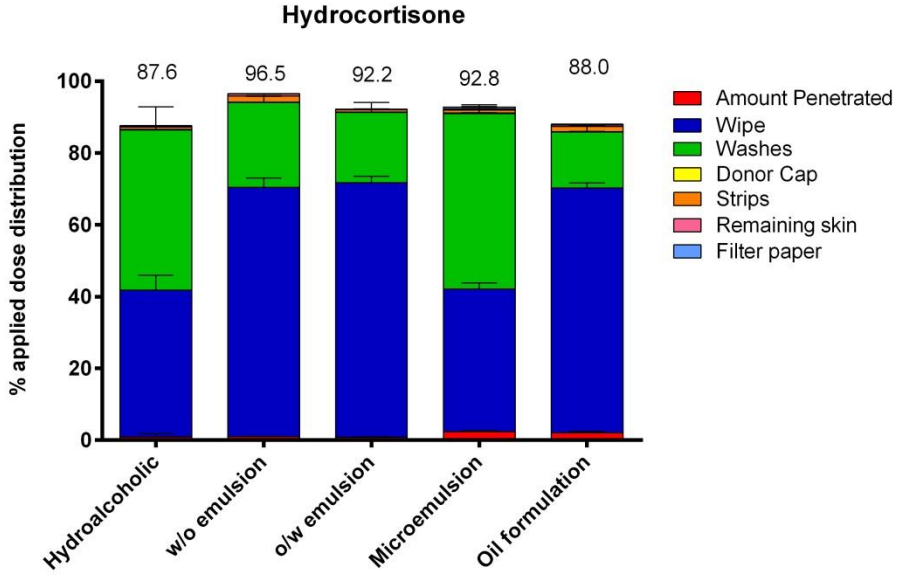


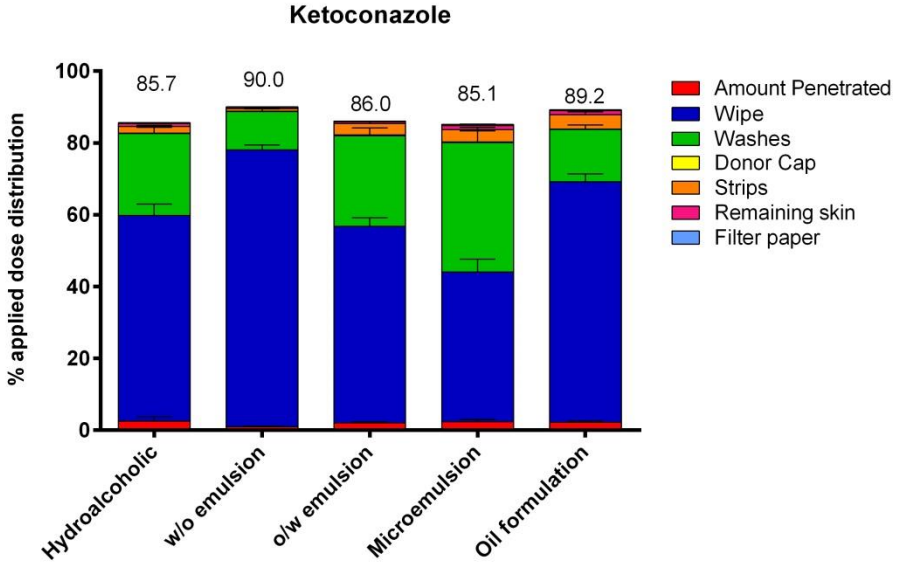
Wiechers et al Int J Cosmet Sci 2012

Recoveries for the various actives from the various dose forms at the end of the study



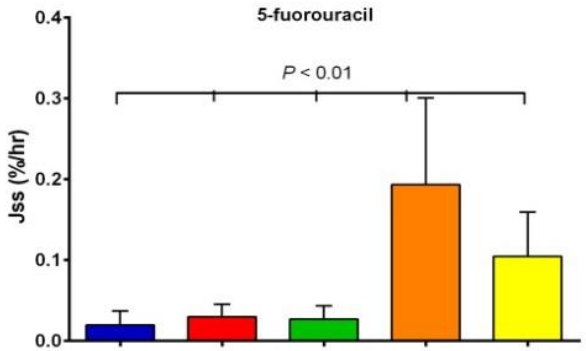


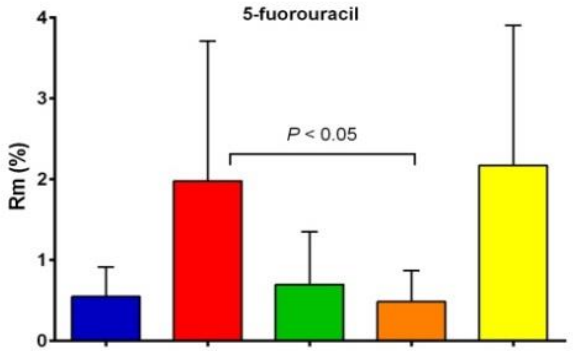


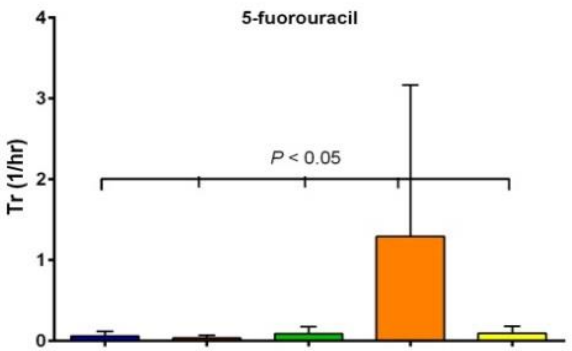


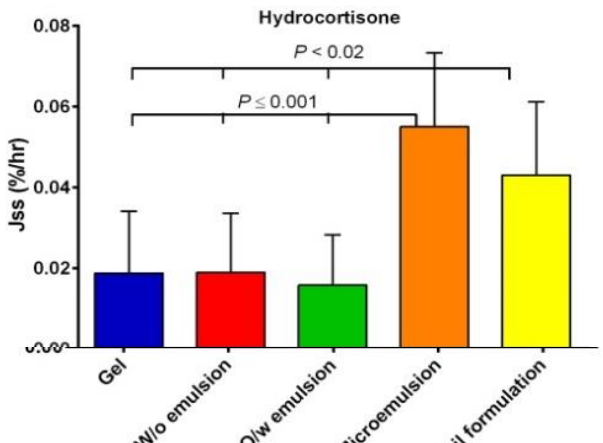
Outcomes

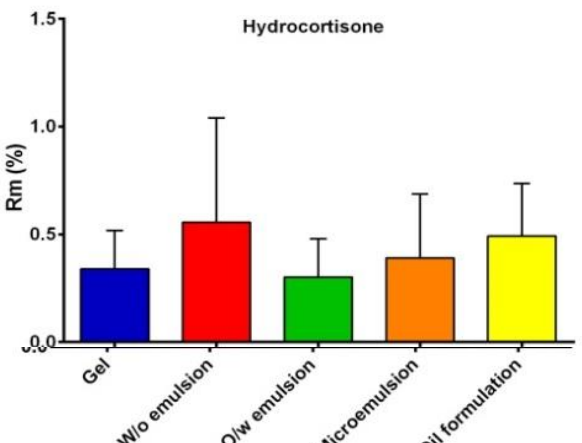
- Essentially saturated flux (Jss) =SC solubility (Rm) X SC diffusivity (Tr)
- Microemulsion is standout highest flux – due mainly to high concentration non-ionic surfactants, e.g. Brij 96 (polyoxyethylene (10) oleyl ether) increasing SC diffusivity
- Oil (fatty acid ester ESTOL 3601 (glycerol monocaprylate/caprate)) promotes the SC solubility & penetration (Jss) for the two most polar solutes

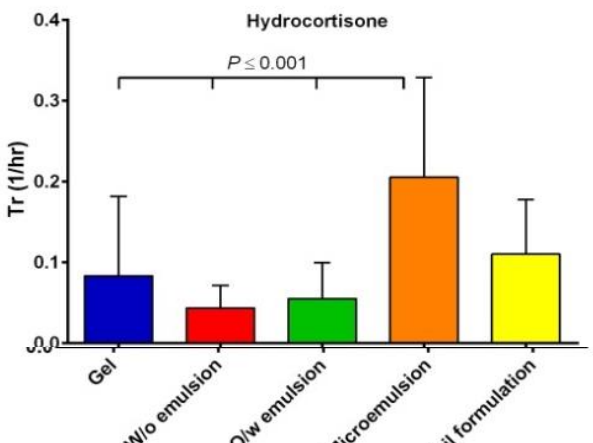






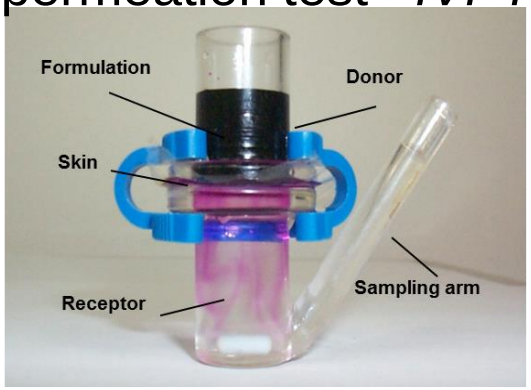




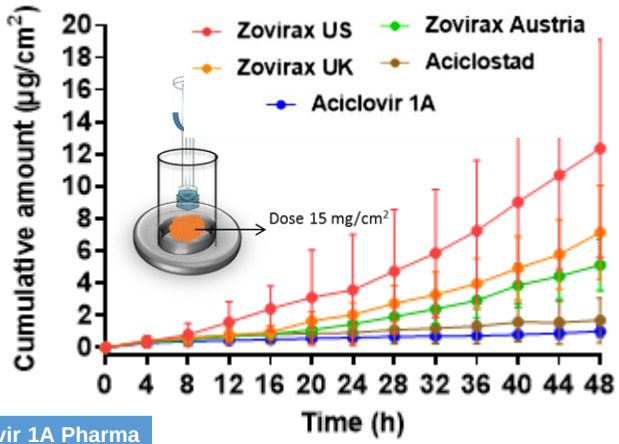


Topical acyclovir products are an example of where permeating enhancing excipients make a real difference

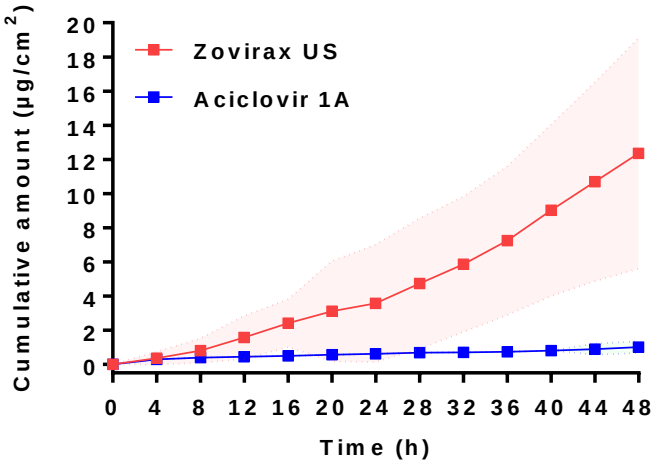
In vitro skin permeation test - *IVPT*



Our group applied 15mg/cm² accurately with a syringe plunger

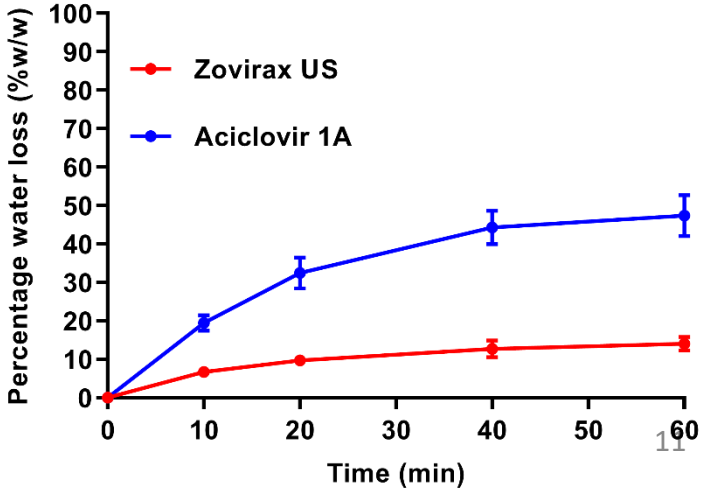


Let us look at two extremes!



Ingredient Name	Zovirax (U.S.)	Aciclovir 1A Pharma (Austria)
Acylovir concentration	5% w/w	5% w/w
Propylene glycol (PG) 40% w/w		**15% w/w*1**
Water Content	**≈ 1/3 w/w**	**≈ 2/3 w/w**
Cetyl alcohol	No	w/w)
Other Ingredients:	Cetostearyl alcohol Mineral oil Poloxamer 407 Sodium lauryl sulfate Water White petrolatum	White Vaseline Viscous paraffin Glycerol monostearate Polyoxyethylene stearate Dimethicone Purified water

Product metamorphosis when applied to skin - slower evaporation of water in Zovirax due to PG

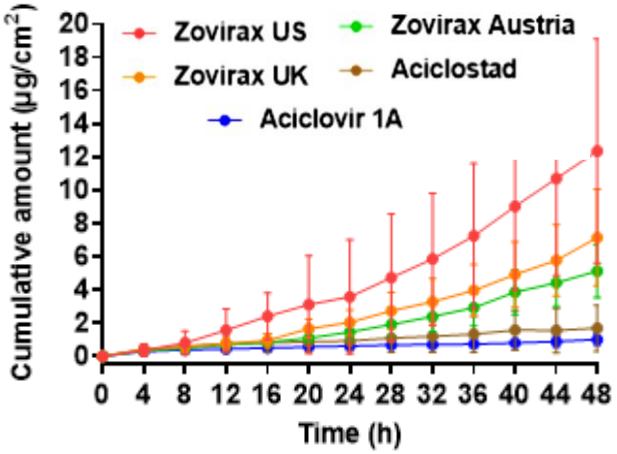


Note differences in :

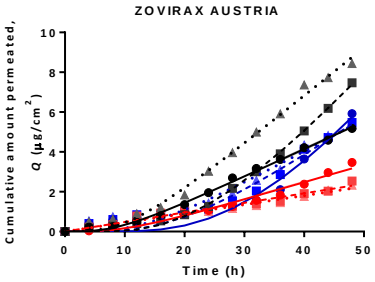
- Q1 (Qualitative – nature of ingredient)
- Q2 (Quantitative - amounts)

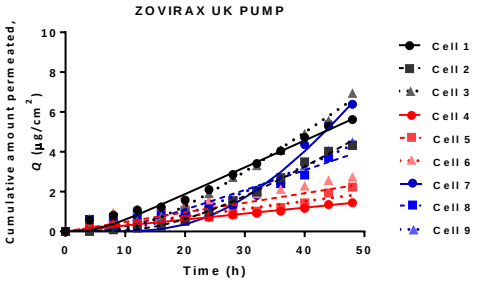
*1 Trottet,LH et al Int J Pharm 304(1-2): 63-71.

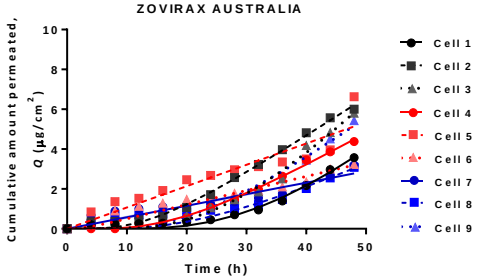
Diffusion *PBPK* modelling of individual acyclovir products

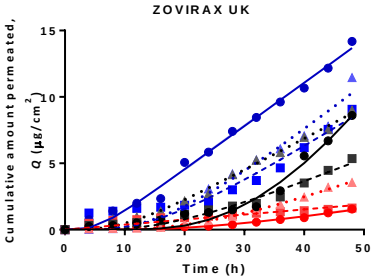


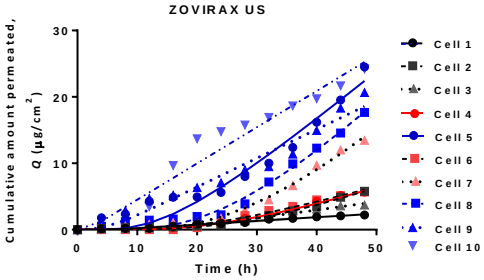
$$\hat{Q}(s) = \frac{J_{ss}A}{s^2}\frac{\sqrt{st_d}}{\sinh\sqrt{st_d}}$$

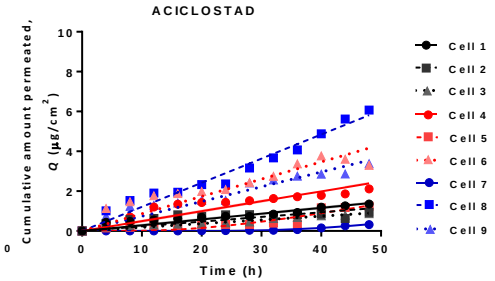




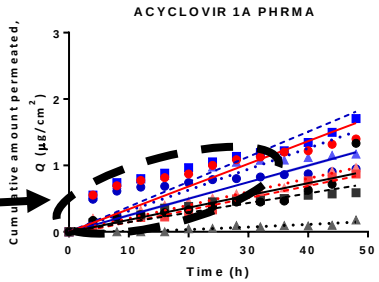






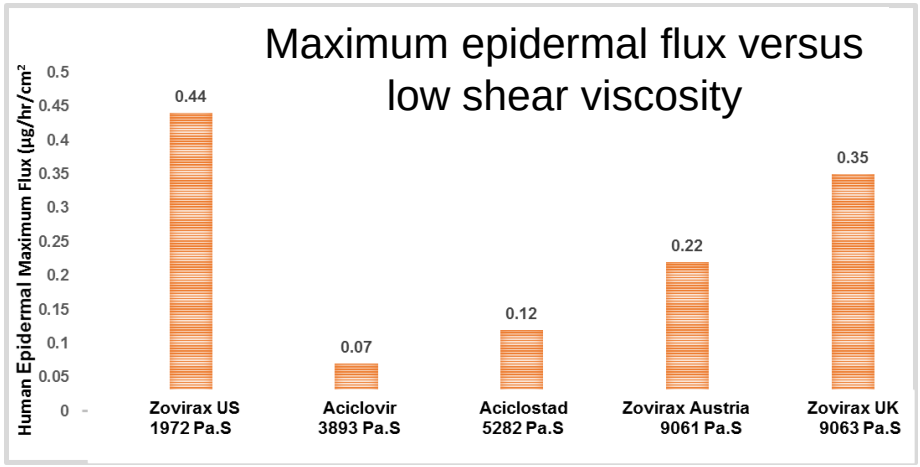


Note Acyclovir 1A Pharma not included

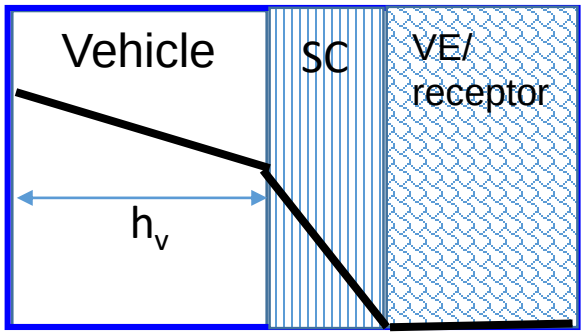


	J_{ss} (µg/cm²/h)	*lag* (h)
ZOVIRAX AUSTRIA	0.19±0.14	16±14
ZOVIRAX UK PUMP	0.15±0.14	13±14
ZOVIRAX AUSTRALIA	0.19±0.09	22±15
ZOVIRAX US	0.46±0.30	21±14
ZOVIRAX UK	0.28±0.24	21±15
ACICLOSTAD	0.07±0.04	13±30

Could flux differences be a viscosity effect?



Expect:



Some insight provided by *IVPTs* for oxybenzone from various dose forms with varying viscosities

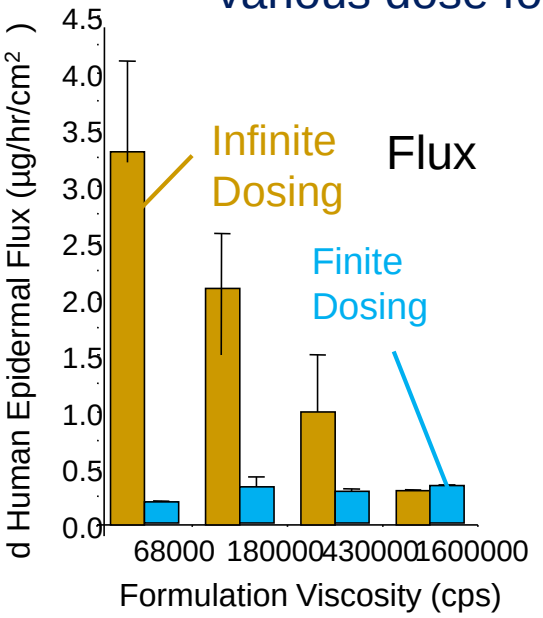
The total flux J = concentration gradient divided by sum of resistances across product & skin. For sink conditions:

$$J = \frac{C_v}{\frac{h_v}{D_v} + \frac{1}{k_{p,sc}}}$$

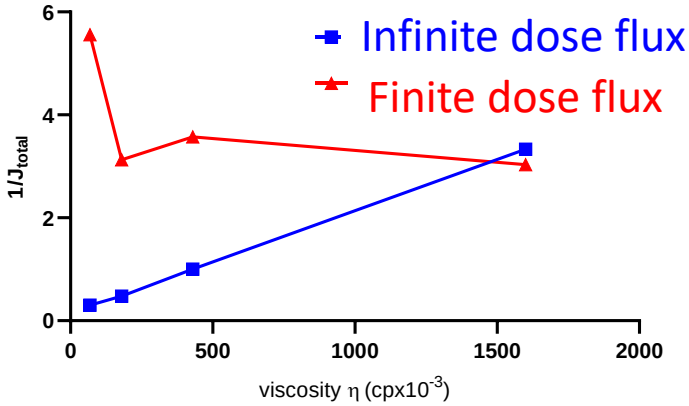
Inverting: $\frac{1}{J} = \frac{h_v}{D_v C_v} + \frac{1}{k_{p,sc} C_v}$

Applying the Stokes-Einstein relationship $D_v = \frac{k_B T}{6\pi\eta r_0}$

$$\frac{1}{J} = \frac{h_v 6\pi\eta r_0}{k_B T C_v} + \frac{1}{k_{p,sc} C_v}$$



Cross et al. J Invest Dermatol 117: 147-150 (2001)



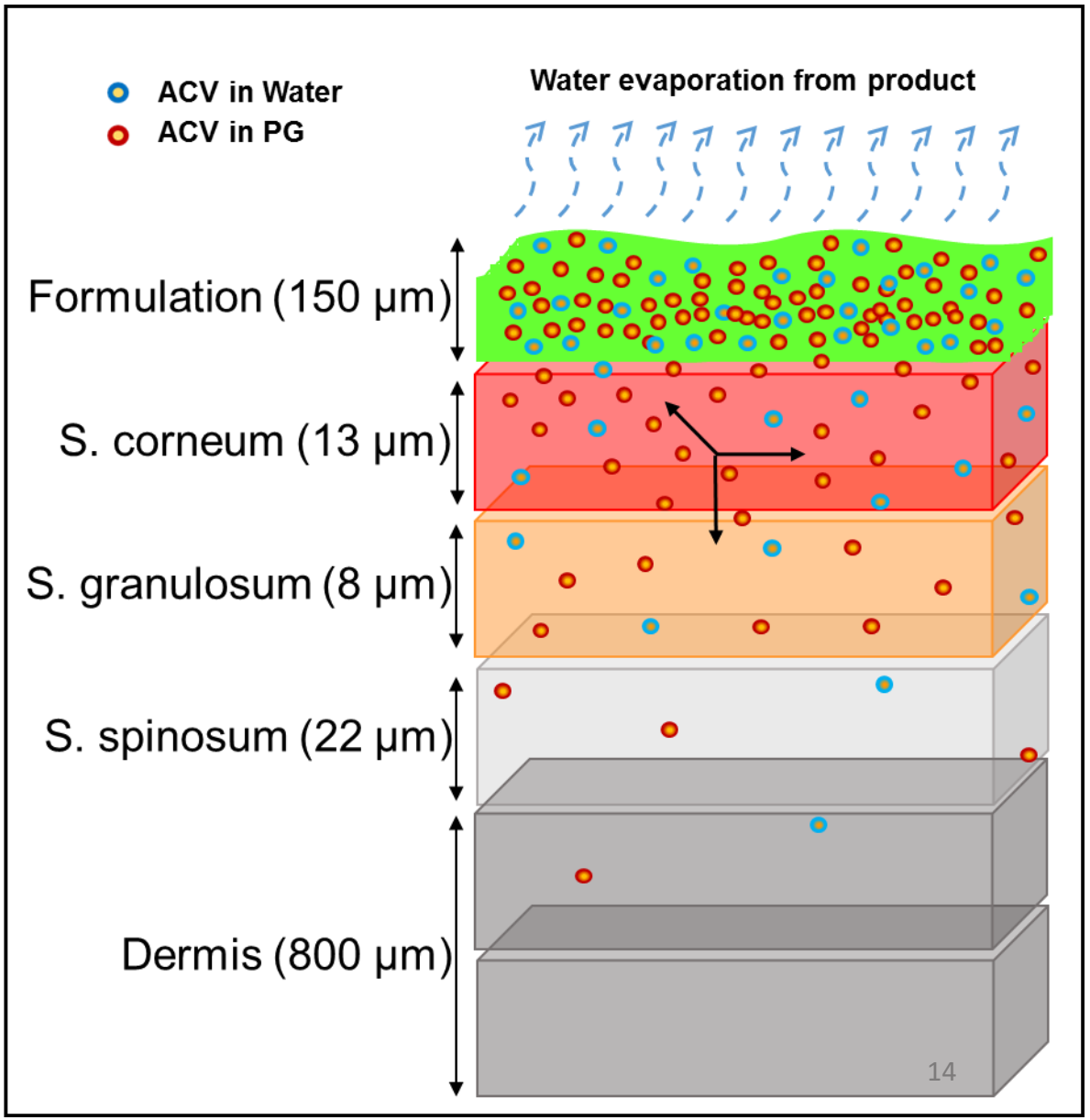
Here, a higher viscosity at lower shear stress for both acyclovir and oxybenzone equals a higher maximum flux.

Due to easier evaporation of the lower viscosity products or occlusion with more viscous residue?

Zovirax US, with 15-18% water, is an exception.

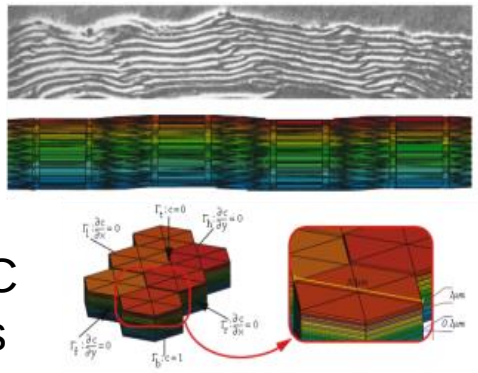
More likely an excipient effect as they can interact directly with the stratum corneum (SC) & impact on *IVPT*

- Propylene glycol (PG) and water, known penetration enhancers, are two excipients present in all products
- Our work has also shown that PG and water can carry solutes into the SC & promote their permeation
- Both are likely to promote direct acyclovir uptake into the stratum corneum
- Potentially, product microstructure (Q3) can impact on acyclovir & enhancer bioavailability to the stratum corneum



Understanding *PBPK* differences in *IVPT* profiles for acyclovir for 2 products

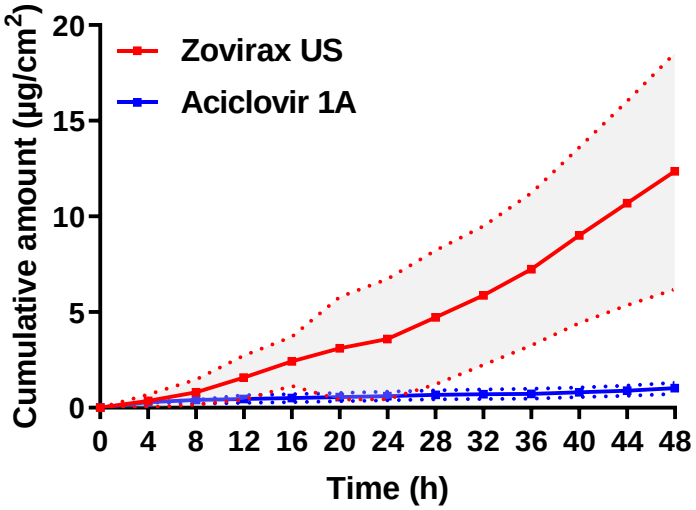
Use complex multi-layer 3D diffusion model (Naegel, Wittum & team) with our data (Mohammed & team)

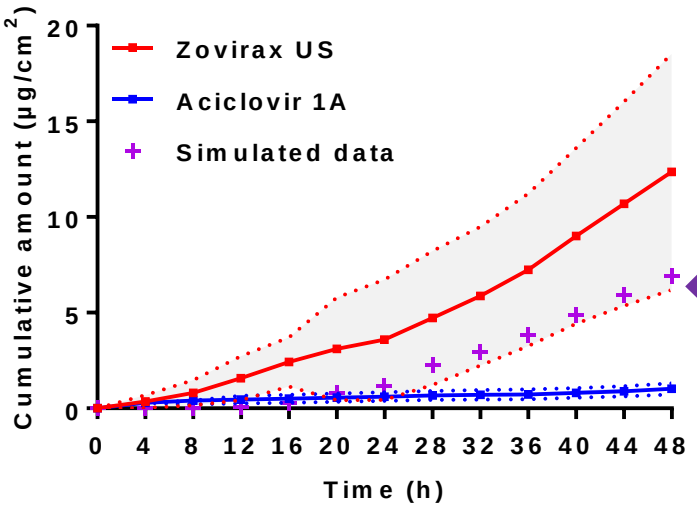


Experimental *IVPT* profiles

Can we predict acyclovir permeation theoretically?

1. We first consider diffusivity of AC V in SC with no product excipients (PG, water etc.) – SC interactions



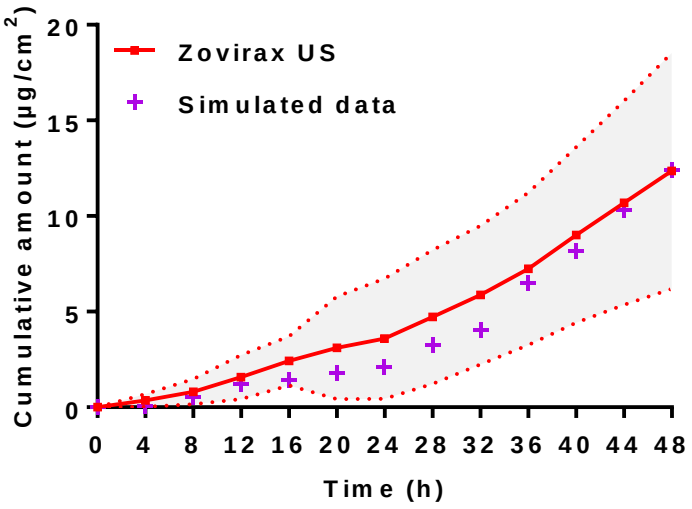


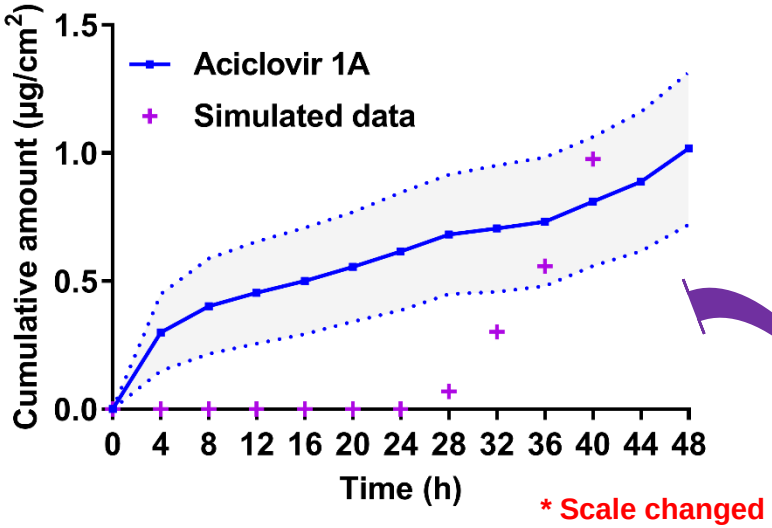
$K_{ACV,SC}$ = 0.24; h_{SC}= 13 µm;
$D_{ACV,SC}$= 2.54 x 10^{-7} µm²/s

The predicted profile by simulation is intermediate between the two observed profiles

Understanding differences in *IVPT* profiles for acyclovir for 2 products

2. Now include impact of PG in SC on Acyclovir permeation predictions





* Scale changed

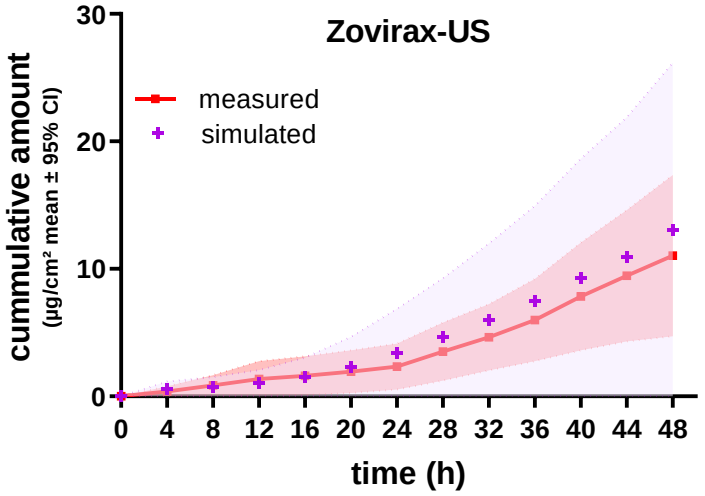
- When the effect of PG, a known ingredient in the formulations and a known solubility and penetration enhancer, is taken into account the simulated profile for Zovirax matches with the *IVPT* data.
- However, Aciclovir 1A still does not fit. Is there something more going on?

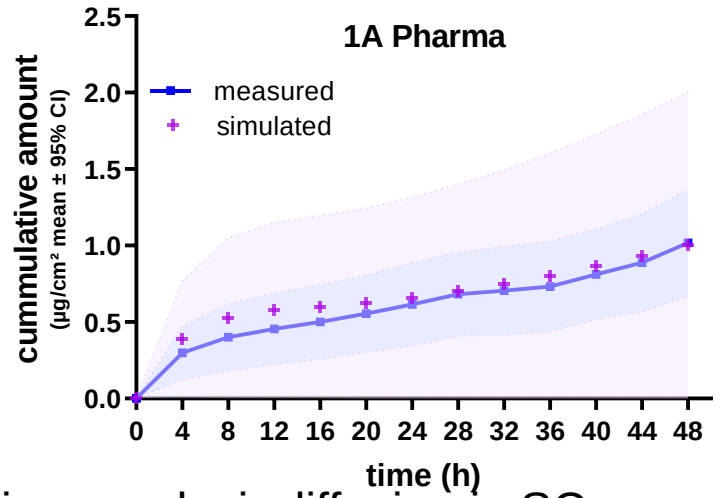
$K_{PG,SC}$ = 0.29; h_{SC}= 13 µm;
$D_{PG,SC}$= 1.03 x 10^{-4} µm²/s

$D^*_{ACV,SC} = D_{ACV,SC} + 0.00003 \times C_{PG,SC}$

Understanding differences in *IVPT* profiles for acyclovir for 2 products

3. Now including impact of PG and water in SC and water evaporation from the product





- As well as interactions of PG affecting acyclovir diffusion in SC,
- Evaporation of water from product modifies acyclovir availability, and

$$D_{\mathrm{don,H_2O}} \nabla u_{\mathrm{H_2O}}(x)\vec{n} = \omega\, u_{\mathrm{H_2O}}(x)$$

$D_{donor,water}$= 6.88 µm²/s; ω= 0.02

- Water can modify acyclovir chemical activity and diffusion in SC

$K_{PG,SC}$ = 0.29; h_{SC}= 13 µm;
$D_{PG,SC}$= 1.03 x 10^{-4} µm²/s

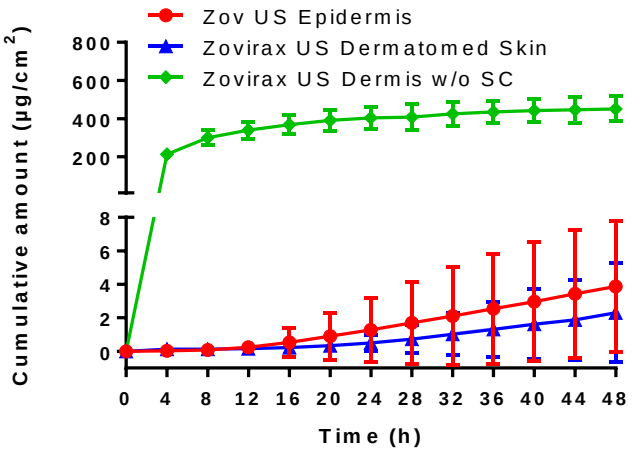
$K_{water,SC}$ = 0.18; h_{SC}= 13 µm;
$D_{water,SC}$= 1.07 x 10^{-3} µm²/s

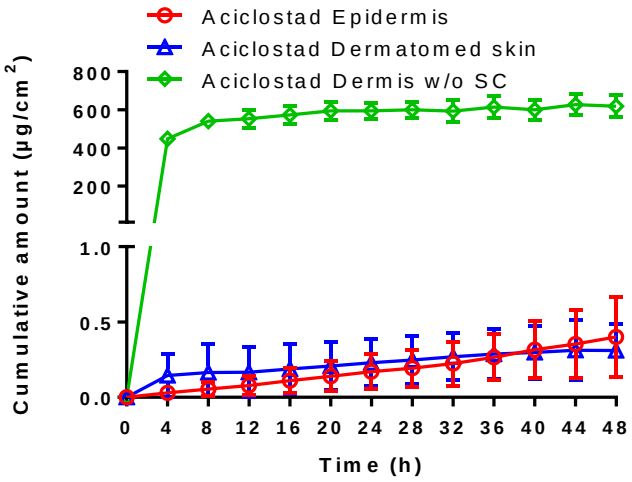
$D^*_{ACV,SC} = D_{ACV,SC} + 0.00003 \times C_{PG,SC} + 0.000043 \times C_{water,SC}$

- Now both Zovirax and Aciclovir 1A are both well fitted.

Support for vehicle enhancing effects using different membranes & use of infinite versus finite doses

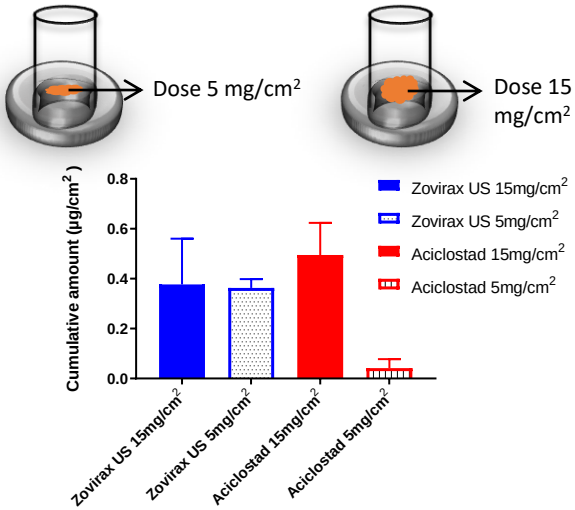
- US Zovirax and Aciclostad products using different skin membranes in the *in vitro permeation test* (IVPT)





- Note two products had different epidermal IVPT but were similar between epidermal membranes and dermatomed skin, i.e. SC is main barrier
- Note also the dermal absorption for the dermal absorption of the two formulations is similar but many orders higher than when SC is present

- Skin permeation of Acyclovir from small and larger dose at 4hrs



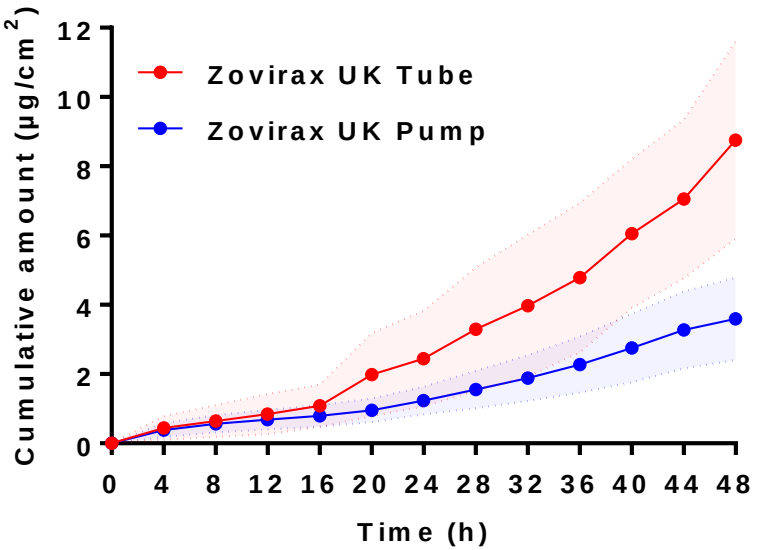
- Note infinite & finite dose of US Zovirax similar
- Also, both similar to infinite dose Aciclostad
- Also, note Aciclostad had a high water content and almost all water is lost from the applied product within one hour – maintained in Zovirax due to the higher propylene glycol content.
- And as water is important hydration of the SC but not the dermis, product water loss not so critical

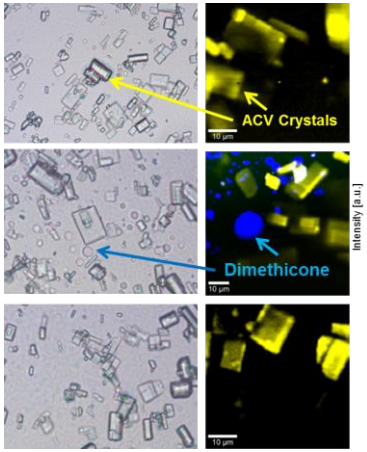
How acyclovir is dosed really matters *IVPT* profiles

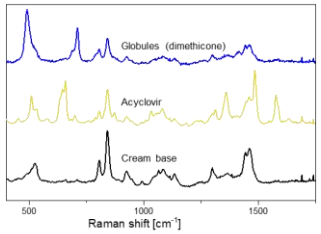
Zovirax UK Tube

Zovirax UK Pump

Zovirax UK Pump (container opened)







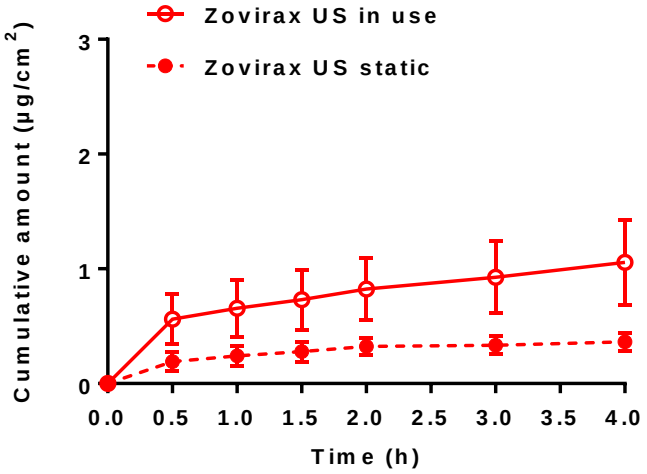
Yield stress from strain sweep (Pa)

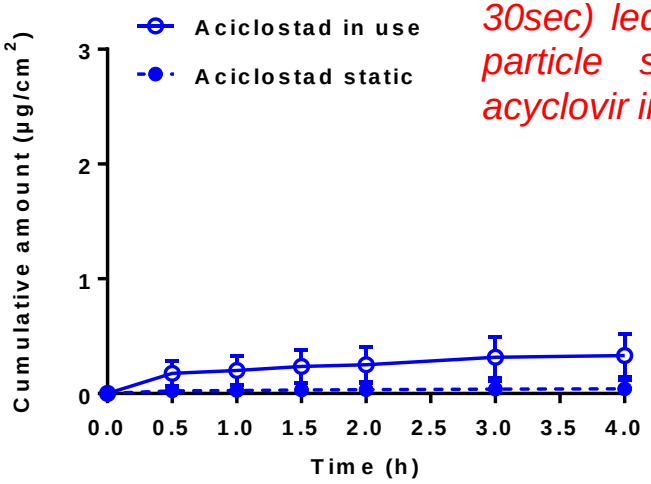
78 ± 1.3

182 ± 0.6

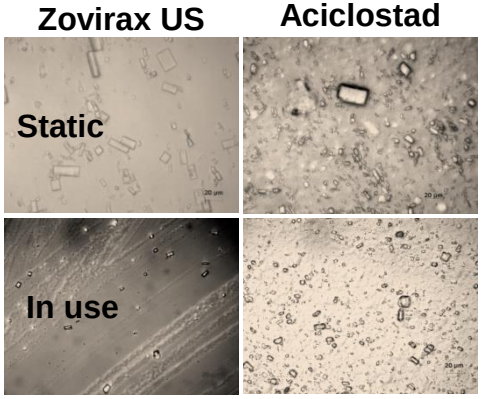
70 ± 10

The *IVPT* for both Zovirax and Aciclostad suggests that rubbing enhances permeation and that this effect is more pronounced for the Zovirax product – indeed the ratio for rubbing/static amount permeated for Zovirax is 8-10 times higher than Aciclostad.





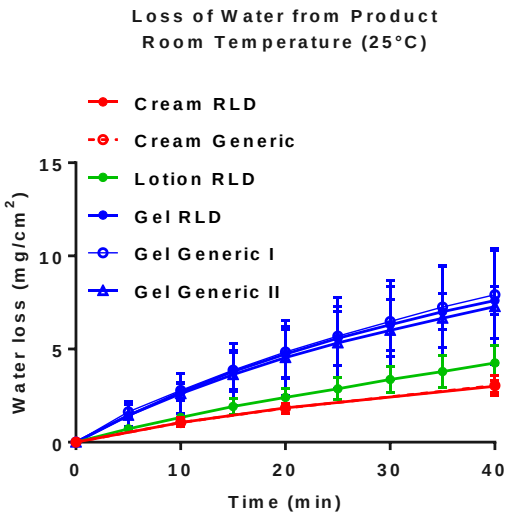
In use (rubbing onto the skin for 30sec) led to a reduction in acyclovir particle size and redistribution of acyclovir in the various phases

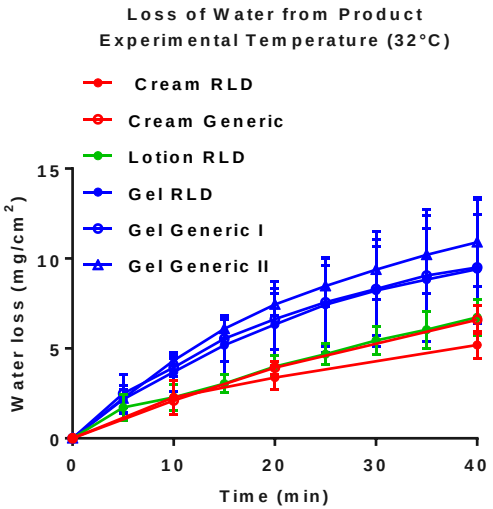


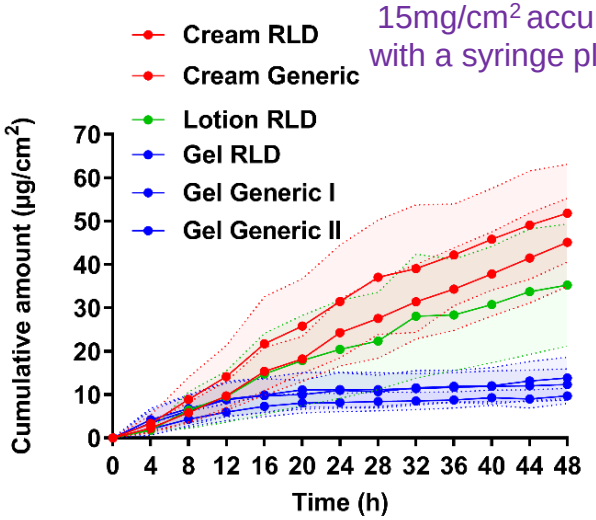
We also see importance of evaporation in the IVPTs for metronidazole products

- The gels have a very high water content and would therefore evaporate much quicker
  - ❖ How would this impact the Metronidazole in solution?
- We observed the product drying on the skin surface
- To what extent does this contribute to the observed *IVPT* differences?

Our group applied 15mg/cm^2 accurately with a syringe plunger







Audra Stincombe, who reported cumulative absorption (µg) over 24-h study duration, had values that corresponded well with **our data in red for the same time:**:

- Generic cream (21.0 ± 10.32, n=3) (~25)
- RLD gel (8.93 ± 2.33, n=3), (~10) and
- Generic metronidazole gel (9.70 ± 2.42, n=3)(~10),
- Applied with iInverted HPLC vial

Target dose: 10 mg/cm2
Flow rate: 1.0 mL/h
Skin surface temperature: 32 ± 2°C (circulating water bath)
Receiver solution: Isotonic phosphate buffer (pH 7.4 ± 0.1)
Skin: human abdominal skin from three donors with four replicate skin sections per donor per product
Audra Stinchcome
https://www.fda.gov/downloads/Drugs/NewsEvents/UCM591900.pdf

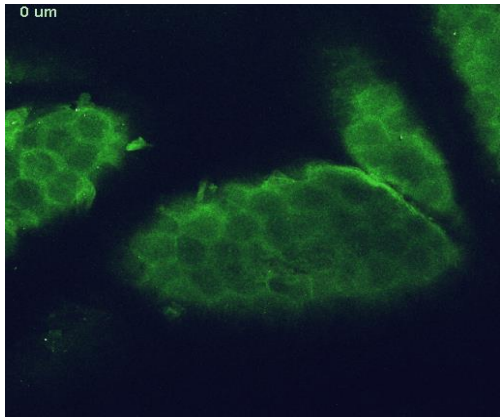
In contrast, data from Murthy appears about half our extent of absorption as our data in red, although the relative differences between products were similar. He reported cumulative absorption (µg/cm^2) over 48-h study duration as follows::

- RLD cream (18.41 ± 4.31), (45.1 ± 4.4)
- Generic cream (17.53 ± 4.68) (51.8 ± 4.9)
- RLD gel (3.76 ± 0.59). (12.3 ± 1.6)
- Generic gel I (4.18 ± 0.76), (13.8 ± 2.1) and
- Generic gel 2 (3.48 ± 0.41) (9.7 ± 0.8)
- Applied with positive displacement pipette

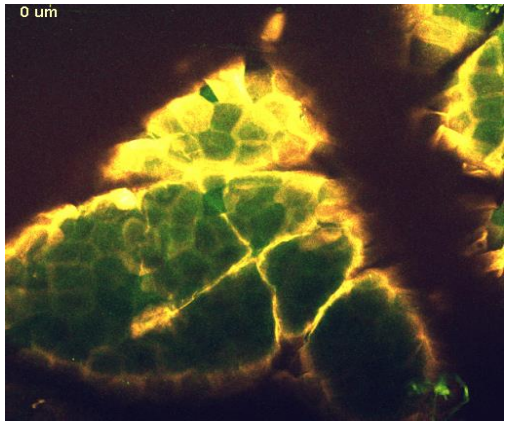
S. Narasimha Murthy
https://www.fda.gov/downloads/Drugs/NewsEvents/UCM591897.pdf

Conclusions

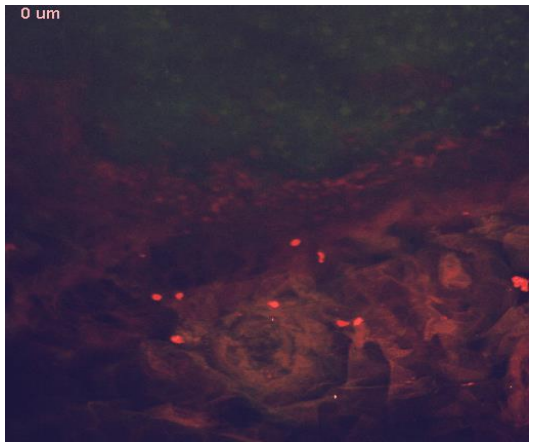
- Q1 (ingredients), Q2 (concentrations) and Q3 (product microstructure) all affect *IVPT* for actives and *in vivo* PBPK for different formulations and actives
- However, *in vitro – in vivo* relationships (*IVIVR*) can be derived from *in vitro* permeation test (*IVPT)* data
- Dose and method of application can have significant effects on *IVPT* outcomes
- Excipient evaporation, viscosity and modulation of skin permeability can also greatly impact on *IVPT* kinetics
- Similar *IVPT* behaviour with various in *in use* dose formulation effects on epidermal *IVPT* kinetics seen for acyclovir, metronidazole and oxybenzone
- More to be done in relating *IVPT* and in vivo behaviour to skin morphology, physiology and pathology
- Understanding the complex interactions between dose forms and their environment and with the skin under *in use* application conditions is crucial to being able to successfully apply predictive *PBPK* analyses for new, re-formulated and generic dose forms



Untreated control



Acriflavine 5 ug/ml **Topical Treatment**



Acriflavine 5 ug/ml **Transdermal Incision**

Thank you!

WHO International Program Team - Environmental Health Criteria for Dermal Absorption

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