A Computational Study on Multi-Component Nutrient Delivery System and its Binding Interaction with Liposomal Membrane

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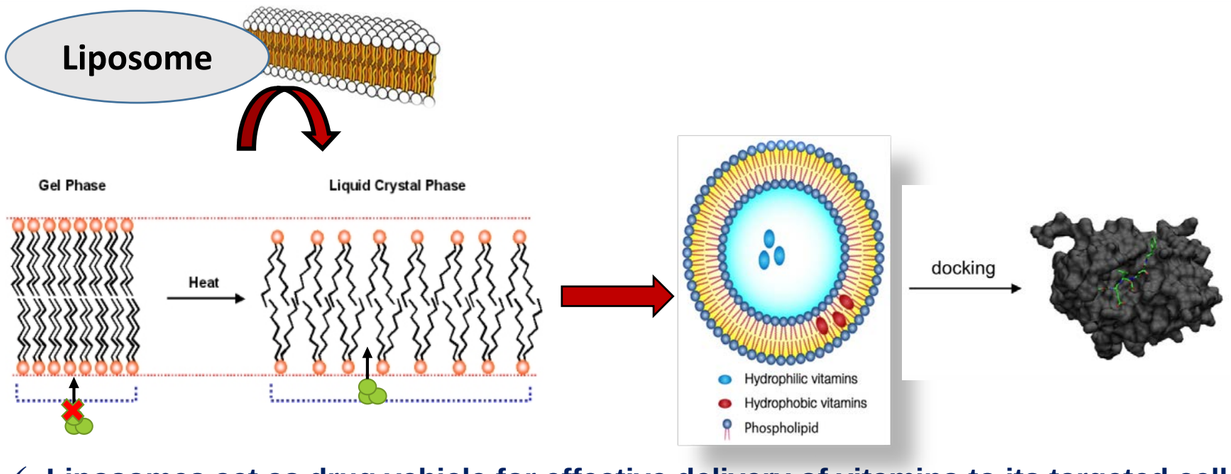
Introduction



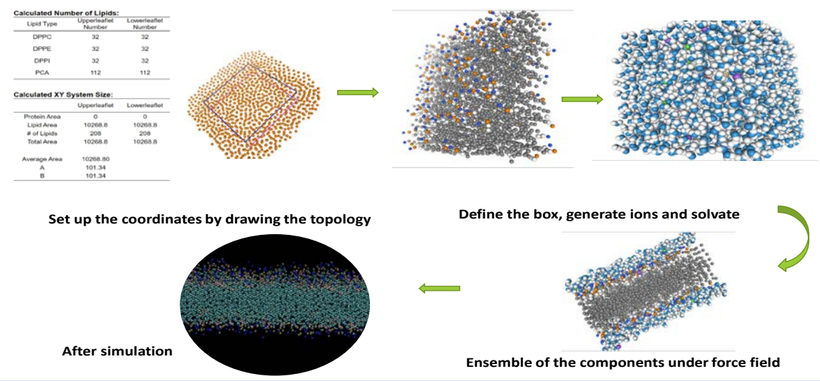
- ✓ Liposomes act as drug vehicle for effective delivery of vitamins to its targeted cells.
- ✓ Phospholipid's transition from gel to liquid crystal phase is important to include nutrient inside its membrane.
- ✓ A computational study on the ligand-receptor interaction will provide comprehensive knowledge about the bilayer composition and aid in liposome structuring.

Objectives

- To determine the phase transition temperature of the different liposomal bilayer membrane combinations.
- To study the binding interaction of vitamins (B_{12}, B_9, A, D) with the lipid bilayer membrane.

Methodology

Steps for liquid crystal phase determination

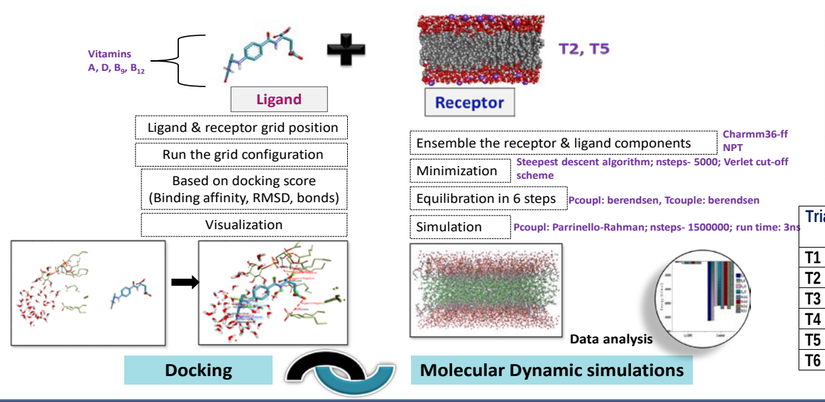


Minimization method: steepest descent method
Ensemble conditions:
- NPT- pressure and temperature fixed.
- Verlet integration algorithm

For production of equilibrated topology:
- Nsteps: 2500000
- Number of frames: 500
- Run time: 50 ns

Force field: Martini force
Box: Hexagonal
Ions: Na^+, Cl^-

Steps for docking behaviour study



TYPE	T2 [no. of lipids UL=LL]	T5 [no. of lipids UL=LL]
DPPC	34	37
DPPE	34	37
DPPI	34	37
PAL	17	-
OLE	17	-
LIN	102	111

Trial No.	DPPC#		DPPE#		DPPI#		PCA#	
	UL*	LL$^{\alpha}$	UL	LL	UL	LL	UL	LL
T1	39	39	39	39	39	39	78	78
T2	34	34	34	34	34	34	102	102
T3	32	32	32	32	32	32	112	112
T4	30	30	30	30	30	30	120	120
T5	27	27	27	27	27	27	135	135
T6	22	22	22	22	22	22	154	154

Results and Discussion

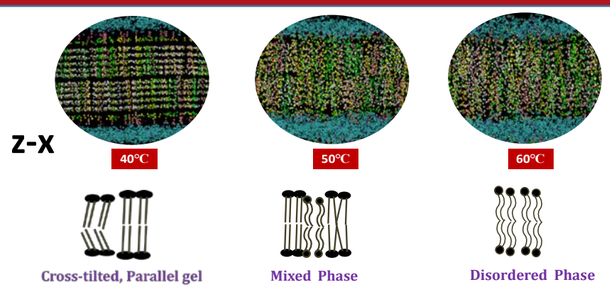


Fig. 1: Snapshots at 50 ns simulation run time as a function of temperature in z-x plane

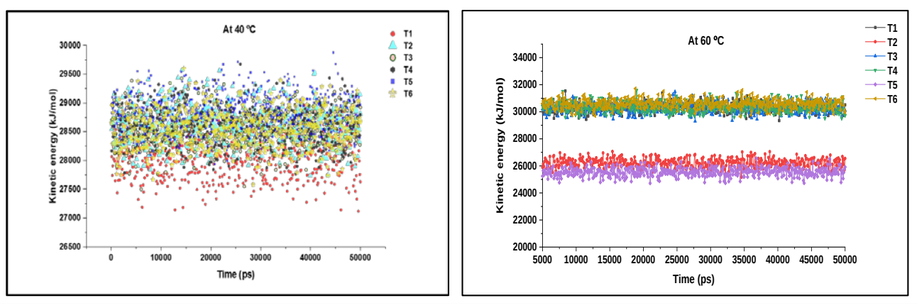
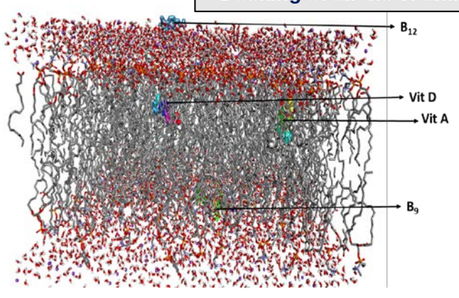


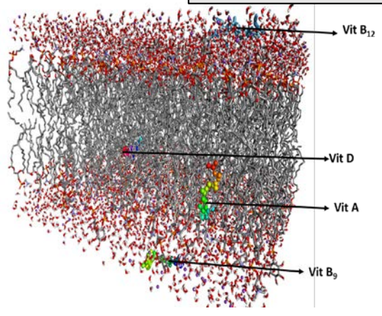
Fig. 2: Kinetic energy (kJ/mol) of different bilayer combinations as a function of simulation time (ps) at (a) 40, (b) 60 ℃

Docking of all the vitamins in T2 membrane



Vitamin	Binding affinity (kcal/mol)	D[membrane] ×10-5 cm²/s
A	-10.8	0.194± 0.06^{d}
D	-11.7	0.133± 0.05^{h}
B_9	-5.4	0.231 ± 0.03^{c}
B_{12}	-5.7	0.150 ± 0.00^{g}
RMSD	0.00	

Docking of all the vitamins in T5 membrane



Vitamin	Binding affinity (kcal/mol)	D[membrane] ×10-5 cm²/s
A	-10.9	0.132± 0.07^{h}
D	-12.5	0.125 ± 0.01^{p}
B_9	-5.1	0.174 ± 0.06^{e}
B_{12}	-5.5	0.150 ± 0.00^{g}
RMSD	0.00	

Table 1: Interaction of Vitamin i) A; ii) D; iii) B_9 and iv) B_{12} with T5

i)

Name	Distance	Type
DPPI 239 (C): VD	4.948	Hydrophobic alkyl
DPPI 243 (C): VD	4.391 4.572	
DPPI 257 (C): VD	4.590 5.453	
LIN 256 (C): VD	3.788 4.721 5.348 5.482 4.608 5.199 4.035 4.244	
DPPC 279 (C21): VD	5.325	
DPPE 244 (C21): VD	4.088	
DPPE 276 (C): VD	4.557	

ii)

Name	Distance	Type
DPPI 409 (C): LIG	4.847 5.181 5.030	Hydrophobic alkyl
LIN 389 (C): LIG	4.649 5.244	
DPPC 364 (C): LIG	3.982 5.024	
DPPE 351 (C12/11): LIG	4.481	
DPPE 351 (C21): LIG	5.052	
DPPE 351 (C21): LIG	4.684	
DPPE 351 (C21): LIG	3.824	
DPPE 410 (C34-37):LIG	4.073	
DPPE 410 (C31): LIG	5.169	

iii)

Name	Distance	Type
TIP2779:HH - :FOL201:O1	2.0892	Water hydrogen bond
TIP2847:HH - :FOL201:OE1	2.33929	
TIP3174:HH - :FOL201:O4	2.57515	
TIP3228:HH - :FOL201:O4	2.3499	
TIP3228:HH - :FOL201:N5	2.129	
FOL201:H3 - :TIP2743:OH2	2.921	
FOL201:H8 - :TIP992:OH2	2.548	
FOL201:H19 - :FOL201:O	2.01397	Conventional hydrogen bond
TIP3228:HH - :FOL201:H8	2.35698	Unfavourable bond

iv)

Name	Distance	Type
:TIP599:HH - :LIG1:N1	2.7532	Water hydrogen bond
:TIP608:HH - :LIG1:O6	2.74529	
:TIP608:HH - :LIG1:O6	2.55705	
:TIP638:HH - :LIG1:O2	2.85219	
:TIP639:HH - :LIG1:O2	2.67662	
:TIP650:HH - :LIG1:O6	2.89942	
:TIP650:HH - :LIG1:O6	2.44264	
:TIP658:HH - :LIG1:O4	2.75859	
:TIP658:HH - :LIG1:O4	2.81268	
:TIP659:HH - :LIG1:O4	2.46724	
:TIP662:HH - :LIG1:O5	3.00166	
:TIP662:HH - :LIG1:O5	2.99645	
:TIP672:HH - :LIG1:O8	2.68787	
:TIP677:HH - :LIG1:O8	2.70726	
:LIG1:H39 - :TIP719:OH2	2.42033	
:LIG1:H56 - :LIG1:O6	2.70294	Conventional hydrogen bond
:LIG1:C48 - :LIG1:O14	3.54183	Carbon hydrogen bond
:LIG1:C56 - :LIG1:O11	3.00367	Carbon hydrogen bond
:TIP608:HH - :LIG1:H56	0.996064	Unfavourable bond

Table 2: Interaction of Vitamin i) A; ii) D; iii) B_9 and iv) B_{12} with T2

i)

Name	Distance	Type
:DPPE 249:C26 - :LIG1	5.0517	Hydrophobic alkyl
:DPPE 301 - :LIG1	5.21975	
:OLE263 - :LIG1	3.9198	
:OLE263 - :LIG1	5.30805 4.12196 4.30598 4.90344	
:LIN261 - :LIG1	5.32652 4.3234	
:LIN283 - :LIG1	4.40935	
:DPPI 274 - :LIG1	4.74709 5.01569	

ii)

Name	Distance	Type
:DPPE12 - :VD3163	5.11418	Hydrophobic alkyl
:DPPE28:C21 - :VD3163	4.43269 4.6318	
:DPPE35 - :VD3163	4.89119 4.77223	
:DPPE36:C21 - :VD3163	4.5853 4.87977	
: DPPE249:C26 - :VD3163	3.86212	
:DPPE249:C31 - :VD3163	4.46145	
:OLE263 - :VD3163	4.12781 4.73004	
:OLE263:C17 - :VD3163	5.05068	
:LIN18 - :VD3163; :LIN18:C18 - :VD3163	4.41302 5.16551	
:LIN245:C14 - :VD3163	4.79955 4.69967	
:LIN255:C18 - :VD3163	3.67693	
:LIN261 - :VD3163	4.96204 4.4809 5.30148 4.08318	
:LIN283 - :VD3163	4.94916	
:DPPC 266:C29 - :VD3163	4.62567	
:VD3163:C27 - :OLE263	5.12832 4.51841	
:VD3163:C27 - :LIN261	4.1705 4.6991	

iii)

Name	Distance	Type
:TIP3028:HH - :FOL201:OE2	2.47299	Water hydrogen bond
:TIP3070:HH - :FOL201:O1	2.26457	
:TIP3451:HH - :FOL201:O2	2.40584	
:TIP3503:HH - :FOL201:N5	2.34399	
:TIP3511:HH - :FOL201:O4	2.1221	
:TIP3574:HH - :FOL201:O4	2.76557	
:TIP3588:HH - :FOL201:O4	2.7182	
:TIP3588:HH - :FOL201:O4	2.28313	
:FOL201:H20 - :FOL201:OE2	2.31854	Conventional hydrogen bond
:TIP3512:HH - :FOL201:H13	1.67477	Unfavourable bond
:TIP3512:HH - :FOL201:H20	1.36054	

iv)

Name	Distance	Type
:TIP193:HH - :LIG1:O10	2.54395	Water hydrogen bond
:TIP179:HH - :LIG1:O6	2.30244	
:TIP193:HH - :LIG1:O12	3.03731	
:TIP208:HH - :LIG1:O14	2.6584	
:TIP242:HH - :LIG1:O9	2.19563	
:TIP312:HH - :LIG1:O5	2.76143	
:TIP318:HO - :LIG1:O5	2.138	
:TIP699:HH - :LIG1:O6	2.69887	
:TIP747:HH - :LIG1:N1	2.9559	
:LIG1:H55 - :TIP257:OH2	2.35622	
:LIG1:H56 - :TIP265:OH2	2.62625	
:LIG1:H19 - :TIP726:OH2	2.71373	
:LIG1:H18 - :TIP766:OH2	2.72841	
:LIG1:C54 - :TIP183:OH2	3.61677	
:LIG1:H89 - :TIP211:OH2	2.79334	
:LIG1:H68 - :LIG1:N13	2.59837	Conventional hydrogen bond
:TIP176:HH - :LIG1:H84	2.51602	Unfavourable bond
:TIP188:HH - :LIG1:H84	2.54976	
:TIP295:HH - :LIG1:H39	1.76375	
:TIP768:HH - :LIG1:H38	2.54518	

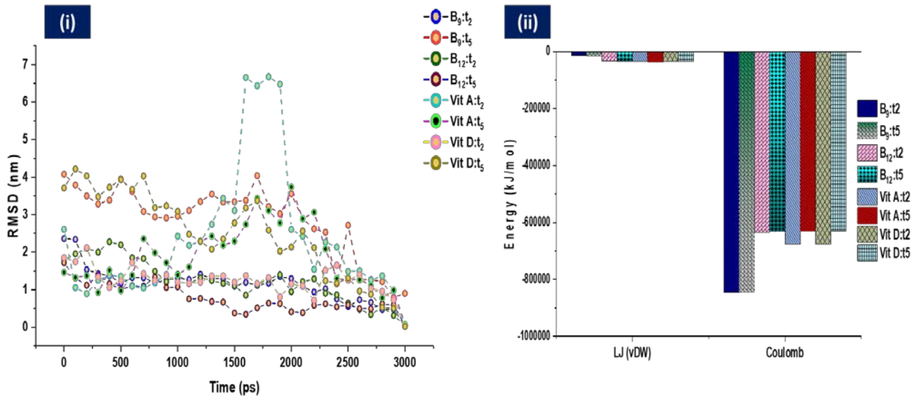


Fig. 3: (i) RMSD (nm), (ii) Energy (kJ/mol), of different bilayer combinations as a function of simulation time (ps) and interaction forces, respectively

Conclusions

- T2 and T5 showed good stability having phase transition at 60 ℃.
- Hydrophobic vitamins showed stronger binding affinity than hydrophilic vitamins.
- Unfavorable interaction was observed in hydrophilic vitamins.
- Electrostatic force showed stronger influence over the molecules than Van der Waals attraction.
- Docking study of multi-vitamins with the lipid bilayer membrane suggests good binding affinity of the ligands (RMSD ~ 0.00) that can be used for co-encapsulation.