Chemical Engineering Science 171 (2017) 485–494

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

A novel multiscale model for the simulation of polymer flash nano-precipitation

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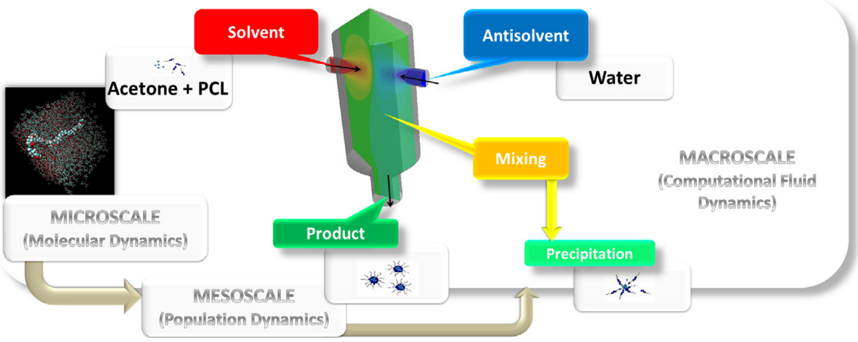
HIGHLIGHTS

- Flash nano-precipitation of polymer nanoparticles is simulated with multiscale modeling.
- Molecular dynamics, population balances and computational fluid dynamics are employed.
- Particle formation is described as the aggregation of molecular building blocks.
- The multiscale model overcomes the standard nucleation-and-growth description.
- The multiscale model with no fitting parameters is validated with experiments.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 30 September 2016
Received in revised form 21 February 2017
Accepted 27 April 2017
Available online 14 June 2017

Keywords:
Multiscale modeling
QMOM
Population balance equation
Computational fluid dynamics
Solvent-displacement
flash-nano precipitation

ABSTRACT

Numerous models describe the flash nano-precipitation (FNP) process to form polymer nanoparticles, however most of them are based on equilibrium approaches and are not capable of predicting kinetically stable configurations. Moreover, since FNP occurs through solvent-displacement, the way in which the solvent and anti-solvent are mixed plays an important role, which is often overlooked. Here we propose a multiscale approach, which combines molecular dynamics (MD), a Smoluchowski population balance equation (PBE) and computational fluid dynamics (CFD), to model the FNP process, from the atomistic-scale up to the macro-scale. The particle formation process is not described with the usual nucleation-and-growth approach, but as Brownian aggregation of the polymer molecules into nanoparticles. Being the final nanoparticles amorphous, no energy barrier to the aggregation process is considered, whereas the effects of both turbulent mixing and turbulent aggregation on the evolution of the nanoparticles are accounted for. The main novelty of this work is that the aggregation kernel appearing in the PBE, coupled in turn with CFD, is calculated from MD simulations, following the multiscale modeling paradigm. The model is tested on the FNP of poly-ε-caprolactone nanoparticles in acetone-water mixtures. Predictions for the final mean nanoparticle size are found in good agreement with experiments, especially at high initial polymer concentrations, where the hypothesis of no energy barrier is more realistic.

1. Introduction

Although the flash nano-precipitation (FNP) process of polymer nanoparticles has been extensively investigated, both with

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http://dx.doi.org/10.1016/j.ces.2017.04.047

experimental and modeling approaches, numerous are the challenges and the issues that still need to be addressed. Above all, this kind of systems is simulated by using models, designed to describe what happens at the equilibrium (Jones, 2002). These neglect therefore kinetic effects, which are also well-known to play an important role (Johnson and Prud'homme, 2003b; Lince et al., 2008), in determining, for example, the size and structure of the final nanoparticles (Celasco et al., 2014; Valente et al., 2012a,b). Another important limitation of the developed models is that the nanoparticle formation process is investigated and modeled only at one scale, by using for example molecular dynamics (MD), Monte Carlo (MC) methods and various coarse-grained models (Sun and Yang, 2014; Wang and Larson, 2015; Yuan et al., 2010). While these methods can capture the molecular interactions, they are unable to account for the effect that the fluid flow has on the nanoparticle formation process, particularly important when investigating the scale-up of these processes or their transfer from batch to continuous, as it happens in continuous manufacturing. Moreover they are inherently constrained at time- and length-scales which are too small to model system size comparable to the experimental ones (Capretto et al., 2011; Li et al., 2006; Rajagopalan, 2001; Yan and Xie, 2013).

We want to overcome these limitations by developing a novel multiscale model, which accounts for kinetic effects and that addresses both the molecular- and meso-scale, as well as the macro-scale. The model is here validated for the case of FNP of poly-ε-caprolactone (PCL) nanoparticles in acetone–water mixture. PCL is a saturated aliphatic polyester with hexanoate repeated units, employed in a wide range of applications, ranging from biomedical devices to controlled drug-delivery systems. Its popularity is due to its biocompatibility with the human body (Who et al., 2000), as well as to the harmlessness of the degradation products (Maeda, 2001). The methodology developed and tested in this work has however a wider range of applications, as it can be used also to describe other "soft systems" such as surfactants, colloids, liquid crystals, proteins, DNA (Bockstaller et al., 2005; Cohen et al., 2011a,b,c,d; Collins et al., 2004; Ferrone et al., 1985; Knowles et al., 2009; Oosawa and Asakura, 1975; Oosawa and Kasai, 1962; Zhou and Ferrone, 1990). Moreover, it could also be used as an exploratory tool to estimate the effect of fluid dynamics on nucleation, following recent works on this topic (Mura and Zaccone, 2016).

The experimental technique used to induce the FNP is the solvent-displacement method, where the PCL polymer molecules are dissolved in a so-called "good" solvent (e.g. acetone) and the solution is then mixed with a "bad" solvent or anti-solvent (e.g. water) for the polymer, but with which the "good" solvent is fully miscible. The presence of the poor solvent induces the polymer molecules aggregation in clusters or nanoparticles of variable sizes (Jones, 2002). Solvent-displacement often takes place in very small continuous mixers, such as the confined impinging jets mixer (Johnson and Prud'homme, 2003a) (CIJM), where solvent and anti-solvent are mixed together continuously and in a controlled way (Johnson and Prud'homme, 2003b), completely defining the environment in which FNP occurs.

The multiscale model developed in this work describes the FNP as an aggregation process, as also proposed by other authors (Cheng et al., 2010), but for the first time it calculates the rate with which polymer molecules interact (via the so-called aggregation kernel) directly from MD simulations (Di Pasquale et al., 2014). MD data are, in fact, used to fit the Flory law (Flory, 1953; Rubinstein and Colby, 2003) for the radius of gyration and the Stokes–Einstein law for the diffusion coefficient of single PCL polymer molecules, completely defining the aggregation kernel appearing in the Smoluchowski population balance equation (PBE). This fitting is then extended to clusters of polymer molecules to predict the evolution of the cluster mass distribution (CMD), in turn employed to quantify the polydispersity of the nanoparticles in terms of the number of polymer molecules belonging to a polymer nanoparticle. The evolution of the CMD is dictated by the PBE, solved with the quadrature method of moments (QMOM) (Marchisio et al., 2003) inside a computational fluid dynamics (CFD) code, to account for the inhomogeneous mixing between the acetone and water streams and for the influence of turbulence on the process. Including mixing in the description of FNP is particularly important, as FNP is very fast, almost instantaneous, mixing-limited (Cheng et al., 2010) and irreversible, and is therefore strongly influenced by spatial inhomogeneities (Johnson and Prud'homme, 2003a,b). Being, for the test cases considered in this work, the flow turbulent, it is also necessary to consider the effect of turbulent fluctuations on the aggregation process. This is done, in the Favre-averaged Navier-Stokes equations (FANS) framework by using the direct quadrature method of moments coupled with the interaction and exchange with the mean (DQMOM-IEM) model (Fox, 2003). As it clearly emerges the FNP process is here described on three different scales: molecular-scale, by using MD, cluster-scale, by means of the Smoluchowski PBE, and macro-scale, by means of CFD.

The model is in this work validated against experimental data referring to different mixing conditions in a CIJM, different initial polymer concentrations and two different molecular weights for the PCL. Comparison with experimental data allows to assess the range of validity of the approach, in line with the theory, and to conclude that this multiscale approach not only provides a molecular insight into the structure of the polymer nanoparticles but also seems to be more effective than other alternatives, based for example on the classical nucleation theory (CNT) (Di Pasquale et al., 2012; Garcia et al., 2014) or other more detailed, but similar, theories in predicting macroscopic data (Di Pasquale et al., 2013).

2. Governing equations

As already mentioned, turbulent mixing between acetone and water is described here with CFD. Turbulence is treated by using the standard $k - \varepsilon$ turbulence model, coupled with the enhanced wall treatment. Since two fluids (i.e. acetone and water) with different densities are involved the FANS approach is adopted. The continuity equation for the acetone–water mixture is solved together with the Navier-Stokes equations, the equations for the turbulent kinetic energy, k, and the turbulent dissipation rate, ε, as common practice with the standard $k - \varepsilon$ model. As these equations are very well known and are already implemented in the CFD code, they are omitted here and readers interested in the details can refer, for example, to our previous work (Di Pasquale et al., 2012). A detailed summary on how the PBE is solved and how equations are implemented in the CFD code follows.

In order to efficiently describe the evolution of the population of polymer molecule clusters, a Smoluchowski PBE is employed. In what follows we will refer to the polymer particles as nanoparticles or molecular clusters, interchangably. The PBE operates on the CMD, $f(\mathbf{x}, n)$, defined in such a way that the quantity, $f(\mathbf{x}, n)\mathrm{d}n$, represents the number density of molecular clusters or nanoparticles containing n polymer molecules at position $\mathbf{x}$. The variable n, referred to in what follows as dimensionless cluster mass, is discrete, but since it varies between one and very large numbers, is treated here as a continuous variable. It is also useful to highlight here that, in the acetone inlet, when the polymer molecules are dissolved in the solvent, and do not show any tendency to self-assemble, the CMD is always equal to zero, except for $n = 1$, where it assumes the value corresponding to the initial polymer molecule number density in acetone. Moreover, as the