in-silico Design of Nanoparticles for Transdermal Drug Delivery Application

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Supporting Information

S1 Projected area on XY plane per lipid and over all order parameter

In a molecular dynamics simulation of lipid bilayer, which has normal along the z direction, the area per lipid (APL) can be calculated using the following equation:

$$APL = 2\frac{Lx\,Ly}{Nlipid} \quad \text{(S1)}$$

Where L_x, L_y is the box length in X and Y direction, respectively and N_{lipid} is total number of lipids in the bilayer.

The second rank order parameter for the bilayer, which has normal in z direction, could be defined as:

$$Sz = \frac{1}{2}(3cos^2\theta - 1) \quad \text{(S2)}$$

where θ is the angle between the bond and the bilayer normal. Sz = 1 means perfect alignment with the bilayer normal, S_z = −0.5 anti-alignment, and S_z = 0 random orientation of the lipid chains.

The overall order parameter was calculated using following relationship:

$$S = \frac{\sum_{i=1}^{n} Sz(i)}{n} \quad \text{(S3)}$$

Where n is number of beads in the ceramide molecules and Sz is order parameter for i^{th} bead of ceramide chain.

S2. **Area compressibility**

The Area compressibility of a bilayer whose normal is oriented along the Z axis is calculated as:

$$K_A = k_b T \frac{<A>}{<A^2>-<A>^2} \quad \text{(S4)}$$

$$A = (APL)\frac{N_{lipids}}{2} \quad \text{(S5)}$$

Where, A is projected area on XY plane, N_{lipids} is number of lipids, k_b is the Boltzmann constant, and T is the temperature. The angular brackets denote the ensemble averages taken over the course of the simulation.

S3. Nanoparticle Structure

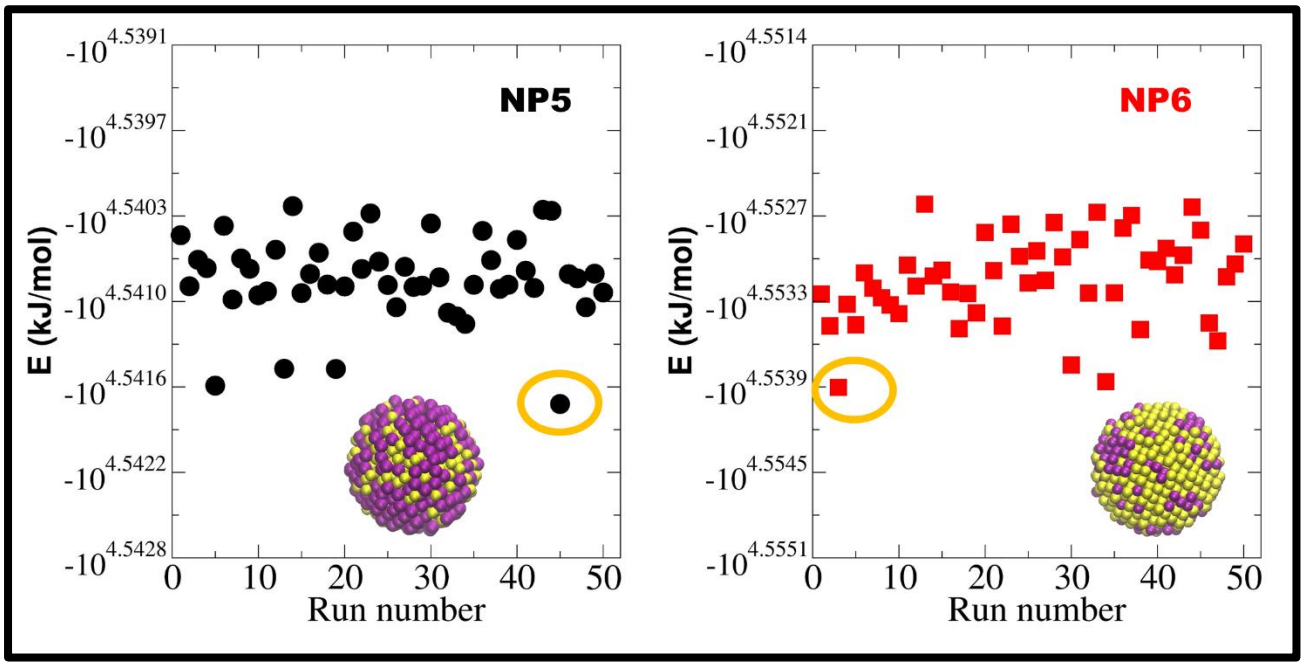

Figure S1. Potential energy of nanoparticle NP5 and NP6 system in different runs. The hydrophobic and hydrophilic beads were arranged randomly on the surface. Configuration which having lowest energy was used for the actual simulations.

S4. Interaction of NPs with skin lipid bilayer

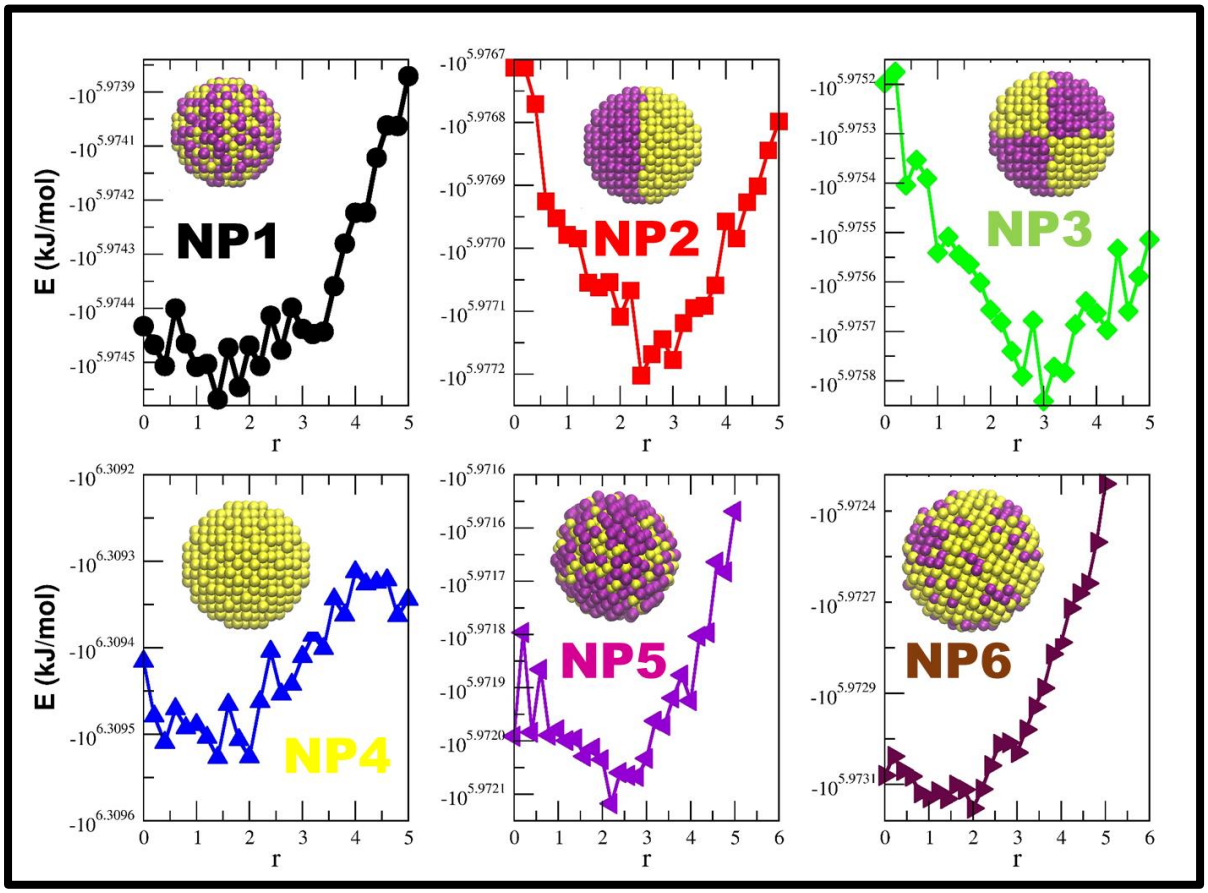

Figure S2. Interaction energy between bilayer and nanoparticle, along the bilayer normal z, calculated in last 150 ns run of constrained simulations. Here z=0 corresponds to the bilayer center. The results are shown only for the upper leaflet of the bilayer.

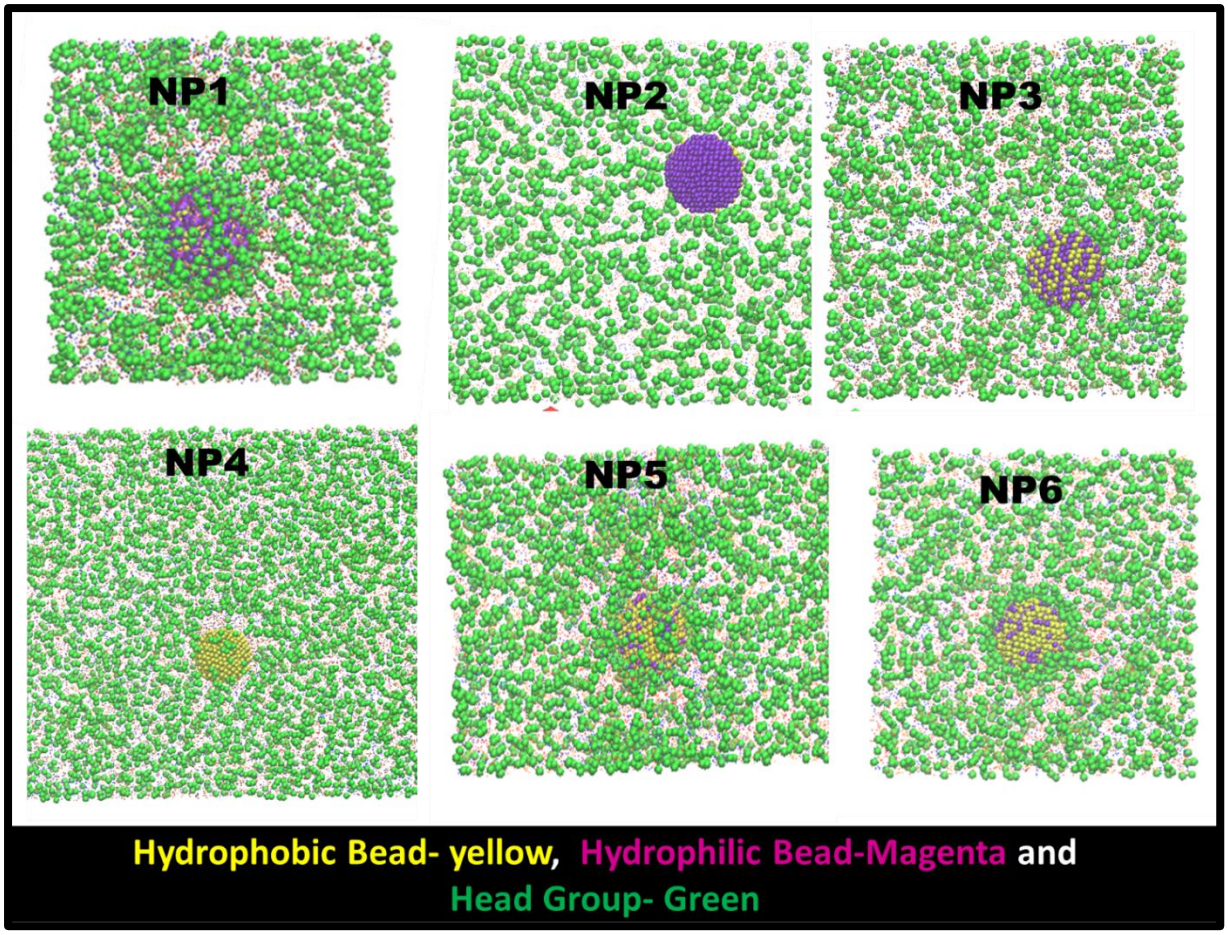

Figure S3. Top view Final snapshot of each nanoparticle and skin lipid bilayer system in the end of 6 μs unconstrained simulation. The water molecules have been removed for the purpose of clarity. The snapshots were created using the VMD software.[1] The CER, FFA and CHOL are shown in orange, red and green color respectively. For color code please refer to the web version of the article.

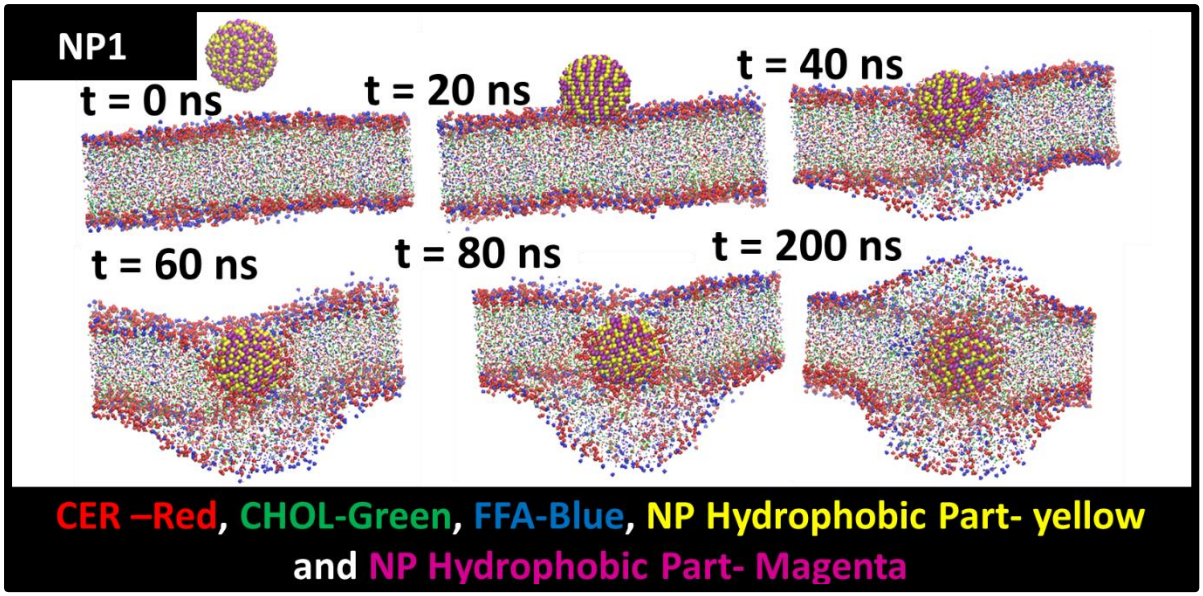

Figure S4. Interaction of NP1 with mixed 1:1:1 (CER: CHOL: FFA) bilayer. Structural changes induced by the NP in the bilayer with simulation time. The CER, CHOL, FFA, hydrophobic part of NP and hydrophilic part of NP are shown in red, green, blue, yellow and magenta respectively. Water molecules were removed for the purpose of clarity. Images/snapshots were created using the VMD software.[1]

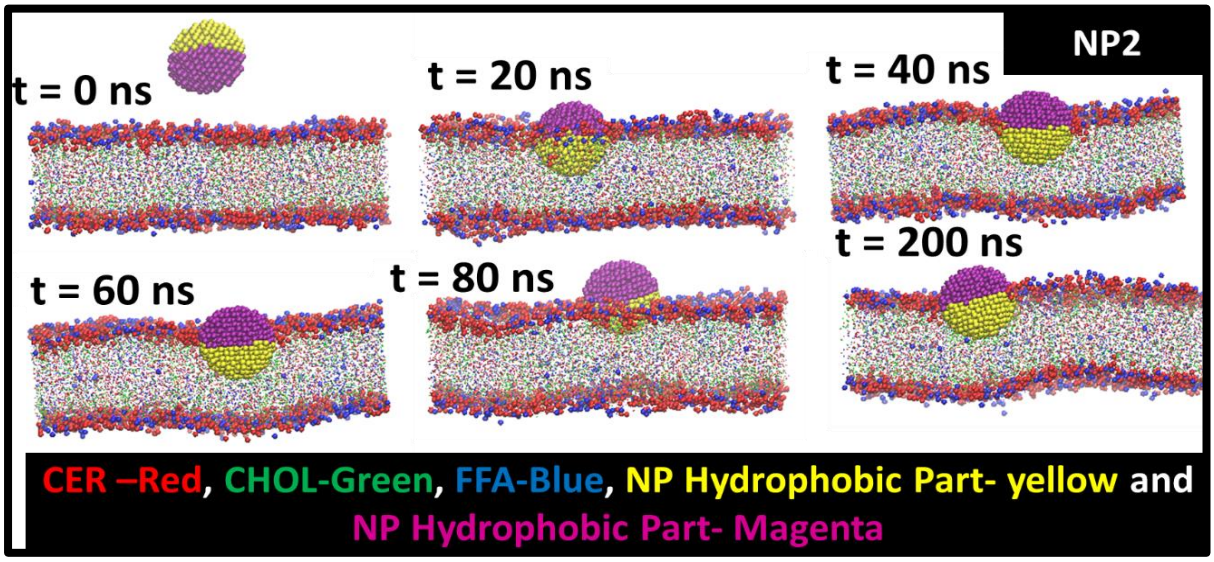

Figure S5. Interaction of NP2 with mixed 1:1:1 (CER: CHOL: FFA) bilayer. Structural changes induced by the NP in the bilayer with simulation time. The CER, CHOL, FFA, hydrophobic part of NP and hydrophilic part of NP are shown in red, green, blue, yellow and magenta respectively. Water molecules were removed for the purpose of clarity. Images/snapshots were created using the VMD software.[1]

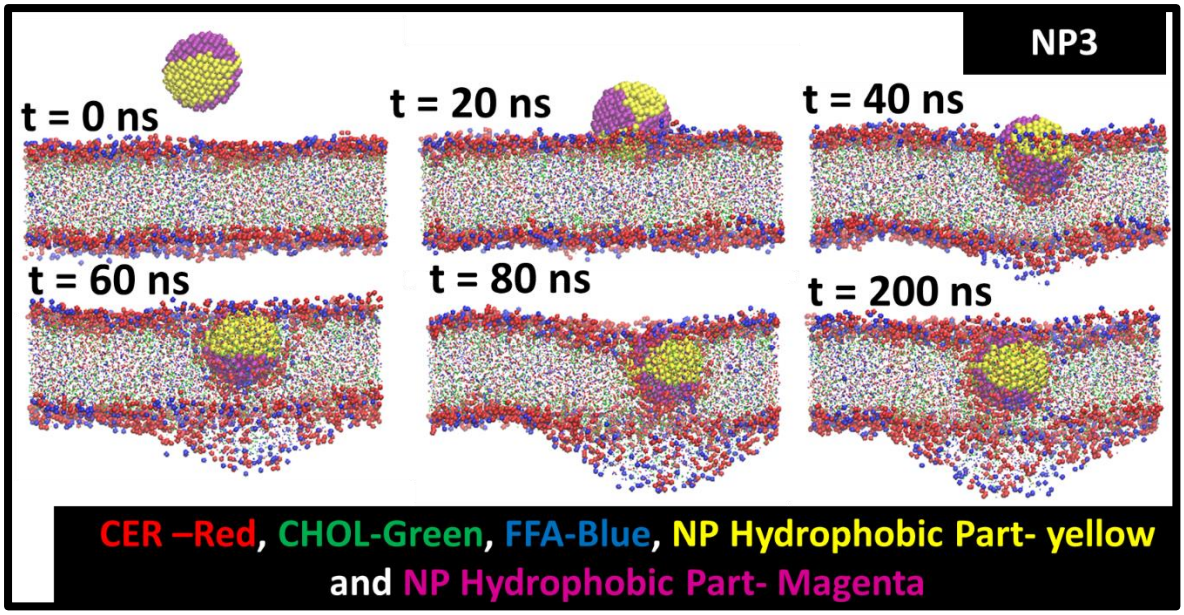

Figure S6. Interaction of NP3 with mixed 1:1:1 (CER: CHOL: FFA) bilayer. Structural changes induced by the NP in the bilayer with simulation time. The CER, CHOL, FFA, hydrophobic part of NP and hydrophilic part of NP are shown in red, green, blue, yellow and magenta respectively. Water molecules were removed for the purpose of clarity. Images/snapshots were created using the VMD software.[1]

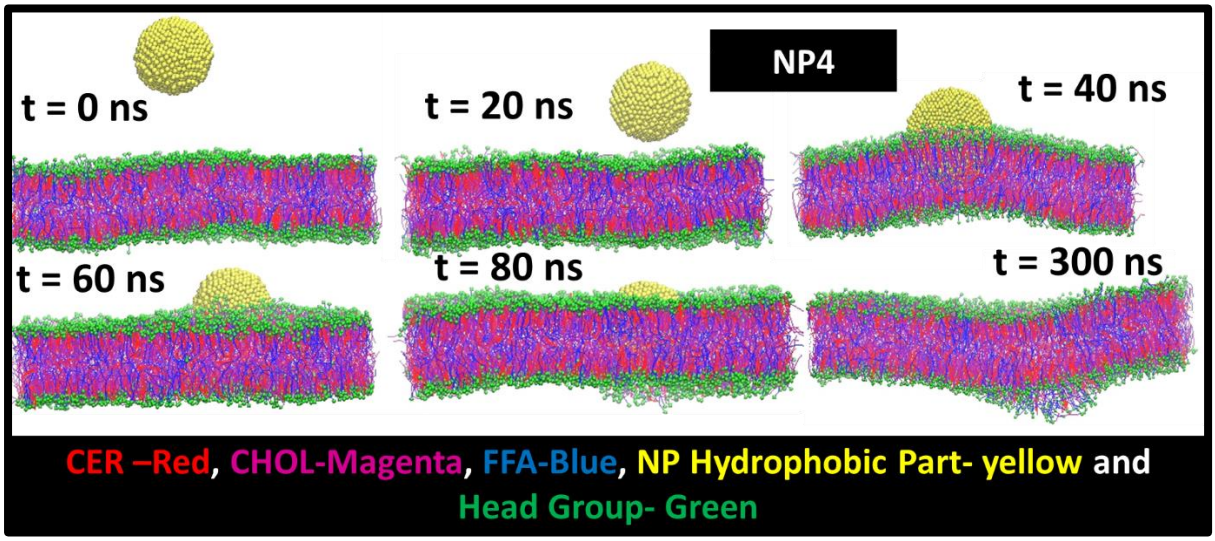

Figure S7. Interaction of NP4 with mixed 1:1:1 (CER: CHOL: FFA) bilayer. Structural changes induced by the NP in the bilayer with simulation time. The CER, CHOL, FFA, hydrophobic part of NP and hydrophilic part of NP are shown in red, green, blue, yellow and magenta respectively. Water molecules were removed for the purpose of clarity. Images/snapshots were created using the VMD software.[1]

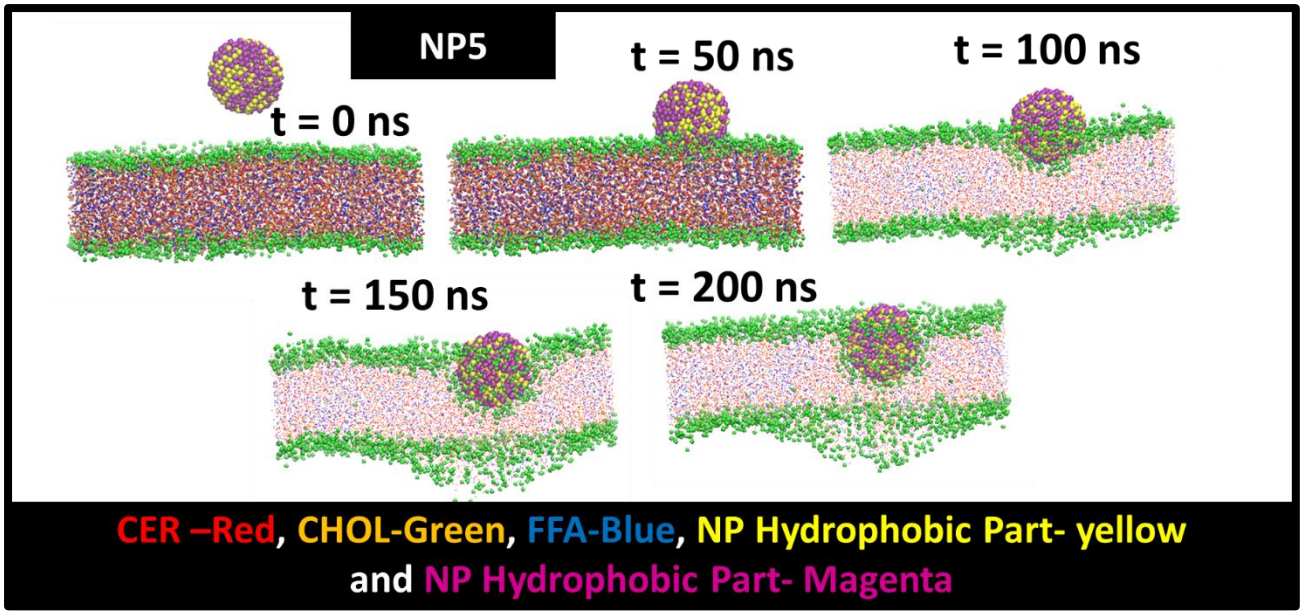

Figure S8. Interaction of NP5 with mixed 1:1:1 (CER: CHOL: FFA) bilayer. Structural changes induced by the NP in the bilayer with simulation time. The CER, CHOL, FFA, hydrophobic part of NP and hydrophilic part of NP are shown in red, green, blue, yellow and magenta respectively. Water molecules were removed for the purpose of clarity. Images/snapshots were created using the VMD software.[1]

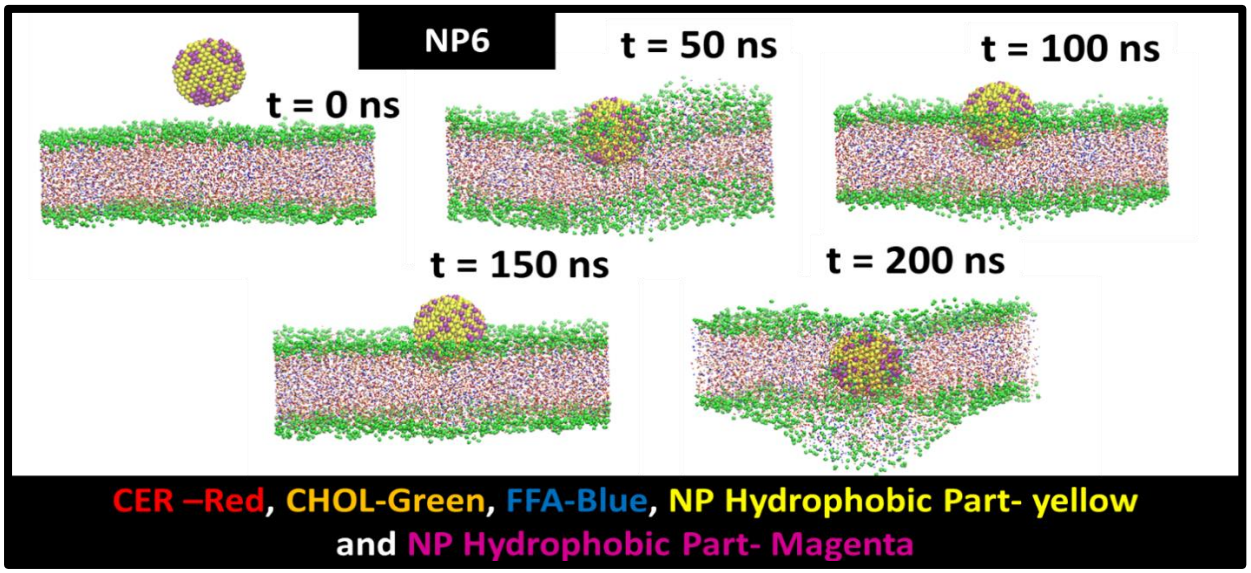

Figure S9. Interaction of NP6 with mixed 1:1:1 (CER: CHOL: FFA) bilayer. Structural changes induced by the NP in the bilayer with simulation time. The CER, CHOL, FFA, hydrophobic part of NP and hydrophilic part of NP are shown in red, green, blue, yellow and magenta respectively. Water molecules were removed for the purpose of clarity. Images/snapshots were created using the VMD software.[1]

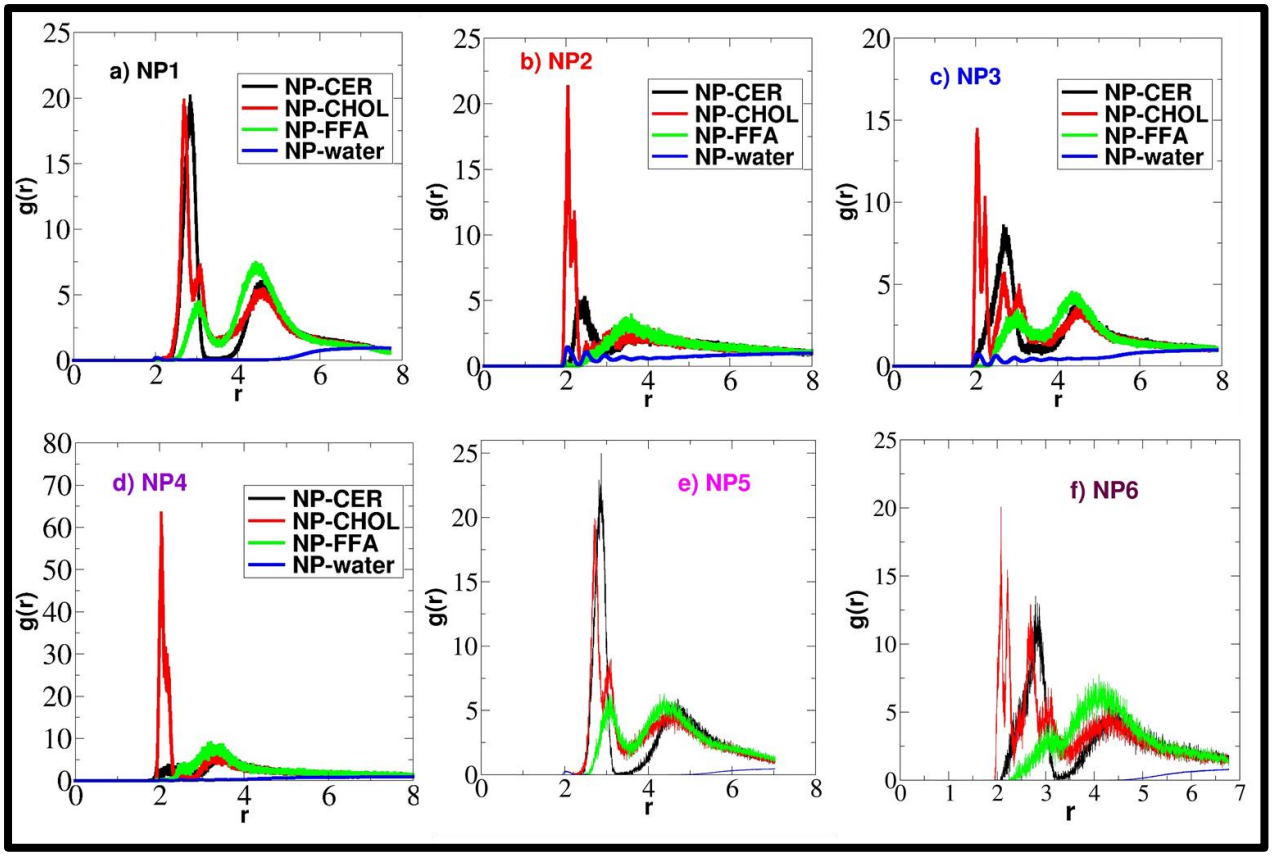

Figure S10. Radial distribution function of skin constituents and water around the nanoparticle in each case calculated in unconstrained simulations

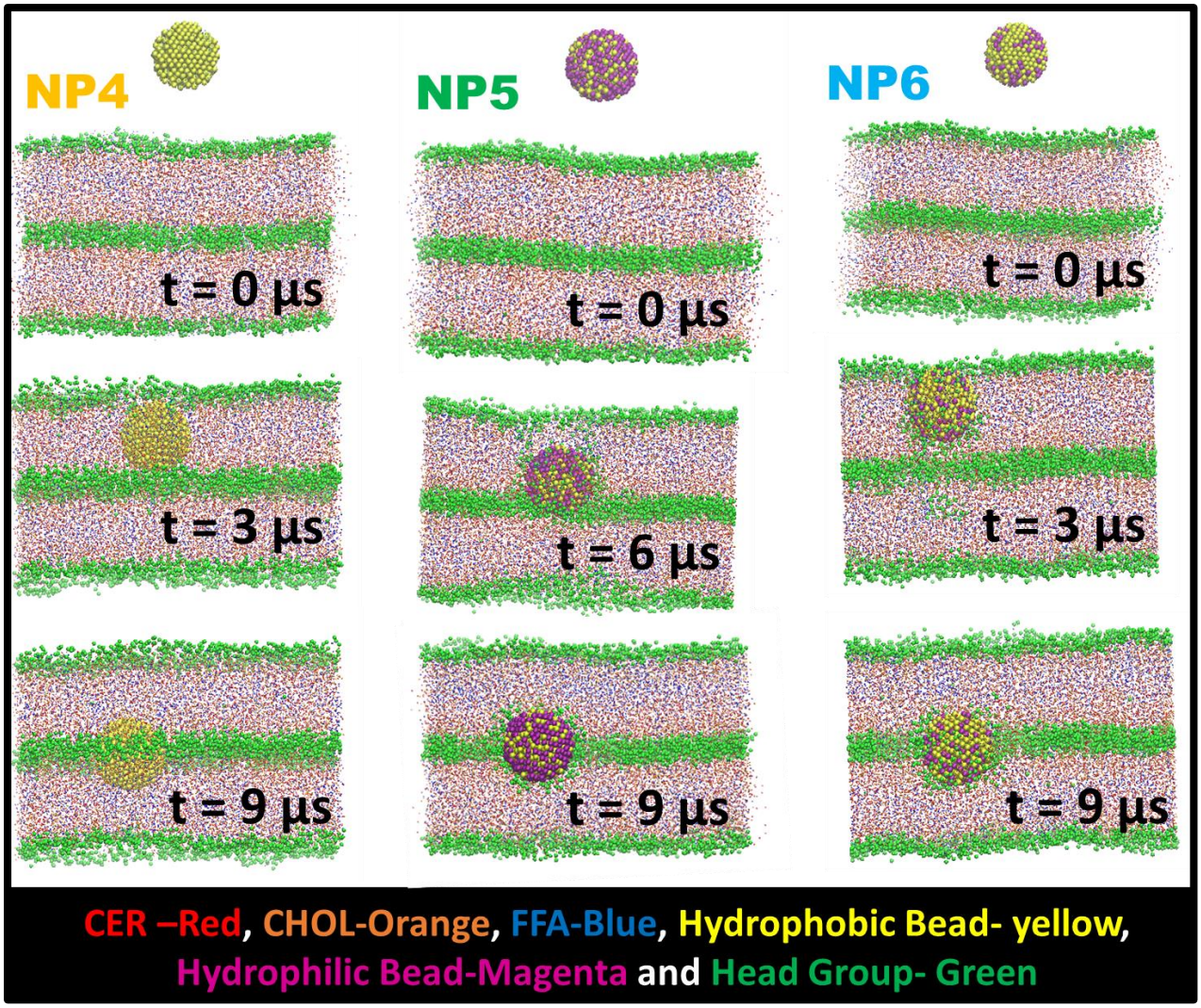

Figure S11. Nanoparticle Permeation through skin double lipid bilayer. Snapshots of each nanoparticle and skin double lipid bilayer system during the 9 µs unconstrained simulation run. The water molecules have been removed for the purpose of clarity. The snapshots were created using the VMD software.[61] The CER, FFA and CHOL are shown in orange, red and green color respectively.

References

1. Humphrey, W., Dalke, A. & Schulten, K. VMD: Visual molecular dynamics. *J. Mol. Graph.* **14,** 33-38 (1996).