

Formulating at the Interface

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Common questions and beliefs

- 60% absorbed
- Generic 'do all' formulation
- Formulation does not affect permeation
- Is it possible to target different strata of the skin?
- Liposomes and nanoparticles penetrate skin

60% absorbed!

Safe, organic beauty products for moms-to-be

By: Isabel Roces

Philippine Daily Inquirer

3:18 am | Friday, February 24th, 2012

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Valentine's Day is no treat if you're pregnant. You know how frustrating it can be to be forbidden so many things. You feel it even more when the hallmark holidays kick into high gear, because so many things on the table are no-no's.

It's not just food that makes up a large chunk of the prohibited list. Even dolling yourself up presents so many hindrances. Expecting moms, as I've found out lately, aren't allowed to color their hair or go through chemical salon treatments. Even manicures and pedicures should be avoided because studies show that you absorb through your skin about 60 percent of whatever you put on it. Some of these things can be full of harsh chemicals that are bad for your overall health and especially your baby.

<http://lifestyle.inquirer.net/36077/safe-organic-beauty-products-for-moms-to-be>

2. **The average woman absorbs more than 4 pounds of cosmetics during her lifetime. Guys, you're not off the hook.** Your skin -- the body's largest organ -- absorbs up to 60 percent of the products you put on it every day, from soaps to shampoos to sunscreens. Considering that most of us use about 10 different products daily?that can really add up. Choosing green personal care products often means using plant-based ingredients in place of petrochemicals, preventing these chemicals from being absorbed into your skin. Learn

Poor bioavailability



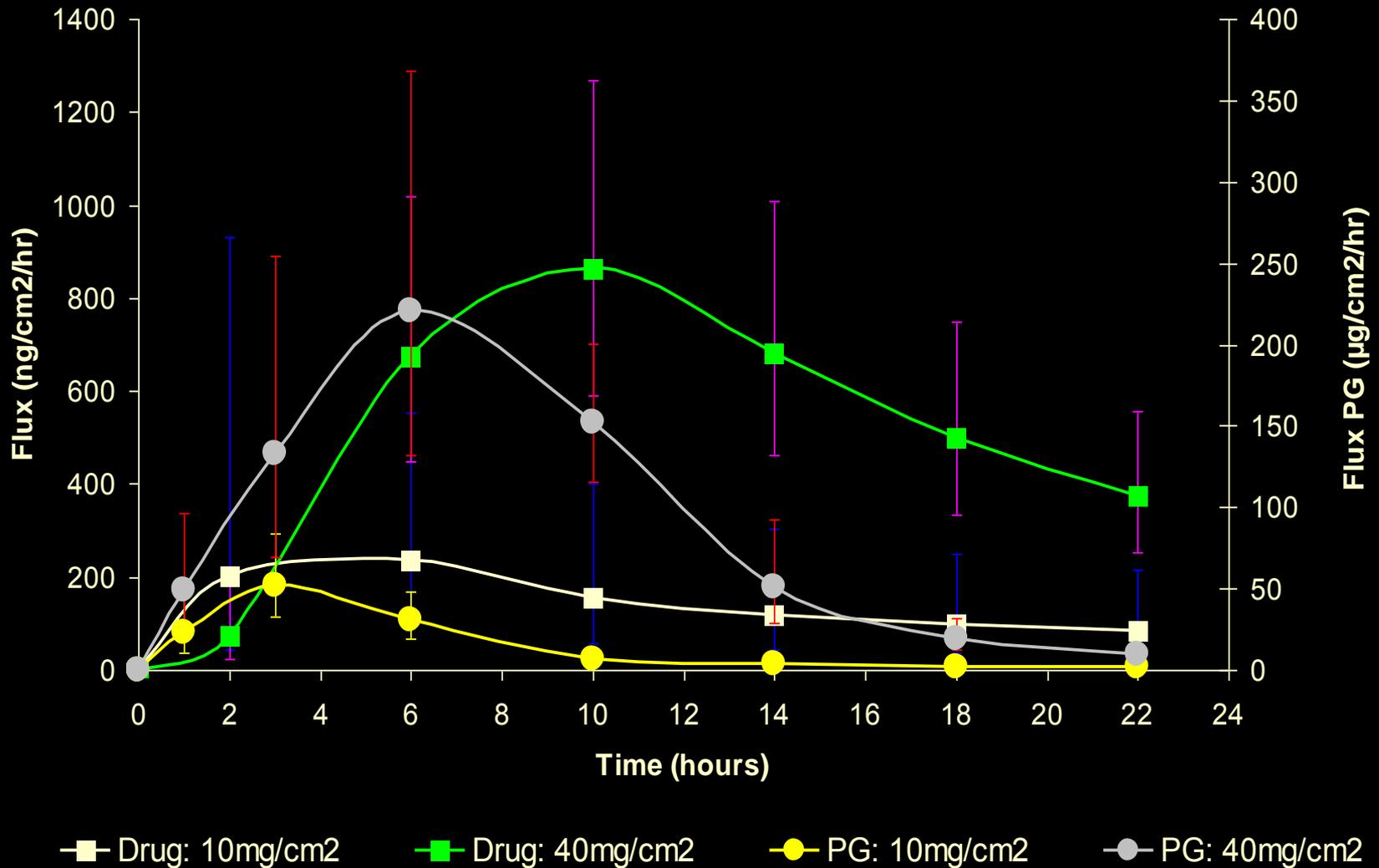
- e.g. 0.25% hydrocortisone alcohol applied to forearm (unoccluded) gives 1.04% excreted
- corresponds to 1.7% absorbed
- equivalent to 0.2 mg/cm²
- Over total body only 4 mg absorbed

Where does it go? And can we improve it?

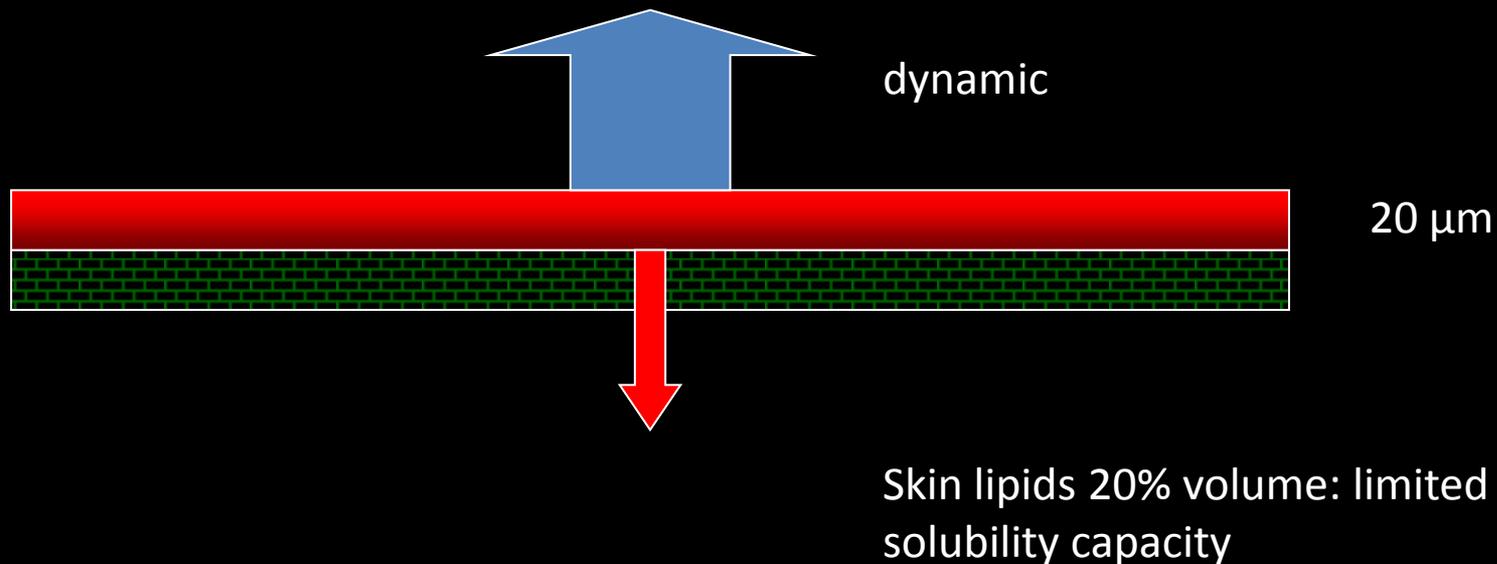


- Role of excipients
- What do they do?
- How long are they there?

Permeation of propylene glycol and drug: effect of the amount of gel applied

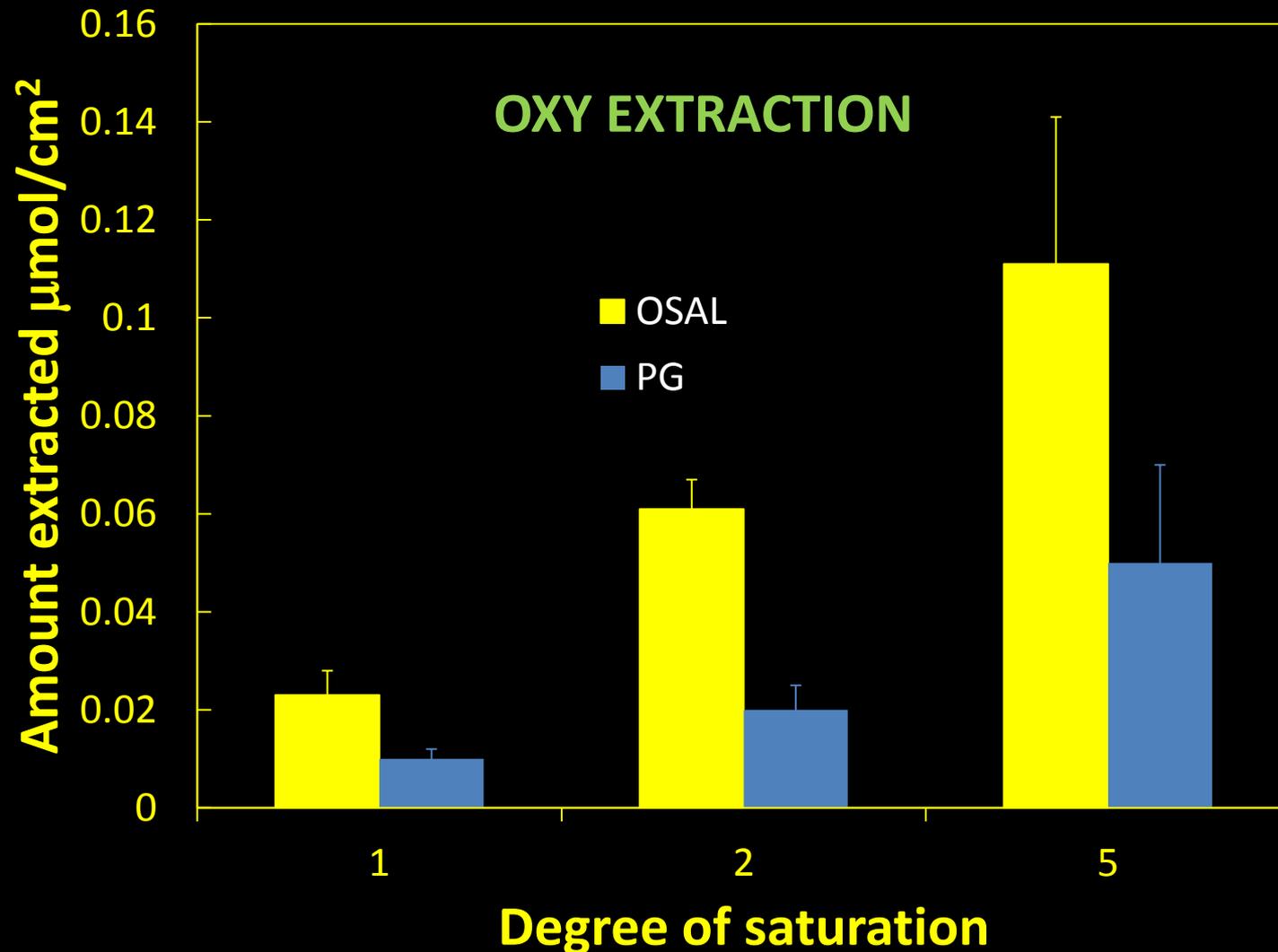


Clinical dosing: 2 mg/cm²

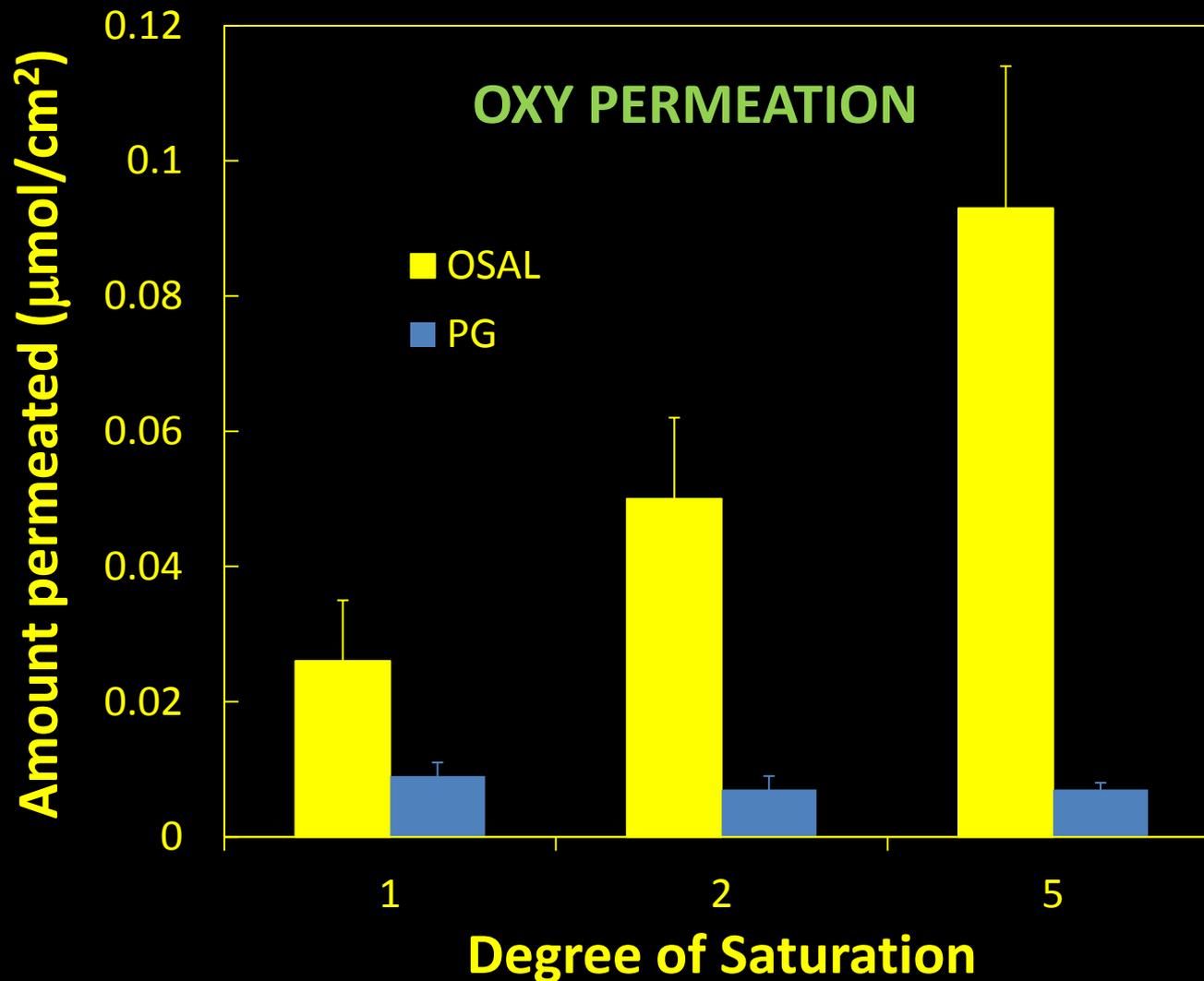


In vitro experiments difficult to mimic dose:
volatile component *cf* spray technology

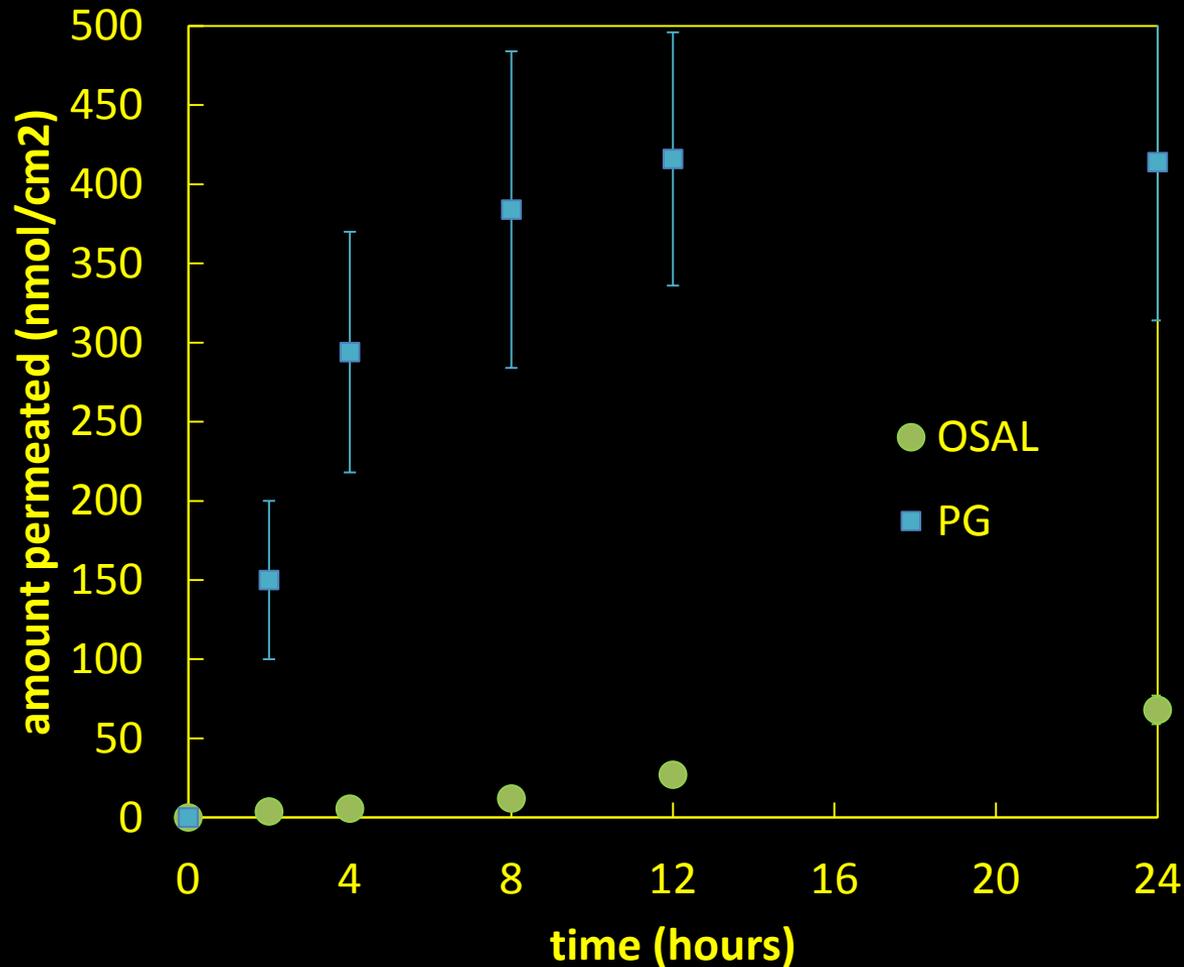
Finite dose of OXY in OSAL: EtOH or PG: EtOH



Finite dose of OXY in OSAL: EtOH or PG: EtOH

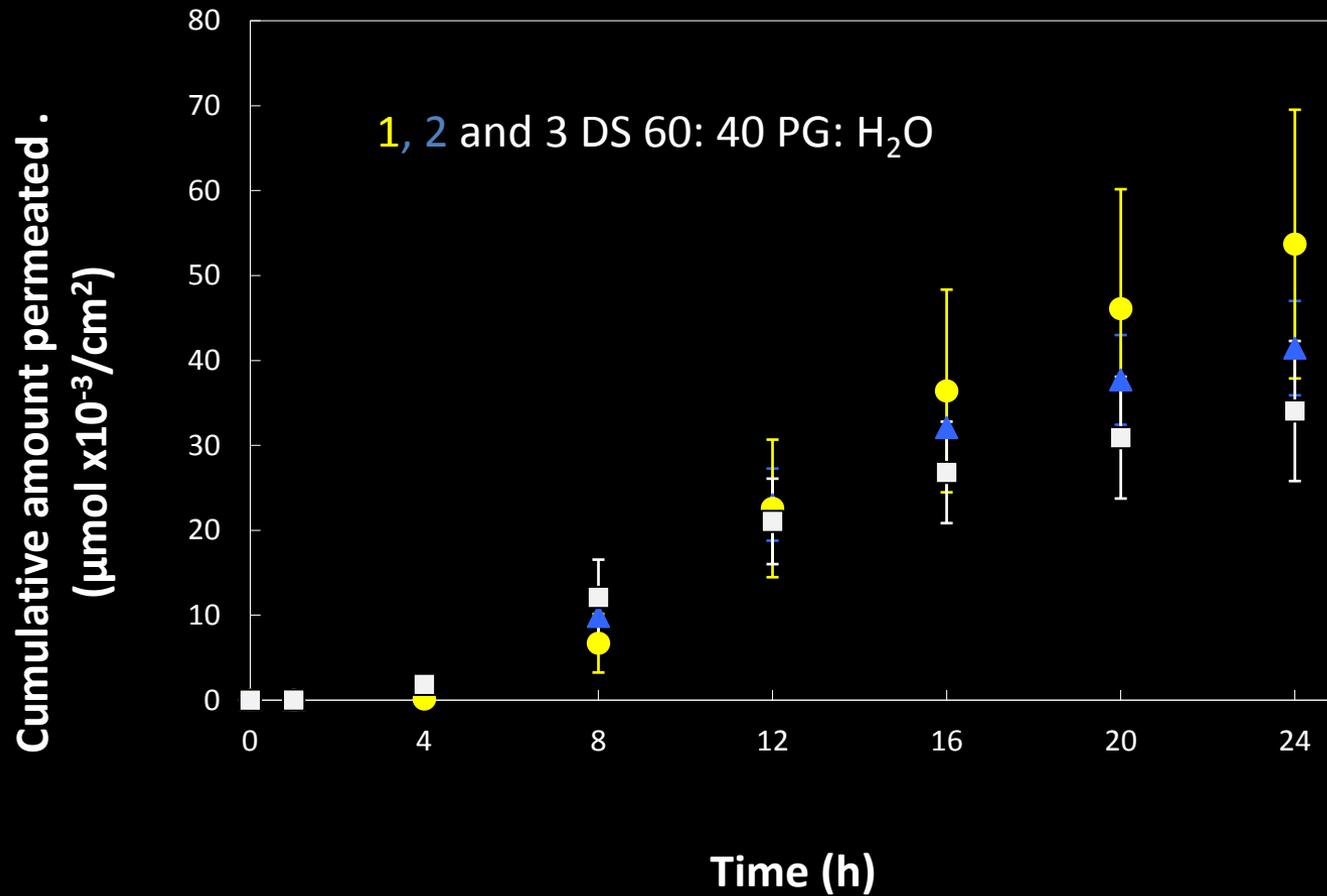


Finite dose of OSAL: EtOH or PG: EtOH: penetration of excipient



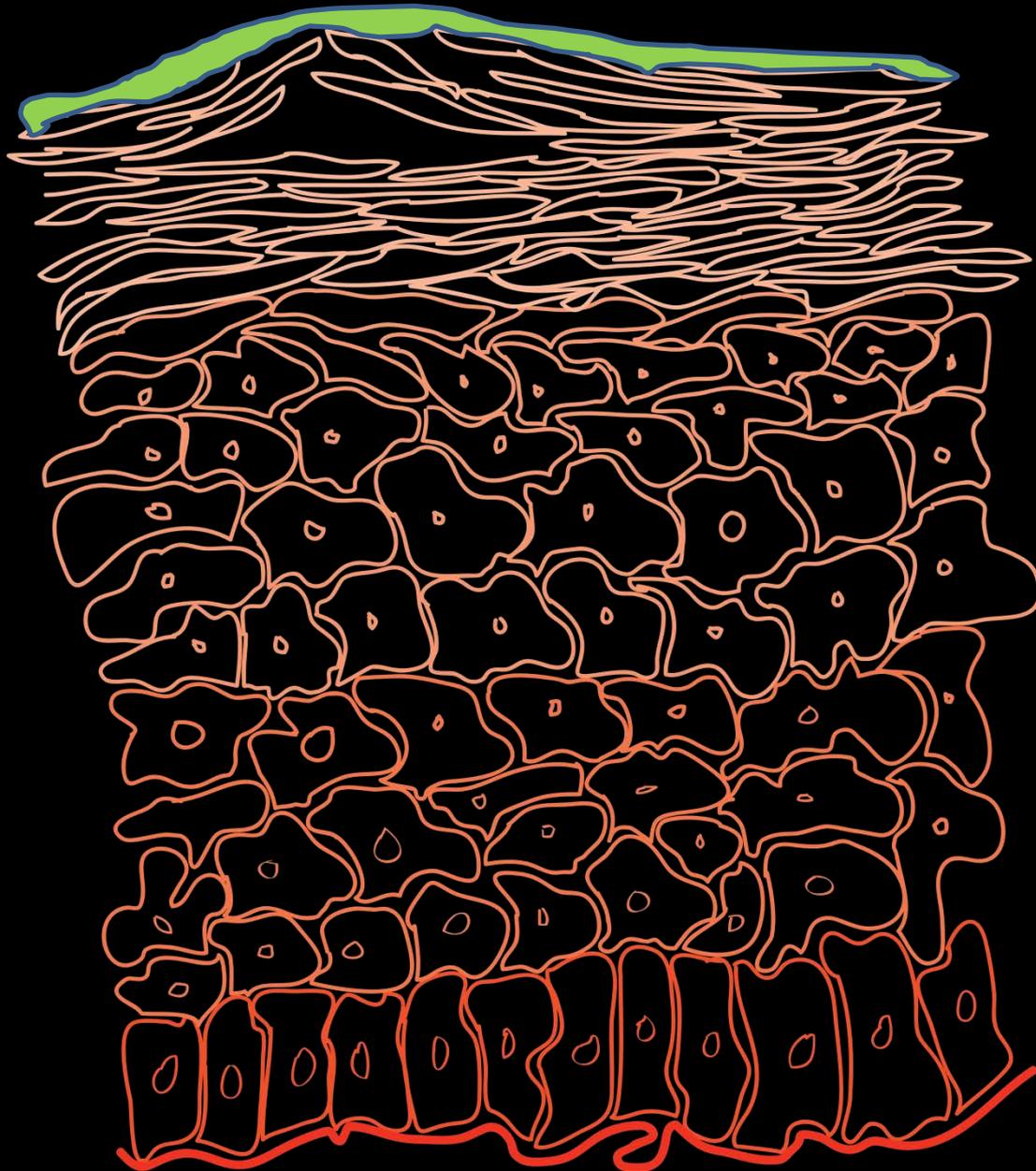
80% OXY left on or in the skin from PG

Finite dose fentanyl, in vitro skin



Contact with intercellular channels or deposition in skin lipids

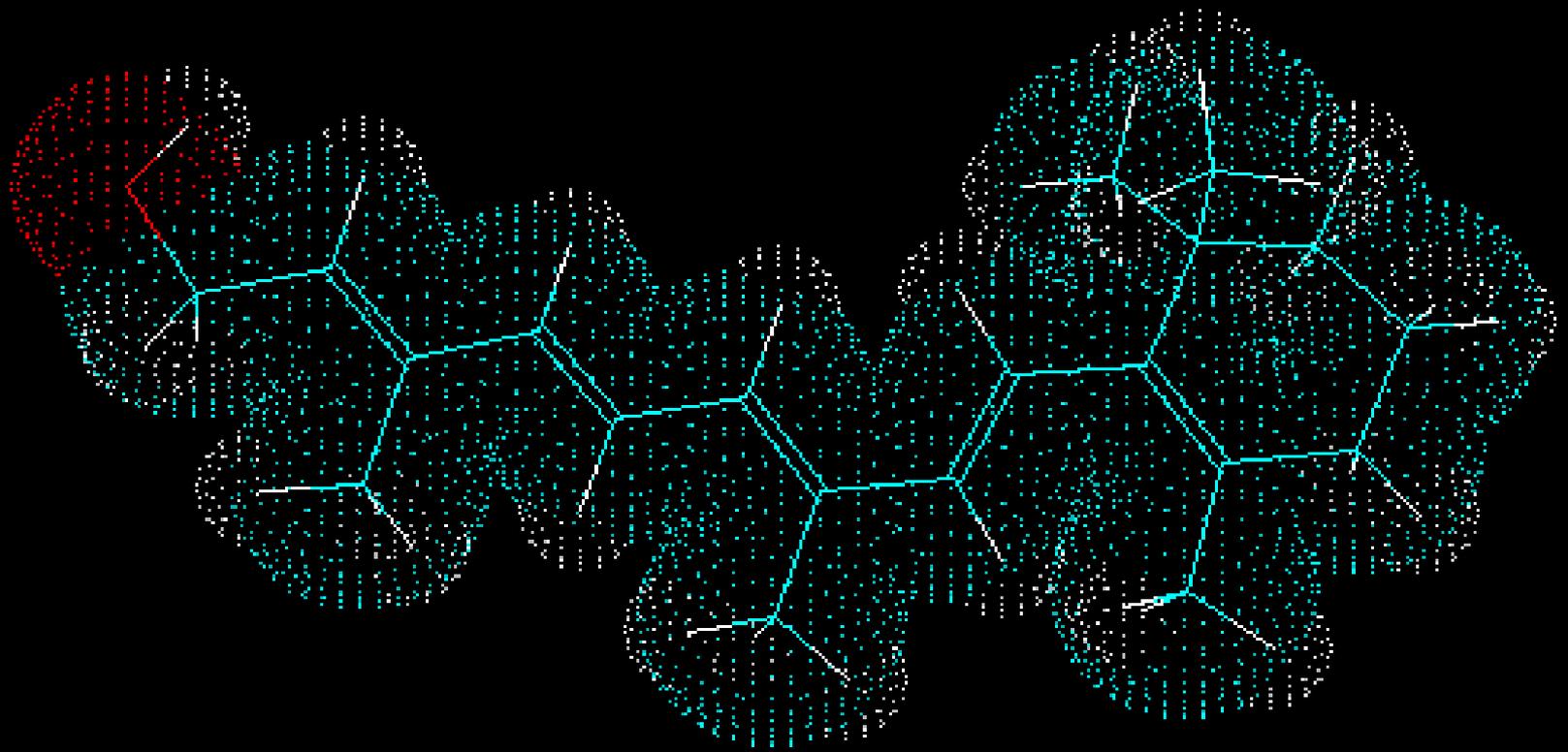




Surface effects

Targeting?

Retinol

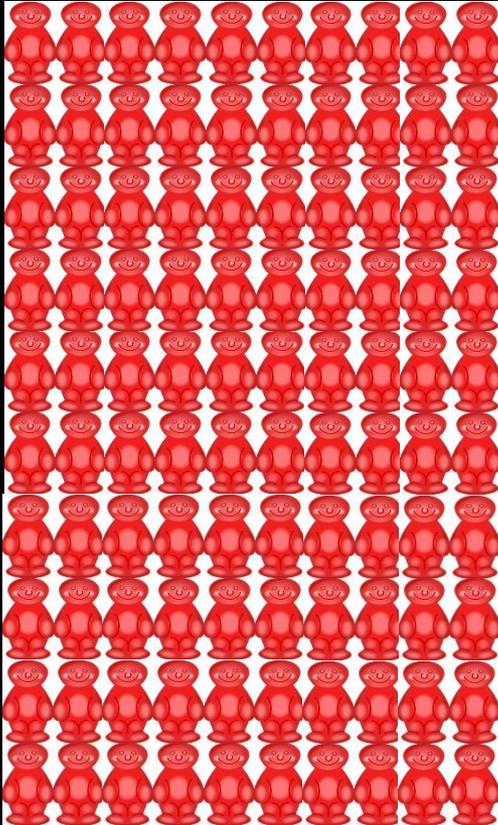


1 nm

Retinoids: concentration effects

Normal formulation, average skin

On Skin



Across Skin



About 1% permeates (lot of waste)

Retinoids: concentration effects

Super deluxe formulation, average skin

On Skin



Across Skin



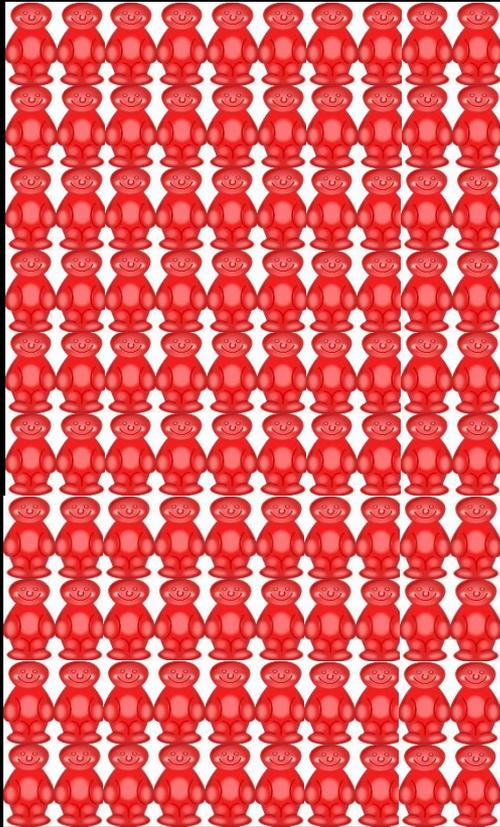
Drop concentration by factor of 20 but has same bioactivity

Use of supersaturation and enhancers

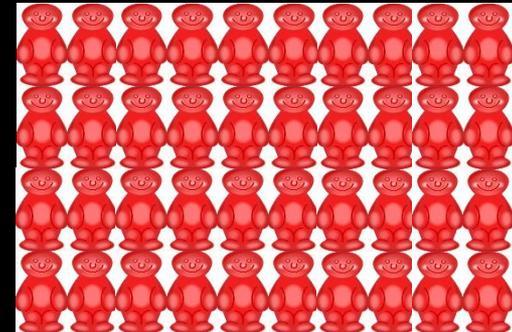
Retinoids: concentration effects

Normal formulation, high permeability skin

On Skin



Across Skin



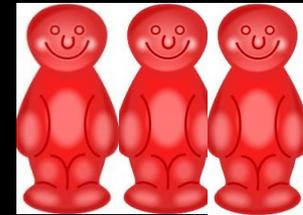
Retinoids: concentration effects

Super deluxe formulation, high permeability skin

On Skin



Across Skin



Drop concentration by factor of 20 far less goes through skin

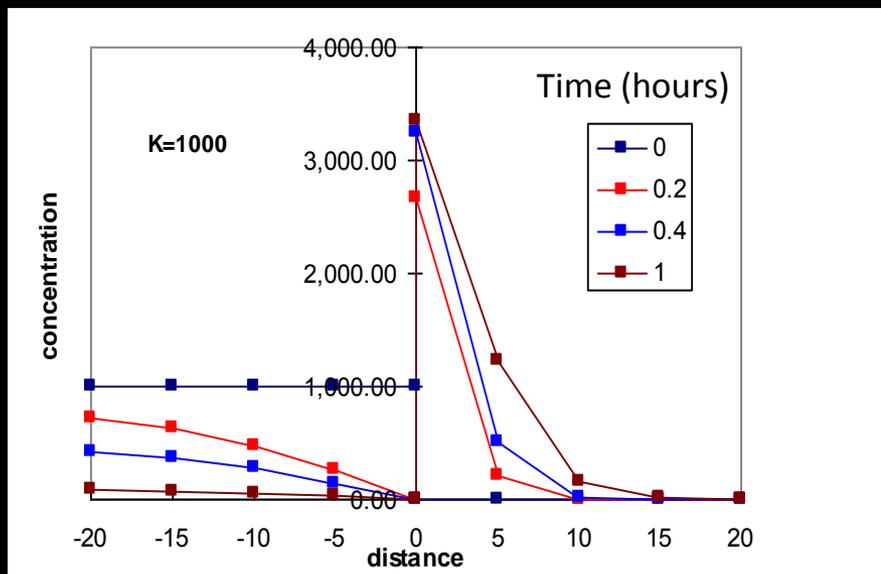
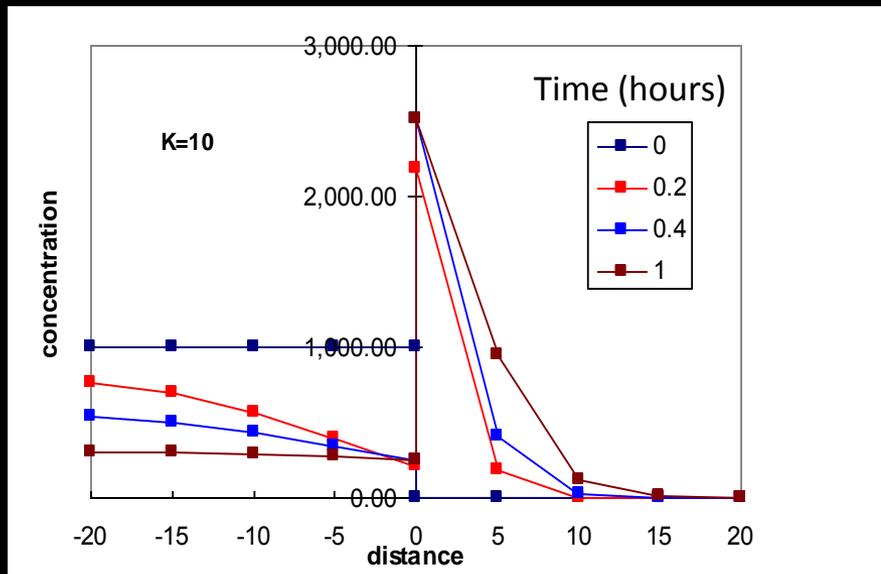


Finite dosing

role of partition & solubility

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}$$

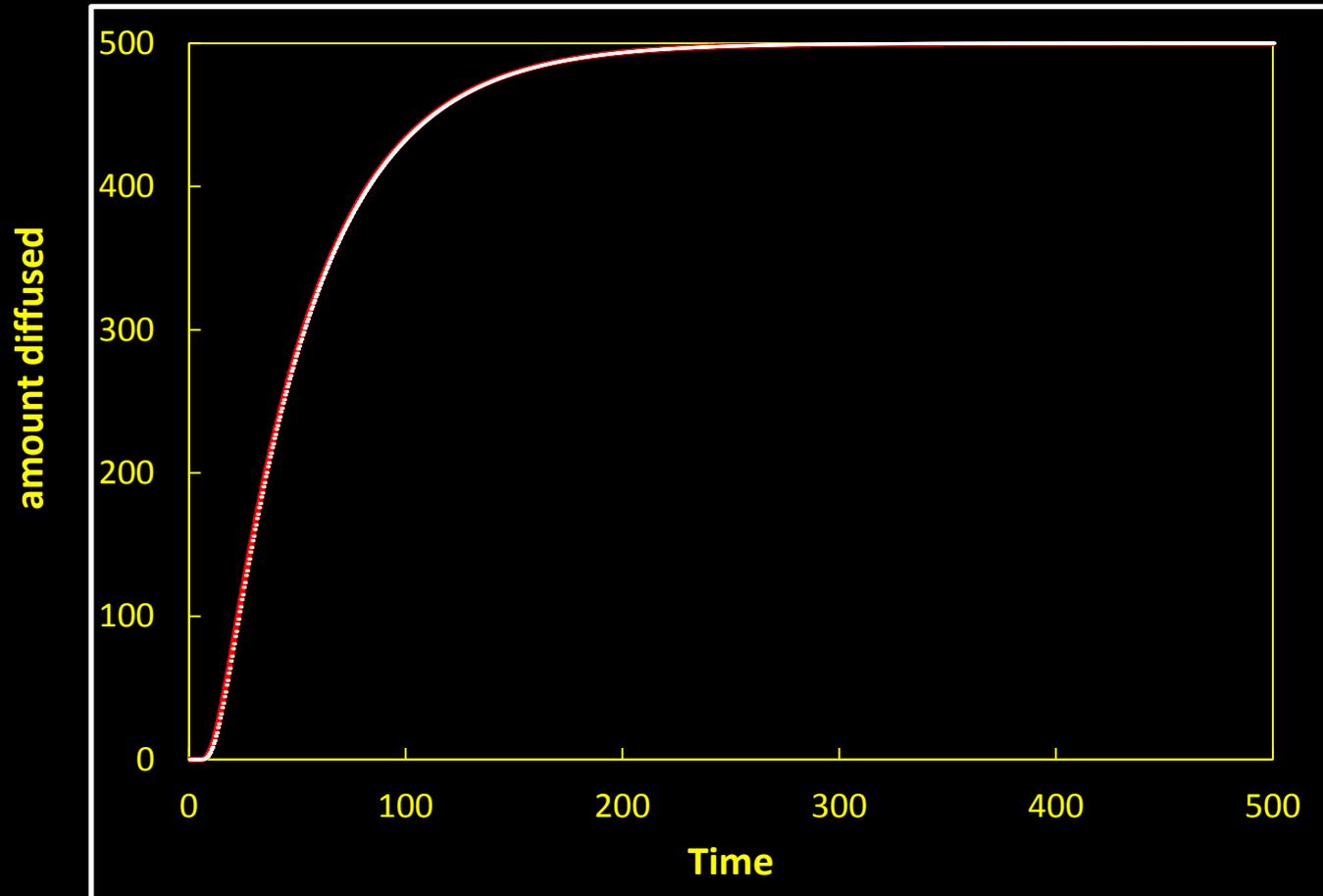
Finite dosing



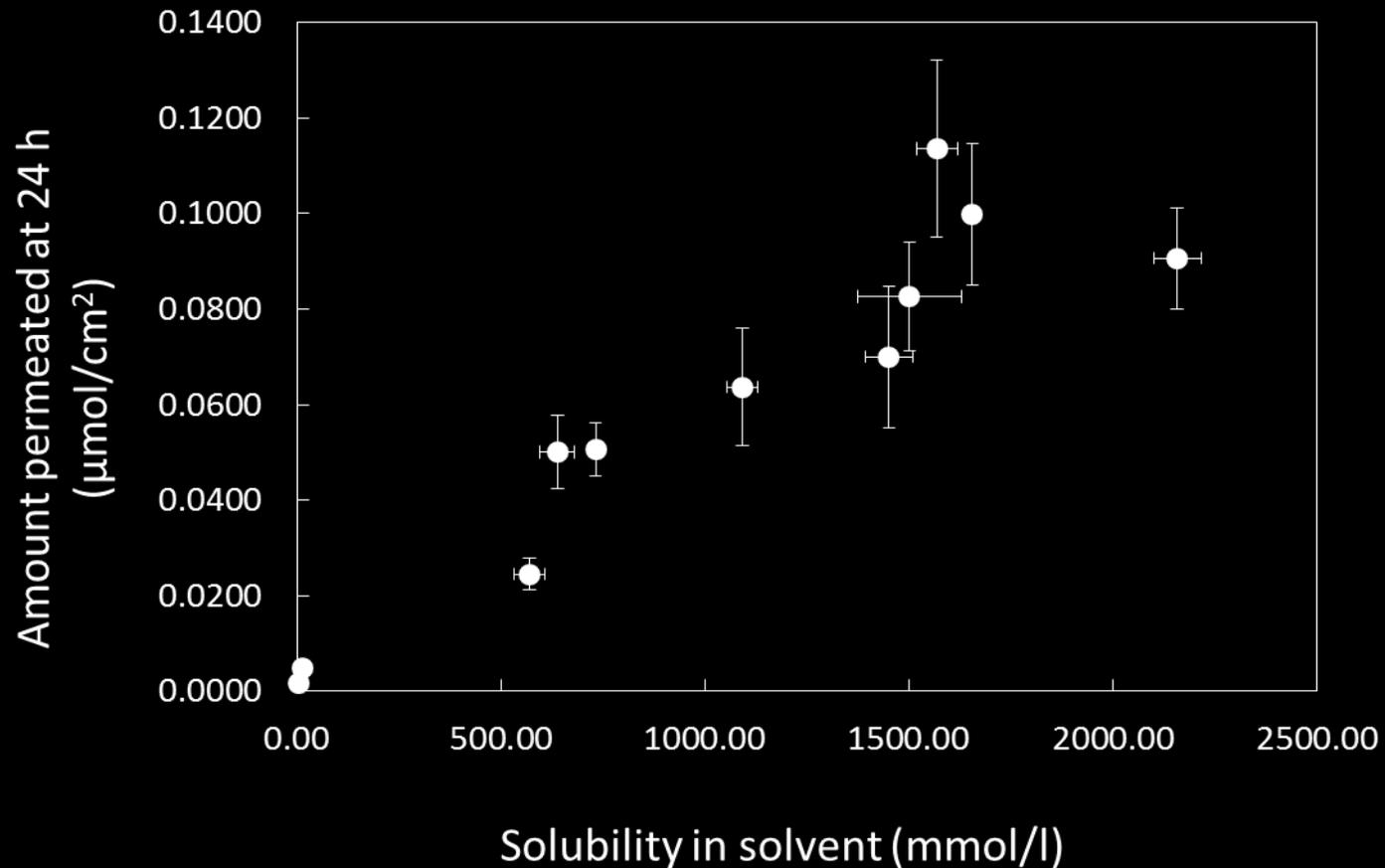
May have to rethink design strategies in dermal drug design

Validity of *in vitro* studies and importance of dosing

Finite dose simulations: effect of changing K by factor of 100



Perhaps solubility dominates in finite dose application



Ibuprofen permeated at 24 hours through human skin (*in vitro*) and solubility of ibuprofen in the applied solvent.

Formulating for efficacy¹

J. W. Wiechers*, C. L. Kelly†, T. G. Blease† and J. C. Dederen‡

*Uniqema Skin R&D, Gouda, The Netherlands, †Uniqema R&D Department, Redcar, U.K. and ‡Uniqema Personal Care Applied Research and Technical Service Group, Redcar, U.K.

Two **opposing factors** are necessary to obtain sufficient skin delivery:

- 1) High **absolute** solubility of the active in the formulation for skin penetration
- 2) Low **relative** solubility of the active in the formulation, so that the drug or active ingredient leaves the formulation and preferentially moves into skin

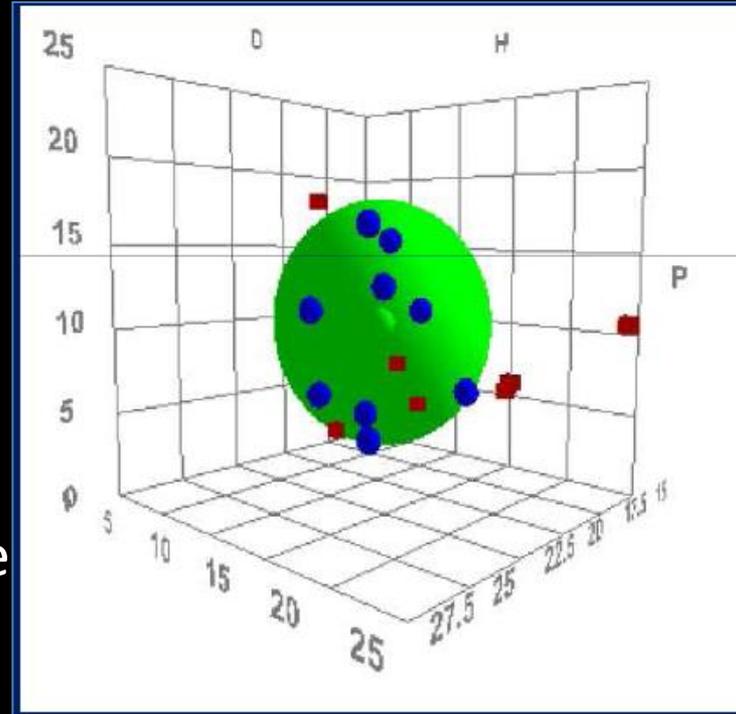
Formulating for efficacy

Computer-aided formulation design

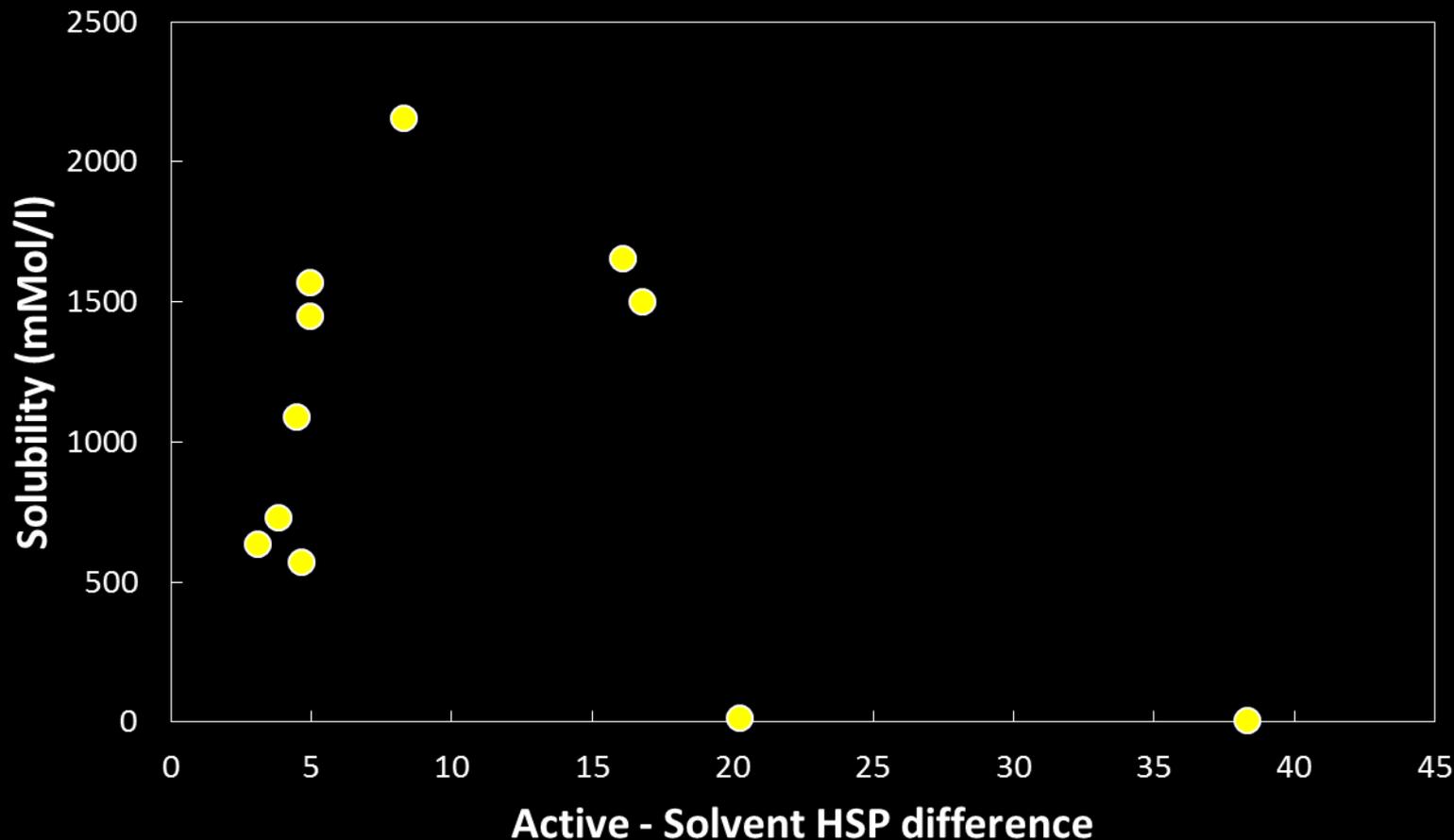
3D plot of active based on solubility parameter

Distance between active and solvent determines how well active dissolves in solvent

Match formulation to skin solubility parameter for optimal flux

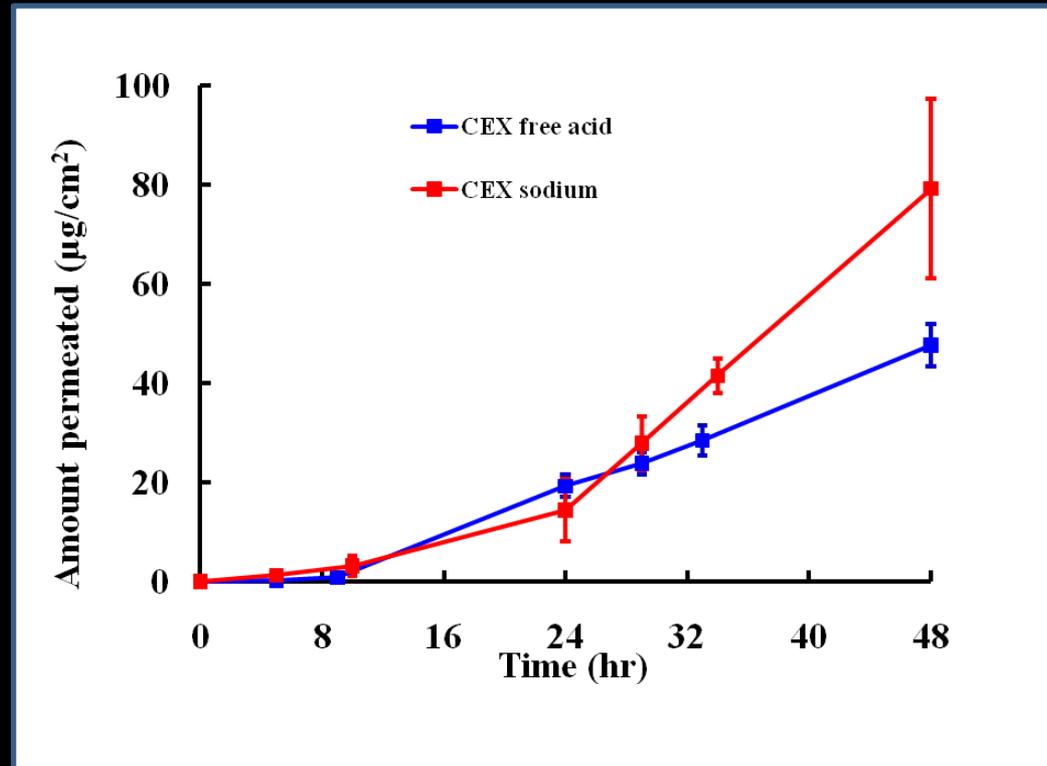


Solubility parameter and solubility



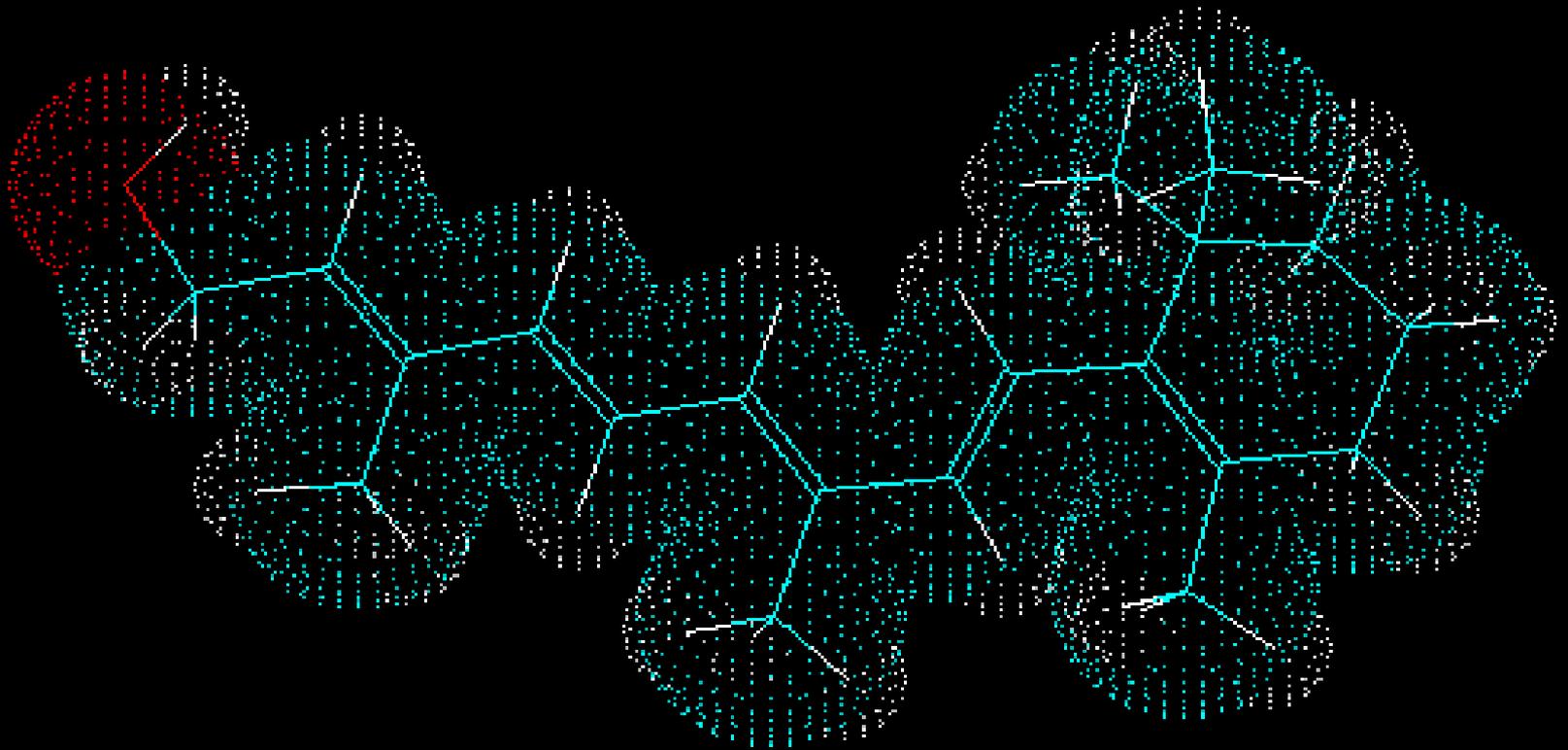
Ibuprofen experimental solubility and the HSP difference between ibuprofen and solvent.

Ionised or free acid / base?



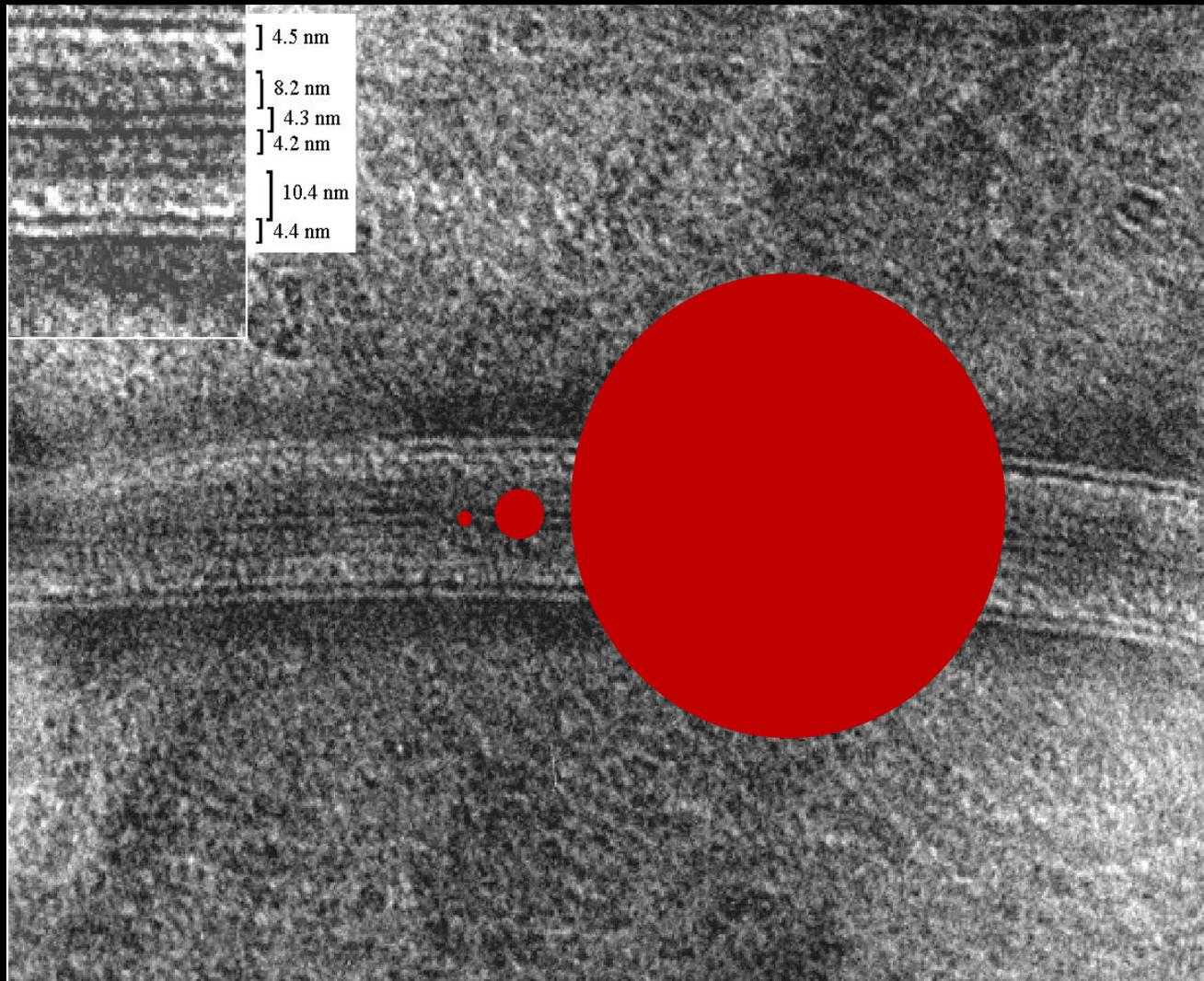
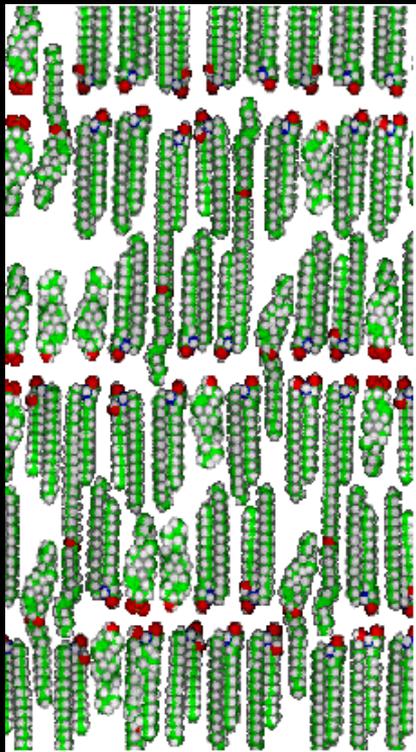
Comparison between the transport of CEX and CEX sodium in the TC-PG-IPM/PGL (36-29-36) formulation through human skin at infinite doses.

Nanotechnology: Retinol, molecular size



1 nm

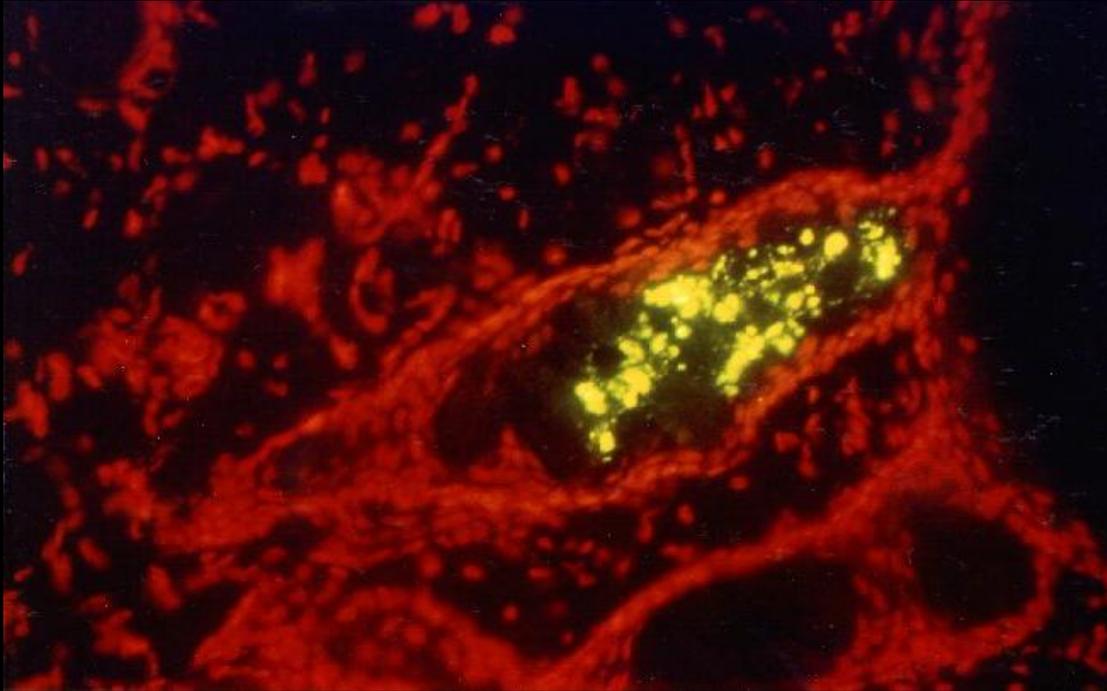
Nanotechnology



10 50 500 nm

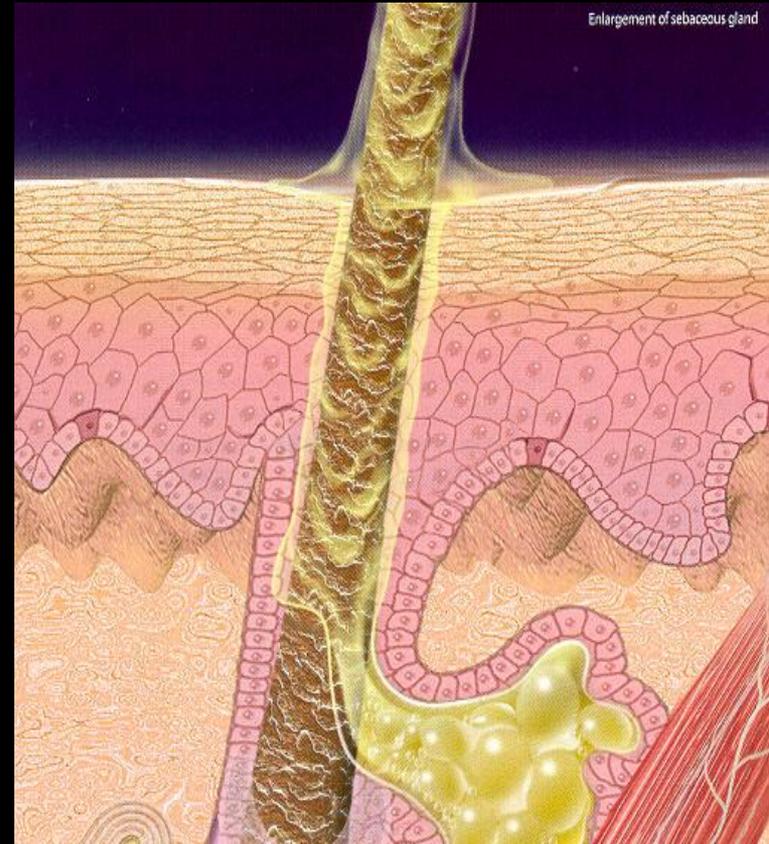
Follicular targeting

1-10 μm particles of dansyl aniline as 10% suspension in silicone fluid



Hair Follicles

Khavari *et al.* Nature Biotechnology 1999



Future developments

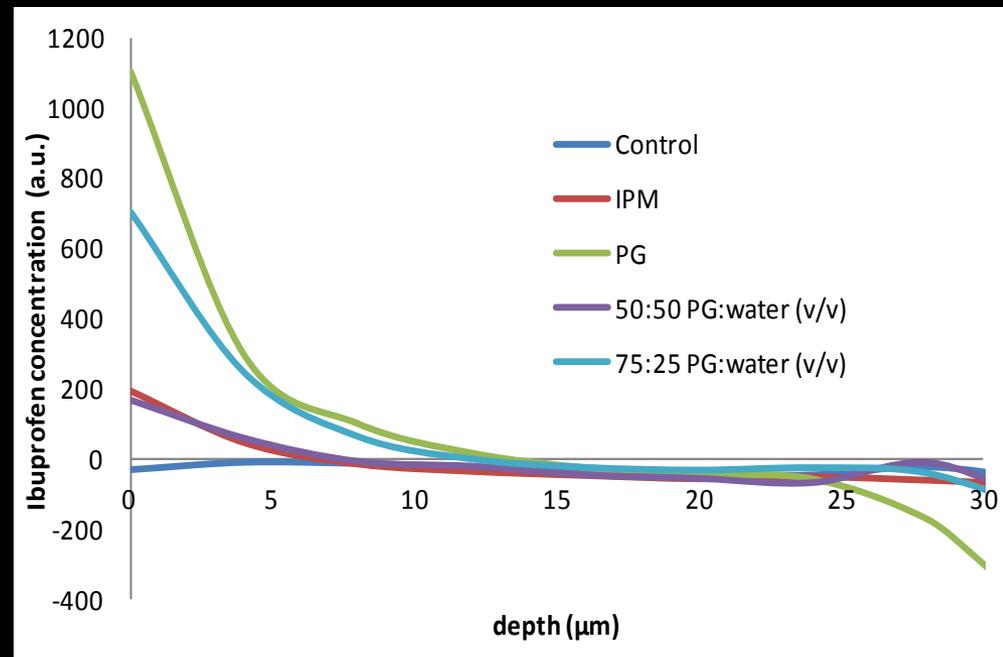
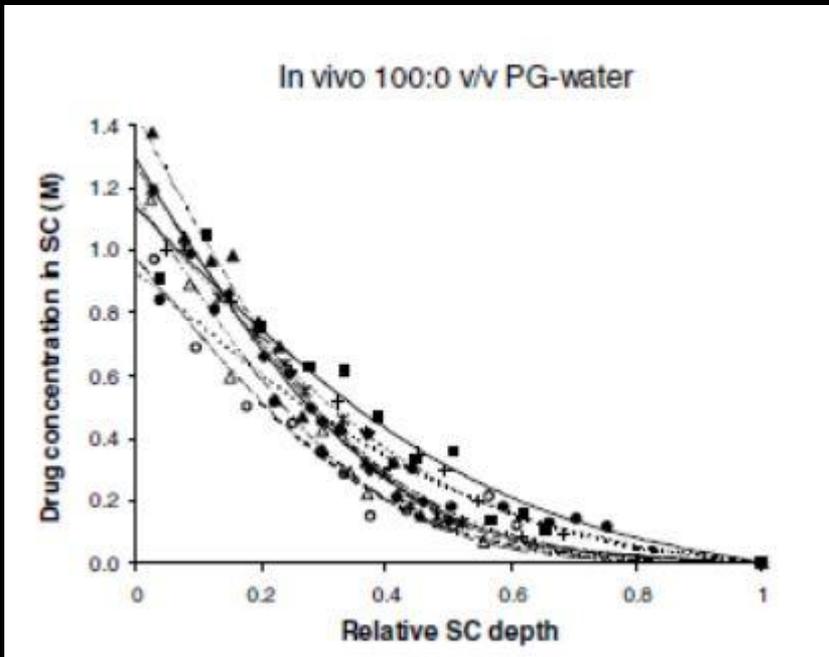
New techniques

Monitor active

Monitor excipient

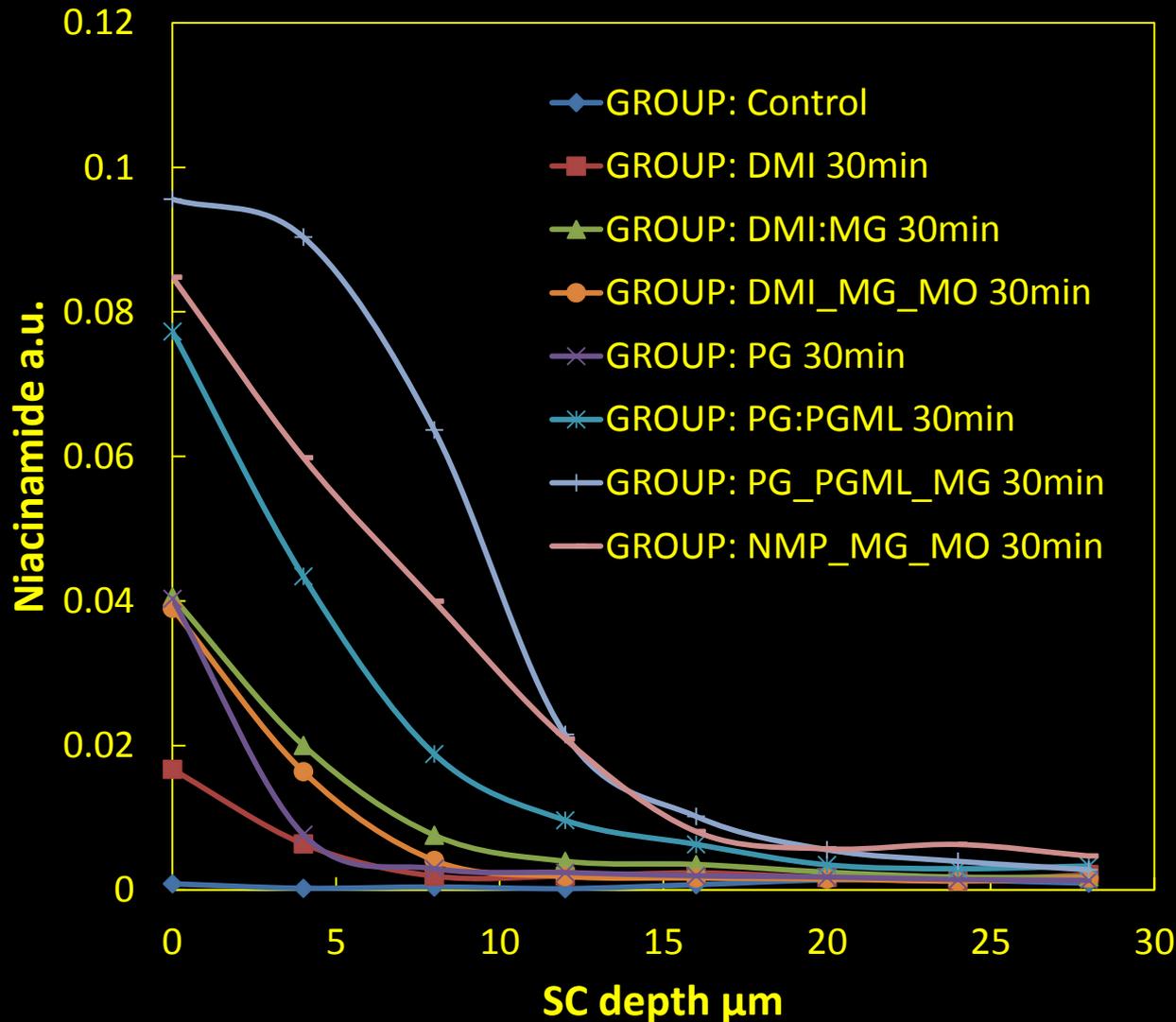
e.g. confocal Raman spectroscopy

Confocal Laser Raman *in vivo*: permeation of ibuprofen



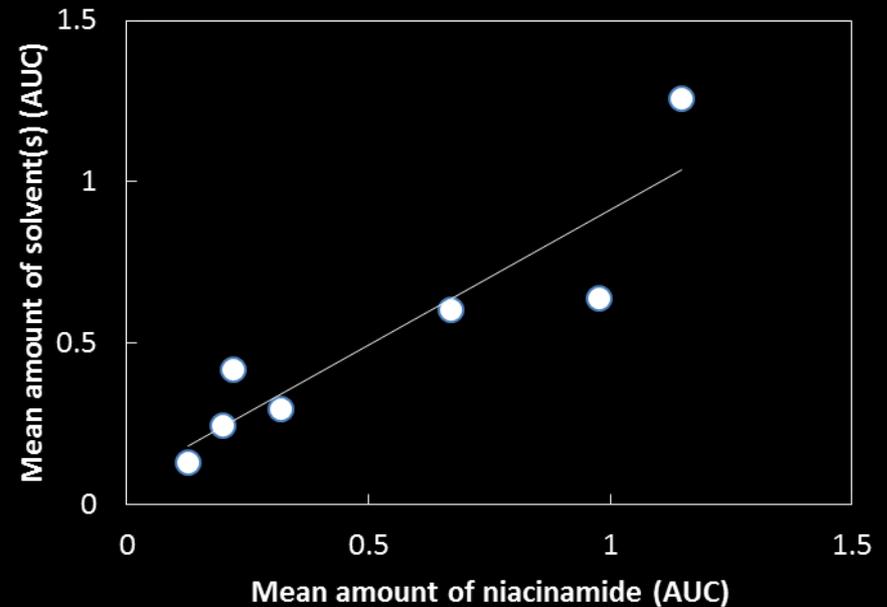
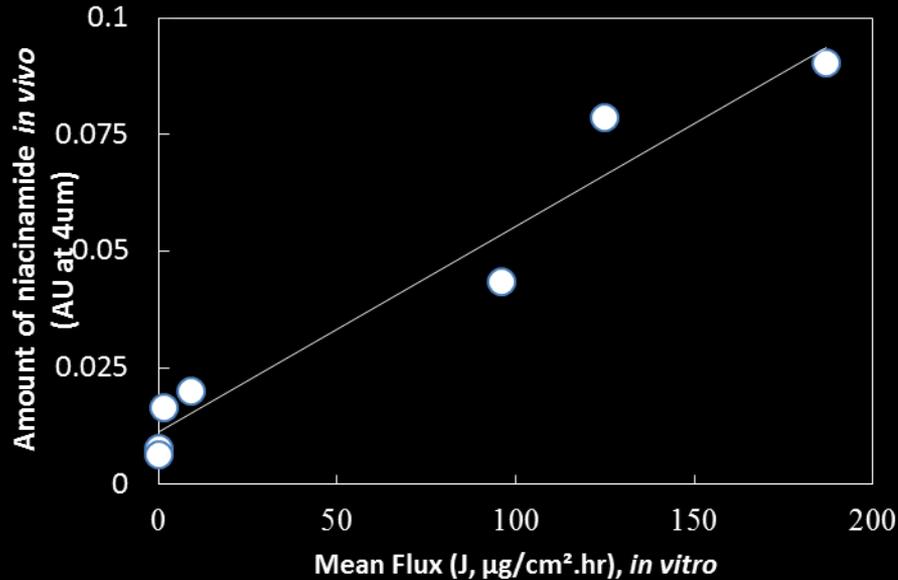
Herkenne *et al.* Pharm. Res. 23 (2006) 1850-1856

Confocal Laser Raman *in vivo*: permeation of nicotinamide



Confocal Laser Raman:

in vivo in vitro correlation and
active: solvent correlation *in vivo*





Conclusions

Significance of solubility

More consideration of role of excipient

Residence time

Monitor active and excipient