How membrane permeation is affected by the donor delivery solvent

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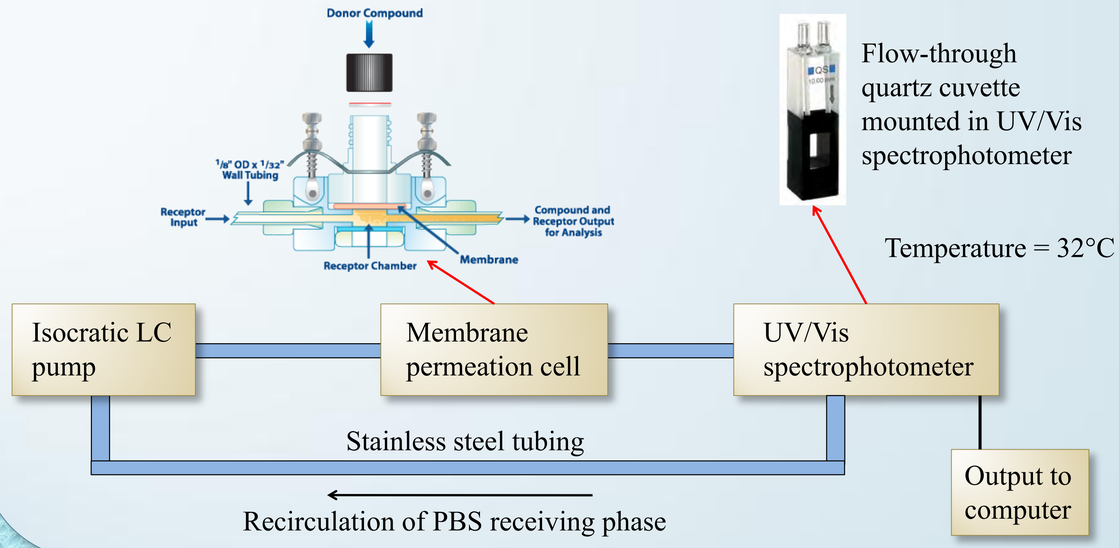
Purpose of Research

We derive a single unified theoretical model to accurately predict the extent and rate of membrane permeation for all possible variations of permeant drug hydrophobicity, membrane wettability and topical formulation type (oil or aqueous solution).

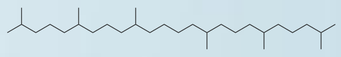
Experimental Apparatus



Materials

Donor solutions

Squalane oil — Oleic

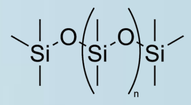


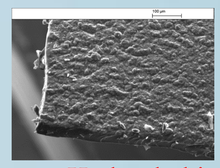
Phosphate buffered saline solution (PBS) — Aqueous

pH = 7.3 at 32°C. Contains 137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4 and 2 mM KH_2PO_4.

Membranes

PDMS

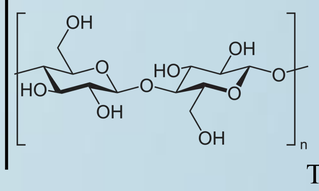


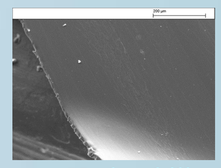


Hydrophobic

Thickness = 81 µm

Cellulose



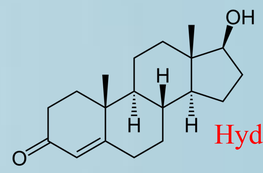


Hydrophilic

Thickness = 47 µm

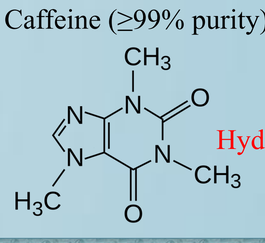
Permeant drugs

Testosterone (>98% purity)



Hydrophobic

Caffeine (≥99% purity)

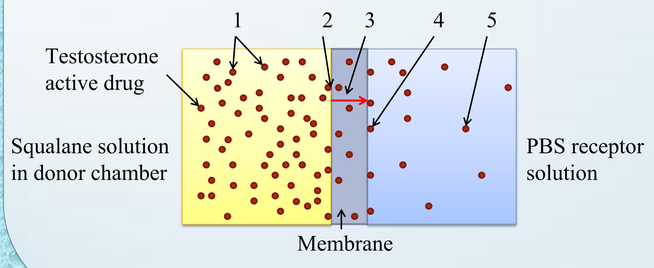


Hydrophilic

Theory of membrane permeation

Mechanism of membrane permeation:

1. Diffusion within and release from the formulation.
2. Partitioning into the outermost layer of the membrane.
3. Diffusion across the membrane.
4. Partitioning from the membrane into the systemic circulation.
5. Diffusion within the systemic circulation.



Assumptions:

Assumptions required for the derivation of a theoretical model for membrane permeation:

1. Diffusion across the membrane is the rate determining step (step 3).
2. Drug concentrations in the donor and receiver phase are uniform up to the membrane surface.
3. The lag time required to establish a steady-state mass transfer rate is negligibly small compared with the overall timescale of the permeation.
4. No membrane swelling is observed and the diffusion coefficient of the permeant within the membrane is uniform and constant throughout permeation.
5. Only the drug permeates across the membrane.
6. The drug is non-charged and behaves ideally.

The validity of these assumptions has been vigorously investigated and confirmed acceptable.

Theoretical model:

Derived from Fick's laws of diffusion

$$C_{rec} = C_{rec,\infty} + \left(C_{rec,0} - C_{rec,\infty}\right)\exp\left(-kt\right)$$

Variation of C_{rec} with time is predicted to follow an exponential curve.

C_{rec} describes the [drug] in the receiving phase at time t.

Where:

Permeation rate coefficient

$$k = \left\{\frac{AD\left(K_{mem-don}Z + K_{mem-rec}\right)}{XV_{rec}}\right\}$$

Permeation rate coefficient is predicted to be independent of initial drug concentration.

$K_{mem\text{-}don}$ = eqm. [drug in membrane] / eqm. [drug in donor solution]

Extent of membrane permeation

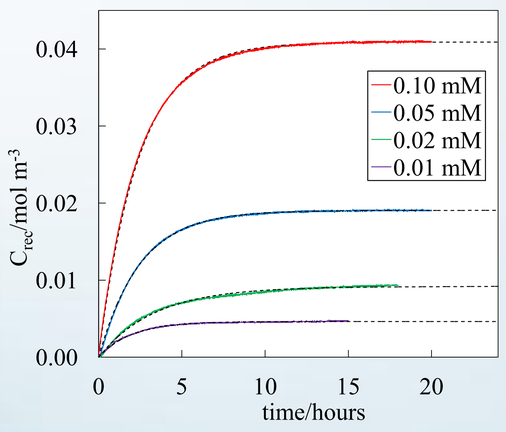
$$C_{rec,\infty} = \left\{\frac{K_{mem-don}Y}{K_{mem-don}Z + K_{mem-rec}}\right\}$$

For full derivation see: *Langmuir*, **2012**, *28*, 2510-2522.

Results and discussion

Example of permeation results:

Caffeine in a PBS donor solution permeating a cellulose membrane



Colour lines = experimental raw data
Black dotted lines = fitted exponential curves

⇩

Raw data is described exceptionally well by exponential curves, as theory predicts.

⇩

Permeation rate coefficient (k) is independent of initial drug concentration (see half-lives), as theory predicts.

⇩

$C_{rec,\infty}$ scales with initial donor drug concentration, as theory predicts.

Numerical values of experimental $C_{rec,\infty}$ and k are accurately extracted from the exponential fits

Predicting membrane permeation:

Fixing all experimental geometrical parameters; k and $C_{rec,\infty}$ are predicted to depend on the nature of the drug, donor and receiver solvents and the membrane, expressed by values of the membrane diffusion coefficient (D) and the two partition coefficients $K_{mem\text{-}don}$ and $K_{mem\text{-}rec}$.

Theory simplifies further:

$$\frac{kXV_{rec}}{AD} = K_{mem-don} + K_{mem-rec}$$

Dimensionless quantity that describes the rate of membrane permeation

$$\frac{C_{rec,\infty}}{C_{don,0}} = \left\{\frac{K_{mem-don}}{K_{mem-don} + K_{mem-rec}}\right\}$$

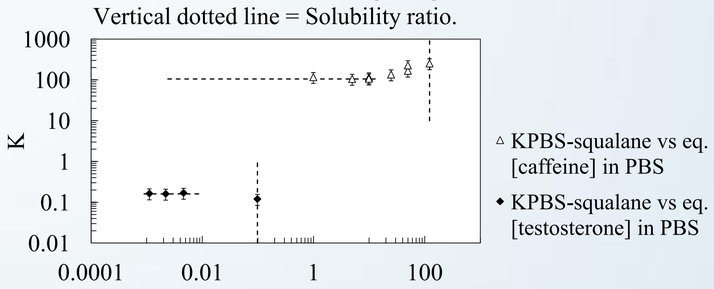
Dimensionless quantity that describes the extent of membrane permeation

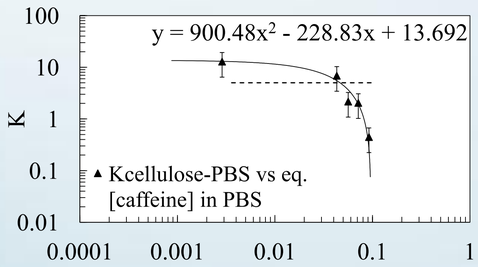
Theoretical partition coefficients for 3 example combinations of drug hydrophobicity, membrane wettability and donor solvent type. Let magnitude of affinity = 40x.

Donor solvent	Permeant	Membrane	$K_{mem\text{-}don}$	$K_{mem\text{-}rec}$	Fraction permeant extracted	Dimensionless permeation rate coefficient (kXV_{rec}/AD)
Oil	Hydrophilic	Hydrophilic	High (40)	Medium (1)	High (0.98)	High (41)
Oil	Hydrophobic	Hydrophilic	Low (0.025)	Medium (1)	Low (0.024)	Medium (1)
Water	Hydrophilic	Hydrophobic	Low (0.025)	Low (0.025)	Medium (0.5)	Low (0.05)

Experimentally recorded partition coefficients:

Horizontal dotted line = [drug] range used.
Vertical dotted line = Solubility ratio.

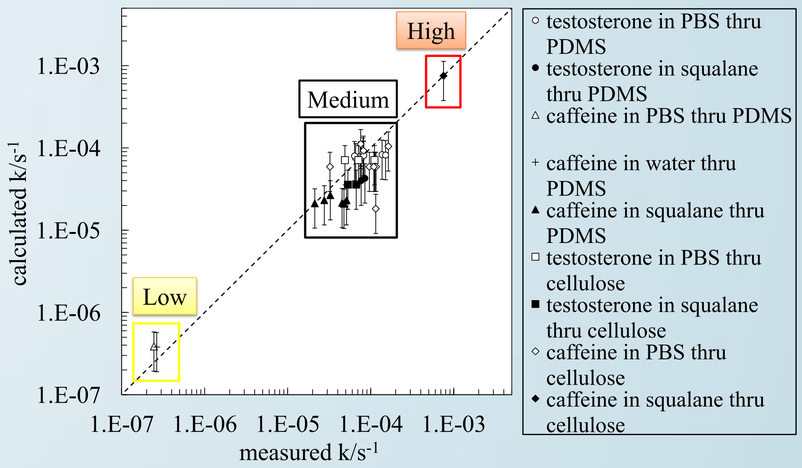




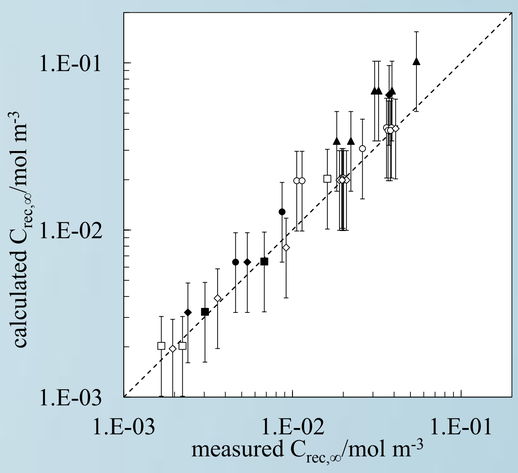
Non-ideal K values are calculated for [drug] used.

Comparing experimental and theoretical results:

Calculated vs. measured k



Calculated vs. measured $C_{rec,\infty}$



Related work & outlook:

1. The mechanics of drug delivery from Pickering emulsions has been investigated (see *Langmuir*, **2012**, *28*, 2510-2522).

2. Future studies aim to understand the mechanism of drug permeation through human skin (a matrix of both hydrophobic and hydrophilic regions).

Conclusions:

1. An accurate and reproducible method for measuring the membrane permeation of a drug from a topical formulation has been developed

2. Successfully derived a theoretical model which accurately describes the membrane permeation characteristics for all combinations of hydrophobic/hydrophilic permeant, membrane and donor type.