CASE STUDY: **OPTIMIZING LIPID-BASED DRUG FORMULATIONS**

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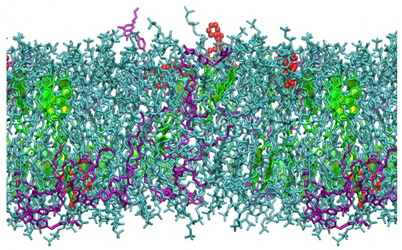
BACKGROUND:

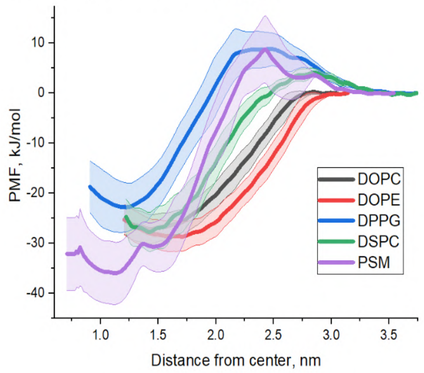
Two IND-stage drug candidates, which act simultaneously as agonists of toll-like receptors TLR4 and TLR7. The compounds are intended to be delivered in liposomes or lipidic nanoparticles, but the drug load was insufficient. The goal was to perform the computational search for optimal lipid composition for both formulations, which maximizes the drug load in liposomes and ensures structural integrity and optimal size of nanoparticles for different molar ratios of the drugs.

METHODOLOGY:

- 24 different lipid compositions were tested computationally using a combination of Molecular Dynamics techniques such as:
  - Spontaneous incorporation into the bilayers.
  - Alchemical free energy simulations of incorporation.
  - Self-assembly of drug-lipid mixtures.
  - Umbrella sampling simulation of drug incorporation.
- Self-assembly of nanoparticles formed by pristine drugs and their mixtures was simulated at different conditions.



Self-assembled bilayer with incorporated drugs.



Potentials of mean force for drug incorporation into the bilayer.

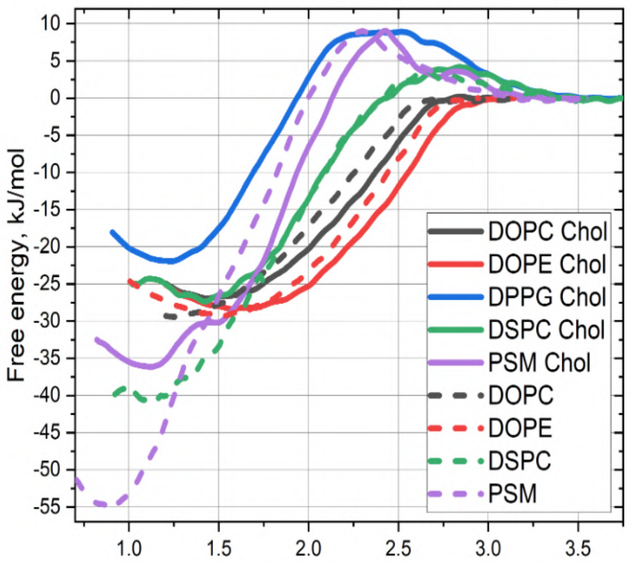
23	3	X20	Stability range
compositions tested	compositions selected for validation	increase of drug load achieved	of nanoparticle formulations assessed

RESULTS:

Results for liposome formulation:

Computational screening of 24 lipid compositions allowed to select 3 compositions, which maximize the free energy of drug incorporation into the lipid membrane and thus should have the best drug load.

Experimental validation confirmed these findings with the increase of drug load up to 20 times in comparison to initial lipid composition.

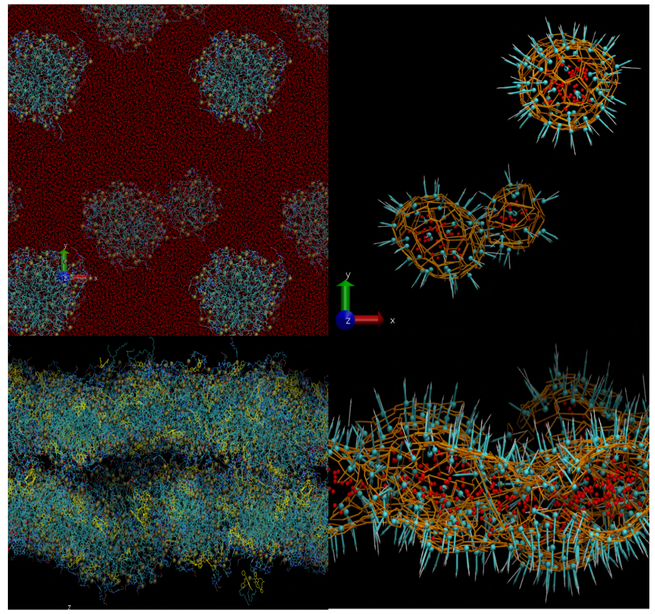


The potentials of mean force for drug incorporation into the bilayers of different composition. The lower the minimum the better.

Results for nanoparticle formulation:

It was shown that the stable nanoparticles of desirable sizes are formed by the compound #1 or by the mixture of both compounds with the molar ratio up to 1:1. Higher ratios lead to formation of undesirable amorphous aggregates.

These results are currently used in experimental optimization of nanoparticle formulation.



Simulation snapshots (left) and the particle surface reconstructions (right) of the nanoparticles with different molar ratio of two studied compounds.