THE MEMBRANE/AQUEOUS PARTITIONING AS AN ESSENTIAL TOOL FOR PHARMACOKINETIC PROFILING TO SUPPORT DRUG DESIGN

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INTRODUCTION

- The **transport of drugs** across cell membranes is a highly complex biological process involving the interaction of drugs with lipid barriers[1]. Numerous significant correlations between **lipophilicity and membrane permeation** have been stablished.
- **Lipophilicity** is the net result of all intermolecular forces, and when measured in the liposome/water systems, it also considers the ionic bounds, providing a better correlation with the intermolecular forces operating in molecular pharmacology and biochemistry[2].
- **Biomembrane mimetic models** provide an alternative platform with very well defined and controlled conditions to help researchers from the drug discovery field to predict drugs' pharmacokinetic properties with therapeutic efficacy implications[3,4].

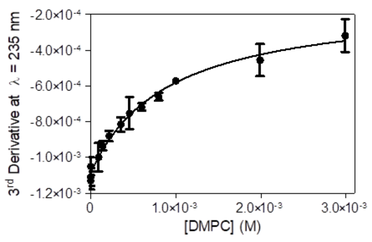
Log $P_{w/m}$ in Permeability: ACYCLOVIR

Permeability Coefficient (PC)

Log PC = -5.51 ± 0.04 $Log\ PC = -6.3 + 0.71 Log\ P_{w/m} - 0.0061 MW$

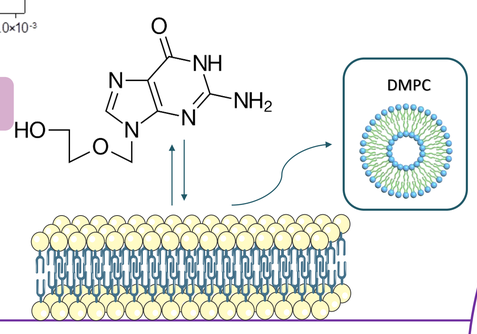
Stratum Corneum Content (SCC)

Log SCC = 20.09 ± 0.47 $Log\ SCC\ (per\ mg) = -3.7 + 7.8 Log\ P_{w/m}$



- ACV is a highly lipophilic drug with low permeability;
- Tends to be retained in Stratum Corneum (SC), inhibiting clearance from this compartment

Log $P_{w/m}$ = 3.05 ± 0.06



- **Distribution coefficient** (*Log* $P_{w/m}$) studies were performed in biphasic membrane/aqueous phase.
- Membrane biphasic systems with **different compositions** were used, accordingly with the main objective.
- **Derivative Spectrophotometry**[3,4] method was applied:

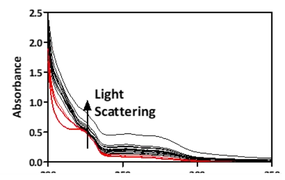
$$D = D_w + \frac{(D_m - D_w) K_D [L] V\phi}{1 + K_D [L] V\phi}$$

Log $P_{w/m}$ in *off-target* Bioaccumulation: CAMPTOTHECIN

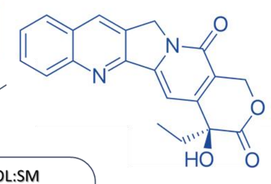
MAIN BIOACCUMULATION SITES

$$K_{bioaccumulation} = \frac{Q}{V P_{w/m}}$$

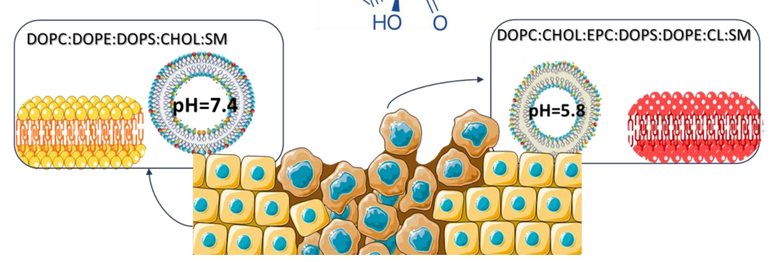
- 61% Adrenals
- 31% Thyroid
- 3% Heart (Basal)
- 3% Kidneys



Log $P_{w/m}$ = 3.14 ± 0.13



Log $P_{w/m}$ = 2.78 ± 0.28



- CPT presents a good distribution profile in both biomembrane models
- Bioaccumulation in off-target sites is predicted

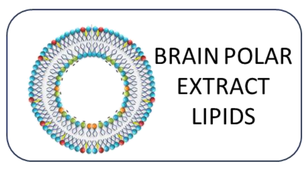
Log $P_{w/m}$ in *target* distribution: NEW DRUG

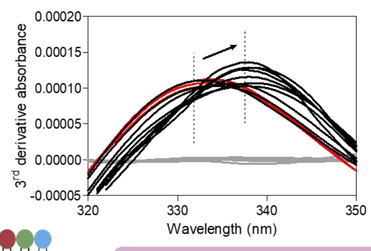
$$LogBB = 0.388 Log\ K_{d\ (BBB)} - 0.00618 V_M + 1.359$$

Log BB = 2.77 ± 0.10

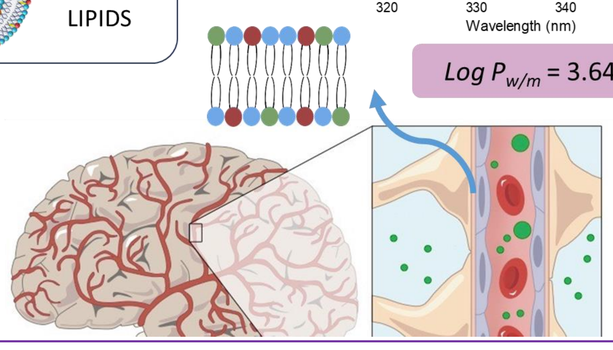
$$Log\ PS = -2.19 + 0.262 Log\ K_{d\ (BBB)} + 0.0583 VWSA\_B - 0.00897 PSA$$

Log PS = -1.88



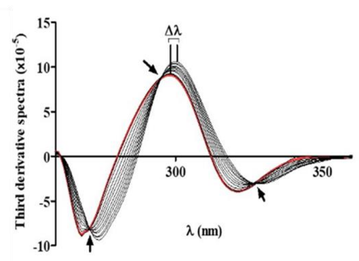


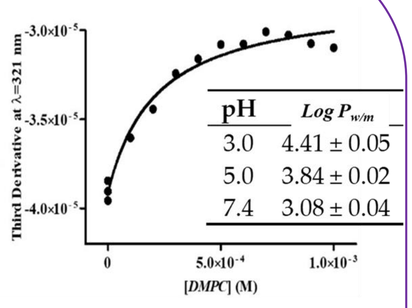
Log $P_{w/m}$ = 3.64 ± 0.25



- The drug is able to pass through Blood-Brain Barrier to reach the therapeutic target

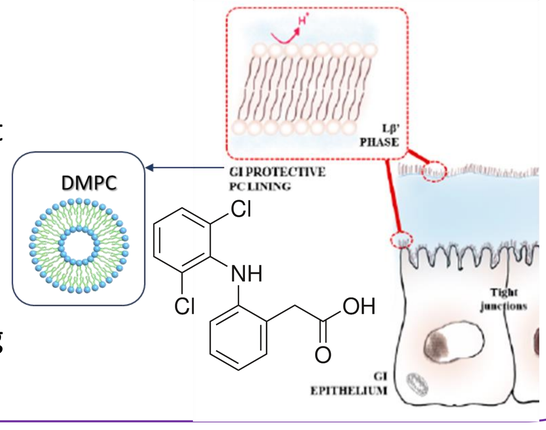
Log $P_{w/m}$ in Gastro-Toxicity: DICLOFENAC[3]





pH	*Log* $P_{w/m}$
3.0	4.41 ± 0.05
5.0	3.84 ± 0.02
7.4	3.08 ± 0.04

- DCF interaction with PC membranes at relevant lipid membrane phases showed that the chemical association is clearly pH dependent.
- At pH 5.0, DCF presented a noticeable distribution at membrane phase despite being partially ionized.



CONCLUSIONS

✓ **Biomembrane Model-Drug** interactions are a promising approach to be adopted for Drug Screening. Providing a solution with more reliable information than octanol/water systems and a better balance of cost:benefit than cell-based assay in such early stage of drug development.

REFERENCES

1. Lúcio, M., et al.; Curr Med Chem. 2010, DOI: 10.2174/092986710791111233
2. Liu, X., et al., Pharm Res., 2011, DOI: 10.1007/s11095-010-0303-7
3. Fernandes, E.: et al.; Int.J.Mol.Sci. 2018. DOI: 10.3390/ijms19113411
4. Fernandes, E.: et al.; Front. Chem. 2018. DOI: 10.3389/fchem.2018.00323

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