

Molecular Modeling of Active Pharmaceutical Ingredient in Amorphous Solid Dispersion Formulations

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Abstract

Oral drug delivery is the most popular route for drug administration due to its convenience, patient preference, and low cost. Approximately 60% of commercial small-molecule drug products are taken orally, making 90% of the global pharmaceutical market.¹ Despite the large number in development, one serious challenge is that a majority of the drugs in the pipeline have low solubility and subsequent poor oral bioavailability. Amorphous solid dispersions (ASDs) are a widely employed formulation technique for addressing solubility of drugs and enhancing their oral bioavailability. A recent experimental study showed that the ASD formulation of hydrophobic Probucol drug with copolymers of 2-hydroxypropyl acrylate (HPA) and hexyl acrylate (HA) with 20 mol% HA composition led to enhanced dissolution performance and higher drug release.² To explain the underlying reasons why the composition of HA and HPA monomers affected Probucol release in experiments, in this project we conducted atomistic molecular dynamics simulations. Specifically, these simulations focused on understanding the interactions between Probucol with HA and HPA in the presence of water to see if the experimental results can be explained purely through the effective interactions. We first confirm that our atomistic simulations' radial distribution functions of HA-HA, HPA-HPA, Probucol-Probucol in explicit water agree with relative hydrophobicity of Probucol, HA, and HPA quantified by the logP values. Then, based on our Probucol-Probucol radial distribution functions (RDFs) in the presence of water and with HA and HPA at various compositions, we conclude that HA-HPA composition only minimally affects Probucol-Probucol RDF as compared to the Probucol-Probucol RDF only in water. We also do not see statistically significant differences in Probucol aggregation in the presence of varying composition of HA and HPA. We hypothesize that the effect of the HA-HPA composition on polymer chain aggregation will have a greater impact on Probucol release and recommend that to be investigated in future.

I. Introduction

Oral drug delivery is the most widely used and convenient method of administering drugs, owing to its ease of use, high level of patient compliance, cost-effectiveness, minimal sterility requirements, and flexibility in dosage form design (tablets, capsules, powders, liquids etc.).³ Despite all the advantages of oral drug delivery, a significant challenge in the design of oral drug formulations is their limited oral bioavailability. Oral bioavailability refers to the amount of a drug or other substance that reaches the systemic circulation (the bloodstream) after being administered orally. In other words, it is the fraction of the drug or substance that actually enters the body and is available to produce an effect. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms.⁴ Despite these factors, the solubility/dissolution of the drug in the gastrointestinal environment (mainly water) and its permeation through the gastrointestinal epithelium are two essential parameters governing this process. Therefore, assessing a drug's solubility and permeability *in vitro* is a reliable method for predicting and comprehending its *in vivo* absorption, by the classification of a drug into 4 different classes of the Biopharmaceutics Classification System (BCS).⁵ A substantial fraction of orally administered drugs on the market and in development can be characterized as poorly soluble.⁶ In the case of BCS Class II drugs (low solubility and high permeability), their low bioavailability mainly results from their low solubility in gastric fluids, rather than absorption. Therefore, increasing solubility of BCS Class II drugs can enhance their bioavailability.⁷

The primary reason for the poor aqueous solubility of drugs is typically attributed to highly stable solid lattice arrangements and/or significant hydrophobicity. One of promising solutions for the solubility problem of BCS Class II drugs is Amorphous Solid Dispersion (ASD) formulation.⁸ ASD involves molecular dispersion of an active pharmaceutical ingredient (API) molecule in an amorphous polymer matrix, which creates a unique molecular environment that stabilizes the drug in its amorphous state and inhibits API molecules from forming a stable crystal lattice. API's exhibit higher solubility and increased dissolution rates in the amorphous state compared to crystalline due to greater free energy and improved wet-ability of ASD particles via incorporation of the hydrophilic polymer, respectively.⁹ However, currently only a limited number of polymers have been utilized in commercial ASD dosage forms such as hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS).^{10, 11} The limited variety of polymer designs available has resulted in a scarcity of commercial options for challenging APIs. Therefore, there is a need to better understand the interactions between API, polymer excipient, and water for a rational design of the polymer excipients for certain API's.

Towards achieving rational design of polymer excipient, in a recent experimental study, random copolymer of HPA and HA (**Figure 1a**) with different monomer mol% ranging from 0 mol% HA (100 mol% HPA) to 60 mol% HA (40 mol% HPA) were applied to form ASD formulations with the drug Probucol (**Figure 1b**). Drug release experiments demonstrated that the polymer design with 20 mol% HA (80 mol% HPA) is the optimal composition to achieve highest Probucol drug release (**Figure 1c**).² The driving force behind the 20 mol% HA copolymer performing the best for Probucol drug delivery remains unclear. We hypothesize that a combination of factors may contribute to the experimentally observed Probucol release profile. One potential contributor is the effective molecular-level interactions between the Probucol drug, HA monomers, HPA monomers and water that result in Probucol release. Another potential contributor is the copolymers' chain aggregation, in which the chain aggregation that occurs with 20 mol% HA copolymer is the most favorable for Probucol release. Simulations for predicting copolymer chain aggregation as a function of HA-HPA copolymer composition and the effect of that microphase separated structure on Probucol solubility and release will require coarse-grained modeling and large-scale simulation. Although we expect that both the copolymers' chain aggregation and the interactions between the monomers and Probucol drug will affect the release profile, we restrict this project to understanding only the latter (monomers, Probucol drug, and water interactions) due to time constraints in a one-semester long 3-credit course work. We aim to contribute to understanding why the 20 mol% HA has the highest drug release through development of an all-atom molecular dynamics simulation.

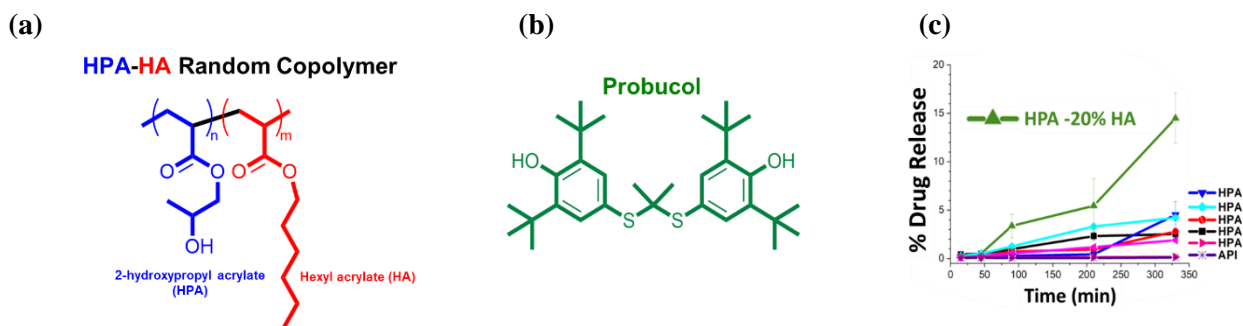


Figure 1. ASD formulation and experimental drug release results. a) Chemical structure of HPA-HA random copolymer, b) chemical structure of Probucol drug, and c) experimentally observed Probucol drug release profiles with varying HA-HPA copolymer composition.²

II. Project Goal

The goal of the project is to develop and optimize a molecular simulation approach that allows us to investigate the molecular-level interactions between the Probucol drug, HA monomer, HPA monomer, and water. Therefore, here we will only focus on studying the effective interactions between four components, Probucol, HA monomer, HPA monomer, and water in the system to see if these can explain why the 80 mol% HPA to 20 mol% HA copolymer composition led to largest Probucol drug release in experiments.²

Our specific objectives are as follows:

1. Determine the relative hydrophobicity/hydrophilicity of HA monomer, HPA monomer, and Probucol drug through their interactions with water. (**Supplemental Figure 1a**) This will validate that our force fields and computational approach are reproducing the same trends in hydrophobicity as the log P values.
2. Investigate how the presence of HA and HPA monomers affects the Probucol drug's interaction with water (**Supplemental Figure 1b**), as we vary the composition of HA and HPA monomers in the system. Specifically, we want to determine to what extent the amount of HA monomer and HPA monomer in our system affects the interaction between the Probucol drug and water. This allows us to conclude if effective interactions play a role in drawing Probucol from the copolymer film to the surrounding water to allow for Probucol release.
3. Identify any factors besides interactions that may also impact Probucol drug release from the HA:HPA systems, such as copolymer composition.

Through successful completion of the above objectives, we will gain insight into the molecular-level interactions between the components of the copolymer system and water, and to potential underlying mechanisms that influence Probucol drug release from HA:HPA random copolymers. Our work focuses on atomistic-level Probucol-monomer interactions and not Probucol-polymer interactions; the latter could certainly be a contributing factor to Probucol drug release that we are not capturing.

III. Computational Approach

Model: There are two main types of molecular dynamics modeling length scales: atomistic and coarse-grained. Atomistic simulations provide a high level of detail for specific atom and monomer-level interactions; however, they require a lot of computational time and resources. Coarse-grained (CG) models are more computationally efficient and are better for modeling macromolecular structure and dynamics by lowering the degrees of resolution.¹² Typically, coarse-grained models use implicit water models, or group four water molecules as a single bead or use single beads to represent monomers or collection of monomers in polymers.¹³ As the problem at hand is related to solubility and specific monomer-water interactions, we chose to take the all-atomistic approach. Using all-atomistic models with explicit water, we can study the atomistic interactions between Probucol and monomers, Probucol with itself, and Probucol with water.

Simulation engine and force field: We perform all simulations using GROMACS version 2018.1 with the Optimized Potentials for Liquid Simulations All-Atom (OPLS-AA) force field.¹⁴ GROMACS is the selected simulation engine because it is open-source, capable of running all-atom models and has been used in other published studies examining Probucol-polymer interactions.^{15, 16} The OPLS-AA force field was selected for this study because it has been shown to accurately predict properties of similarly structured Probucol-polymer systems and reproduce experimental data.^{17, 18}

System initialization: The contents of the various systems modeled can be seen in **Appendix Table 1**. The initial structure files for hexyl acrylate (HA), hydroxypropyl acrylate (HPA), and Probucol were obtained as .mol files from the Chemical Book Database.¹⁹ We converted the formatting of each .mol structure file to a .pdb file format to be read by the simulation engine. Each system consisted of a 15 x 15 x 15 nm³ cubic box and was solvated with TIP3P water molecules using the ‘gmx solvate’ command, giving an approximately equivalent density for all systems studied. For the water molecules in the system, we used the TIP3P rigid 3-point water model, as it is computationally efficient and is parameterized for OPLS.¹⁸ This water model has been shown to be less computationally intensive, allows fast diffusion, and works well with small molecule systems.^{20, 21}

Energy Minimization: In the initial energy minimization step, we utilized the steepest descent minimization algorithm, first published by Peter Debye in 1909, but dating back to a method published by Augustin-Louis Cauchy in 1847, differently named the ‘gradient descent method’.²²⁻²⁴ The steepest descent minimization algorithm finds energy minima by computing the maximum scalar force applied to each atom. The algorithm stops when either a specified number of force calculations have been performed or when the maximum of the absolute values of the force components is smaller than a specified value.¹⁴ In this work we specified in our minimization file for the minimization to stop when maximum force of each atom in our system was less than 100 kJ/mol/nm. During minimization, nonbonded interactions were cut off at 1.0 nm and long-range electrostatics were included utilizing the Particle Mesh Ewald (PME) method.²⁵ All bonds are constrained with the holonomic constraint algorithm, LINCS.²⁶ In the LINCS algorithm, atoms are allowed to move through equilibration steps without restraints, but after each update the bond lengths are reset to their expected values.²⁶ Following a successful minimization, we plotted the potential energy of the system to confirm that an energy minimum had been reached using the “gmx energy” command.

NVT Equilibration Protocol: Next, we performed an NVT equilibration (NVT stands for constant Number of particles, Volume and Temperature) at 300 K for 20 ps. Temperature of the system was coupled using the velocity rescaling thermostat.^{27, 28} The NVT equilibration step stabilizes the temperature of the system. Using the “gmx energy” command, we plot the pressure over each time step to ensure the system has been adequately equilibrated.

NPT Equilibration Protocol: Following the NVT equilibration, an NPT equilibration (NPT stands for constant Number of particles, Pressure and Temperature) was performed, using the LINCS algorithm to constrain bonds involving hydrogen atoms. This is to reduce the number of degrees of freedom during the simulation and allow for large time steps. The NPT equilibration step, also known as the isothermal-isobaric ensemble, stabilizes the pressure and the density of the system prior to data collection and most closely resembles experimental conditions. During NPT equilibration, the density of our system increased from about 980 kg/m³ to the approximate expected density of a dilute aqueous solution, about 995 kg/m³. After the initial density increase that lasted approximately 25 ps of NPT equilibration, the density reached a plateau and exhibited only minimal fluctuations for the remaining 370 ps of equilibration time, indicating that the system had reached an adequate equilibration. Pressure of 1.0 atm utilizing the Parrinello-Rahman coupling method and temperatures of the systems for the NPT equilibrations remained constant at 300 K utilizing the velocity rescaling thermostat.^{28, 29}

Radial distribution function (RDF) describes the relative likelihood of finding a pair of atoms/beads/molecules at a specific distance r as compared to infinite distance. It is calculated by determining the number density of the atom/bead/molecule pair at distance r , $\rho(r)$, and dividing by the bulk density of particle pairs, ρ_{bulk} . (**Supplemental Figure 2**). RDFs were calculated between monomer-monomer, Probucol-Probucol, monomer-Probucol, monomer-water, and Probucol-water for analysis. In each case, a central atom was selected for each system component to avoid potential intramolecular peaks. RDFs were plotted by averaging the last 2400 ps of simulation, considering one configuration every 120 ps (20 configurations in total).

To perform these calculations, we used an in-house python script that is published in the open-source NRT Merck-2023 GitHub under the file name RDF.py. The height and width of RDF peaks can provide insight to the relative favorability of interactions between the pair of atoms/beads/molecules in that system. For our system, the interactions of interest include: 1. monomers/API–self, 2. monomer/API–water, 3. API–water (in the presence of monomer), and 4. Probucol–water for varying number of HA to HPA monomers.

All simulations were conducted using ACCESS resources obtained through a research proposal led by Prof. Arthi Jayaraman (MCB100140). Preliminary simulations and analyses calculations were conducted on Prof. Arthi Jayaraman's research lab computers (<https://sites.udel.edu/arthij/>).

**All related files including customized topology, minimization/equilibration input files and analysis Python scripts will be published to the NRT GitHub, link: <https://github.com/NRT-hackathon/2023-Merck>*

IV. Results

First, to validate our computational approach we calculated HA-HA, HPA-HPA, and Probucol-Probucol RDFs as well as HA-water, HPA-water, and Probucol-water RDFs. (**Figure 2a/2b**) Using these RDFs, we determined the relative hydrophobicity ranking of these three chemistries and checked it against known logP values. The results indicated that HPA had the most interactions with water and Probucol interacted the least with water, comparatively. The HPA-HPA RDFs indicated that HPA had the lowest aggregation with itself in the presence of water; HA monomers that had more aggregation compared to HPA. Probucol-Probucol aggregation was the highest and illustrated roughly a 3-fold greater $g(r)$ magnitude peak compared to HA. A visual assessment using VMD³⁰ (**Figure 2c**) was also performed to confirm the above quantitative trends. All of the results in Figure 2 confirm that the ranking of hydrophobicity is in the order of Probucol, HA, and then HPA; this ranking matches the experimental ranking of hydrophobicity represented by logP values (10.57, 3.14, and 0.64, respectively)².

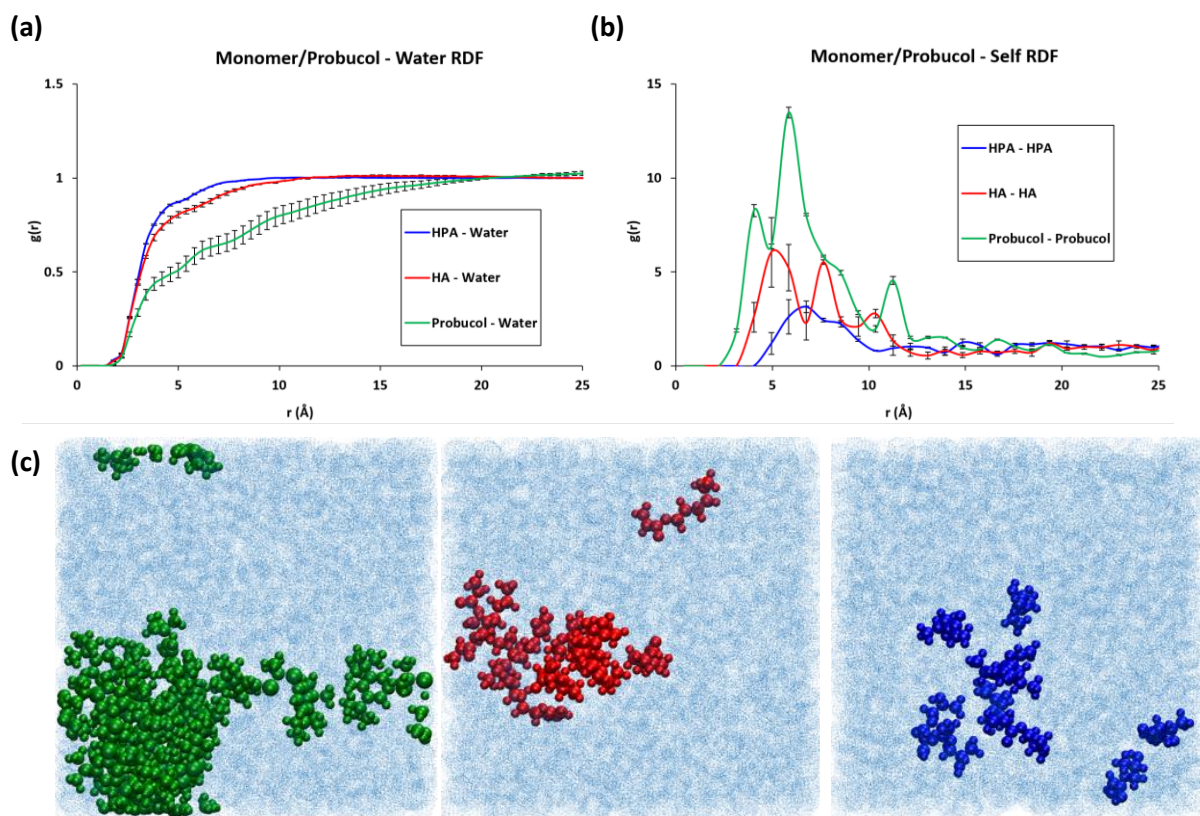


Figure 2. RDF plots. a) Monomer/Drug – Water, b) Monomer/Drug – Monomer/Drug, c) VMD simulations in water of Probucol-Probucol (green), HA-HA (red), and HPA-HPA (blue). The number of non-water molecules in the system was 40 for each condition. Data is expressed as the mean of 3 trials with error bars representing standard deviation³⁰.

After confirming relative hydrophobicity trend with that with known logP values, we next evaluated the effect of varying number of HA to HPA monomers on the Probucol-Water and Probucol-Probucol interactions. The RDFs of Probucol-Water and Probucol-Probucol were assessed with varying HA monomer composition from 0-60 mol% (**Figure 3**). HA monomer composition being X% means that there were number of HA monomers divided by total (HA + HPA) monomers $\times 100$ is X. RDFs of the Probucol-water at varying HA monomer composition shows statistically insignificant differences (**Figure 3a**). The Probucol-Probucol RDF also shows similar aggregation of Probucol with varying HA monomer composition (**Figure 3b**). These interactions were also assessed visually in VMD to validate the quantitative results and there were no apparent differences between groups in regard to aggregation (**Table 1**).

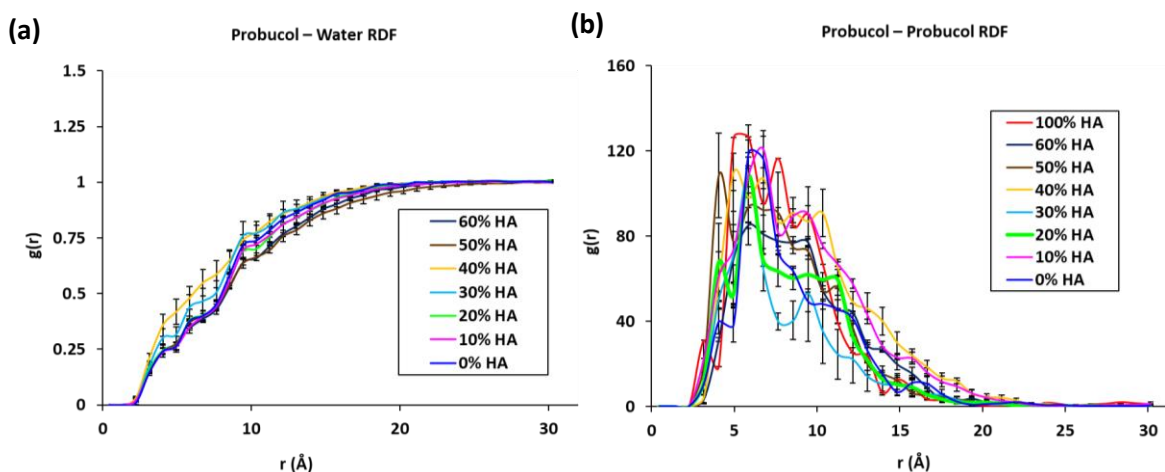


Figure 3. RDF plots. a) Probuco – water, b) Probuco – Probuco. The number of non-water molecules in the system was 40 for each condition. Data is expressed as the mean of 3 trials with error bars representing standard deviation.

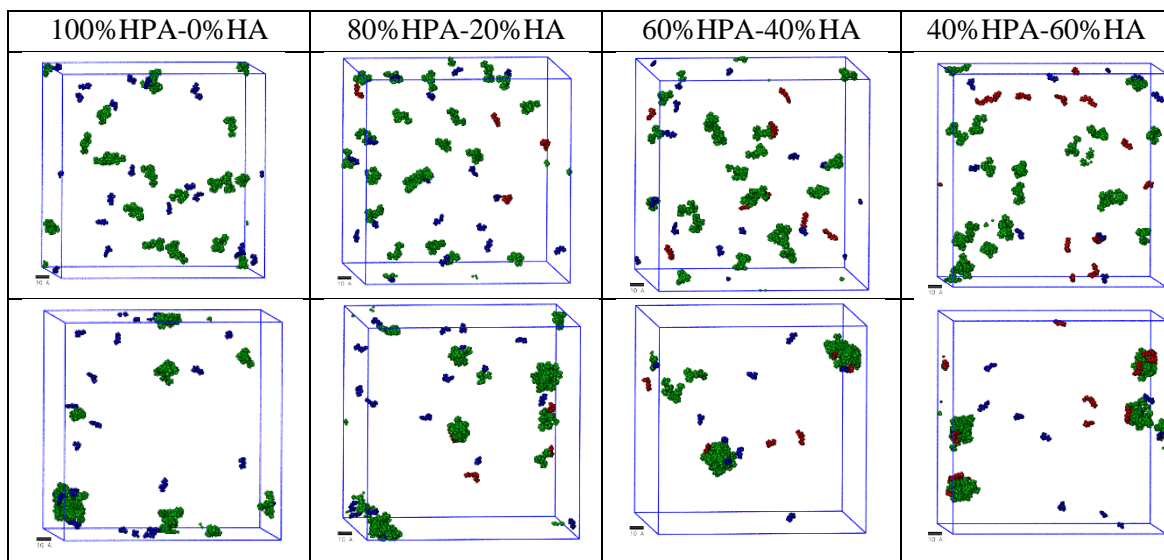


Table 1. Representative configurations. i) Starting configurations and ii) ending configurations for increasing (0-60%) HA monomer composition with Probuco shown in green, HA monomer in red and HPA monomer in blue. Each simulation had a total number of 40 non-solvent molecules (HA, HPA, and Probuco) and between 109,800-109,860 water molecules (not represented to enhance visual clarity).

V. Conclusion

Our computational study examines the interactions of monomers, Probucol drug molecules, and water molecules to give insights into how/if interaction could explain the experimentally observed Probucol release from a copolymer film. Specifically, the goal of this project was to determine why the HPA-20%HA random copolymer formulation has the greatest Probucol release.

For this system, drug release can be attributed to several factors, including the relative hydrophobicity of system components, the effective interactions between system components, and the copolymers' chain aggregation. In this study, we examined the relative hydrophobicity and effective interactions in order to gain insight on how system components behave on a molecular-level and to identify the underlying mechanisms that influence drug release. Although certainly a contributing factor to drug release, polymer-level contributions were not modeled in this system due to time constraints dictated by this course.

We employed an all-atomistic model for all system constituents using OPLS and conducted MD simulations to investigate the relative hydrophobicity and effective interactions between Probucol, monomers, and water through GROMACS. The radial distribution function analyses were conducted to give insights regarding relative hydrophobicity and effective interactions between components.

We validated our computational approach by showing agreement in relative hydrophobicity of HA, HPA, and Probucol from HA-HA, HPA-HPA, and Probucol-Probucol RDFs and their RDFs with water and the known hydrophobicity ranking of HA, HPA, and Probucol from their logP values. Then we explored the effect of varying the number of HA to HPA monomers on the Probucol-water and Probucol-Probucol interactions to determine how effective interactions play a role in drug release. We found that there were no statistically significant differences in Probucol-water and Probucol-Probucol RDFs for varying HA monomer: HPA monomer ratio. The key takeaway from this project is that it is likely that the change in copolymer chain aggregation with varying HA: HPA copolymer composition plays a greater role in deciding Probucol drug release.

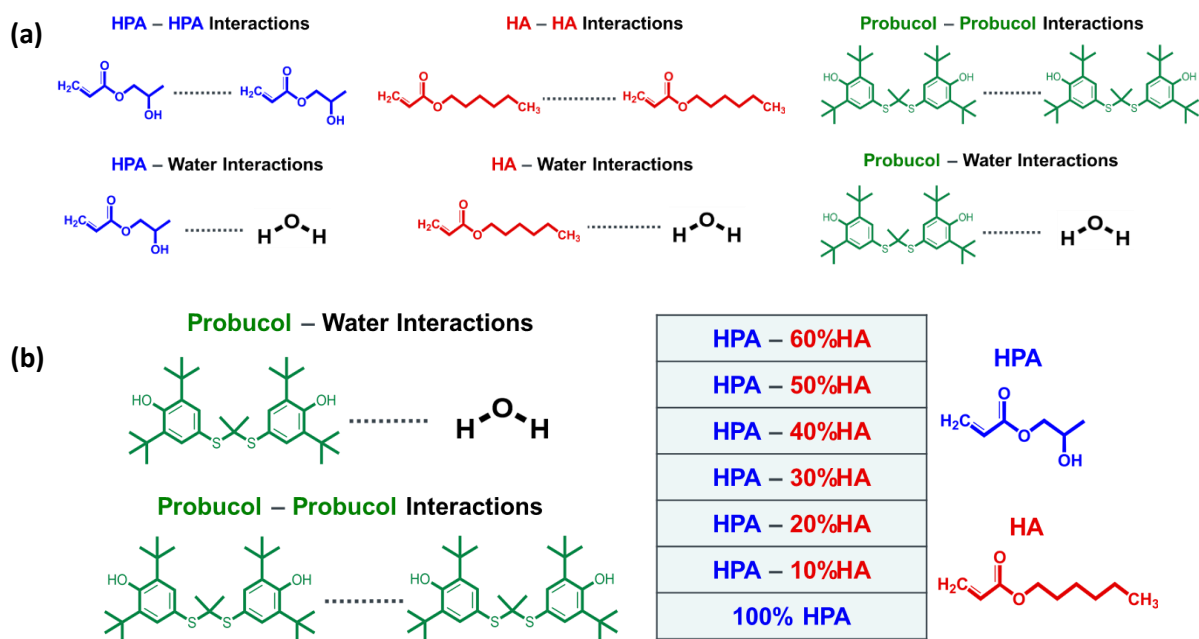
This study is foundational as it explains how varying concentrations of HA and HPA monomers interact with Probucol and water before examining the HA-HPA copolymer induced interactions. The HA-HA, HPA-HPA and Probucol-Probucol RDFs in water can serve as a guide to their relative interactions in implicit water for use in coarse grained copolymer simulations with Probucol at varying HA-HPA copolymer composition. These coarse-grained simulations can then describe if and how the copolymer chain aggregation, and its variations with HA-HPA copolymer composition, affect Probucol drug release.

GitHub Repository Link: <https://github.com/NRT-hackathon/2023-Merck>

Appendix

- Supplementary information regarding atom identification and in-depth GROMACS simulation protocol may be located in the NRT GitHub repository under the name “Supplement.pdf”
- Energy minimization parameter file may be located in the NRT GitHub repository under the name “minim.mdp”
- NVT (Number of Particles, Volume and Temperature) Equilibration input scripts may be located in the NRT GitHub repository under the name “NVT.mdp.”
- NPT (Number of Particles, Pressure and Temperature) Equilibration files input scripts may be located in the NRT GitHub repository under the name “NPT.mdp”
- RDF analysis for multiple trials with standard deviation may be located in the NRT GitHub repository under the name “RDF.py”

S1)



Supplemental Figure 1. Interactions of Interest. a) Monomer-Monomer and Monomer-Water interactions, b) Drug-Water and Drug-Drug interactions when varying monomer concentration.

S2)

$$g(r) = \frac{\langle \rho(r) \rangle}{\rho}$$

Supplemental Figure 2. RDF formula utilized for calculations.

S3)

Determining the Number of Water Molecules Replaced by 10 Hexyl Acrylate (HA) Monomers to Maintain Effective Crowding:

Simulation box volume = 1000 nm^3

Volume of a single HA monomer:

Assuming the density of HPA is 1.1 g/cm^3 , and the molar mass of HPA = 142.17 g/mol .

$$\text{Mass of a single HPA monomer: } \text{Mass} = \frac{\text{molar mass}}{\text{Avogadro Number}} = 142.17 \text{ g/mol} / 6.022 \times 10^{23} \text{ mol}^{-1} \\ = 2.364 \times 10^{-22} \text{ g}$$

Now, volume of a single HPA monomer: $\text{Density} = \frac{\text{Mass}}{\text{Volume}}$

$$\text{Volume} = 2.364 \times 10^{-22} \text{ g} / (1.1 \text{ g/cm}^3 \times 1.0 \times 10^{21} \text{ nm}^3/\text{cm}^3) = 2.13 \times 10^{-3} \text{ nm}^3$$

To bring in 10 HA monomers, we need to remove the equivalent volume of water molecules from the simulation box. The volume occupied by 10 HA monomers is:

$$\text{Volume of 10 HA monomers} = 10 \times \text{volume of a single HA monomer} \\ = 10 \times 2.13 \times 10^{-3} \text{ nm}^3 = 2.13 \times 10^{-2} \text{ nm}^3$$

So we need to remove $2.13 \times 10^{-2} \text{ nm}^3$ of water molecules from the simulation box and replace it with the same volume of HA monomers.

$$\text{Number of water molecules needed to be removed} = \frac{\text{Vol to Remove}}{\text{Vol of Single Water}} \\ = 2.13 \times 10^{-2} \text{ nm}^3 / 0.03 \text{ nm}^3 = 7.1 \times 10^{-1} = 0.71 \text{ (rounded to two decimal places)}$$

Therefore, we need to remove 0.71 water molecules from the simulation box and replace them with 10 HA monomers to keep the overall crowding constant.

S4)

Determining number of water molecules needed to allow one Probucol molecule to “dissolve”:

Probucol water solubility $\sim 5 \text{ ng/mL}$ in water³¹

Probucol M.W.= 516.842 g/mol ,

H₂O M.W.= 18.01528 g/mol $300 \text{ K}=26.85 \text{ }^\circ\text{C}$,

Density of water= 0.996567 g/cm^3 @ $26.8 \text{ }^\circ\text{C}$,

$$1\text{mL of water} = (0.996567/18.01528 \text{ mol}) * 6.02214076 \times 10^{23} = 3.33132 \times 10^{22} \text{ water molecules}$$

$$5\text{ng of Probucol} = (5 \times 10^{-9}/516.842 \text{ mol}) * 6.02214076 \times 10^{23} = 5.82590 \times 10^{12} \text{ Probucol molecules}$$

Therefore, one Probucol molecule needs 5.71811×10^9 water molecules to dissolve.

S5) System Components

System Index	# HPA	#HA	#PBL	Box Size (nm ³)	%HPA-%HA
1	18	2	20	3375	90%HPA-10%HA
2	18	2	20	3375	90%HPA-10%HA
3	18	2	20	3375	90%HPA-10%HA
4	16	4	20	3375	80%HPA-20%HA
5	16	4	20	3375	80%HPA-20%HA
6	16	4	20	3375	80%HPA-20%HA
7	14	6	20	3375	70%HPA-30%HA
8	14	6	20	3375	70%HPA-30%HA
9	14	6	20	3375	70%HPA-30%HA
10	12	8	20	3375	60%HPA-40%HA
11	12	8	20	3375	60%HPA-40%HA
12	12	8	20	3375	60%HPA-40%HA
13	10	10	20	3375	50%HPA-50%HA
14	10	10	20	3375	50%HPA-50%HA
15	10	10	20	3375	50%HPA-50%HA
16	8	12	20	3375	40%HPA-60%HA
17	8	12	20	3375	40%HPA-60%HA
18	8	12	20	3375	40%HPA-60%HA

S6) LogP values for system components

2-Hydroxypropyl Acrylate (HPA)	0.64
Hexyl Acrylate (HA)	3.14
Probucol Drug	10.57

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