New transdermal drug delivery agent: a multiscale characterization

Kathryn Piston, Huilin Ma, Eden Tanner, Kelly N. Ibsen, Samir Mitragotri, and Shikha Nangia

Department of Biomedical and Chemical Engineering, Syracuse University | School of Engineering and Applied Sciences, Harvard University

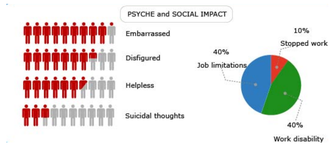
Introduction

A unique class of ionic liquids represents a promising new transdermal drug delivery agent for dermatological diseases. Understanding their characteristics under water contact is critical for applications and potential future commercialization.

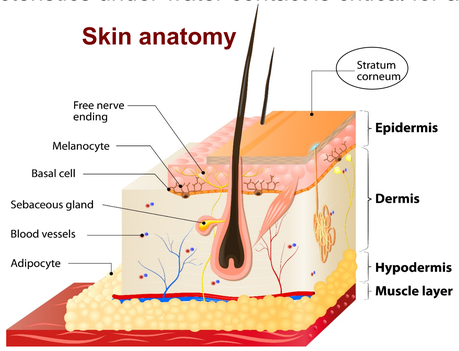
Motivation

5-20% of children affected worldwide

125 million affected worldwide



Skin anatomy

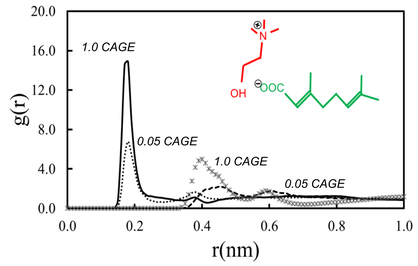


- Low permeability of the stratum corneum is a challenge for topical treatments
- Ionic liquids, in particular Choline and Geranate (CAGE), can navigate the stratum corneum making them ideal drug delivery candidates [1,2]

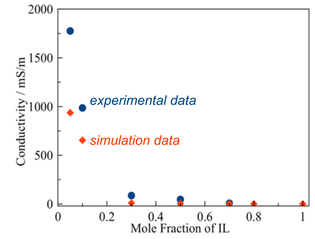
Results

Using a synergistic experimental and computational approach, we elucidate the impact of water on the microscopic interactions and the bulk physical properties of CAGE.

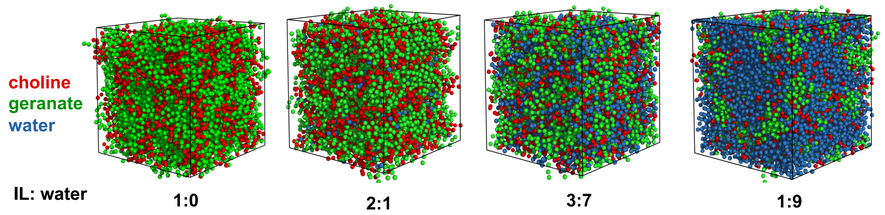
1 μs AA MD simulation:



Experimental and Computational Comparison



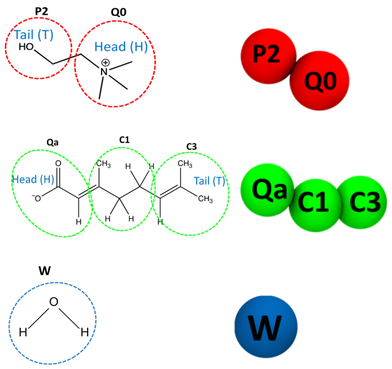
20 μs CG MD simulation: Snapshot of each CG 10 × 10 × 10 nm simulation box



Methods

Choline **a**nd **Ge**ranate (CAGE) mixed in 1:1 ratio with varying mole fractions of water randomly distributed in molecular dynamics (MD) simulation box in both all atomistic (AA) and coarse grain (CG) systems. CG according to Martini force field mapping.

Simulation details

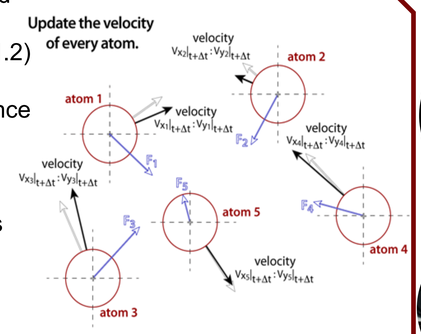


Coarse-grain mapping scheme

The simulations were performed using the molecular dynamics engine GROMACS (version 5.1.2)

GROMACS is a high-performance software package designed to perform molecular dynamics.[3]

The workflow of the simulations involved construction of a box, energy minimization, short isothermal-isochoric (*NVT*) and isothermal-isobaric (*NPT*) equilibration runs, and long-production *NPT* runs.



Molecular dynamics

Conclusions

This work uses MD simulations and physical characterization to investigate the effect of water on choline and geranate (CAGE) ionic liquid. It was experimentally determined that under atmospheric conditions CAGE contains ~11% water by mole.

- Experimental data conferred by molecular dynamics find an increase in conductivity and diffusion coefficient, and a decrease in viscosity with increasing water content plateauing between 30-10% IL
- Simulations suggest that above 30% IL geranate ions begin to reorganize to minimize contact of their hydrophobic tails with water forming a micelle like structure.
- This structure could be exploited for drug delivery applications via solvation of hydrophobic drugs
- The lack of microscopic reorganization in solutions containing up to 65% water by mole suggest that atmospheric CAGE can be used with no change in efficacy without pre-drying

This collaborative work pioneers the understanding of CAGE and its potential use for transdermal applications and commercialization in the future and is under review for publication.

Acknowledgments

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References

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2. Tanner EEL, Ibsen KN, Mitragotri S. *Transdermal insulin delivery using choline-based ionic liquids (CAGE)*. J Control Release 286, 137–44 (2018).
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