Influence of bile composition on membrane incorporation of transient permeability enhancers

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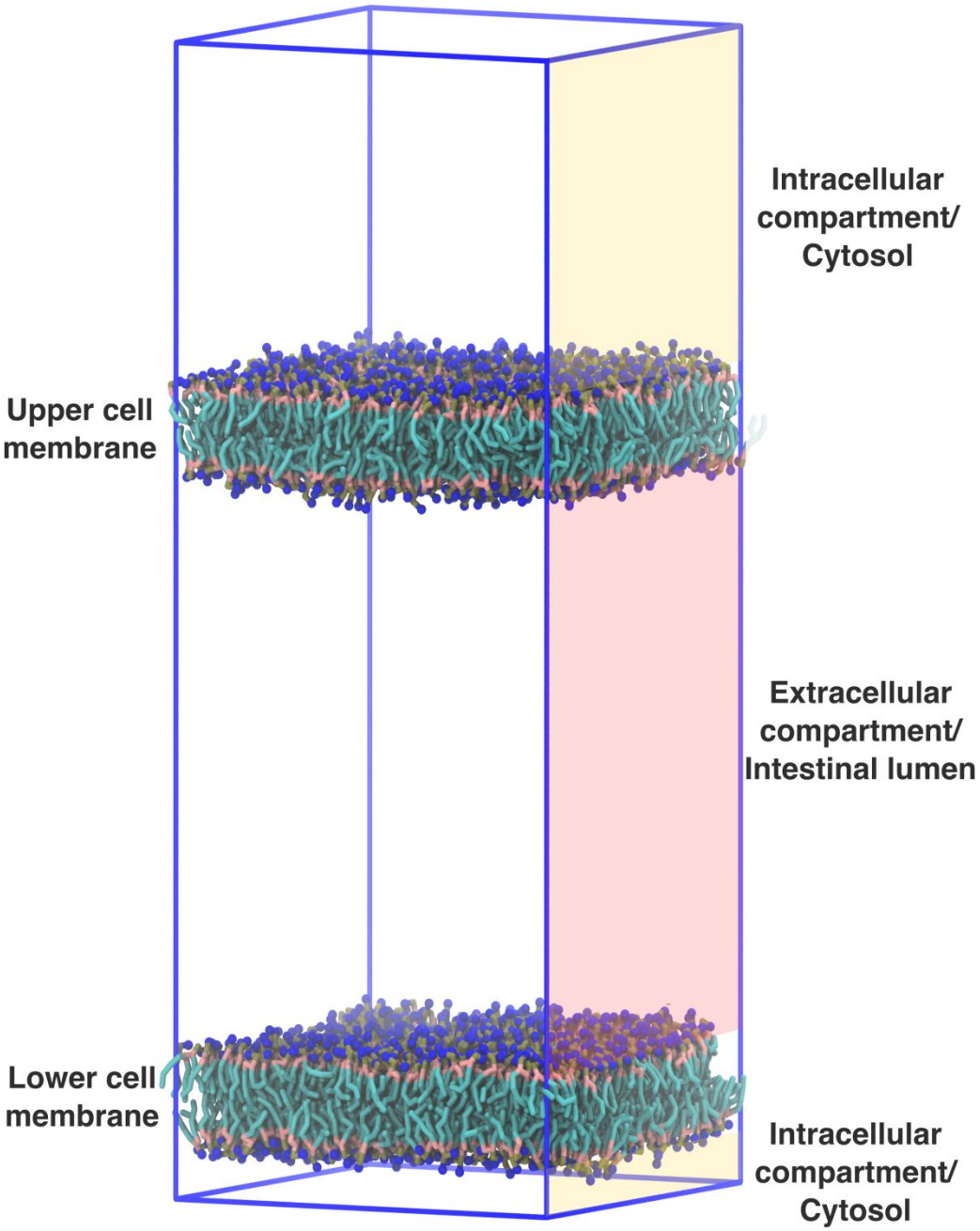
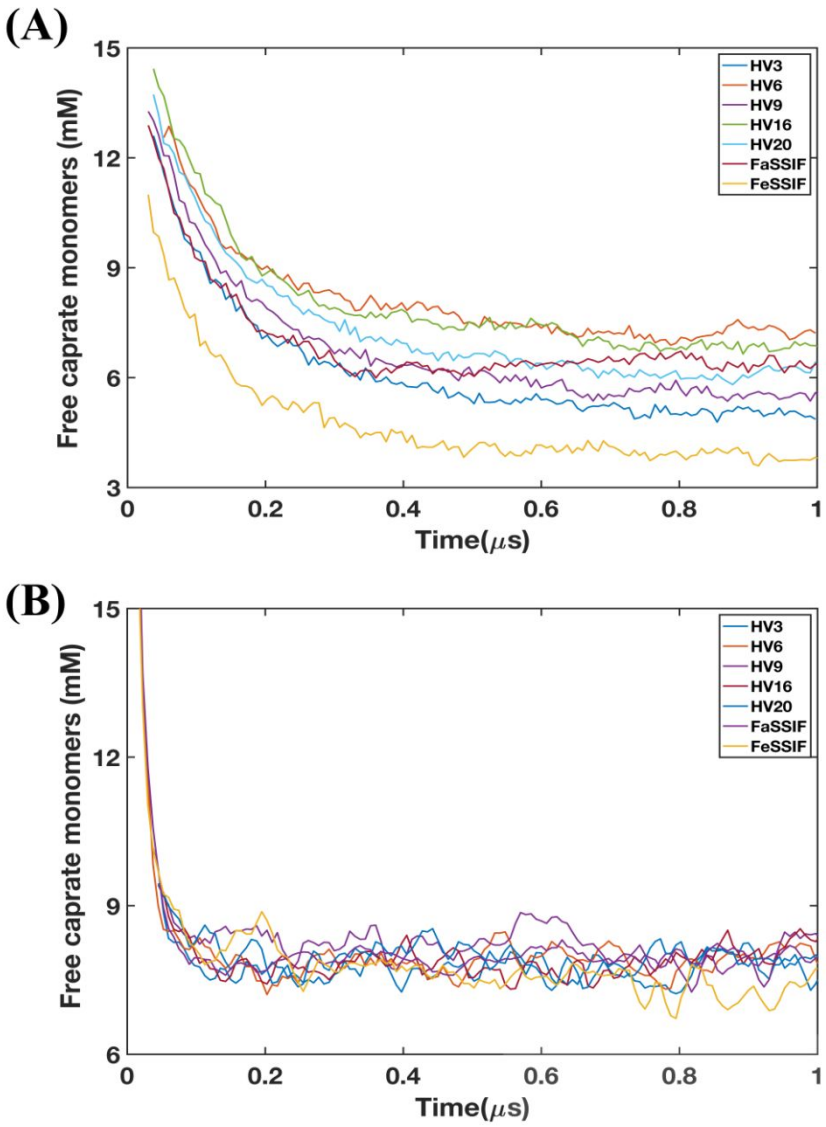
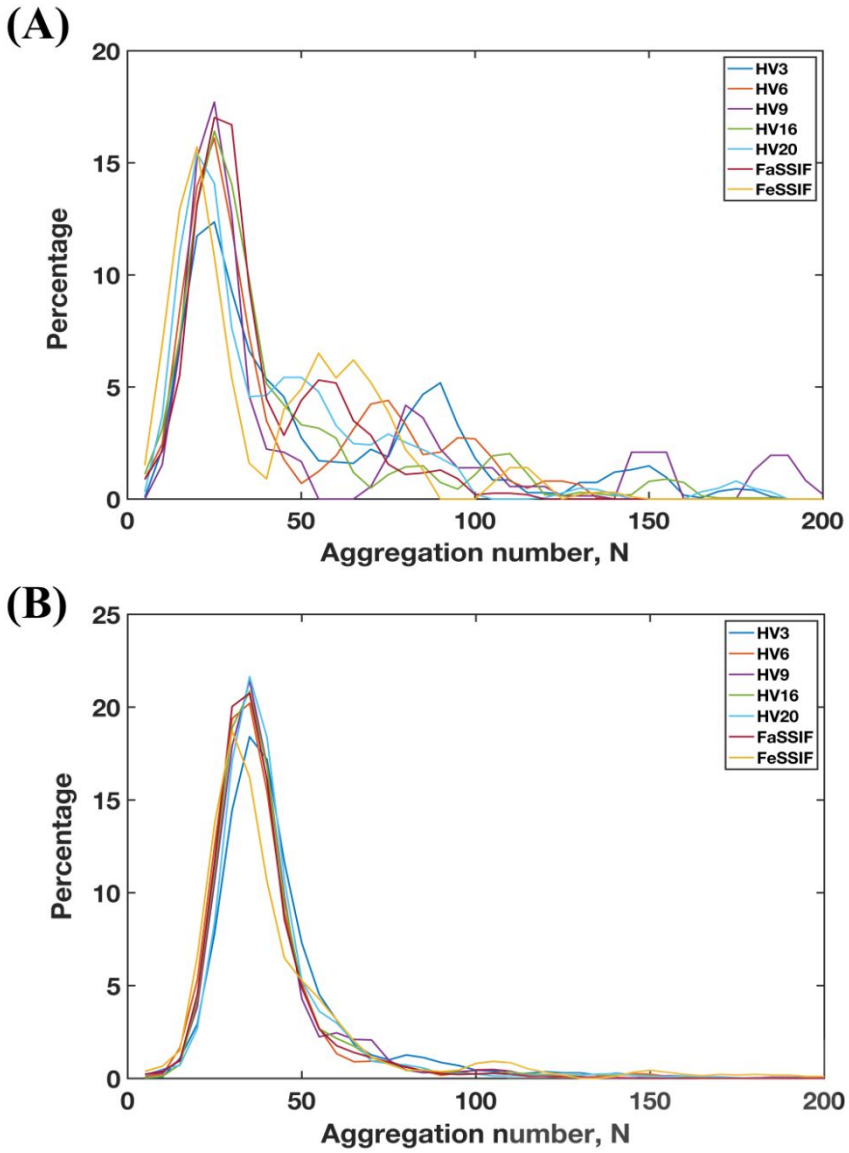


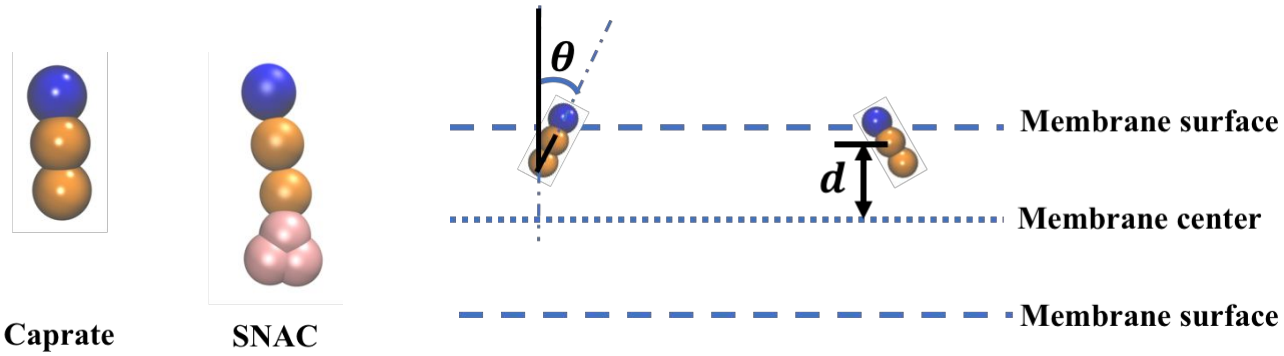
Supplementary Figure 1: Simulation system used to study the interaction of permeability enhancers (PEs), bile components and membrane. Different PE and bile components were placed in between POPC membranes as indicated by extracellular compartment. Such systems were used so that PEs and bile components can only interact with one side of the membrane. Intracellular compartment was used to restrict the interaction between the membranes itself.



Supplementary Figure 2: Variation of free caprate monomers during the simulation with the addition of (A) 20 mM and (B) 100 mM of caprate.



Supplementary Figure 3: Distribution of the micelle sizes from the simulations of different intestinal fluids with the addition of (A) 20 mM and (B) 100 mM of caprate.



(A) (B)

Supplementary Figure 4: (A) Coarse-grained representation of the caprate and SNAC molecules. The blue, orange and pink beads represent headgroup, fatty acid chain and salicylamide region, respectively. (B) Representation of d, which is the distance between the membrane center and the center of mass of the caprate and SNAC fatty acid chain in the membrane normal direction. θ represents the angle between membrane normal and the vector from two consecutive beads of the fatty acid chain.

Supplementary Table 1: Composition details of the four different micelles in the US simulations. Note that, in the first column, the names of the micelles are the same as presented in Figure 8A.

Micelle	Composition
OA	25 OA and 1 caprate molecules
BS	10 NaTC and 1 caprate molecules
Mixed (BS+PL)	14 NaTC, 4 POPC and 1 caprate molecule
C10	22 caprate molecules

The following abbreviations are used: Phospholipids (PL), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), oleate (OA), bile salts (BS), sodium taurocholate (NaTC), C10 (caprate)

Supplementary Table 2: QCM-D experiments using different combinations of fasted and fed state simulated intestinal fluids and permeability enhancers.

Experiment	Combination of Intestinal fluid and PE added in Step (iii), see Section 2.3
A	FaSSIF
B	FeSSIF
C	FaSSIF with 100 mM of caprylate
D	FeSSIF with 100 mM of caprylate
E	FaSSIF with 100 mM of caprate
F	FeSSIF with 100 mM of caprate
G	FaSSIF with 100 mM of SNAC
H	FeSSIF with 100 mM of SNAC

Supplementary Table 3: Description of the micelle sizes from the simulations of different intestinal fluids with the addition of caprate

Intestinal fluid	With addition of 20 mM Caprate		With addition of 100 mM Caprate	
	Aggregate size (in nm) Max/Min	Aggregate size (in nm) Average	Aggregate size (in nm) Max/Min	Aggregate size (in nm) Average
HV3	10.7/2.8	4.9	11.8/2.6	5.1
HV6	7.3/2.7	3.8	7.9/2.3	4.3
HV9	11.3/2.6	5.1	11.5/2.6	5.1
HV16	7.4/2.4	3.6	9.4/2.5	4.5
HV20	10.4/2.7	3.9	10.1/2.4	4.9
FaSSIF	7.9/2.8	3.8	9.5/2.5	4.5
FeSSIF	11.2/3.1	5.2	11.6/2.9	4.9