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## **ACKNOWLEDGEMENT**

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## **SUMMARY**

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# 1 INTRODUCTION

In crystalline forms, most of the newly discovered active pharmaceutical ingredients (APIs) are poorly soluble in water, which limits their bioavailability, dissolution, and then their distribution through the organism. This fact limits potential wider use of numerous API as a solid drug in medical treatment. Today, combinatorial chemistry techniques and high-throughput screening have led to a sharp increase in the quantity of proposed nonsoluble API molecules, so the oral administration of poorly soluble drugs has become the biggest challenge for formulation scientists in the pharmaceutical industry. [1] There are different strategies to overcome this issue, such as cocrystal formation [2], conversion of an API to its salt [3] or using dispersions of API in various matrices. [4]

In 1961, Sekiguchi and Obi provided the earliest account of the so-called first-generation solid dispersion, when they discovered that the creation of eutectic mixtures enhances the rate of drug release and bioavailability. First-generation solid dispersions were built from crystalline carriers such as urea or sugars, forming crystalline solid dispersions. The second generation of solid dispersions is based on replacing crystalline carriers by amorphous carriers such as polymers, forming an amorphous product in which API is dissolved. There exist also a third generation of solid dispersions using a surfactant carrier or a combination of amorphous polymers and surfactants. [5]

The aim of researchers is to overcome the poor solubility of APIs by using amorphous solid phases of APIs and to avert the rearrangement of their molecules into a crystal lattice. However, crystalline forms of APIs are advantageous because of their better stability during long-term storage and more reliable predictions of material properties at the molecular level under defined conditions. [6] The better solubility of APIs in amorphous forms comes from a higher Gibbs energy of the amorphous form compared to the crystalline forms. During processing, storage, and after contact with water or humidity, the thermodynamically metastable amorphous forms tend to crystallise. Solid mixtures of API and excipients (e.g. polymeric excipients) create amorphous solid dispersions (ASD) and offer a way to inhibit crystallisation of the API before and after oral administration of the dose. [7]

The creation of an amorphous dispersion of an API can generally have a twofold effect on the rate of solid-state crystallisation, affecting both thermodynamic and kinetic aspects. Thermodynamically, it reduces the Gibbs energy of the dispersion due to strong beneficial intermolecular interactions between API and its excipient, as well as it increases kinetic barriers to recrystallisation. On the atomic scale of

individual interactions stabilizing such solid dispersions, hydrogen bonding makes the most significant contribution. [8]

Other suitable biocompatible and biodegradable polymers for ASD could be polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP). [9]

## 1.1 Studied compounds

### 1.1.1 Polylactic acid

Polylactic acid (PLA) was chosen as a biocompatible polymer excipient. PLA is a biodegradable polymer formed by the polymerisation of lactic acid. The formula of the PLA monomer unit is shown in Figure 1. In this work, two condensed units of D-PLA were considered as the simplest building block for creating all of the other longer polymer chains. Polymer samples of a length up to 100 dimer units were created by replicating these dimer units. The molar weight of our dimer unit considered in the investigation is  $M_w = 162.14 \text{ g mol}^{-1}$ , which means that the longest polymer chain used in the simulations has a molar weight equal to  $M_w = 14\,431 \text{ g mol}^{-1}$

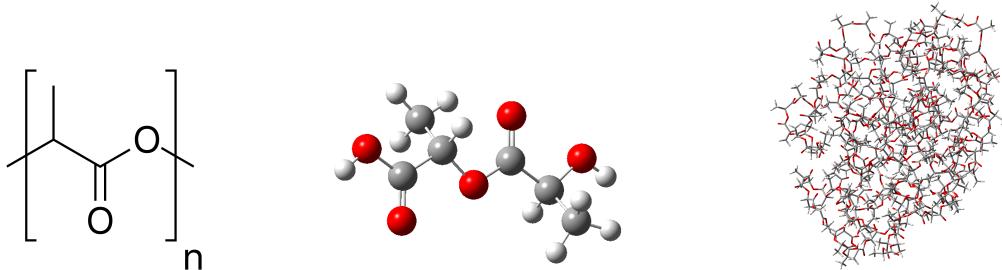


Figure 1: PLA formula on the left, PLA dimer block representing the chain unit used to build up polymer chain in the middle and a folded PLA chain containing 100 dimer block used to create mixtures with APIs on the right.

### 1.1.2 Active pharmaceutical ingredients

The first selected API is **ibuprofen**, systematically 2-(4-Isobutylphenyl)propanoic acid ( $C_{13}H_{18}O_2$ ) as an example of a widely used analgesic, antipyretic, anti-inflammatory drug. The racemic mixture of ibuprofen is commonly used in medical treatment. The S-enantiomer has a stronger pharmaceutical activity than the R-enantiomer, which is metabolically transformed to S-form in the organism. [10] In this work the S-form, which is visualised in Figure 2, is used. The molar weight of ibuprofen is  $M_w = 206.28 \text{ g mol}^{-1}$  and the melting temperature of the enantiopure crystal is 324.4 K. [11]

The second selected API is **naproxen**, systematically 2-(6-Methoxynaphthalen-2-yl)propanoic acid ( $C_{14}H_{14}O_3$ ), a non-steroidal anti-inflammatory drug, used as a

painkiller. Naproxen contains three oxygen atoms (one carboxyl group and one ether bond), the structure is shown in Figure 2 in the upper right corner. On the basis of its structure, naproxen can donate one hydrogen bond and accept up to six hydrogen bonds, steric factors limits the actual coordination. Naproxen is a white crystalline powder, with a molar weight of  $M_w = 230.263 \text{ g mol}^{-1}$  and melting temperature is 429.3 K. [11]

**Carbamazepine**, alternatively 5-Carbamoyl-5H-dibenzo(b,f)azepine ( $C_{15}H_{12}N_2O$ ) is a representative anticonvulsant, which is used for the treatment of seizures and neuropathic pain. Carbamazepine contains two nitrogen atoms (amide group) and one oxygen in the carbonyl group; its structure is shown in Figure 2 on the left side. According to its structure, carbamazepine can theoretically accept up to two hydrogen bonds and donate up to four hydrogen bonds. Carbamazepine is a white crystalline powder, with a molar weight of  $M_w = 236.273 \text{ g mol}^{-1}$  and melting temperature of 463.6 K. [11]

**Indomethacin**, 2-1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-ylacetic acid ( $C_{19}H_{16}ClNO_4$ ), whith structure depicted in Figure 2, is used in the treatment of musculoskeletal and joint disorders. The molar weight is  $M_w = 357.8 \text{ g mol}^{-1}$  and the melting temperature is 433.3 K. [11]

The last selected API was **sulfathiazole** with systematic name 4-amino-N-thiazol-2-ylidenebenzene-sulfonamide as a representative antibiotic drug from the sulfonamides group, which is used in the treatment of pyogenic cutaneous infections. Sulfathiazole is a white crystalline powder, with a molar weight ( $M_w$ ) = $255.3 \text{ gmol}^{-1}$ , which is highly polymorphic, five polymorphs have been discovered so far [6]. All known polymorphs of sulfathiazole crystallise in the  $P2_1/c$  space group, but there are differences in intermolecular bonding and structural properties [12]. The II polymorph structure, shown in Figure 3, is used in this work. There are four molecules of sulfathiazole in the crystal monoclinic unit cell.

## 1.2 Objective

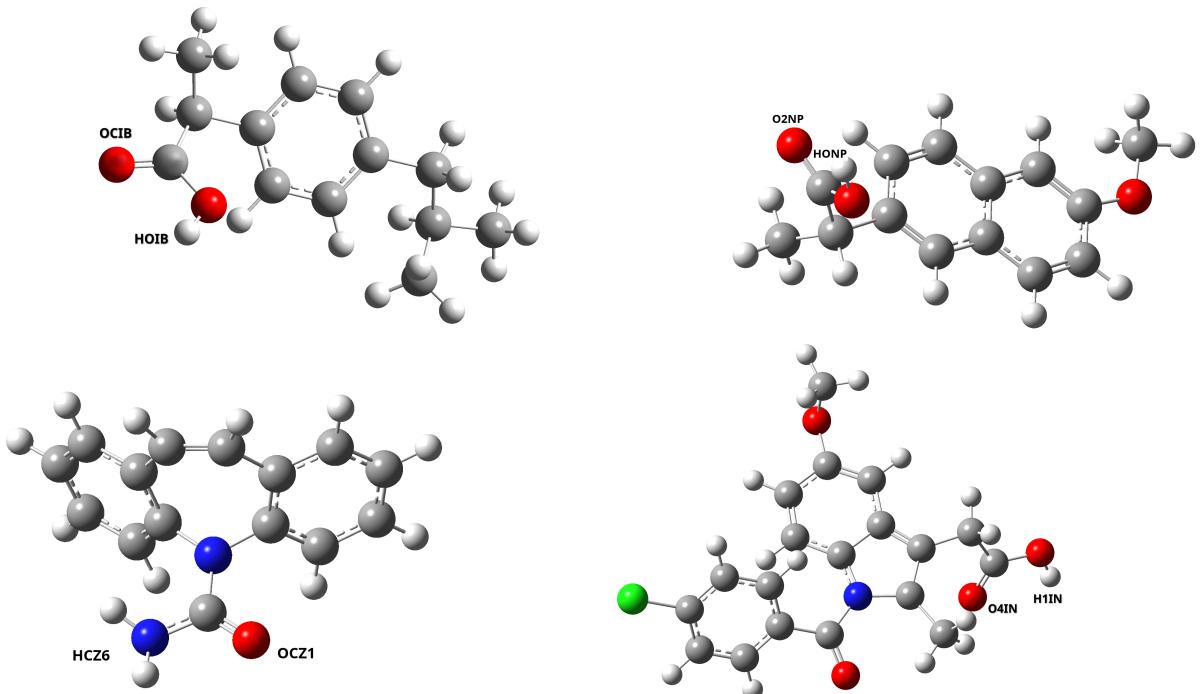


Figure 2: Molecular structures of ibuprofen (**top left**), naproxen (**top right**), carbamazepine (**bottom left**) and indomethacin (**bottom right**). Atom types contributing most to the hydrogen bonding are tagged for each molecule.

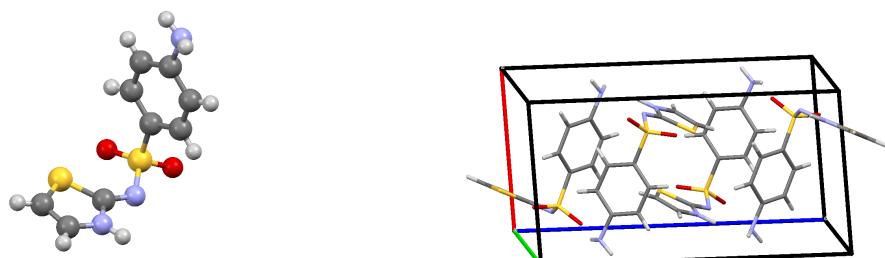


Figure 3: Sulfathiazole - molecular structure on the left and a unit cell of its II polymorph on the right.

## 2 THEORETICAL PART

In order to convert a real system consisting of individual molecules into a form that can be understood by a computer software, we must define individual parameters that are essential for describing mutual interactions of atoms. When describing real systems, it is usually necessary to consider a certain degree of approximation due to the possible computational complexity. In computational chemistry methods, we often encounter the so-called Born-Oppenheimer approximation, which is based on the decoupling of the motion of nuclei and electrons. The basis of the approximation is the orders-of-magnitude difference in mass between the electron and the nucleus. The latter thus move very slowly relative to the electrons and can thus be considered as a fixed point charge. This allows us to calculate the energy of a molecule as a function of the positions of the nuclei, in quantum chemistry we talk about the so-called Potential Energy Surface (PES), which is a function of  $3N$  coordinates, where  $N$  is the number of nuclei. [13]

For small systems it is possible to calculate the PES based on quantum chemistry methods using reasonable resources, for very large systems this is not yet realistic. We therefore introduce a classical-mechanics set of analytic functions, yet empiric parameters called the Force Field (FF), which enable to evaluate the energy of simulated systems depending on the positions of the nuclei. Methods based on the use of such Force Fields are called molecular mechanics, which are applied especially when quantum phenomena are not of great importance and we can use classical mechanics approach or big amorphous systems where quantum-based calculations would be extremely expensive and resource taking. [14]

### 2.1 Force fields

The total energy calculated using the force field can be broken down into two contributions, a binding and a non-binding term, which are further expanded in Equations 2.1 and 2.2.

$$E_{\text{bonded}} = E_{\text{bond}} + E_{\text{angle}} + E_{\text{torsion}} \quad (2.1)$$

$$E_{\text{nonbonded}} = E_{\text{electrostatic}} + E_{\text{Van der Walls}} \quad (2.2)$$

By the level of functional description (number of terms) of the interactions in the

force field, we distinguish force fields of three classes. Class 1 force fields contain the 5 terms mentioned in the two equations above (bond, angle, torsion, Lennard-Jones and electrostatic), examples of such FF are the DREIDING, AMBER [15], GAFF and OPLS. In addition, class 2 force fields include bond-bond and bond-angle coupling terms, anharmonic terms simultaneously with all class 1 terms, examples of such fields are PCFF or ReaxFF. The third class includes fluctuations of charge distribution in time (charge polarization effect), and they are called polarizable FF. [16]

During the parameterization of force fields (FF), we start from the assumption of transferability, similar chemical groups of different molecules interact in the same way. When constructing a force field for large molecules, we can use parameters obtained from data for small molecules, which are much more easily graspable and contain the same functional groups. [14] In model development, our aim is to achieve the most universal description of the system while still closely corresponding to its actual state. This can be facilitated by employing higher-order terms; however, incorporating anharmonic and cross terms introduces the need for a greater amount of FF parameters. We strive to avoid situations where we employ an overly adapted and detailed model that merely reproduces inserted information without providing any predictive capabilities. [16]

According to the level of parameterization, there are 3 basic types of force fields. In the first case, where the parameters are determined for each individual atom in the system, including hydrogens, we speak of an all-atom force field. A united atom force field is one where we parameterize the individual functional groups (interaction centers), such an interaction center could be for example a methyl group. The third type of force field is coarse grained, used mainly for protein and polymer simulations, offering higher computational efficiency for long simulations of large molecules by grouping them into "superatoms". [17]

### 2.1.1 OPLS force field

Optimized Potential for Liquid Simulations (OPLS) force field was developed by William L. Jorgensen [18] at Purdue University and later at Yale University based on previously released Assisted Model Building and Energy Refinement (AMBER) force field developed by Peter Kollman's group. [19] The OPLS force field consists of following terms written in Equation 2.3.

$$\begin{aligned}
U_{\text{OPLS}} = & \sum_{\text{bonds}} \frac{1}{2} k_b (r - r_0)^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 \\
& + \sum_{\text{torsions}} \left( \frac{V_1}{2} [1 + \cos(\phi)] + \frac{V_2}{2} [1 - \cos(2\phi)] + \frac{V_3}{2} [1 + \cos(3\phi)] + \frac{V_4}{2} [1 - \cos(4\phi)] \right) \\
& + \sum_{i=1}^{N-1} \sum_{j=i+1}^N \left\{ 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j e^2}{r_{ij}} \right\} f_{ij}
\end{aligned} \tag{2.3}$$

$i$  and  $j$  denote different atom types,  $N$  is the total number of atom pairs,  $\epsilon_{ij}$ ,  $\sigma_{ij}$  are LJ parameters,  $r_{ij}$  is the distance between atoms  $i$  and  $j$ , and  $f_{ij}$  is scaling factor equals 0.5 for 1-4 interactions ( $i, j=1,4$ ) and 1 otherwise.

**Bonds and angles** are described as harmonic oscillators in OPLS FF. The equilibrium parameters are obtained by structural methods, such as x-ray diffraction NMR experiments. The values for force constants are then fitted to experimental data taken from vibrational spectroscopy. In Figure 4 is the visualization of the constants.

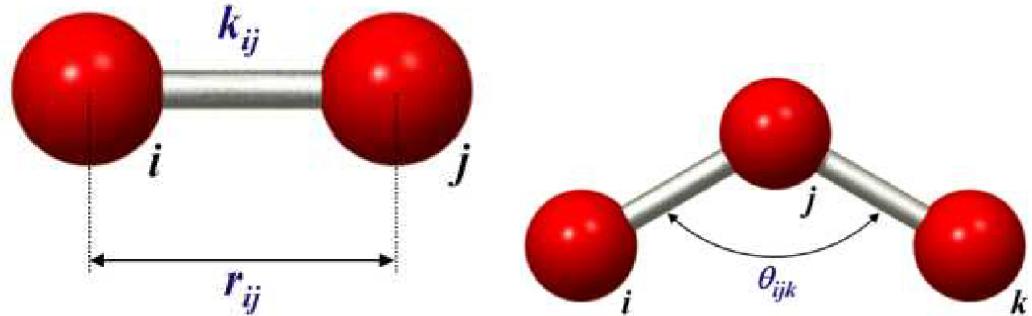


Figure 4: caption

Proper **dihedral angle**  $\phi$  between atoms  $i,j,k,l$  is represented in Figure 5. The torsional energy is described as a cosine expansion, where the first term corresponds to the rotation periodic after  $360^\circ$ , second term by  $180^\circ$ , the third term by  $120^\circ$  and the fourth term by  $90^\circ$ . Each of this term has the  $V_n$  constant, representing the barrier for rotation along the proper dihedral angle, which is dependent both on the torsional energy and non-bonded forces. Different approaches could be chosen, one of them is obtaining the parameters by QM calculations. [20] We first optimize the molecular geometry using QM methods and then we run scanning of dihedral angle of interest. At each step, we optimize geometry and calculate the change in

potential energy. Then we compute potential energy of each optimized geometry using MD with dihedral parameters set to zero. Then we can fit the parameters by subtracting the results of MD from QM, this corresponds exactly to the influence of dihedrals. To do this procedure first all the other FF parameters should be known.

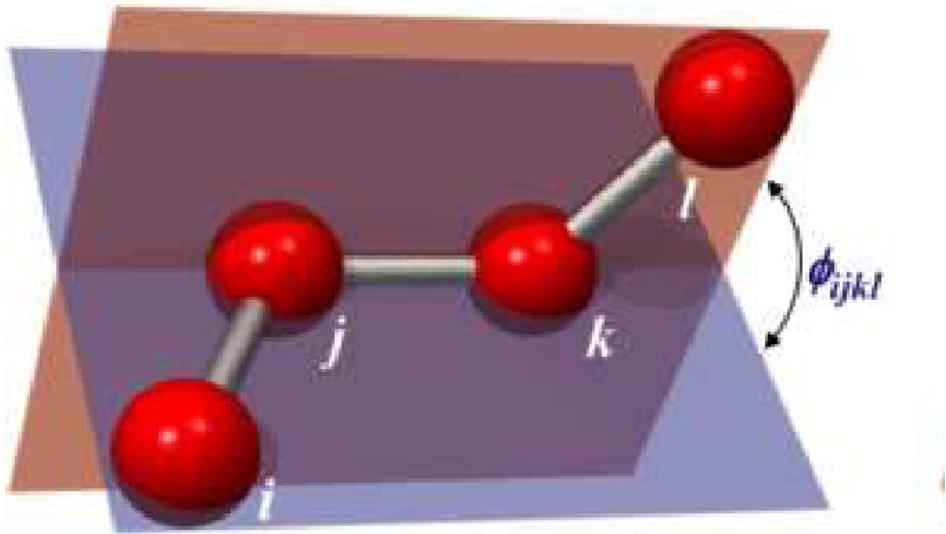


Figure 5: caption

**Charges** parametrization is also done by ab initio methods. When we are using the classical FF, the charges used to calculate the Coulomb potential remains the same during the simulations. Due to that, it is crucial to obtain the charges from equilibrium state of the molecules in order to avoid any errors from having the charges taken from structures with higher energy. When obtaining the charges, the first step is to optimize the geometry using the appropriate level of theory, meaning the basis set to be better or equal to 6-31G. Commonly used method to achieve the charges is CHELPG (CHarges from ELectrostatic Potentials using a Grid based method) [21], based on adjusting the partial charges at the centers of the nuclei in order to get the best representation of the electrostatic potential given by the wave functions. Calculation of the charges are often done using higher-level methods and basis sets such as B3LYP/cc-pVTZ or HF/6-31G\*\*.

**Van der Waals** forces are most often represented by the Lennard-Jones (LJ) potential. The functional form with the illustration is in Figure 6. Lennard-Jones potential is a combination of two terms, repulsive term describes the Pauli repulsion at short distances and the attractive term describes the London dispersion

force. The  $\epsilon$  values are adjusted to experimental values of heats of vaporization and  $\sigma$  parameters are adjusted to experimental densities and structural data.

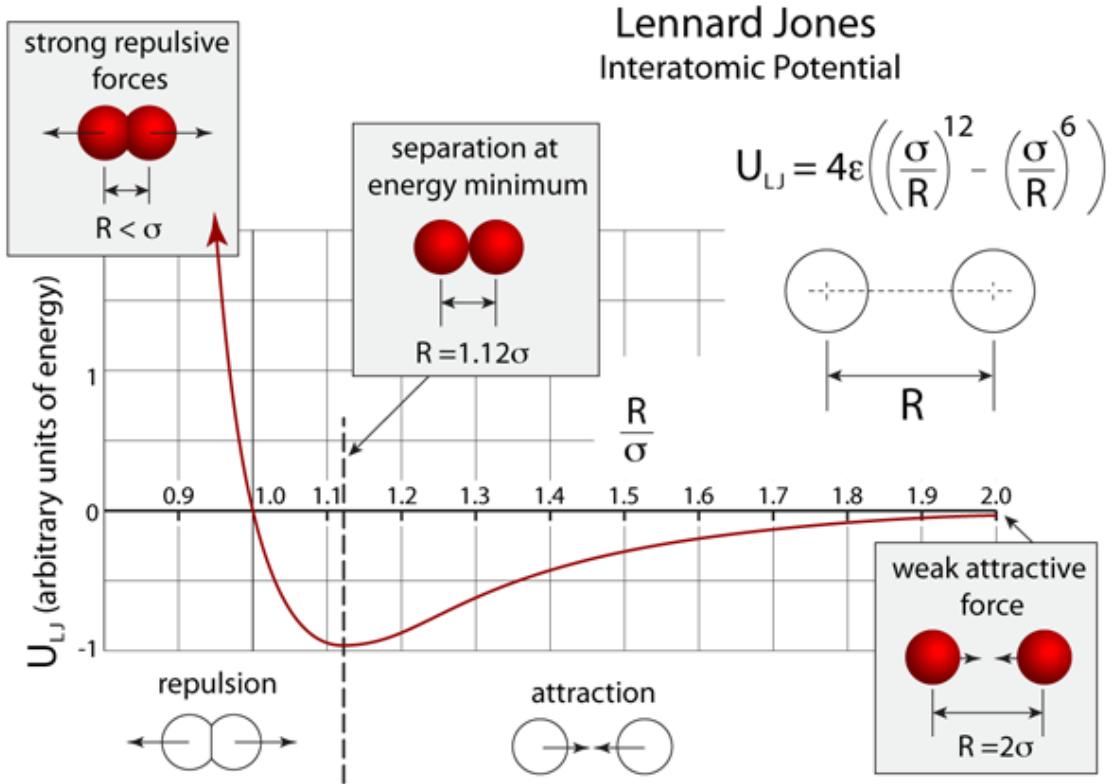


Figure 6: caption

### 2.1.2 Polarizability

## 2.2 Periodic boundary conditions

Due to the computational complexity, we are focused on only small region of a very complex real system. In order not to introduce errors caused by the boundaries of the system and interaction on them, we introduce periodic boundary conditions (PBC). This method is based on surrounding the simulated system with periodic images, thus achieving an approximation by a surface less system. We choose a shape of the simulation box that can be used to fill the space without problems, in our case a cubic box. For simulations in three dimensions, we usually introduce PBCs in the direction of all axes, which means that our simulated box is surrounded on all sides by a total of 26 replicas of the system. The behavior of the system is the same in all replicas, so we must include all the particles appearing in the replicas when calculating the pair interactions.

### 2.2.1 Setting the cutoff

From the preceding paragraphs it is evident that the main problem in time complexity of the simulations is the evaluation of non-bonding energies. While the number of bonded terms increase linearly with the system size, the non-bonded terms show a quadratic increase in the number of contributions. A common strategy for reducing the computational time is to set specific cutoff distance, beyond which we neglect or estimate the non-bonded interaction energy contribution. We distinguish two type of interactions based on their decay with distance. First the so-called short-range interactions decreasing faster than  $1/r^3$  such as van der Waals ( $1/r^6$ ) that could be neglected on relatively short distance. By neglecting the van der Waals contributions at long distances, we introduce only a small numerical deviation for each pair, but the cumulative effect when all pairwise interactions are summed introduces larger deviations into the simulations. Theory says that van der Waals interactions are negligible beyond about 20 Å, we choose 12 Å as the optimal cutoff in this work because of the optimal computational complexity.

For the long-range interactions, such as Coulombic interactions ( $1/r$ ) the situation is not that easy and they require larger cutoff than van der Waals due to their long-range nature. The easiest option, as mentioned above, is to solve this issue by neglecting any contributions beyond the cutoff distance. The problem in that approach is that we introduce discontinuities in the potential and its derivatives. Better and more effective approach, especially for periodic systems is called Ewald summation.

### 2.2.2 Ewald summation

### 2.2.3 PPPM

## 2.3 Molecular dynamics

The molecular dynamics method is based on solving the equations of motion of classical Newtonian mechanics for atoms. Let us choose the assumption that the interaction potential  $U$  is continuous and differentiable. The force acting on the  $i$  particle can thus be written as an equation 2.4

$$f_i = -\frac{\partial U(r^N)}{\partial r_i}, \quad i = 1, \dots, N. \quad (2.4)$$

In molecular dynamics, we are focused on the time development of the model. In other words, we are looking for the trajectory of the solution of the respective systems

of differential equations. In Newtonian mechanics, acceleration is directly related to forces through the equations of motion. Formally, we can write the equation 2.5

$$\ddot{r}_i = \frac{f_i}{m_i}, \quad i = 1, \dots, N, \quad (2.5)$$

where the second time derivative of the positions appears on the left side. The equation 2.5 is a system of  $3N$  ordinary differential equations for a set of  $N$  atoms. As initial conditions, we usually choose the knowledge of all atomic positions  $r_i$  and velocities  $\dot{r}_i$  at the initial time  $t = t_0$ .

We solve equation 2.5 using the finite difference method when we track the desired solution in the form of the function  $r_i(t), i = 1, \dots, N$ , in the time interval  $[t_0, t_{max}]$  at discrete points of the form  $t = t_0 + kh$ , where  $h$  is the integration step and  $k$  is a non-negative integer.

To find a solution, it is necessary to calculate the forces acting on individual particles at each step of the simulation. One of the methods that is applied in this area is the Verlet integration method. It is a simple and very effective method that provides sufficiently accurate results in the physico-chemical context. Its great advantage is the time-reversibility and the conservation of the total energy of the system [22].

### 2.3.1 Verlet integration

Verlet integration method is a numerical method for integrating the equation 2.4. We express the second derivative using finite differences. From the second-order Taylor expansion  $r_i(t \pm h)$  centred at  $t$ , we obtain the formula

$$\ddot{r}_i = \frac{r_i(t - h) - 2r_i(t) + r_i(t + h)}{h^2}, \quad (2.6)$$

binding values at three points in a row ( $t - h$ ,  $t$  and  $t + h$ ). We will use this characteristic to calculate  $r_i(t + h)$ . By substituting 2.6 into 2.4 we get

$$r_i(t + h) = 2r_i(t) - r_i(t - h) + h^2 \frac{f_i(t)}{m_i}. \quad (2.7)$$

In this formulation, we are able to calculate the new positions at time  $t + h$  from knowledge of the forces at time  $t$ , the positions of the particles at time  $t$  and the previous time  $t - h$ . The time reversibility of the method is clearly visible here. The advantage is that the force is calculated only once in each step of the simulation. For the position preceding the initial position ( $r_i(t_0 - h)$ ), we can use the expansion

2.8

$$r_i(t_0 - h) = r_i(t) - h\dot{r}_i(t_0) + h^2 \frac{f_i(t_0)}{2m_i}. \quad (2.8)$$

### 2.3.2 Constraint dynamics

When integrating equations of motion, we often impose constraints on certain aspects of molecular geometries. The main reason is to enable using a longer simulation time step. If we simulate with a too large time step, we introduce large errors into the simulations, leading in extreme cases to a crash of the simulation. The calculated particle positions at time  $t + h$  may lead to overlapping of particles, the calculated force acting on the particles may divert from physically reasonable configurations. Conversely, the use of inappropriately short simulation steps reduces the efficiency of the simulations (the most computationally and therefore time consuming element of the simulations is the calculation of the forces when integrating the equations of motion). [22] The criterion determining the optimal step length is the accuracy of the conservation of total energy. The step length can be determined by an Nyquist-Shannon [23] sampling theorem that says that the time step must be half or less of the period of the quickest dynamics exhibited in the system. Thus, for systems containing very light hydrogen atoms, we can either artificially increase the mass of the hydrogen atom while redistributing the masses of the other molecules to conserve the overall mass of the molecule, or fix the bond angles or bond lengths terminating in the hydrogen atoms. It is the fixation of hydrogen bond lengths that is most often implemented in the Verlet method, using an algorithm called SHAKE.

The SHAKE algorithm is based on Verlet's integration method and is iterative. The first step is to initialize the initial velocities and positions of the atoms, then calculate the positions using Verlet's method without considering bond length constraint. We then create the  $\lambda$  correction of the atom positions to constrain the bond length. Fixing the bond length allows us to use a longer time step (we are no longer limited by the motion of very light particles) and, unlike fixing angles, does not introduce large deviations in the simulations.

## 2.4 Measuring the properties

### 2.4.1 Statistical ensembles

MD gives us insight into the total energy of the system, which is naturally conserved in simulations. However, real systems are rarely thermodynamically closed and we often expose the system to external pressure or heat exchange. Thus we speak of

different statistical ensembles depending on the conservation of quantities.

As already mentioned, the natural ensemble is the so-called microcanonical ensemble, **NVE**. Thermodynamically it is an adiabatic system, there is no heat exchange while maintaining the total number of particles, total energy and volume.

Another ensemble is isothermal, or sometimes called the canonical ensemble **NVT**. As the name implies, the thermodynamic temperature and volume are constant, heat exchange occurs with the thermostat. It is used for applications where we are not interested in pressure or pressure is not definable.

For chemists, the most interesting is the **NPT** ensemble where temperature and pressure are constant.

#### 2.4.2 MSD

#### 2.4.3 RDF

### 3 COMPUTATIONAL METHODS

LAMMPS software [24] (version 5 May 2020) was used for all molecular dynamics calculations. The placement of molecular chains in the simulation boxes was done by Packmol [25], the chains were randomly distributed in the space of a cubic box. The input files for the LAMMPS software were generated using the fftool [26] script written in the Python programming language.

We also used periodic boundary conditions in the directions of all axes and the velocity Verlet integrator. Contributions of long-range charge interactions of distant atoms were calculated using the long-range solver using the particle-particle-particle mesh (PPPM) algorithm [27]. The bonds and angles were considered as harmonic oscillators, and for dihedral angles, OPLS (Optimised Potentials for Liquid Simulations) was used for every atom. Coulombic point charges and the Lennard-Jones potential were used, the cut-off distance for dispersion and Coulombic interactions was set to 12 Å. The SHAKE atom algorithm [28] was applied to constrain the lengths of covalent bonds that terminate in hydrogen atoms. The simulations were run under  $NpT$  conditions using the Nosé-Hoover thermostat and barostat [29], with relaxation times for temperature control as 100 fs and pressure control as 1000 fs. The simulations contained around 25 000 atoms in a simulation box. From previous research, this was considered to be a suitable setting. [9]

All-atom non-polarisable force fields were used during MD simulations, the parameterisation of the PLA force field was obtained from the literature [30], the parameterizations of APIs were also taken from the literature. [31]

#### 3.1 Simulations of neat PLA

The PLA was first simulated separately from two initial conformers, a fibrilar and a globular chain. We try to verify that the resulting state of the system does not depend on the initial conformations that were used for the simulations. The Cartesian coordinates of the positions of atoms forming a globule were obtained from the last frame of a simulation of one linear polymer molecule in a large virtual empty box.

The initial simulation of the polymers led to the equilibration of the system. The simulation was carried out at 500 K and 1 bar in three blocks with a gradually increasing simulation step. First with a step 0.2 fs for 0.5 ns, followed by steps 0.4 fs and 0.7 fs for 0.7 ns, then 1 ns of simulation with step a 1 fs.

### 3.2 Simulations of neat APIs and mixtures with PLA

We started all simulations with an equilibration simulation run from randomly packed simulation boxes under the temperature of 500 K and pressure of 1 bar in three blocks with a gradually increasing time-integration step. The simulation began with an equilibration procedure using a step of 0.25 fs, followed by steps 0.5 and 0.75 each for a simulation time of 0.5 ns, then 1 ns of simulation with a step of 1 fs. From this point, we cooled the system, down to 300 K for 2 ns with a step of 1 fs. After this cooling, we continued with a 10 ns long production run with a temperature of 300 K and pressure equal to 1 bar.

From these production runs, we evaluated the MSD (Mean Squared Displacement) of API and PLA molecules in the mixture and the RDF (radial distribution function) of atom interactions. We also performed a production run at the higher temperature of 500 K and the same pressure of 1 bar starting from conformations after the first equilibration under 500 K. We also sampled RDFs and MSDs. Those simulations were performed for neat APIs, PLA polymer, and mixtures with different concentrations of API. For each API, the concentration ratio API:PLA in terms of the number of molecules in a simulation box was 100:17, 200:17, and 300:17. The corresponding molar and mass fractions are available in the Table 1.

Table 1: The concentration of API in mixtures with PLA, expressed in molar and mass fractions.

$N_{\text{API}}$	$N_{\text{PLA}}$	$x_{\text{API}}$	$w_{\text{nap}}$	$w_{\text{cbz}}$	$w_{\text{ibu}}$	$w_{\text{indo}}$
100	17	0.85	0.086	0.088	0.078	0.13
200	17	0.92	0.16	0.16	0.14	0.23
300	17	0.95	0.22	0.22	0.20	0.30

To determine the glass transition temperature ( $T_g$ ) of the mixtures, we performed simulated annealing simulations with a gradually decreasing temperature cooling rate ( $30 \text{ K ns}^{-1}$ ) starting at 800 K and ending at 200 K. Systems containing a mixture of API and PLA were first heated from 500 K to 800 K over 2 ns. To have statistically more reliable data, simulated annealing simulations were performed from 5 different initial conformations. To obtain those conformations a 4 ns long simulation at 800 K was done sampling atomic coordinates within the image of the box every 1 ns.

## 4 RESULTS AND DISCUSSION

The results section is divided into three logical blocks. First, simulations of the neat polymer were performed to verify the force field and to determine the key properties of the polymer. Subsequently, a series of neat API simulations were performed. Then, simulations of mixtures of different API concentrations in polymer were performed to see the behavior of the mixtures.

### 4.1 Simulations of neat PLA

#### 4.1.1 Structural properties

First, the simulations from 2 initial states were done (fibrillar and globular). The Figure 7 shows an example of the shortest polymer in a fibrillar conformation state, whereas Figure 8 displays globular conformations of chains containing 20 and 200 monomer units on the left and right, respectively.

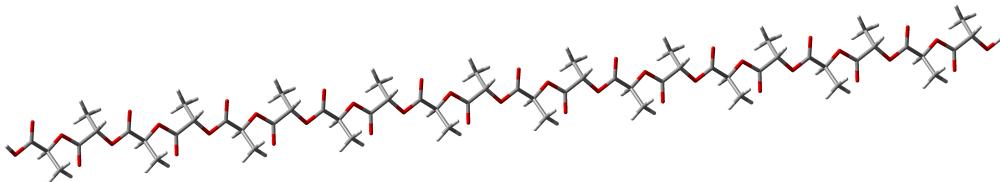


Figure 7: Fibrillar PLA polymer chain, 20 units



Figure 8: Globular PLA polymer chain, 20 and 200 units

To see the effects of initial conformations, molecular weight and thermal history of the polymer on bulk densities following simulations were performed. The design of the simulation boxes is in Table 2. The simulations were first performed at the temperature of 500 K (run 1), then the box was heated up to 1000 K followed by re-cooling and simulating at a temperature of 500 K (run 2). All subsequent simulations were observing the system for 10 ns with a step 1 fs at 1 bar. From

these simulations, the densities and the root mean square distance of the polymer chain termini with their standard deviations were evaluated.

Table 2: Design of the neat PLA simulation boxes

$N_{\text{units}}$	$n_{\text{chains}}$	$N_{\text{atoms}}$	$M, \text{ g mol}^{-1}$	$d, \text{ \AA}$
20	140	25620	1459.3	67.9
40	70	25410	2900.5	67.7
60	40	24978	4341.8	64.3
80	35	25305	5783.1	67.7
100	28	25284	7224.3	67.7
120	23	24909	8665.6	67.3
140	20	25260	10106.8	67.6
160	17	24531	11548.1	67.0
180	15	24345	12989.4	66.8
200	14	25242	14430.6	67.6

The following graphical representation of the results (Figure 9) shows a trend of an increasing density depending on the length of the chain (molecular weight), which is independent of the initial conformation of the molecule. There is also visible that densities for longer chains converge to constant value. From this finding, we can consider a system above  $M_w = 9\,000 \text{ g mol}^{-1}$  as sufficiently polymeric.

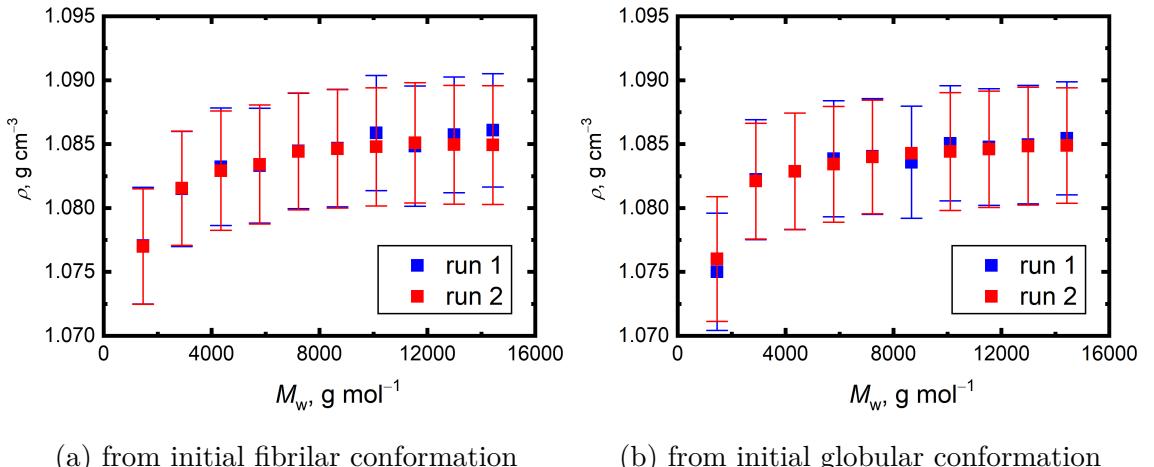


Figure 9: Average densities with their standard deviations for PLA polymer chains at 500 K and 1 bar as a function of chain length before (run 1) heating and (run 2) after cooling.

From the density data, any impact of the conformation memory cannot be assessed, since the bulk density is too a crude point of view on the polymer structure. That is the reason why the distances of the polymer chain termini that are displayed in the Figure 10 were calculated. The simulated time of 10 ns at the elevated temperature

1000 K was not enough to completely erase the polymer conformational memory, there is a noticeable deviation of the data sets representing the initial fibrilar and globular conformations.

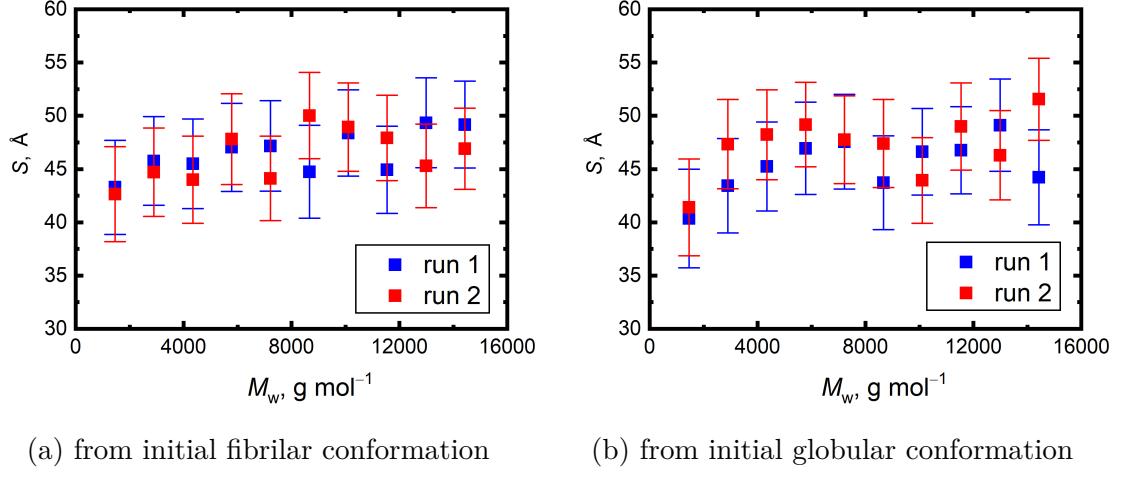


Figure 10: Distances of the polymer chain termini with their standard deviations for PLA polymer chains as a function of chain length before (run 1) heating and (run 2) after recooling.

The dynamics of the polymer is slow due to complex entanglement of individual chains even at elevated temperatures, for a complete loss of memory it would be necessary to simulate the system for a longer period of time, especially for longer chains.

To investigate the effect of the box size on the molecular simulations, the simulations with box containing 5-50 polymer chains inside, each having a molar mass  $12\ 989 \text{ g mol}^{-1}$  were performed. The simulations were performed with a 3-block initial equilibration at 1000 K and 1 bar and subsequently cooled to 500 K and simulated for 10 ns. Mean densities obtained from these simulations are shown in the Figure 11a on the left. The simulation results prove that the initial size of the box has no significant effect on resulting average density. However, there is a visible effect of a lower uncertainty of standard deviations of densities for larger boxes. To have a better insight what is going on the structural level, we also analyzed the root-mean-squared end-to-end distance of the polymer chain termini shown in Figure 11b on the right. From the obtained data there is visible growing trend in end-to-end distances. That means that the small boxes do not represent correctly the distribution of the end-to-end distances in the polymer. We can say, that the value converge for box containing more than 40 polymer chains. As a conclusion, when we are focused on macroscopic values such as density we can use smaller number of chains in the simulation boxes in order to save the computational resources. However, when

dealing with structural properties we should be careful and set the number of chains in a simulation box more carefully.

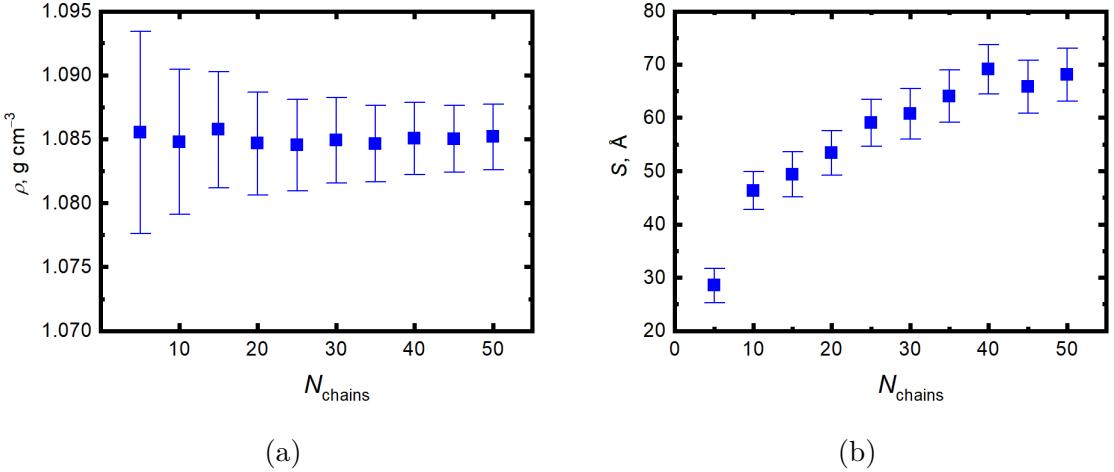


Figure 11: (a) dependence of density on number of chains containing 90 dimer units in the box on the left and (b) density of PLA at 500 K and 1 bar extracted from MD simulations depending on the polydispersity coefficients on the right.

To validate the calculated densities, the corresponding experimental data was obtained from literature. The comparison for two temperatures (300 and 500 K) in following Table 3 was taken from [9], where the methodology is also described in more details.

Table 3: Comparison of calculated and experimental PLA densities taken from [9].

$T$ , K	$\rho_{\text{exp}}$	$\rho_{\text{calc}}$
300	$1.373 \pm 0.003$	$1.193 \pm 0.001$
500	$1.181 \pm 0.003$	$1.086 \pm 0.001$

#### 4.1.2 Polydispersity effect

Under real conditions, it is hardly possible to experimentally prepare a monodisperse polymer containing only one selected chain length. For this reason, we simulated several polydisperse systems, each exhibiting a different distribution of molar masses of individual molecular chains, containing a total number of 50 chains. The lengths come from interval 8-244 units. Polydispersity index PDI = 1 corresponds to 50 chains of length 124 units, the other values were calculated using the equation 4.1. We then build the other systems using the Gaussian distribution with mean value of 124 units. By this procedure we were able to obtain the PDI equal to 1.3. For PDI 1.4 and 1.5 we had to adapt the number of very short and long polymers randomly to get the desired PDI. Designed compositions of systems based on PDI values are

displayed in the Figure 12. The density was again evaluated from the simulations, in this case as a function of the PDI.

$$\text{PDI} = \frac{\sum_i N_i \cdot \sum_i N_i M_i^2}{(\sum_i N_i M_i)^2} \quad (4.1)$$

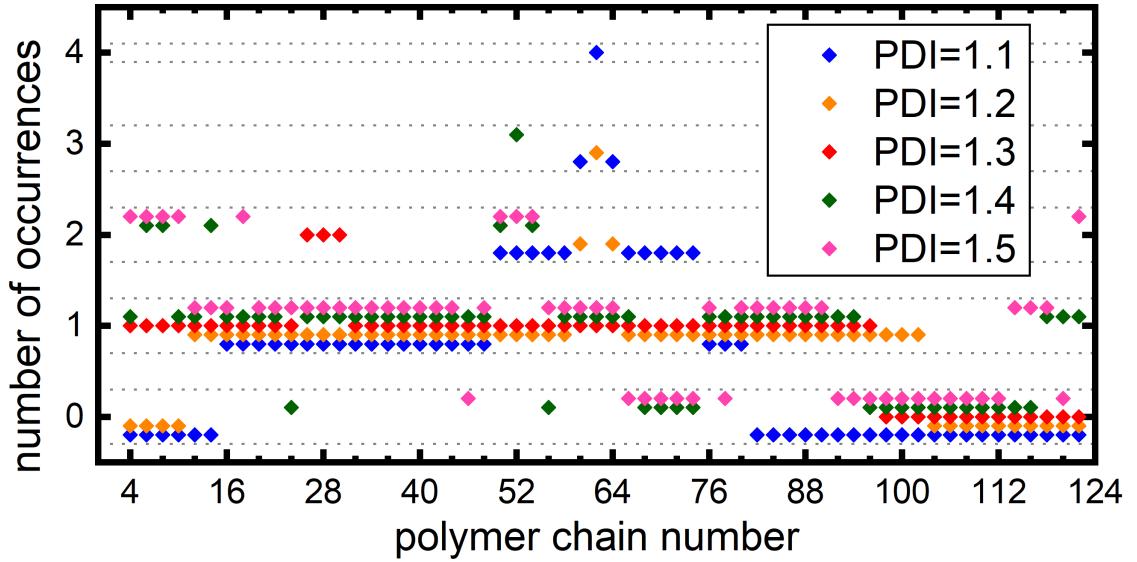


Figure 12: Number of occurrences of chains of a given length in the polydisperse systems with corresponding PDI.

Calculated densities depending on the PDIs are in the Figure 13. There is not a massive difference among the densities obtained for different values of the polydispersity index, for the subsequent simulations we will use monodisperse systems as it will not introduce big errors.

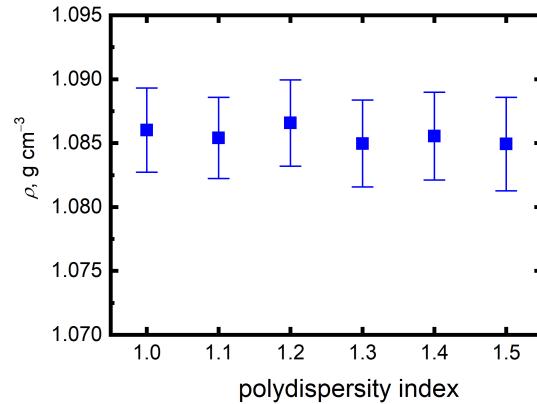


Figure 13: Density of PLA at 500 K and 1 bar extracted from MD simulations depending on the polydispersity coefficients.

### 4.1.3 Glass transition modeling

To obtain the glass transition temperature of PLA ( $T_g$ ), we started by simulating ten different polymer chain lengths for a set of temperatures in a range 140-485 K with a step of 15 K. For the system equilibration, each polymer chain simulation runs for 1 ns with a step of 1 fs. After the equilibration, the temperature interval for the following simulations was limited to the range of 200-485 K with a step of 15 K. Then, we run a  $NpT$  production simulation with this limited temperature interval for 10 ns with a step of 1 fs from which the equilibrium bulk phase densities were calculated and displayed as a function of temperature. To get the glass transition temperature ( $T_g$ ) for PLA from that function, the trend shift method was used [32].

The trend shift method is illustrated for one length of the polymer chain in the Figure 14. When we plot the bulk phase densities as a function of temperature, there is a visible trend shift which has the meaning of the transition between the glassy state and the rubbery state. The point of the transition divides the density dataset into two intervals. Coordinates of the breakpoint and one surrounding point from each side were excluded from the further processing and the two resulting intervals were interpolated by a linear function. The  $x$ -coordinate of the intersection of these two lines determines the glass transition temperature. For this purpose a script in Maple software solving the system of linear equations to get the  $T_g$ .

Available experimental  $T_g$  of L-PLA varies in the literature, the value of  $T_g = 333 \pm 4$  K [33] was chosen. Our obtained PLA  $T_g = 337 \pm 10$  K as an arithmetic mean of the values for all polymer chain lengths. The calculated  $T_g$  for each polymer chain are displayed as function of polymer chain weight in the Figure 14 with their arithmetic mean value drawn as a blue line. The calculated  $T_g$  value is very close to the experimental one. There is no significant trend in  $T_g$  of PLA from the calculated data.

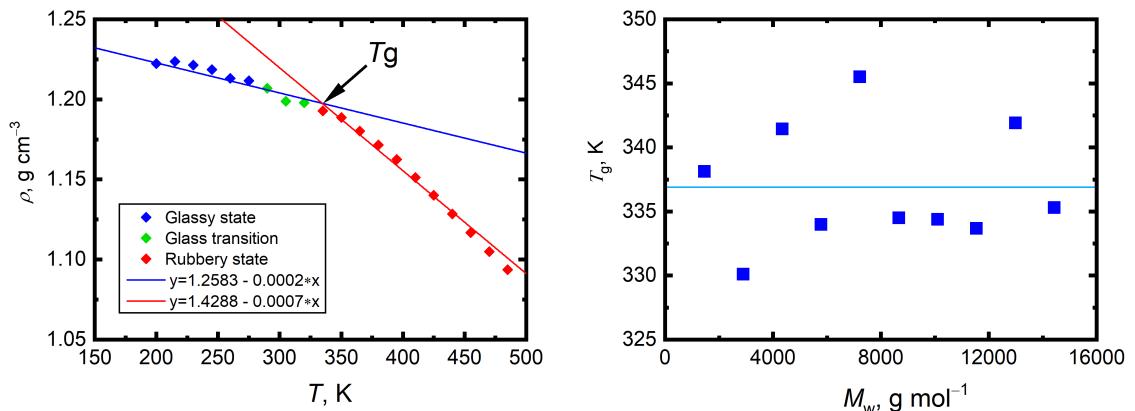


Figure 14: Illustration of the trend shift method for one polymer chain length on the left, and calculated  $T_g$  for all lengths of polymer chains by this method where blue line represents mean value on the right.

## 4.2 Simulations of neat API

The properties of API simulation boxes after equilibration run ( $T=500$  K) is presented in Table 4, showing the number of API molecules ( $N_{\text{API}}$ ), the total number of all atoms ( $N_{\text{atoms}}$ ) and size of the cubic box ( $l_{\text{box}}$ ).

Table 4: Properties of equilibrated API simulations boxes,  $T=500$  K.

API	$N_{\text{API}}$	$N_{\text{atoms}}$	$M, \text{ g mol}^{-1}$	$l_{\text{box}}, \text{\AA}$
carbamazepine	800	24 000	6	66
naproxen	800	24 800	6	66
ibuprofen	800	26 400	6	67
naproxen	600	24 600	6	66

To validate the force fields computed densities were compared with experimental values, the comparison is in the Table taken from literature. UPRAVÍM [31]

Table 2. Comparison of simulated and experimental bulk phase densities  $\rho$  ( $\text{g}\cdot\text{cm}^{-3}$ ).

Compound	Phase	Temperature, K <sup>a</sup>	$\rho_{\text{MD}}$	$\rho_{\text{exp}}$	$100(\rho_{\text{MD}}/\rho_{\text{exp}} - 1)$
Carbamazepine	Crystal III	293	1.335	1.333 [41]	0.1
Ibuprofen	Crystal I	296	1.115	1.117 [40]	-0.2
	Liquid	350	1.006	0.966 [43]	4.1
		400	0.968	0.924 [43]	4.7
Indomethacin	Crystal $\alpha$	203	1.408	1.420 [39]	-0.9
	Crystal $\gamma$	120	1.418	1.401 [38]	1.2
	Liquid	400	1.284	1.231 [43]	4.3
		450	1.264	1.183 [43]	6.9
Naproxen	Crystal	293	1.308	1.263 [37]	3.6
	Liquid	430	1.154	1.088 [43]	6.1
		480	1.116	1.048 [43]	6.5
Adenine	Crystal	293	1.506	1.494 [35]	0.8
Cytosine	Crystal	293	1.537	1.502 [36]	-1.6

<sup>a</sup> Experimental density determination was performed at this temperature.

### 4.2.1 Sulfathiazole FF parametrization

A newly parametrized force field [34] was used for sulfathiazole. The charges on the atoms were calculated by quantum-chemical calculations using the Gaussian code [35]. At first, the structure was optimized using the B3LYP functional with the aug-cc-pVTZ basis set with the dispersion correction GD3BJ [36]. After finding the optimal geometric structure of the molecule, the charges on the atoms were fitted through the CHELPG (Charges from Electrostatic Potentials using a Grid-based method) method and inserted into force field file.

The MD simulations of the sulfathiazole crystal were performed to validate the force field file parameters. The triclinic simulation box and barostat setting was used to

account for the anisotropic character of the molecular crystal, other settings are similar to that with the PLA instead of calculating long-range interactions. The sulfathiazole crystal was simulated for three temperatures of 100, 200 and 300 K at 1 bar. The simulation results and experimental data obtained from literature [12] are given in the Table 5.

Temperature, K	100	200	300
Experimental density $\rho_{\text{exp}}$ , g cm <sup>-3</sup>	$1.575 \pm 0.002$	$1.560 \pm 0.002$	$1.540 \pm 0.002$
Calculated density $\rho_{\text{MD}}$ , g cm <sup>-3</sup>	$1.552 \pm 0.001$	$1.534 \pm 0.002$	$1.515 \pm 0.002$
$100(\rho_{\text{MD}}/\rho_{\text{exp}} - 1)$	-1.5	-1.7	-1.6
Experimental $\beta$ angle, °	94.14	93.905	93.674
Calculated $\beta$ angle, °	91.56	91.64	91.67
Calculated cell a length, Å	8.302	8.325	16.701
Calculated cell b length, Å	8.236	8.275	16.625
Calculated cell c length, Å	7.995	8.027	16.133

Table 5: Comparison of simulated and experimental crystallographic parameters for sulfathiazole.

There is a good match between the experimental and computed quantities. The relative deviations of experimental and calculated densities are very low. Other parameters do not indicate any notable deviations in the simulation box during the simulation, the crystallographic parameters of the unit cell are  $a = 8.1896$  Å,  $b = 8.532$  Å and  $c = 15.447$  Å.

### 4.3 Simulations of mixtures of APIs and PLA

#### 4.3.1 Calculated properties of mixtures

Additive molar volumes ( $V_{\text{m, mixing}}$ ) of the mixtures were evaluated from the simulations for each concentration using the Equation 4.2. For this reason, the average molar volumes of the simulation boxes were evaluated from simulations of pure API ( $V_{\text{m}}^{\text{API}}$ ) and pure polymer ( $V_{\text{m}}^{\text{PLA}}$ ) and from a mixture ( $V_{\text{m}}^{\text{MIX}}$ ).

$$V_{\text{m, mixing}} = V_{\text{m}}^{\text{MIX}} - x_{\text{API}}V_{\text{m}}^{\text{API}} - x_{\text{PLA}}V_{\text{m}}^{\text{PLA}} \quad (4.2)$$

Molar mixing energies were also evaluated in a similar way. The following Equation 4.3 was used

$$E_{\text{m, mixing}} = E_{\text{m}}^{\text{MIX}} - x_{\text{API}}E_{\text{m}}^{\text{API}} - x_{\text{PLA}}E_{\text{m}}^{\text{PLA}}, \quad (4.3)$$

where  $E_m^{\text{MIX}}$  is the average molar energy of the simulation box of the mixture,  $E_m^{\text{API}}$  is the average molar energy of pure API, and  $E_m^{\text{PLA}}$  is the averaged molar energy of pure PLA obtained from simulation. Mixing energies and volumes were calculated for all systems and both temperatures (300, 500 K), and the comparison is shown in Table 6.

Table 6: Calculated mixing energies and volumes for API mixtures of different concentrations, simulations under 500 K.

<b>API</b>	$x_{\text{API}}$	$V_m, \text{mixing, cm}^3/\text{mol}$	$E_m, \text{mixing, kJ/mol}$
carbamazepine	0.85	0.97	4.79
	0.92	0.48	3.17
	0.95	0.21	2.68
naproxen	0.85	-7.07	7.50
	0.92	-8.50	6.24
	0.95	-9.85	4.75
naproxen	0.85	-7.07	7.50
	0.92	-8.50	6.24
	0.95	-9.85	4.75
naproxen	0.85	-7.07	7.50
	0.92	-8.50	6.24
	0.95	-9.85	4.75

The data show that a mixture of naproxen and PLA can create a more advantageous arrangement of molecules in space, meaning that the mixing volumes are negative. For carbamazepine the trend is the opposite; this could be caused by the shape of the carbamazepine molecule when the mixture needs more space. From the positive changes in energies, we can assume that mixing the APIs with PLA can reduce the interactions between API-API molecules, and also that new interactions between API and PLA are not developed in order to compensate for the API-API cohesion.

#### 4.3.2 Glass transition temperature

The glass transition temperatures of the mixtures were evaluated from the simulated annealing simulations by fitting a hyperbola to the temperature-density data. The whole methodology is described in the paper written by Alzate-Vargas[37], the main equation of the fit is Equation 4.4

$$\rho(T) = \rho_0 - a(T - T_0) - b \left[ \frac{1}{2}(T - T_0) + \sqrt{\frac{(T - T_0)^2}{4} + e^c} \right]. \quad (4.4)$$

Since this method is sensitive to the initial state of the simulated box, more simulated data starting from different conformations must be provided to evaluate  $T_g$ . In this work we used 5 simulations from different initial states.

TO DO: DOPOČÍTAT PRO NOVÉ SIMULACE The resulting value for carbamazepine is  $T_{g, cbz} = 385 \pm 4$  ( $k = 2$ ) and for naproxen is  $T_{g, nap} = 365 \pm 2$  ( $k = 2$ ).

#### 4.3.3 Radial distribution functions

Then, all RDFs of mixtures containing the API-API interaction were scaled onto the pure API RDF signal for better visualisation using the following Equation 4.5

$$\text{RDF}_{\text{scaled}} = \text{RDF} \cdot \frac{V_{\text{API}}}{N_{\text{API}}} \frac{N_{\text{mix}}}{V_{\text{mix}}}, \quad (4.5)$$

where  $V_{\text{API}}$  is the average volume of the pure API simulation box,  $N_{\text{API}}$  is the number of molecules in the pure API simulation box and, respectively, for mixtures.

Sampling the radial distribution function from the simulations was done to explore the interactions that are having the highest impact. The hydrogen bonds were mostly studied. All RDF data containing the API-API interaction in the mixtures were scaled for the intensities of the pure API signal. The strongest API-API interaction was chosen and plotted to study the change between simulations with different concentrations of PLA.

For ibuprofen, the interaction between hydrogen from OH group and oxygen from OC was studied. For naproxen, the hydrogen bonding between two carboxyl groups was studied, for carbamazepine, hydrogen bonding was studied between the NH<sub>2</sub> and OC group and for indomethacine the interaction of oxygen from OC and hydrogen from OH was studied. The selected atom types involved in interactions are visualised in the introduction section in Figure 2.

The RDF of the hydrogen bonding interaction of ibuprofen is shown in Figure 15.

The RDF of the selected interaction of naproxen is shown in Figure 16. Here is the situation very different, the height of the first peak changes for different concentrations of PLA. For the higher concentration of PLA, the occurrence of the two hydrogen bonds carboxyl group contact is less important, and the contact of the groups is made only by one hydrogen bond.

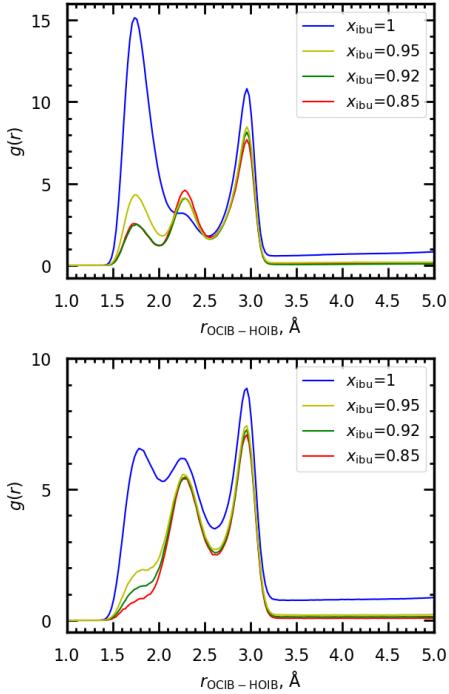


Figure 15: Radial distribution function of the API-API interaction between HOIB hydrogen atom bonded on oxygen and OCIB oxygen atom in a mixture of ibuprofen and PLA for different concentration normalized on values for pure ibuprofen, temperature of 300 K in the left upper corner and 500 K bottom left, coordination numbers on the right.

The RDF of the hydrogen bonding interaction of carbamazepine is shown in Figure 17. The shape and signal response of the peaks for the mixtures are similar for both temperatures, meaning that the impact of the concentration of PLA on the cohesion of carbamazepine in the mixture is very low.

The RDF of the hydrogen bonding interaction of indomethacin is shown in Figure 18.

The hydrogen bonding between API and PLA was also studied. The contact visualization is available in Figure 19.

The RDF of hydrogen bonding with the carbonyl group is shown in Figure 20. For carbamazepine, those interactions are weak, we can see that the intensity of the first peak is really low. Under temperature 300 K slightly above one, but for 500 K the peak is below one, meaning that this interaction occurs less at a small distance than in the rest of the system. The value converges to one in a long distance. For naproxen, the interaction is more relevant, and the intensity of the peak is much higher but still less than in the NAP-NAP interactions.

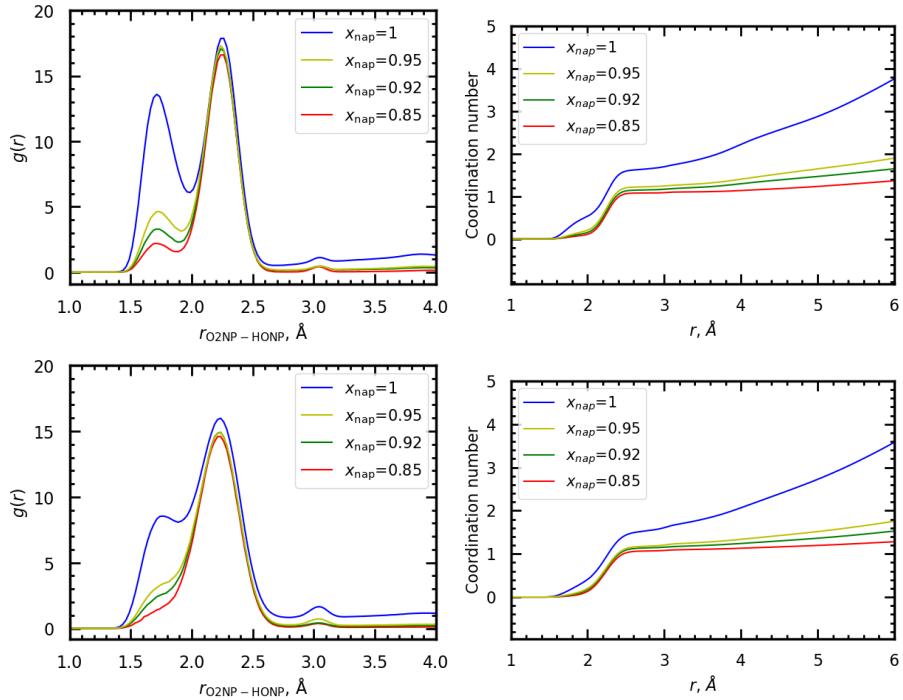


Figure 16: Radial distribution function of the API-API interaction between HONP hydrogen atom and O2NP oxygen atom from COOH group in a mixture of naproxen and PLA for different concentration normalized on values for pure naproxen, temperature of 300 K in the left upper corner and 500 K bottom left, coordination numbers on the right.

The hydrogen bonds with the oxygen bonded by ether bond in PLA are shown in Figure 21. Here is the same situation as in the previous contact with carbonyl oxygen, but for naproxen, the interaction is less relevant. Both values also converge to 1 in a long distance.

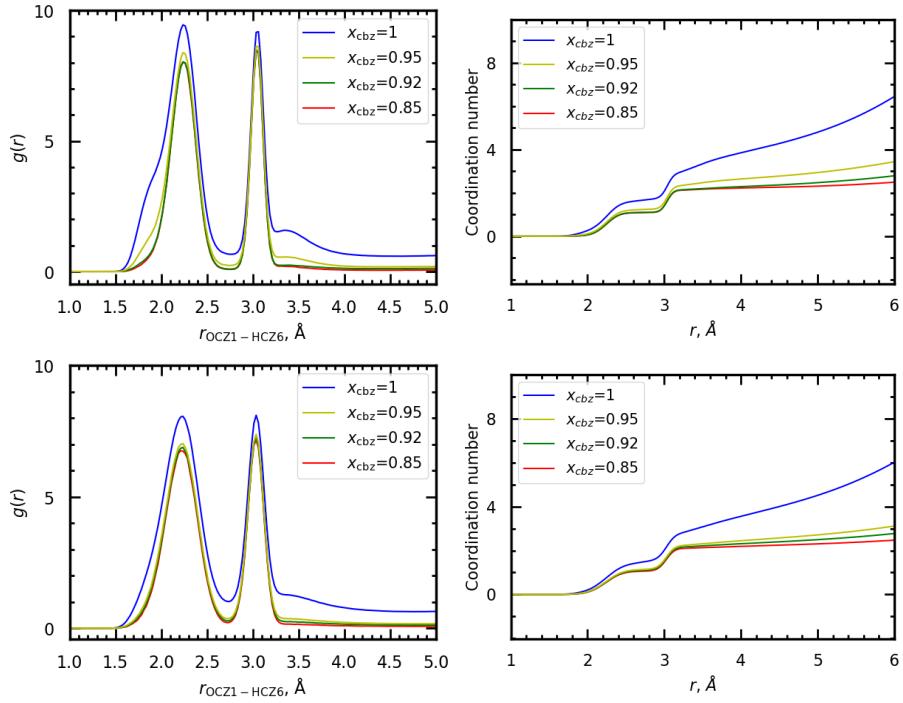
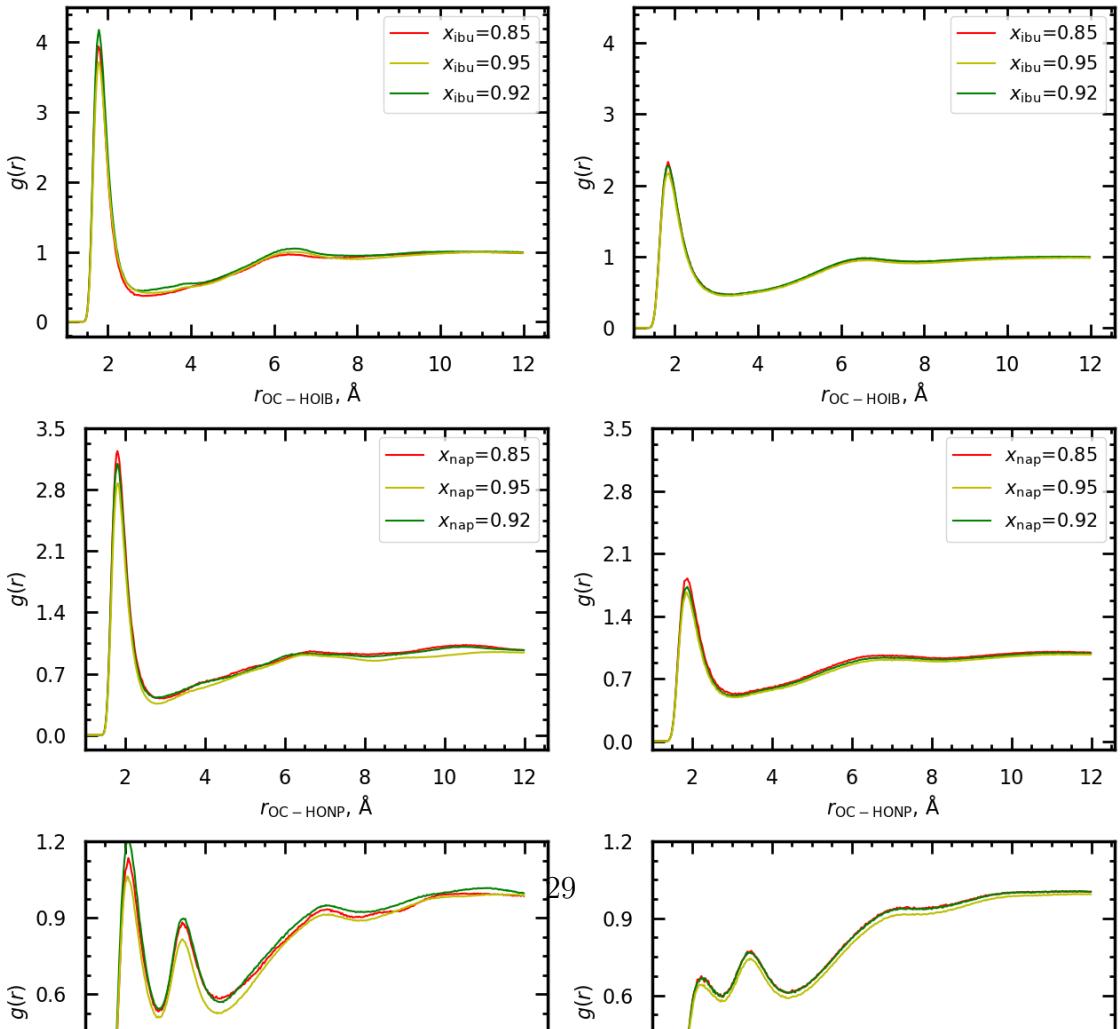


Figure 17: Radial distribution function of the API-API interaction between HCZ6 hydrogen atom bonded on nitrogen and OCZ1 oxygen atom in a mixture of carbamazepine and PLA for different concentration normalized on values for pure carbamazepine, temperature of 300 K in the left upper corner and 500 K bottom left, coordination numbers on the right.



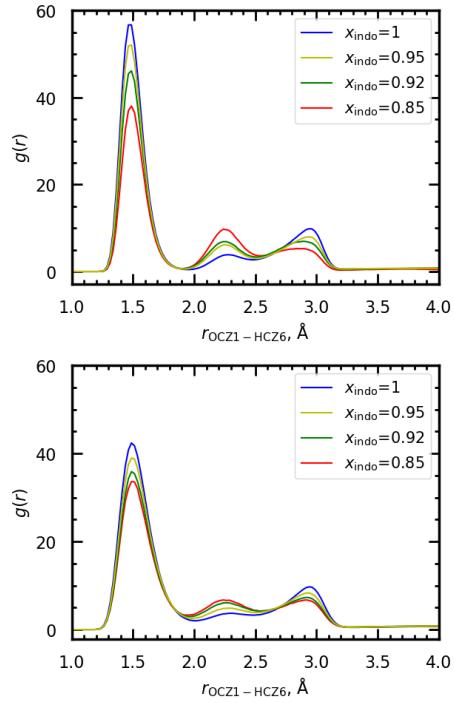


Figure 18: Radial distribution function of the API-API interaction between HCZ6 hydrogen atom and OCZ1 oxygen atom from COOH group in a mixture of indomethacine and PLA for different concentration normalized on values for pure indomethacine, temperature of 300 K in the left upper corner and 500 K bottom left, coordination numbers on the right.

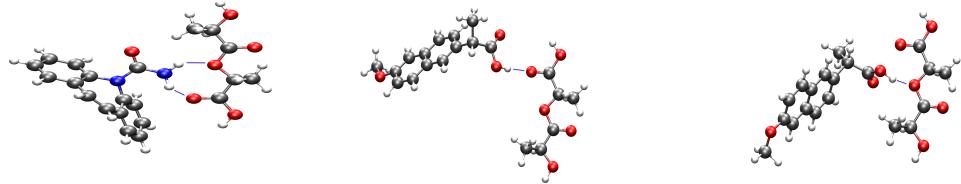
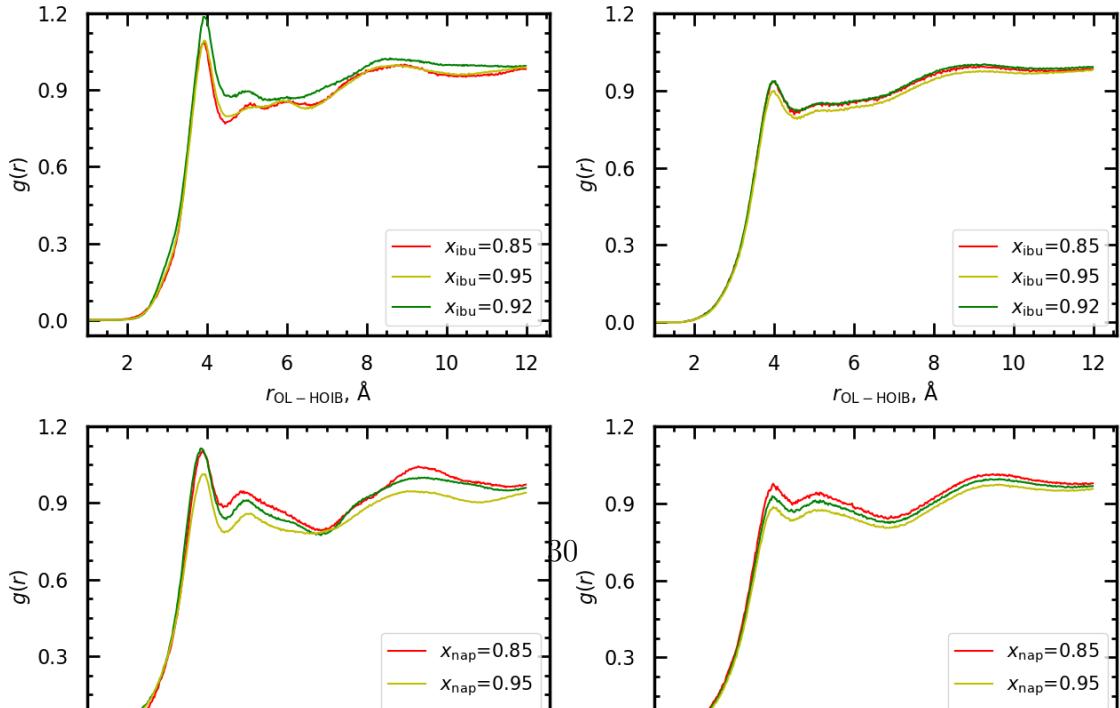


Figure 19: Visualization of studied interactions of PLA-API, for carbamazepine on the left and for naproxen on the right.



#### 4.3.4 Diffusion coefficients

The MSDs were sampled from the 10 ns long run simulations every 1000 fs (integration step 1 fs). At each sampled time step, obtained MSD data were averaged over all API molecules and then plotted as a function of simulation time. The MSD dependencies were then interpolated by a linear functions and related self-diffusivities of the API in the mixtures were evaluated from the slope of the line using the following Equation 4.6

$$D_{\text{API}} = \frac{a}{2d}, \quad (4.6)$$

where  $D$  is the diffusion coefficient,  $a$  is the slope of the line and  $d$  is the dimensionality of the trajectory (3 in our case).

The MSD data for APIs in mixtures with PLA for  $T=500$  K are plotted in Figure 22. For ibuprofen, there is a significant difference between mobility of neat API and API mixed within the polymer. This could be result of very strong API-PLA interaction forming in the mixture. The data of carbamazepine shows that with increasing API concentration, mobility also increases. There is also not that enormous difference between neat API. For naproxen, it seems that there is no change for different concentrations of mixtures, also in neat API the mobility is higher. The situation for indometacine is completely different. For neat API the mobility is really low compared to mixtures with PLA. This behaviour seems strange, the reason could be, that in pure API, there are really strong API-API interactions that decrease the mobility. Also the MSD values are much lower.

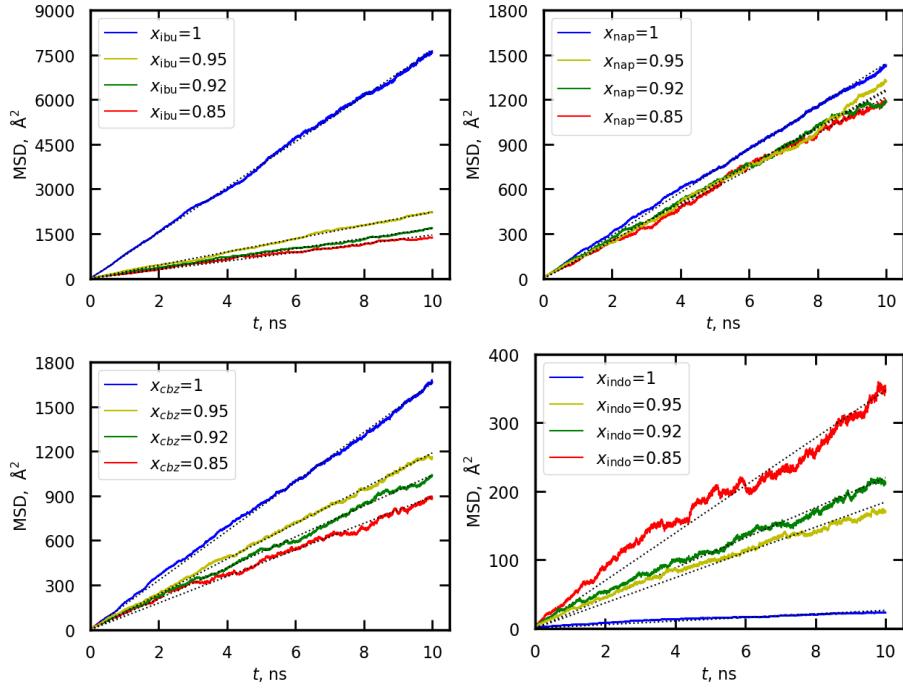


Figure 22: MSD from simulations under 500 K, ibuprofen (**top left**), naproxen (**top right**), carbamazepine (**bottom left**) and indomethacin (**bottom right**).

Self-diffusivities were evaluated from the above data and plotted in Figure 23. The data reveal that in pure liquid carbamazepine the diffusion is faster than in naproxen. For higher temperatures, the main factor affecting diffusion is the shape of the molecules, not the strength of the intermolecular interactions. This is caused because the kinetic energy is higher than the potential for higher temperatures.

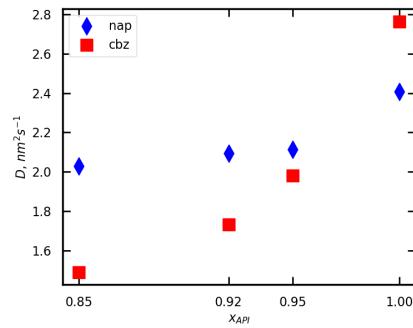


Figure 23: Self-diffusivities for carbamazepine and naproxen as a function of their concentration in the mixtures, temperature 500 K.

MSD was also evaluated at a lower temperature of 300 K, Figure 24. There is the opposite trend. From these data sets, we can assume that carbamazepine has lower interactions with polymer because the mobility in the mixtures is higher than that in

the pure state. The mobility of naproxen is always lower in mixtures, which is related to its stronger interactions with the polymer. The strength of the intermolecular interactions has a greater impact, meaning that paired molecules NAP-API slow the diffusion of other particles.

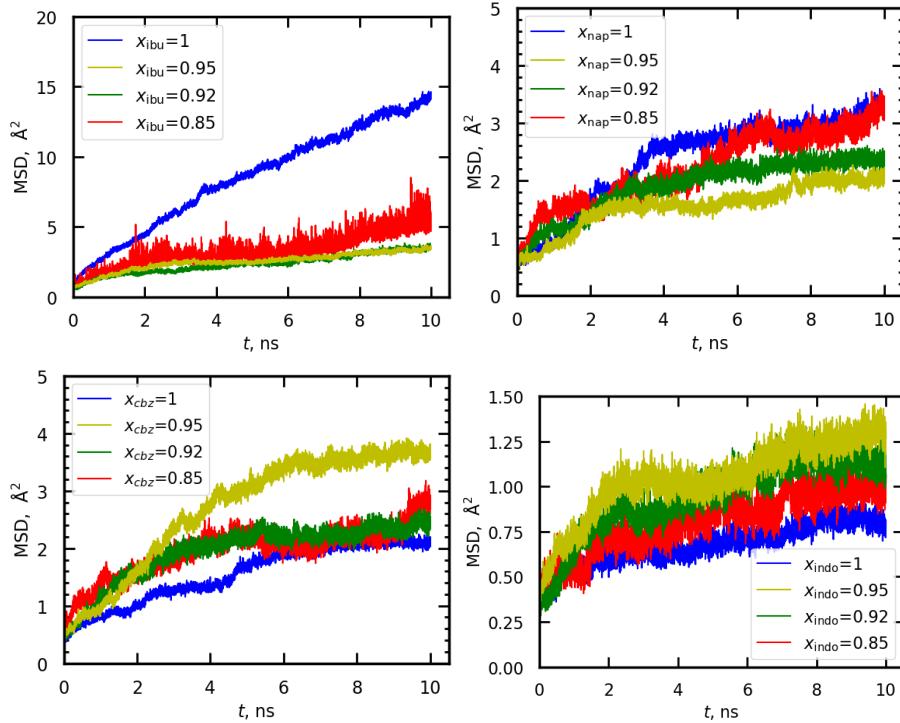


Figure 24: MSD from simulations under 300 K, ibuprofen (**top left**), naproxen (**top right**), carbamazepine (**bottom left**) and indomethacin (**bottom right**).

## **5 CONCLUSION**

text

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## List of Abbreviations

$x$  position

$v$  velocity

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## List of Symbols

$x$  position

$v$  velocity

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## **Appendix A Headline**