Molecular Dynamics of Synergistic Permeation Enhancement:

Propylene Glycol and Isopropanol at the Skin Barrier

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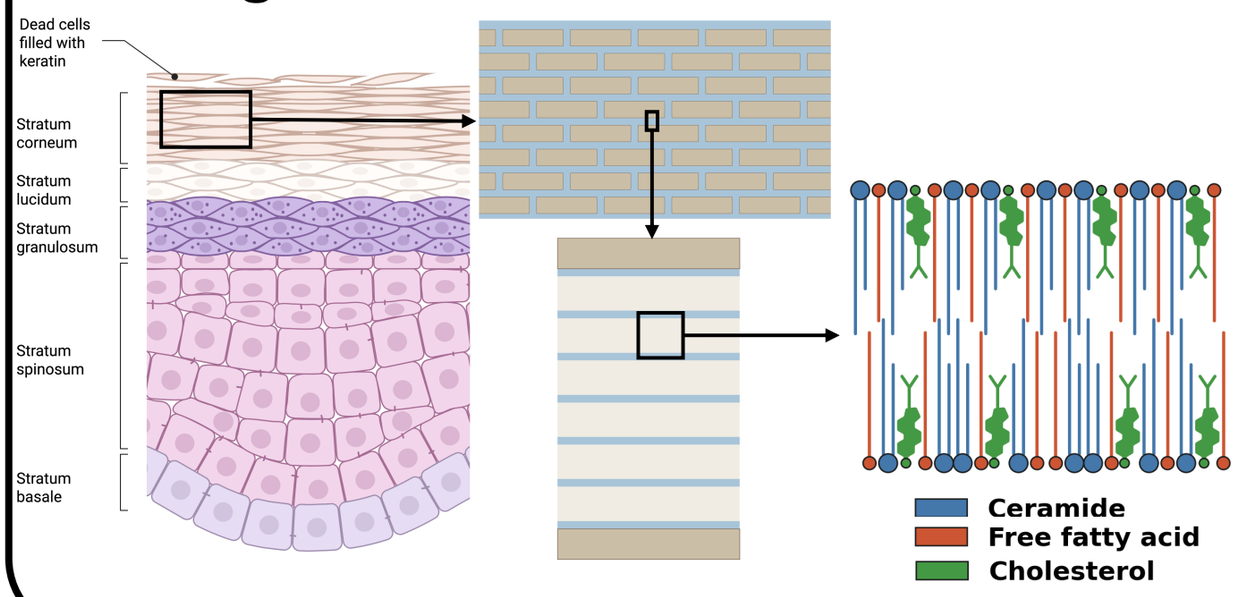
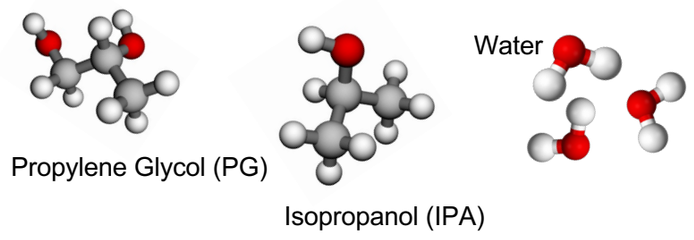
Background: Stratum Corneum



- The skin's outermost layer, the stratum corneum (SC), is a crucial barrier against pathogens, water loss, and environmental damage, and is the main obstacle for topical drug delivery.
- The SC is formed by dense lipid lamellae comprised of ceramides, cholesterol, free fatty acids that surround the skin cells (corneocytes).

Permeation Enhancers

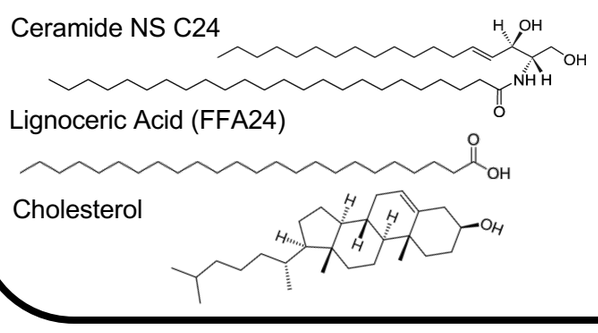


- Permeation enhancers (PEs) such as isopropanol (IPA) and propylene glycol (PG) are widely used to boost drug delivery through skin by disrupting the lipid barrier.[1]
- How PEs trigger changes in SC lipid organisation and structure remains unclear and depends on chemistry.

Simulated Systems

Lipids in 1:1:0.5 molar ratio

- Ceramide NS C24 (CER NS)
- C24 Fatty Acid (FFA24)
- Cholesterol (CHOL)

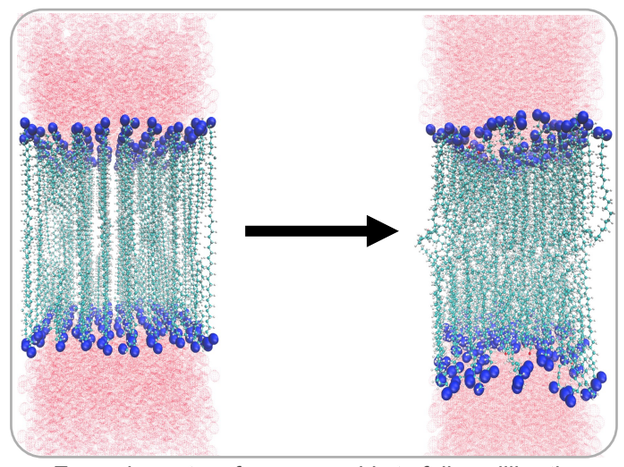


Solvent systems:

- **Water + Isopropanol**
  Concentrations 0, 10, 20 $\%_{w/w}$
- **Water + PG**
  Concentrations 0, 20, 50, 70, 80, 90, 100 $\%_{w/w}$
- **Water + IPA/PG Mixtures**
- **Total 19 simulated systems**
  3 replicas of each system

Methods

- CHARMM based forcefields used for skin lipids, propylene glycol,[2] and isopropanol and *m*TIP3P used for water
  - 64 lipids per leaflet assembled using MoSDeF [3] and then solvated with water
  - 50 ns of RWMD equilibration at 305-355 K [4]
- Water replaced as with PG/IPA/water mixtures and system re-equilibrated
- Production runs for 1μs at 305K and 1 atm
  - Final 400 ns used for analysis

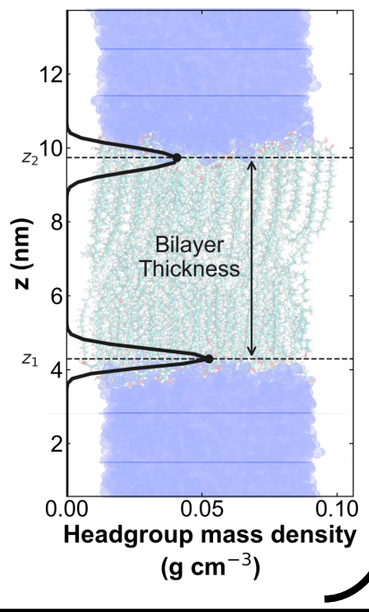


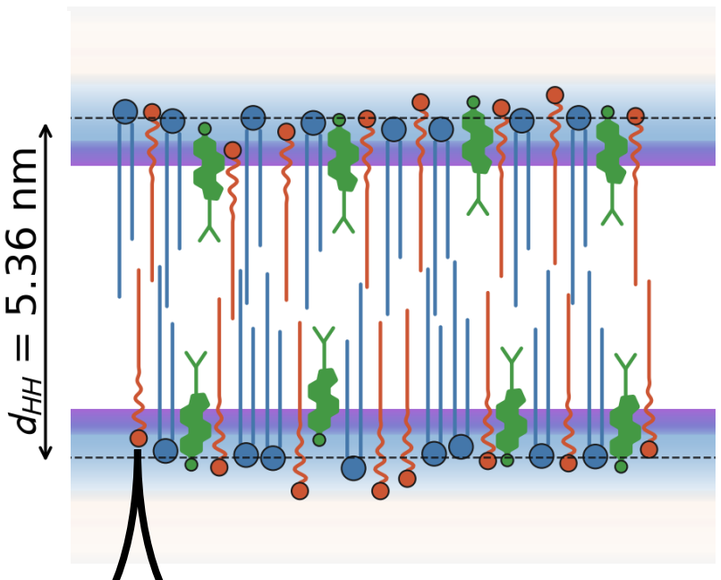
Example system from assembly to full equilibration
Headgroups -Blue, Lipid Tails – Teal, Solvent - Red

Results: Water 30 $\%_{w/w}$, PG 50 $\%_{w/w}$, IPA 20 $\%_{w/w}$

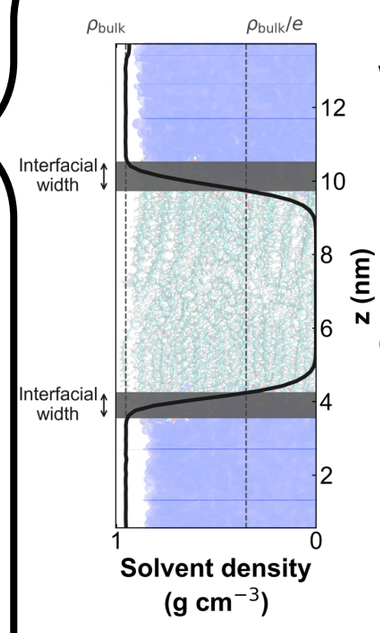
Bilayer Thickness (d_{HH})

d_{HH} and the complementary area per lipid (APL) track how solvent molecules perturb the head-group region. Reduced height with increased APL signals intercalation of solvent molecules in the headgroup region.



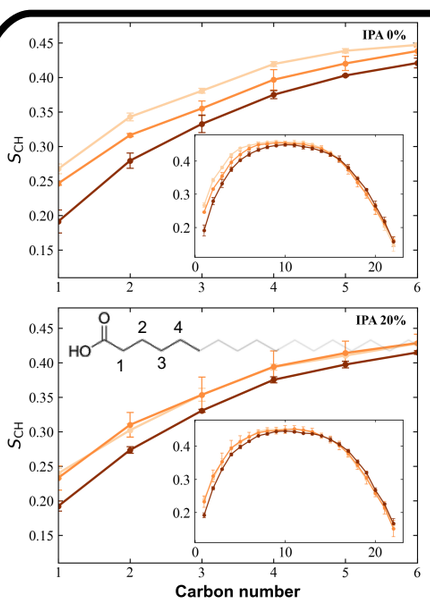


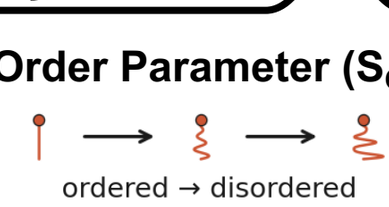
Interfacial Width (δ)



The interfacial width δ measures the sharpness of the lipid–solvent boundary, defined as the distance over which the solvent density rises from bulk/e to its bulk value. It is sensitive to how solvent molecules organise at the bilayer surface.

Tail Order Parameter (S_{CH})

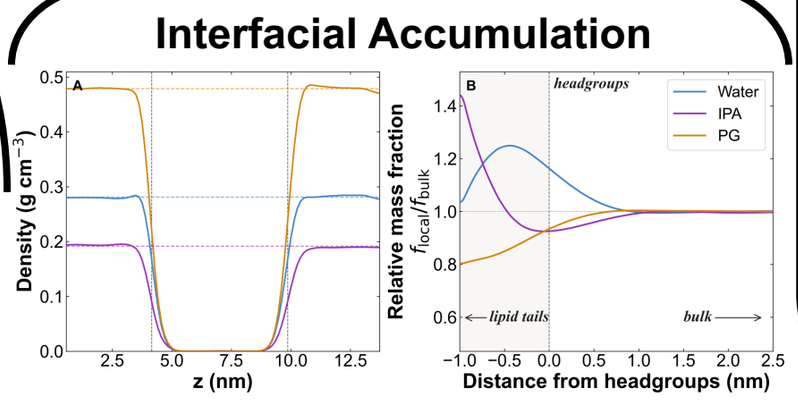


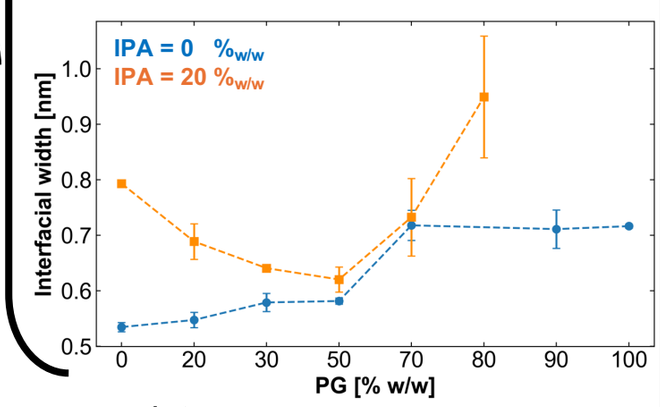


S_{CH} tracks the conformational order of the lipid chains, with the FFA24 tail being the most responsive to the PEs. The composition dependent drop near the head-group region signals disorder as the solvent perturbs the interface. The deeper regions remain largely unchanged (gel-phase).

S_{CH} of FFA24 under different Solvent conditions: Deeper orange shading indicates increasing PG concentration (0%, 50%, 80%(bottom)/100%(top))

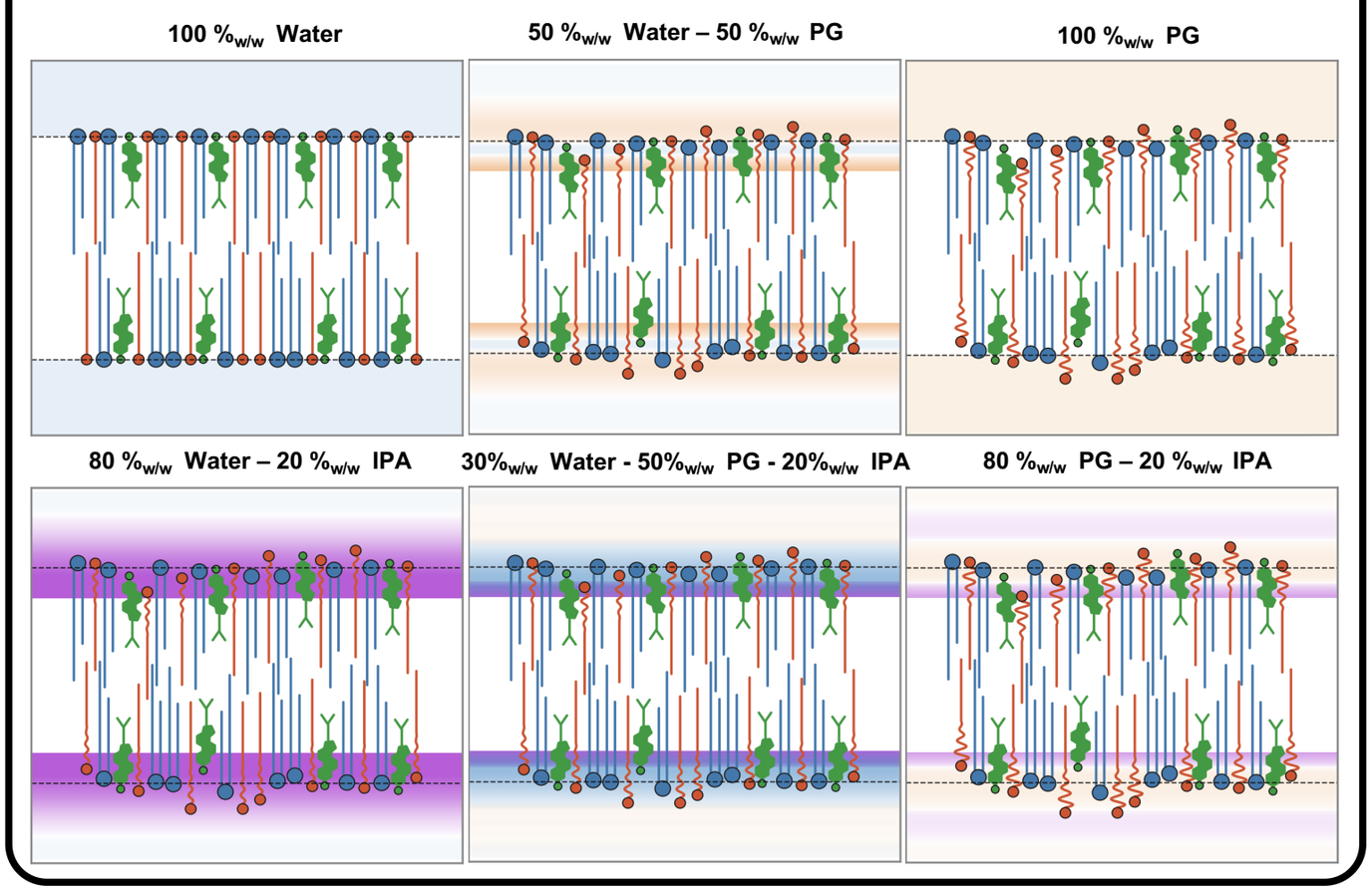
Interfacial Accumulation





Density profiles show where each solvent species accumulates. **(A)** Mass density of water, PG, and IPA across the box; dashed lines mark the headgroups (vertical) and bulk values (horizontal). **(B)** Relative mass fraction $f_{\mathrm{local}}/f_{\mathrm{bulk}}$ vs distance from the headgroup, folded over both leaflets, , where f is each species' mass fraction within the solvent. >1 = accumulation, <1 = depletion, showing how water, PG, and IPA compete for the interface.

Results



Conclusions

- **IPA and PG both work to disrupt the lipid barrier primarily by increasing the interfacial width**
  - Two effects increase the interfacial width:
    - IPA: disruption of the upper tail region
      - Dominant at low PG – concentrations.
    - PG: dehydration of the headgroup-region
      - Dominant at low or no-water concentration (high PG – concentration)
- **The two PEs counter act each other while water is present**
  - Minimum disruption at 30 $\%_{w/w}$ Water, 20 $\%_{w/w}$ IPA and 50 $\%_{w/w}$ PG
  - Cooperative, enhanced disruption in the water free system.
- **In the 30 $\%_{w/w}$ Water, 20 $\%_{w/w}$ IPA and 50 $\%_{w/w}$ PG system**
  - PG curbs IPA's penetration
  - Water aggregates around the headgroups and keeps the solvent-lipid interface relatively sharp.

References

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