Molecular Dynamics of HPMC/SDS Interactions

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Abstract

Hydroxypropyl methylcellulose (HPMC) is a target polymer that has been found to be an efficient way to manipulate the release rate of the active pharmaceutical ingredient in a drug. Our goal is to use Molecular Dynamics(MD) to determine the interaction of HPMC with SDS over two location GP6 and GP2. The surfactant is placed in an environment with HPMC where a water box is created, and the surroundings are neutralized with 0.15 M NaCl. The simulations are accomplished using NAMD, a molecular dynamics program that specialized in biomolecular systems. The advantage of using MD is the ability to control the environment the complex is placed in, such as the concentration of SDS molecules. The overall goal is to generate results that will allow pharmaceutical companies to better select inactive ingredients in drugs reducing the side effects, increasing the efficiency, and essentially improving patient's quality of life.

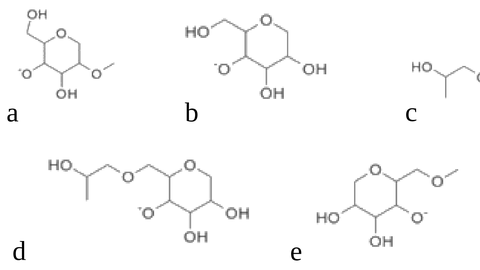


Figure 1. (a) The main molecular structure of Hydroxypropyl methylecellulose (HPMC) BGLC. The molecular structures of the modified glucoses used in this assay: (b) GM2, (c) GP2,(d) GP6, and (e) GM6.

Significance

HPMC/SDS interactions have become an important point of research due to HPMC's ability to modify the release rate of medications and to enhance micelle stability1. A study done by Chiba University focused on the interaction between flurbiprofen and HPMC/SDS. They concluded that the formation of a flurbiprofen nanoparticle using HMPC/SDS as a ternary ground mixture were essential for particle size reduction and presented good stability. They later stated that this can be replicated with other hydrophobic drugs. In our lab, we are going to further explore the precise aspect of the HPMC/ SDS molecule focusing on the location of interactions. It has been proven that HPMC controls the rate of release while the surfactant controls solubility.

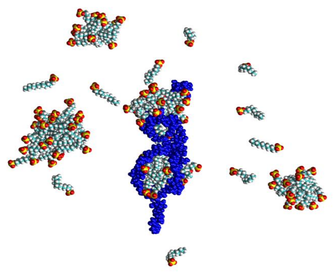


Figure 2. (a) Shows the interaction between SDS and HPMC. The blue molecule is the HPMC with just BGLC. While the other surrounding molecules are SDS. There are two clear and distinct micelles of SDS that have formed around and within the HPMC molecule which are significant.

Method

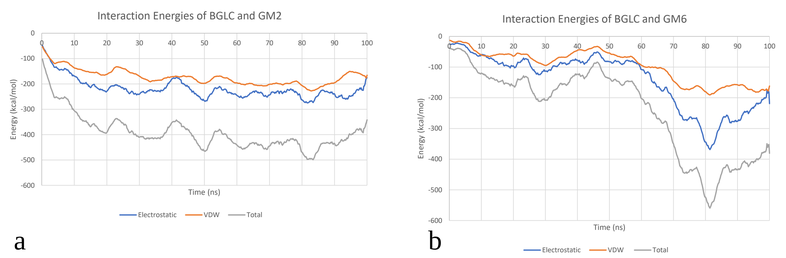
The HPMC molecule was built by randomly assigning the number and position of each of the modified glucose molecules in HPMC. The positions of the modified glucose residues are shown in the figure below, where GM6 is 6-methylglucose, GP2 is 2-hydroxypropylglucose, GP6 is 6-hydroxypropylglucose and GM2 is 2-methylglucose. These are the modified residues found in commercially available HPMC. Packmol was used to amalgamate the HPMC and SDS into the same environment. Nanoscale Molecular Dynamics (NAMD) was used to equilibrate the polymer4, and then placed into a water box containing 0.15 M NaCl. The polymer was then put through a 100 nano second simulation. Once this was completed the final frame of HPMC was extracted and equilibrated with 100 SDS molecules. Another 100 ns simulation was run on the complex. Visual Molecular Dynamics (VMD) was used in order to envision the HPMC and SDS molecule and their interactions.

Creating MD Simulations

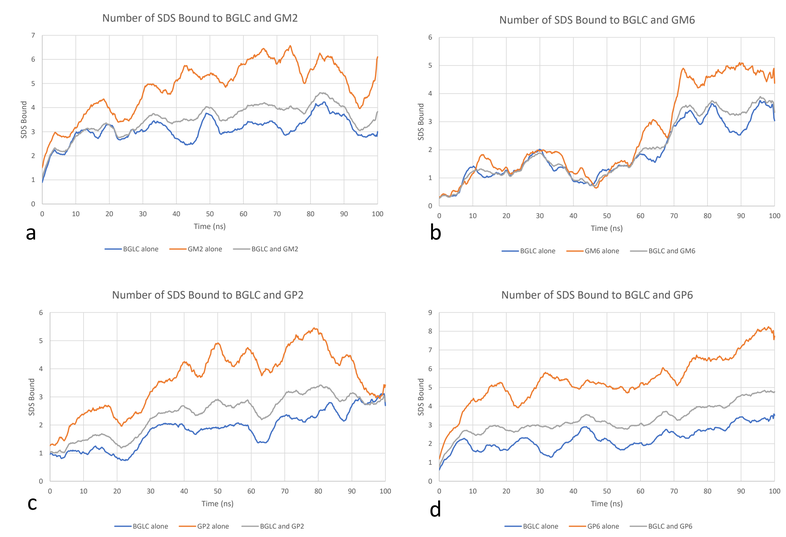
HPMC_	Sequence
GM6	G-G-M6-G-G-G-M6-M6-G-G-G-M6-M6-M6-G-G-G-G-G-M6-M6-M6-M6-M6-G-G-G-G-M6-G-G-G-M6-M6-G-G-G-G-M6-M6-M6-G-G-G-M6-M6-G-G
GM2	G-G-M2-G-G-G-M2-M2-G-G-G-M2-M2-M2-G-G-G-G-G-M2-M2-M2-M2-M2-G-G-G-G-M2-G-G-G-M2-M2-G-G-G-G-M2-M2-M2-G-G-G-M2-M2-G-G
GP6	G-G-P6-G-G-G-P6-P6-G-G-G-P6-P6-P6-G-G-G-G-G-P6-P6-P6-P6-P6-G-G-G-G-P6-G-G-G-P6-P6-G-G-G-G-P6-P6-P6-G-G-G-P6-P6-G-G
GP2	G-G-P2-G-G-G-P2-P2-G-G-G-P2-P2-P2-G-G-G-G-G-P2-P2-P2-P2-P2-G-G-G-G-P2-G-G-G-P2-P2-G-G-G-G-P2-P2-P2-G-G-G-P2-P2-G-G

Figure 3. This Table refers to the modification made to the HPMC molecule. With 48 total residues on each molecule. G stands for Glucose, M stands for Methyl, and P stand for Propyl.

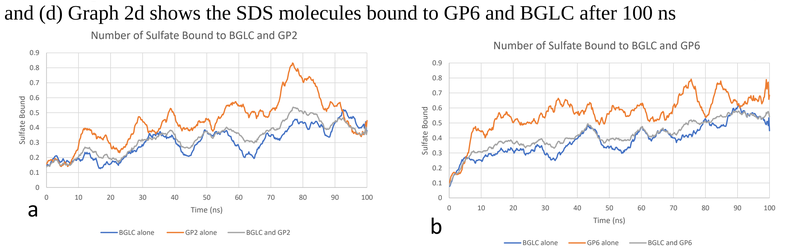
Results



Graph 1. (a) Graph 1a shows the interaction energies for GM2 after 100 ns, (b) Graph 1b shows the interaction energies for GM6 after 100 ns, (c) Graph 1c shows the interaction energies for GP2 after 100 ns, and (d) Graph 1d shows the interaction energies for GM2 after 100 ns all separated into electrostatic, VDW, and total interactions.



Graph 2. Counting the number of SDS molecules that were bound to the modified HPMC molecules in VMD, the (a) Graph 2a shows the SDS molecules bound to GM2 and BGLC after 100 ns, (b) Graph 2b shows the shows the SDS molecules bound to GM6 and BGLC after 100 ns, (c) Graph 2c shows the shows the SDS molecules bound to GP2 and BGLC after 100 ns, and (d) Graph 2d shows the SDS molecules bound to GP6 and BGLC after 100 ns



Graph 3. Shows the interactions of the Sulfate ion in SDS with the glucose molecules. (a) Graph 3a shows the sulfate ions interacting with GP2, and BGLC after 100 ns (b) Graph 3b shows the sulfate ions interacting with GP6 and BGLC after 100 ns.

Results

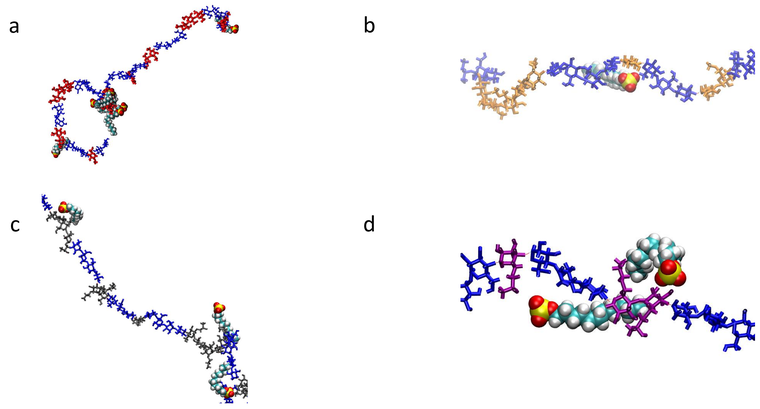
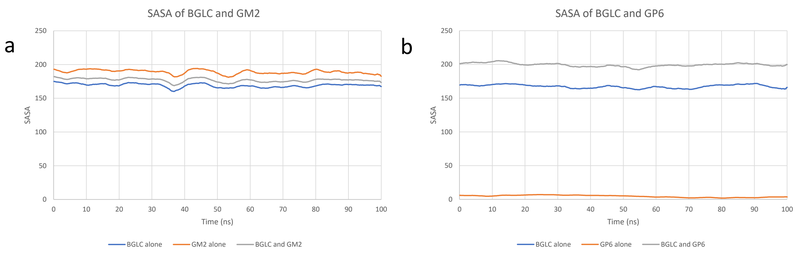


Figure 4. The initial frame of the HPMC/SDS interactions. BGLC is shown as blue and SDS is in VDW form. (a) GM2 shown in red (b) GM6 shown in orange , (c) GP2 shown in gray , (d) GP6 shown in purple



Graph 4. The Solvent Accessible Surface Area (SASA) for (a) GM2 and BGLC after 100 ns, and (b) GM6 and BGLC after 100 ns showing a constant variable.

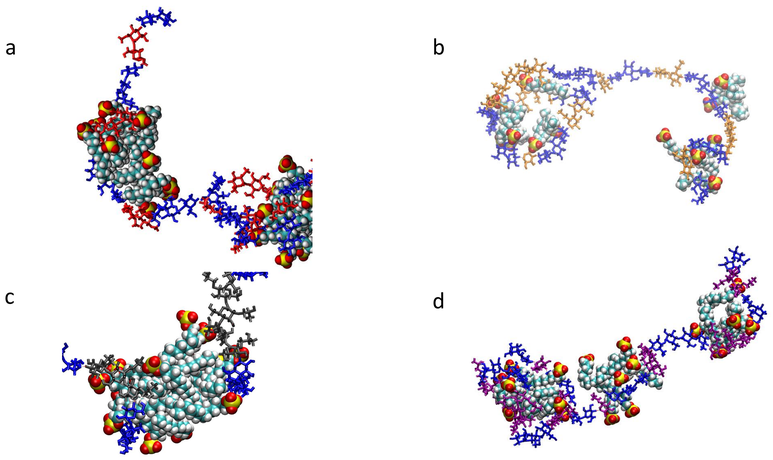


Figure 5. The final frame of the HPMC/SDS interactions. BGLC is shown as blue and SDS is in VDW form. (a) GM2 shown in red (b) GM6 shown in orange , (c) GP2 shown in gray , (d) GP6 shown in purple

Discussion

The HPMC molecule was ran for 100ns and we noticed an interaction with the SDS molecules. However due to the limitations of the water box, the HPMC molecule was sticking out of it. The binding of the surfactants happened sporadically throughout the simulation sometimes coming off as a micelle while at other points attaching onto the HPMC molecule itself. This simulation has been repeated with a larger water box, which will be used on future simulations. The structure of the GP2-HPMC molecule (blue) bound to SDS (atomic colors) after 100ns of simulation is shown in the figure below. The figure shows five mini-micelles of SDS and several free-floating SDS molecules. The HPMC has wrapped itself around two of the SDS micelles.

References

1. Humphrey, W., Dalke, A., Shulten, K. (1996) VMD - Visual Molecular Dynamics. J. Molec. Graphics. 14, 33-38.
2. L. Martínez, R. Andrade, E. G. Birgin, J. M. Martínez. Packmol: A package for building initial configurations for molecular dynamics simulations. Journal of Computational Chemistry, 30(13):2157-2164, 2009.