

Multiscale Modelling of Polymer Self-Assembly in Binary Solvent Mixtures

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ABSTRACT

This thesis focuses on the multiscale modelling and simulation of the formation process of particulate colloidal systems. In particular, the focus is on the self-assembly of polymer molecules in solution, leading to the formation of polymer nanoparticles (NP). The process is also known as flash nano-precipitation (FNP). In FNP, NP formation is induced by solvent displacement: by mixing a good solvent (i.e., acetone) containing polymer molecules (poly- ϵ -caprolactone, PCL, in this study) with a bad solvent (i.e., water) their self-assembly in molecular clusters, or NP, is induced. It usually takes place in very small devices and here the confined impinging jets mixer (CIJM) is considered. It consists of a cylindrical axial symmetric chamber with two inlets on the sides and one outlet at the bottom. NP production finds a wide range of applications; among the others it is worthwhile to mention drug delivery systems, in which NP are responsible for carrying a drug inside the human body, with the specific aim of attacking an ill site (e.g., cancer cells). As drug nano-carriers, control of mean NP size, together with particle size distribution (or, equally, the cluster mass distribution), becomes a crucial aspect in modelling and simulating such complex systems.

Due the complexity of the phenomena involved in this process, three different scales are investigated: the atomistic scale, by means of molecular dynamics (MD) and coarse-grained molecular dynamics (CGMD); the cluster scale, by means of a population balance model (PBM); the vessel scale, in which fluid dynamics effects on NP formation are investigated through computational fluid dynamics (CFD). These three scales are interconnected with each other: the PBM is implemented and coupled into a CFD code and it is, in turn, built up from MD simulations. One of the several advantages in using a multiscale method is that, sometimes, one scale turns out to be useful in understanding or further investigating some peculiar behaviours that cannot be captured at just one level of description.

More specifically, in this work, full-atom MD is used to study the mixing behaviour at the atomistic scale of acetone-water mixtures. MD calculations of acetone-water mixtures exhibit a strong phase separation with most of the standard all-atom force fields, despite the well-known experimental fact that acetone is miscible with water in any proportion at room temperature. The strong de-mixing (particularly stressed at low acetone molar fractions) is demonstrated to be caused by a bad polarization response of the classical all-atom force fields, usually employed to simulate such liquid systems. Therefore, the de-mixing of acetone-water mixtures is here overcome at the molecular scale by means of a Charge-on-Particle model (COP), in which a pseudo-polarizable approach is used. A charge displacement is introduced on the carbonyl group of the acetone molecule, and suitably modified in function of the acetone molar fraction in order to get the desired polarization response. Thanks to the COP model, the dipole moment is shown to increase together with the content of water and de-mixing vanishes. Other dynamical properties, such as viscosity or diffusivity, are also shown to have a better profile with respect to the original all-atom force field, in terms of agreement with experimental trends. Modelling of long PCL chains in solution at molecular level is also investigated by means of coarse-grained molecular dynamics (CGMD). More specifically, the MARTINI CG force field is used, in which both thermodynamics and structural parametrizations are employed to optimise the CG model. It is a four-to-one mapping method, namely four heavy atoms are grouped in one CG bead. The main advantage in using a CG procedure is the possibility of simulating much larger systems than the one explored with all-atom simulations, saving computational time. Non-bonded Lennard-Jones parameters are chosen as tuning functions, for the optimization procedure. The single CG bead types are set up by matching the solvation free energies of the corresponding atomistic compounds, by means of the Bennett's Acceptance Ratio method. The non-bonded intrachain interactions are then optimised by matching the radius of gyration of the corresponding atomic chains. Although the CG model developed here shows the typical limitations of the CG approaches (e.g., the sharp globule-to-coil transition at medium mixture concentrations range), results are quite satisfactory and self-assembly dynamics of several PCL CG chains in solution can be investigated by using this CG model. Both the all-atom and CGMD simulations are carried out by means of the GROMACS simulation package.

Going to the cluster scale, a PBM is developed, in order to describe the evolution of the cluster mass distribution (CMD, i.e., the number of polymer molecules that belong to a NP) thanks to a suitable governing equation (i.e., population balance equation) and, at the same time, to predict the final mean NP size at the mixer outlet. Particle size is described in terms of the mean radius of gyration, by using the Flory's theory. The whole PBM is treated with quadrature-based moments methods (QBMM). The advantage of solving the problem in terms of the moments of the CMD is twofold: on one hand, moments are scalars that correspond to known physical properties; on the other hand, much less equations need to be solved and so the computational cost is lowered. Being FNP an extremely fast process, the effect of turbulent fluctuations (also known as micro-mixing) must be accounted for. Turbulent fluctuation effects on NP formation is then considered in the PBM in the context of the Favre-averaged Navier-Stokes equation approach, thanks to the direct quadrature method of moments coupled together with the interaction-and-exchange with the mean (DQMOM-IEM) method. The rate at which two polymer clusters collide and aggregate is modelled by means of aggregation kernels, built up from MD calculations, and suitably implemented in the PBM. Finally, the effect of fluid dynamics on NP formation (in terms of influence on both CMD and final radius of gyration), is studied by CFD, proving that kinetics effects are one of the key parameters in controlling the mean NP size. The model referring to the latter two scales are coupled together in a simple computational tool, by means of proper user-defined function (UDF) of a CFD code.

The multiscale model is eventually exploited to simulate the effect of different good solvents on the NP formation process with a particular focus on the effect on particle size. Besides acetone, acetonitrile and THF have been studied and the key parameters, responsible for the different NP size have been successfully identified, thanks to both empirical and theoretical (i.e., Flory-Huggins solubility theory) approaches. This fully-predictive model is validated against experiments. Modelling predictions are in a good agreement with experiments, especially for medium and high initial supersaturation ratios (i.e., local PCL to equilibrium PCL concentration ratio). At low supersaturations the model still shows a gap with experiments. Further investigations are required to figure out the key phenomena at low solute concentration, but the multiscale model yields very interesting insights into the solvent effects.

As alternative mathematical framework for the population dynamics scale, the conditional quadrature method of moments is developed here and implemented in an open-source tool, OpenQBMM. PBM and CFD simulations are performed with both commercial (ANSYS Fluent) and open-source (OpenFOAM) packages. Concluding, the achievements of this work can be summarised as follows:

- De-mixing issues in MD simulations of acetone-water mixtures was overcome thanks to a charge-on-particle model, at the atomistic scale;
- A coarse-grained model was developed to properly describe the thermodynamics and the structural behaviour of long polymer chains in binary mixtures, by means of the MARTINI force field.
- A novel population balance model (with different modelling approaches) for FNP is employed in which the number of the polymer molecules that belong to a cluster was used for the first time as internal coordinate of the PBE. This allowed also a better understanding on the different good solvents effects in FNP.

Future investigations can focus on:

- Considering the presence of the active principle or drug (together with the carrier/polymer);
- Using the CG model to achieve a better insight into the key phenomena of the dynamics of the self-assembly at the molecular scale, to be eventually passed to the PBM scale;
- Investigating the different good solvent effects at the atomistic scale.