An Investigation of β–Blocker Association with a Chiral Molecular Micelle by means of Molecular Dynamics Simulations

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Abstract

Molecular dynamics (MD) simulations were used to investigate the intermolecular interactions between two β-blocker drugs and the chiral molecular micelle (MM), poly-(sodium undecyl-(L)-leucine-valine) (poly(SULV)). The MM contained twenty covalently bound surfactants, each with a chiral, hydrophilic dipeptide headgroup and hydrophobic hydrocarbon tail. The MM has been used to separate the enantiomers of chiral drugs. These separations are necessary because drug enantiomers often have different physiological properties. The β–blockers investigated were atenolol and propranolol. These drugs are used to treat high blood pressure and glaucoma. Propranolol has also been shown to have strong chiral interactions with poly(SULV), while the chiral interactions between the MM and atenolol are weak. One enantiomer of each β-blocker was docked into one of four MM binding pockets and fifteen nanosecond MD simulations were carried out. With the propranolol cation, it was found that both enantiomers preferentially bound to MM pocket number one, while the enantiomers of the atenolol cation preferred two separate pockets. Binding free energy calculations showed that (S)-propranolol associated more strongly with the MM than (R)-propranolol. Analogous calculations showed that the binding free energies for the atenolol enantiomers were similar. Solvent accessible surface area analyses showed that the preferred propranolol binding pockets allowed the ligand's aromatic rings to penetrate deeply into the poly(SULV) core. Atenolol, however had much higher solvent accessible surface areas, suggesting that its enantiomers bound primarily near the micelle surface. Finally, (S)-propranolol was also found to form more H-bonds with the MM headgroup than (R)-propranolol.

Chemical Structures

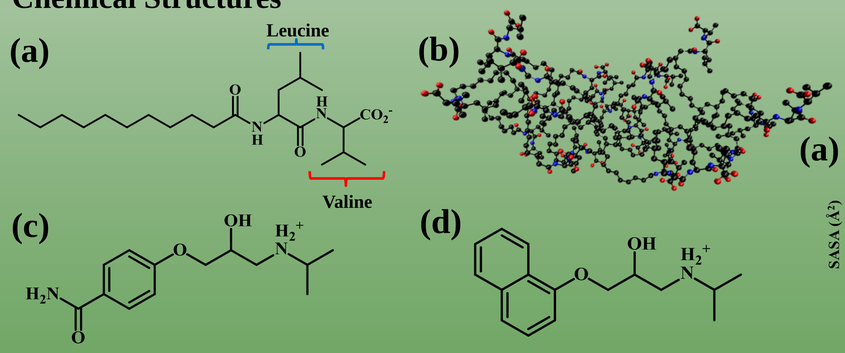

Figure 1:, (a) poly(SULV) molecular micelle monomer chain, (b) poly(SULV) representative structure from MD simulations, (c) atenolol cation structure (d) propranolol cation structure

Experimental Details

- Four poly(SULV) molecular micelle binding pockets were identified using the software package MOE (www.chemcomp.com).
- β-blocker enantiomers were docked into each pocket.
- Classical molecular dynamics simulations were carried out with the docked structures using the software package Amber 12 (www.ambermd.org).
- Amber 12 trajectory analysis tools were used to (1) measure distances between H-bond donor and acceptor atoms, (2) investigate the drugs' solvent accessible surface areas, (3) examine inter-molecular hydrogen bonds, and (4) calculate enantiomer binding free energies.

Results

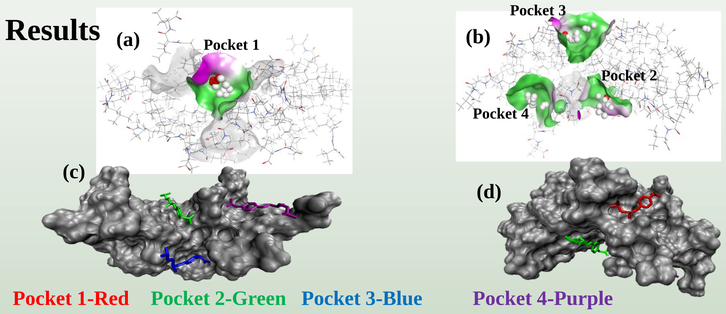

Figure 2: (a) Poly(SULV) ligand binding pockets, (b) alternate view of (a), (c) (S)-propranolol initial docked structures, (d) alternate view of (c).

Ligand: MM Pocket	Ligand: MM Binding Free Energy (kJ•mol^{-1})	MM Pocket Fraction Occupied
(S)-Propranolol: 1	-71.09	0.99
(R)-Propranolol: 1	-38.28	0.99
(S)-Atenolol: 1	-16.73	0.73
(S)-Atenolol: 4	-14.37	0.27
(R)-Atenolol: 1	-21.31	0.58
(R)-Atenolol: 3	-20.51	0.42

Table 1: Binding free energies and fractional populations for propranolol and atenolol enantiomers in their preferred poly(SULV) pockets.

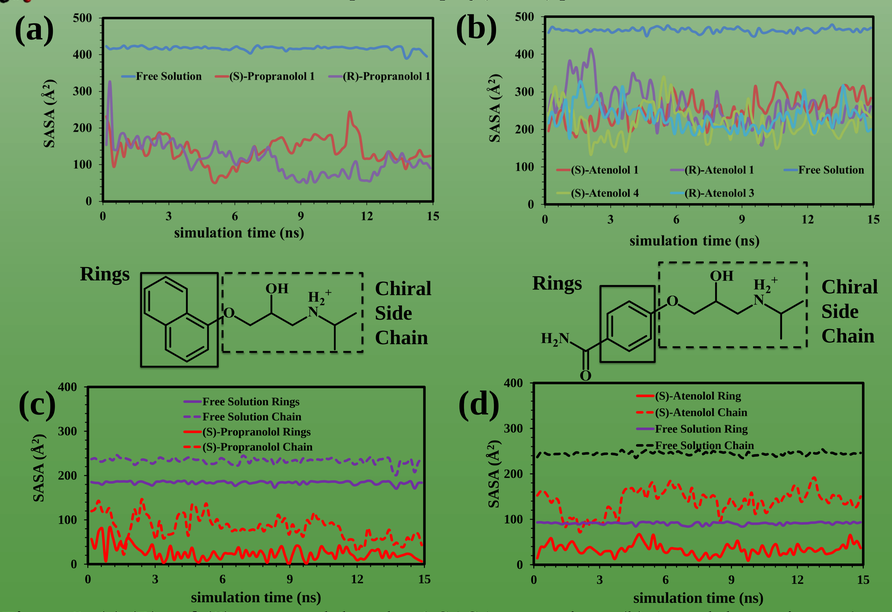

Figure 2: (a) (R) and (S)-propranolol pocket 1 SASA comparison, (b) Atenolol enantiomers' SASA, (c) (S)-propranolol ring and chain pocket 1 SASA, (d) (S)-atenolol ring and chain SASA.

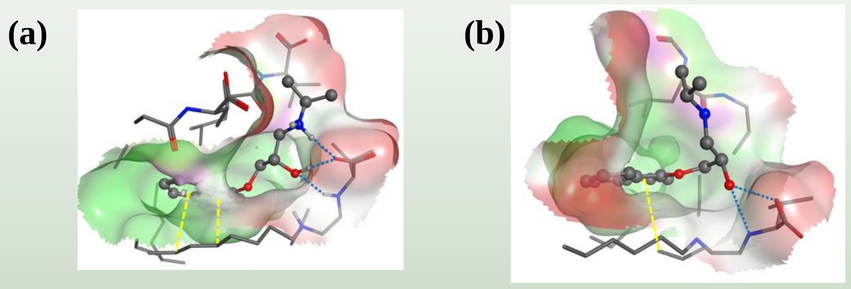

Figure 6: (S)-propranolol (a) and (R)-propranolol (b) in poly(SULV) pocket one with aromatic rings embedded in the micelle core.

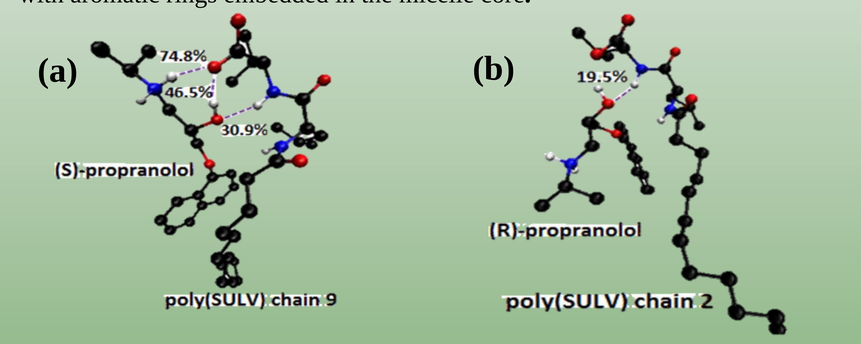

Figure 7: High occupancy H-Bonds between propranolol enantiomers and the MM.

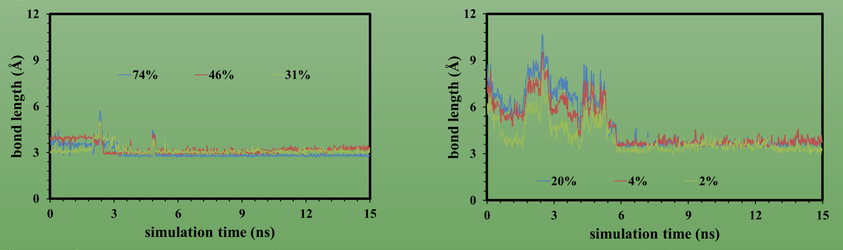

Figure 8: Distance between donor/acceptor atoms in (a) (S)-propranolol and (b) (R)-propranolol poly(SULV) H-bonds. Percent occupancies of the H-bond are in the legend.

Conclusions

1. Both enantiomers of propranolol preferentially bound to poly(SULV) pocket one, while (S) and (R)-atenolol bound to pocket one, and either pocket 4 or 3, respectively.
2. Propranolol enantiomer solvent accessible surface area analyses and structures extracted from the MD simulations showed that each enantiomer's rings were placed deep inside the micelle, while the polar chains were closer to the micelle surface.
3. (S)-propranolol experienced stronger H-bonding interactions with poly(SULV) than (R)-propranolol. Distance analyses showed (S)-propranolol formed simultaneous H-bond with the MM.
4. Atenolol's polarity prevented the ligand from docking deep into the micelle core.

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