Biodelivery across leaf/skin membranes – formulating for biodelivery

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Innovation in Colloid Formulation: Secrets of Formulation III

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Introduction

- How do we design formulation for maximum efficacy?

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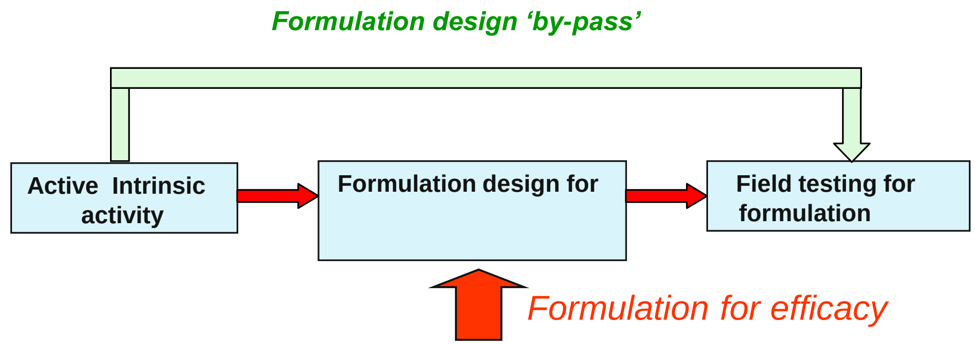


Foliar penetration

- $J = (K.D/ L) \Delta C$
  - J = steady state flux of penetrant across membrane
  - K = partition coefficient i.e. the distribution coefficient of the penetrant between the membrane barrier and the donor vehicle.
  - D= diffusion coefficient through membrane
  - L= path length through membrane
  - ΔC = concentration difference across the membrane

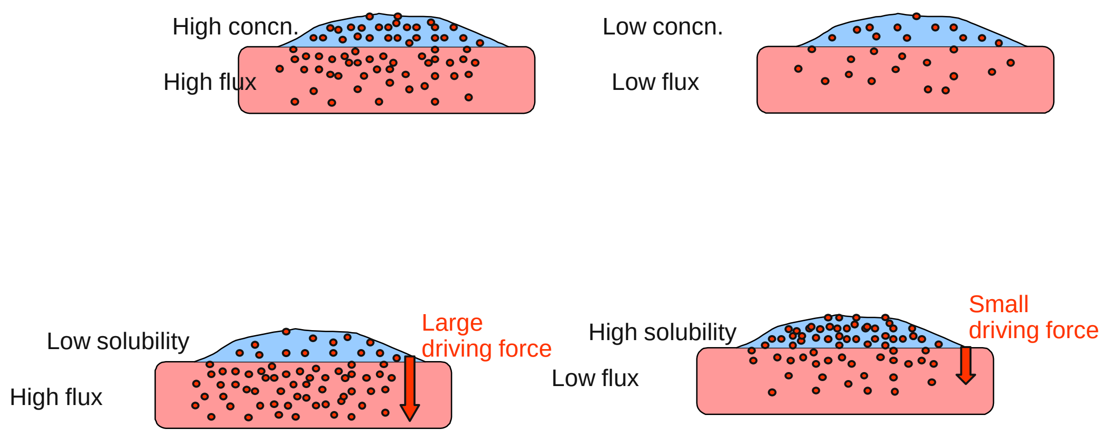
Foliar penetration contd.

- $\text{Activity}_{\text{subst.}} = \text{Activity}_{\text{form.}}$
- $C_{\text{subst.}} / \text{sol limit}_{\text{subst.}} = C_{\text{form.}} / \text{sol limit}_{\text{form.}}$
- $K = C_{\text{subst.}} / C_{\text{form}} = \text{sol limit}_{\text{subst.}} / \text{sol limit}_{\text{form}}$

Foliar penetration contd.

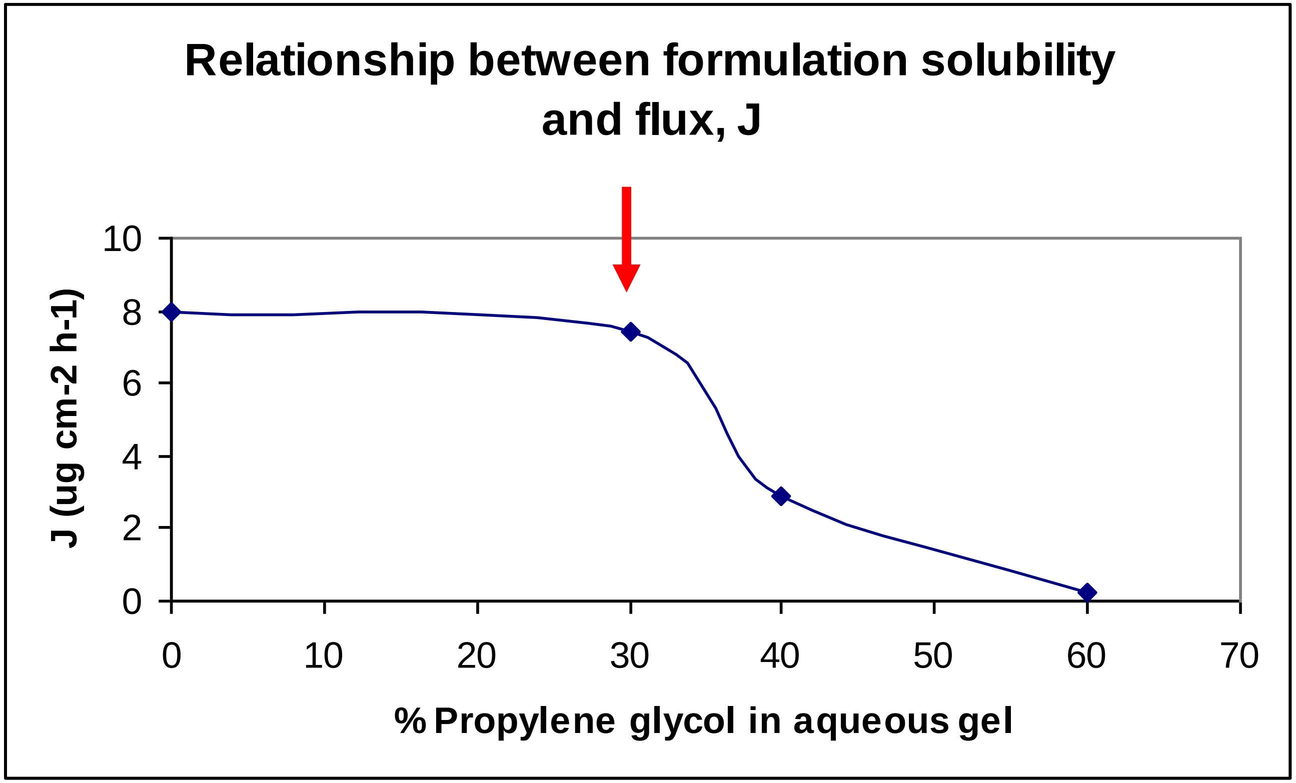
- $C_{subst.} / \text{sol limit}_{subst.} = C_{form.} / \text{sol limit}_{form.}$

- $K = C_{subst.} / C_{form} = \text{sol limit}_{subst.} / \text{sol limit}_{form}$



- $K_{subst./form} \cdot C$ = ‘driving force’

Example of driving force effect : Diclofenac sodium ex-aqueous gel



Increased sol limit $_{form}$ -> Decreased K -> Decreased J

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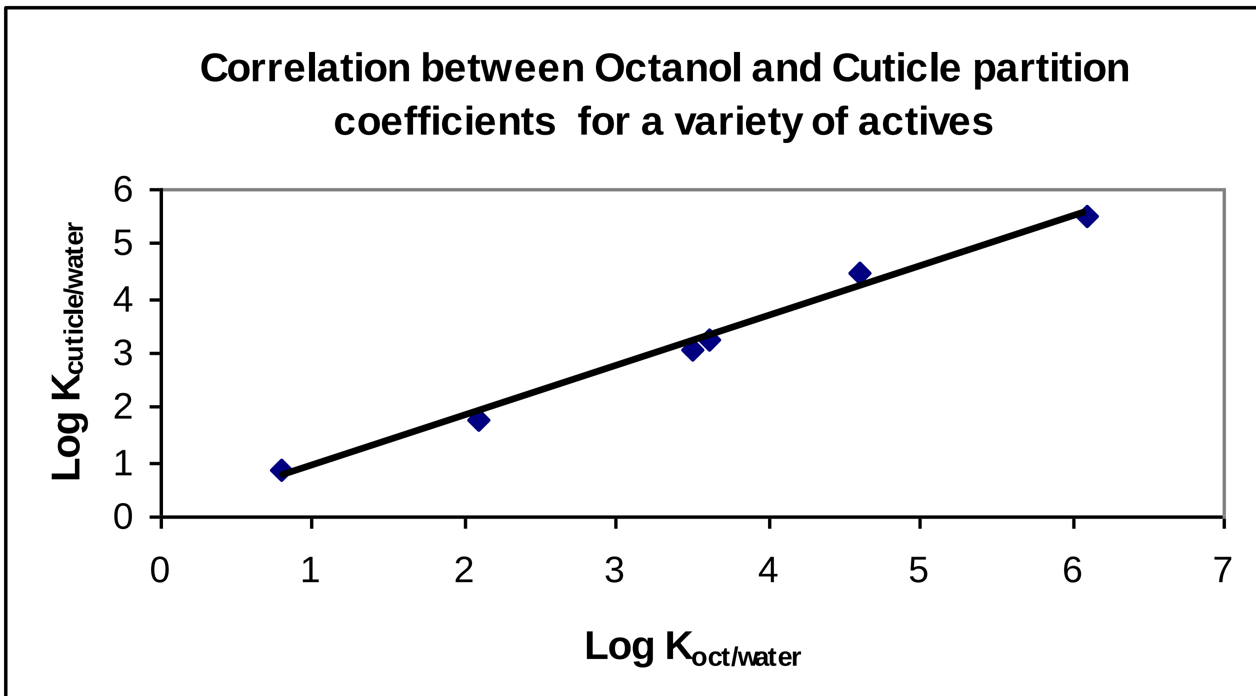
Predicting K values

- Octanol/water partition coefficients (log K $_{oct/w}$)
- Correlation with log $_{cuticle\ /water}$



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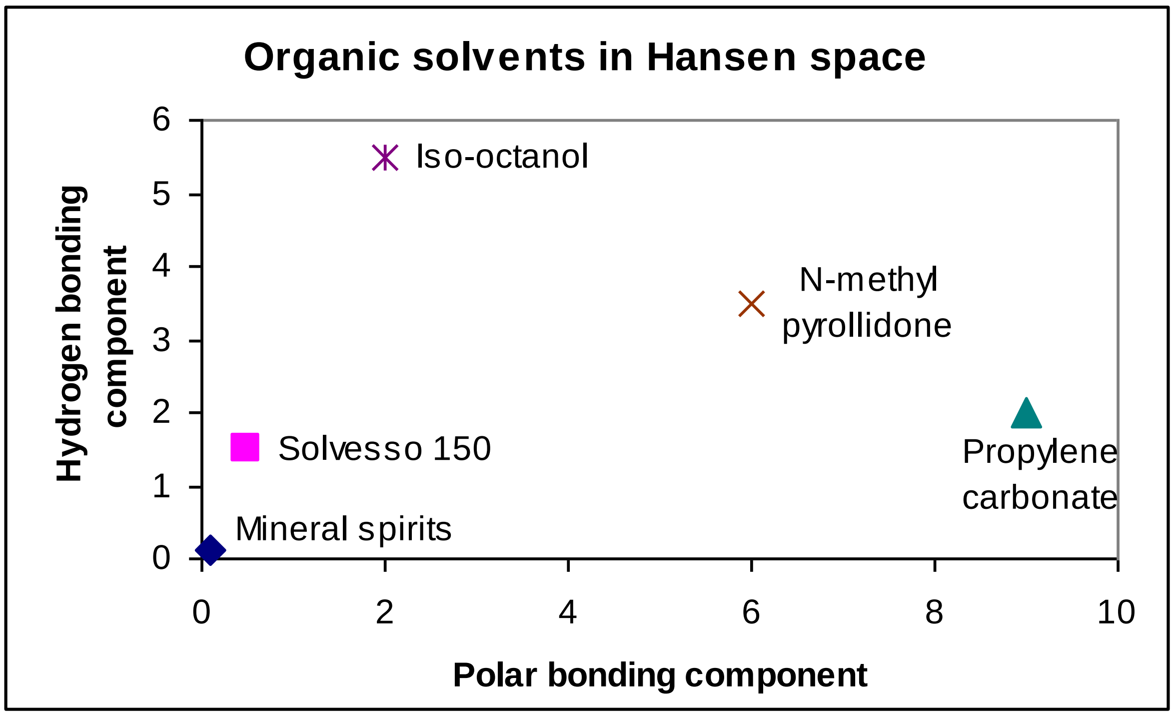
Predicting K values contd.

- Hansen solubility

$$\Delta T = \sqrt{(\delta_d)^2 + (\delta_p)^2 + (\delta_h)^2}$$



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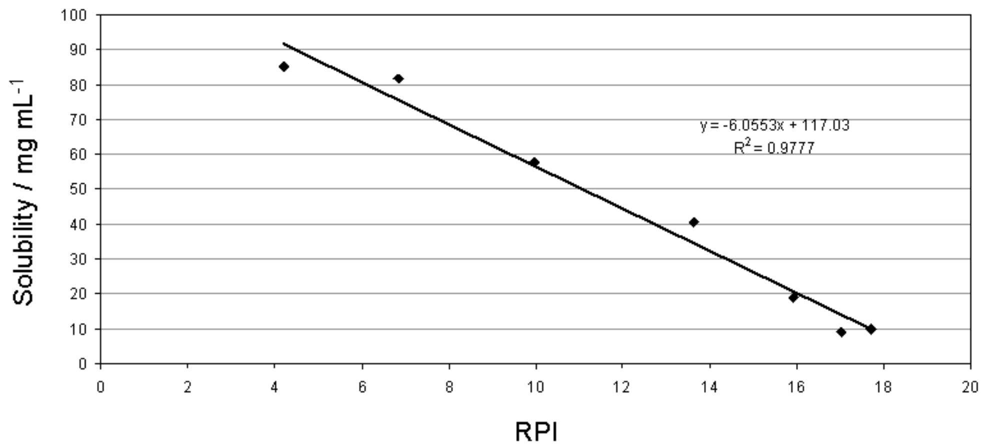
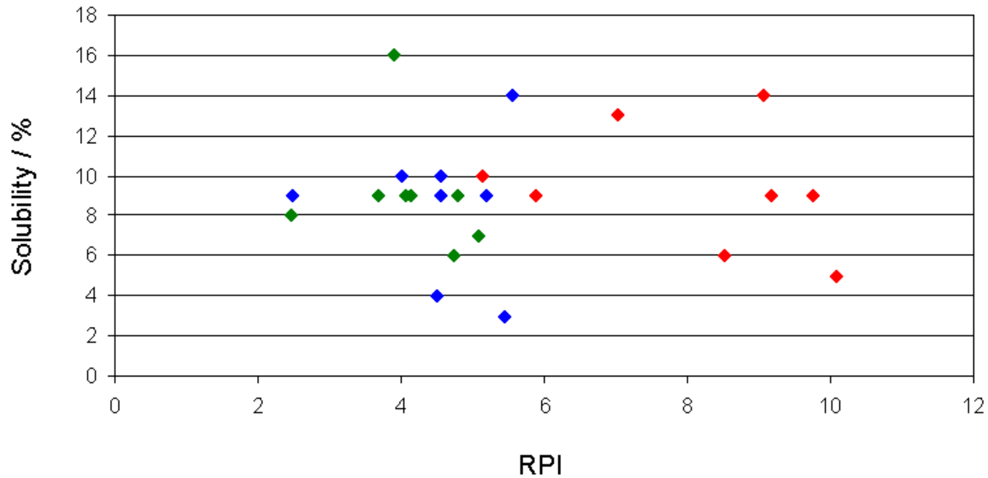
Hansen solubility contd.





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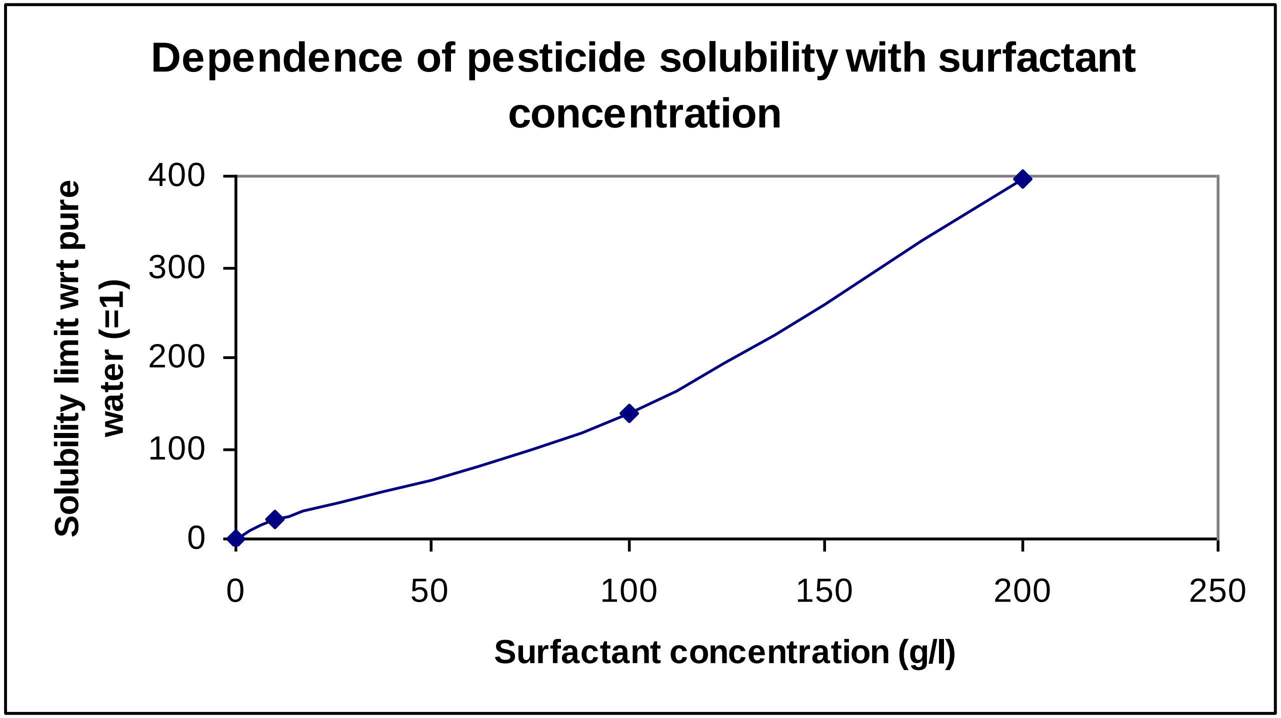
Measuring K values - donor medium

- Evaporation effects



- Absorption effects

Measuring K values - substrate medium

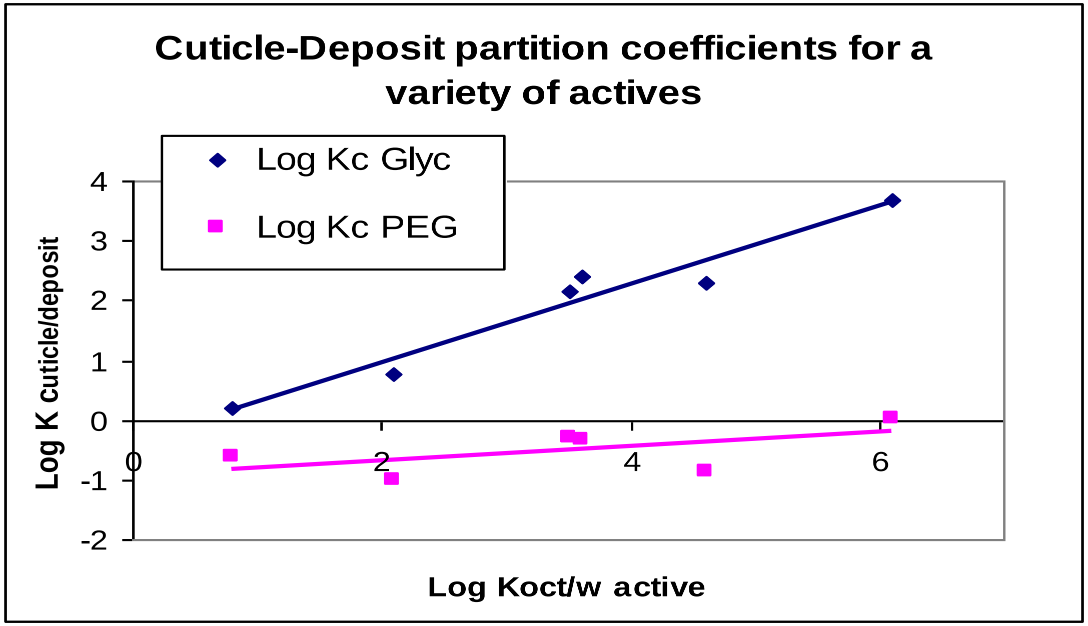
- Leaf structure complicated
- Focus on rate-determining step
- Wax extraction ->massive permeability increase
- Permeation of reconstituted extractable wax ~ that of cuticle
- Intracuticular rather than epicuticular wax shown to be transport-limiting

Active K values

- Lipophilic systemic actives
  - Log $K_{o/w}$ 3 +/- 1 is good balance
    - <2 - limited partitioning into substrate
    - >4 - accumulation in cuticle rather than underlying tissues

- Hydrophilic actives - Log $K_{o/w}$ <<1
  - ‘Polar pathway’
  - Transport limiting stage less obvious

Driving force effect on cuticle-deposit partitioning



- PEG 400 good solvent for all actives
- Glycerol only for hydrophilic actives
- Water uptake reduces PEG solvency for lipophilic actives

Effect of adjuvant absorption into substrate : partition coefficient

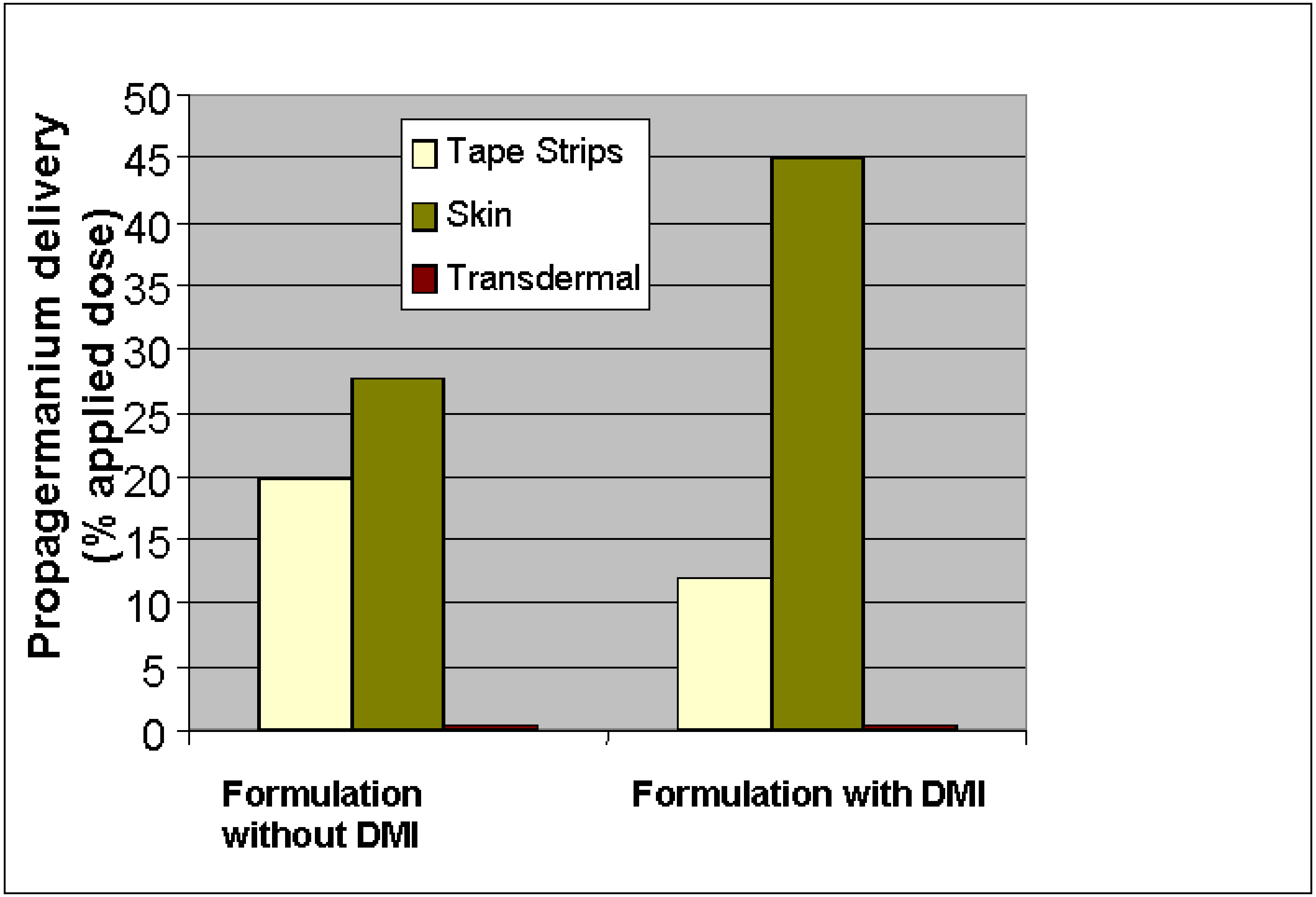
- $K = C_{subst.}/C_{form} = \text{sol limit}_{subst.}/\text{sol limit}_{form}$

- Adjuvant classification
  - Passive (donor, dissolving)
  - Active (accelerator, plasticising)
- Examples of active adjuvants
  - Surfactants e.g. alcohol ethoxylates
  - Crop oils
  - Transcutol®
  - Dimethyl isosorbide (DMI)

DMI effect on dermal uptake of hydrophilic active

- EW Formulation
  - 18% ester moisturising oils
  - 6% surfactant
  - 0.5% Propagermanium
  - 4% glycerine
  - 0 or 10% Arlasolve® DMI
  - q.v. water
- Skin penetration after 24 hours
- Tape stripping removed successive layers of the membrane
- Inductively coupled plasma mass spectrometry analysis

Effect of adjuvant absorption into substrate contd.



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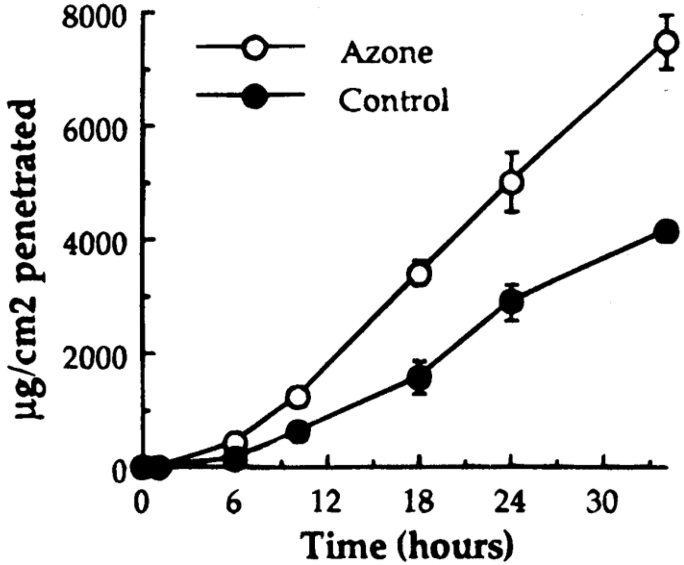
Effect of adjuvant absorption into substrate : diffusion coefficient

- J = (K.D/ L) ΔC
- ‘Accelerator’ adjuvant – Active penetration rate matching

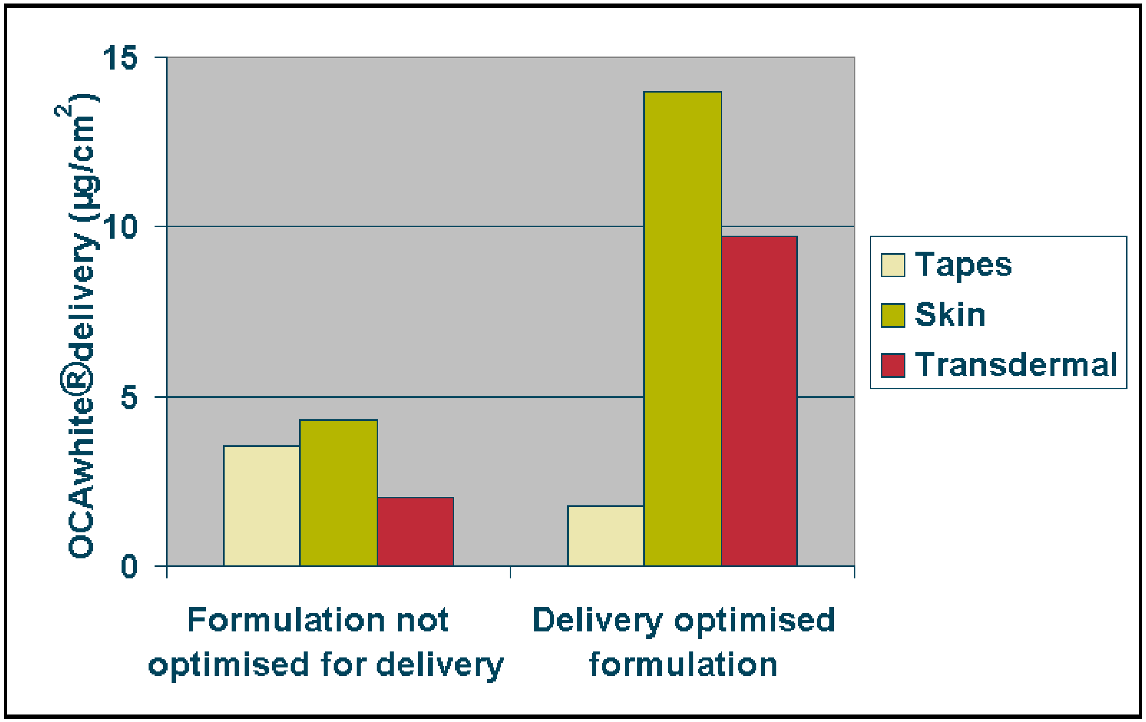


'2 in 1' enhanced delivery EW formulation

- 2% Lipophilic active
- 18% Ester moisturising oil selection
    - Accelerator oils chosen
    - Oil blend such that active at solubility limit (max. activity)

- Tape stripping after 24 hours
- Radioactivity detection

Effect of adjuvant absorption into substrate



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Deposit formation

- Crystallisation v. Partitioning dilemma

Deposit formation

- Crystallisation v. Partitioning dilemma
- Phase diagram for non-volatiles
  - Surfactant-free
  - Surfactant-containing

Surfactant	Chemical description	20%	30%	40%	50%	60
Atplus® 450	Alkyl polysaccharide blend	L_1	L_1	L_1	L_1	L_1
Atplus® MBA 13/15	POE(15) C13 monobranched alcohol	L_1	L_1	V_1	H_1	H_1
Synperonic® A7	POE(7) C13-15 alcohol	L_1	L_1	H_1	H_1	L_a
Synperonic® A20	POE(20) C13-15 alcohol	L_1	V_1	V_1	V_1	H_1

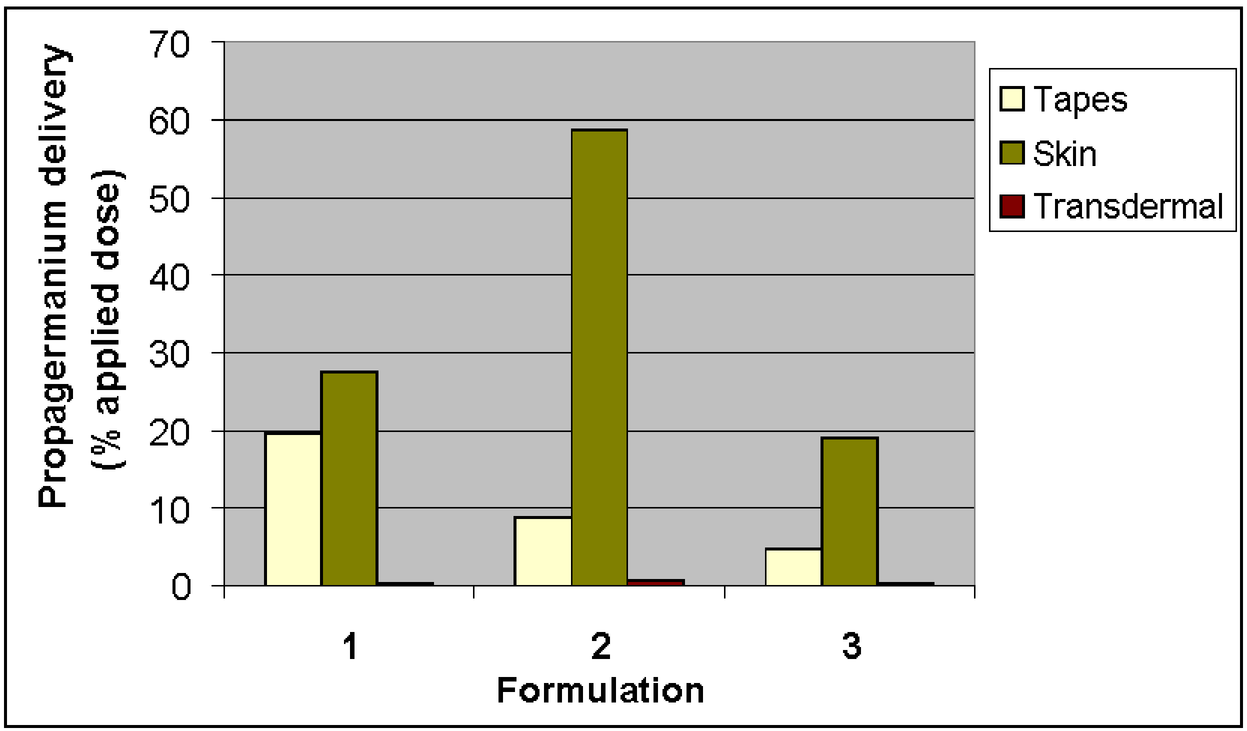
L_1 = isotropic micelle phase; V_1= cubic phase; H_1= hexagonal phase; L_a=lamellar phase; L_2= inverse micelle phase.

Surfactant dry down effects

- Viscosity

Surfactant dry down effects

- Viscosity
- Water retention



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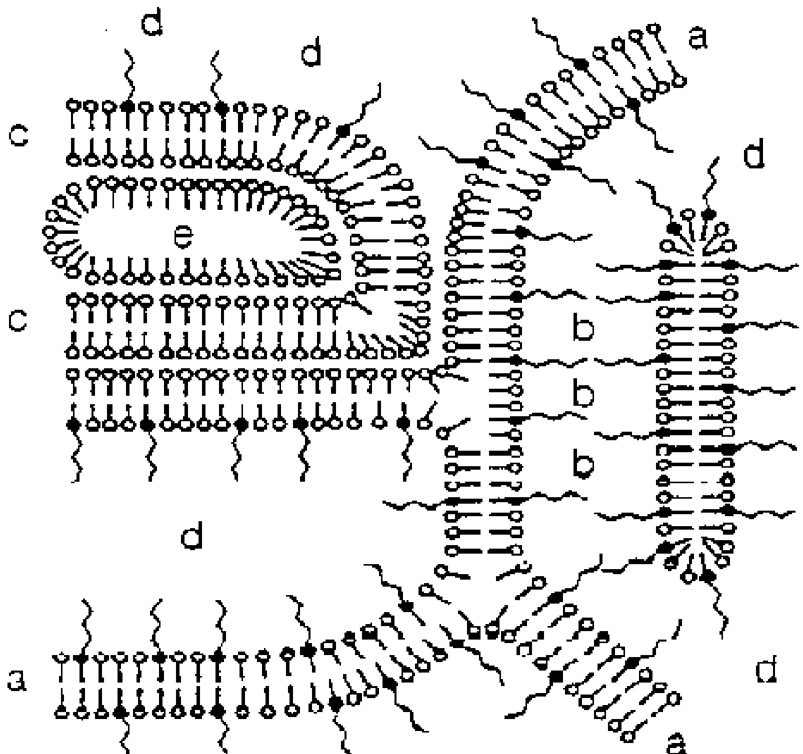
‘Hydrosome’ mesophase structure



a: hydrophobic part
b: trapped water
c: hydrophilic part
d: bulk water
e: oil

Summary

- Maximise activity of lipophilic actives in oil phase
- Use carefully selected range of formulants e.g. surfactants
  - Passive v. active
  - Different phase behaviour
- Study state of active in dried down deposit
- Environmental factors