

KINETIC MODELING OF NANOPRECIPITATION USING CFD, MICRO-PIV, AND POPULATION BALANCE EQUATION

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Summary

A model study was conducted for Flash Nanoprecipitation, a novel approach to produce protected functional nanoparticles. First, the quality of mixing in a custom-designed microscale multi-inlet vortex (MIV) reactor was investigated experimentally using a parallel-reaction system and then modeled using computational fluid dynamics (CFD), which showed great agreement. Next, CFD turbulence models (RANS, LES) were validated using microscopic particle image velocimetry (microPIV). Finally, a bivariate population balance equation (PBE) was derived to model the aggregation kinetics of nanoprecipitation. By coupling with the CFD model for scalar mixing, the role of mixing effects in Flash Nanoprecipitation was investigated.

Keywords

nanoprecipitation, CFD, microPIV, PBE.

Introduction

Functional nanoparticles are becoming increasingly important in the development of materials for dyes, cosmetics, pharmaceuticals, and numerous other applications, resulting in great interest in the techniques controlling the stability and size range in their production. For example, studies have shown that colloidal drug carriers such as liposomal and micellar dispersions consisting of particles 50-400 nm in diameter have great promise in formulating anticancer therapeutics, which can selectively target tumors¹. The Flash Nanoprecipitation technique – a novel approach to produce functional nanoparticles stabilized by amphiphilic copolymer directed assembly – is able to produce particles in such size ranges. In addition, the nanoparticles encapsulated by copolymer also make it possible to afford long circulation times in the body².

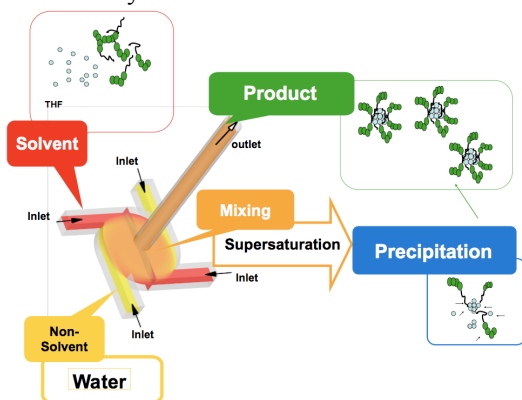


FIG 1. Flash Nanoprecipitation process.

During the Flash Nanoprecipitation process, the drug and copolymer are dissolved in a solvent and injected into a customized micro-scale mixing device (Fig. 1). The solvent is mixed rapidly with a nonsolvent to create supersaturation and therefore precipitate drug and/or copolymer particles. The copolymer attaches to the organic aggregates to stabilize them by preventing further aggregation³. In this process, mixing is thought to be uncoupled from particle aggregation in order to attain homogeneous kinetics for the precipitation, which is crucial for obtaining particles within a narrow size range.

Mixing Model for the Micro-Reactor

The evaluation of the quality of mixing has been carried out in two microscale devices: the confined impinging jet (CIJ) and the multi-inlet vortex (MIV) reactors. An MIV reactor shown in Fig. 1 is comprised of a round mixing chamber and four injectors arranged in directions allowing vortical turbulent flow. The MIV reactor is of special interest due to its wide range of operating conditions. In contrast, the CIJ reactor requires equal inlet momenta for the impinging jets. To simulate the mixing process in the MIV reactor, a computational fluid dynamics (CFD) model was developed and its predictions compared with the experimental data. The characteristic mixing times were measured by applying a parallel reaction system, which employs two competitive reactions (acid-base reaction and DMP hydrolysis) as a “chemical ruler”. In the CFD model, the two-environment DQMOM-IEM model was applied to solve the mixture fraction and reaction progress variables⁴.

Investigation of Fluid Dynamics in the MIV Reactor

In order to validate the turbulence model applied in the mixing study, the fluid dynamics were investigated experimentally using microscopic particle image velocimetry⁵ (microPIV), a technique for measuring instantaneous velocity field data in microfluidic devices (Fig. 2).

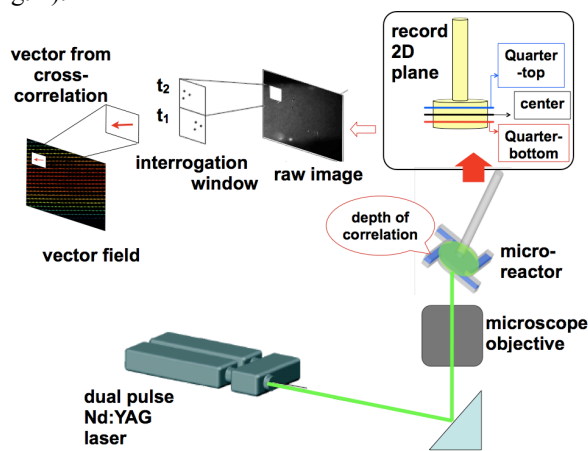


FIG 2. Illustration of the microPIV experiment.

The microPIV data were used to evaluate the accuracy of the CFD models in simulating the flow within the MIVR. Laminar simulations were performed for the low Reynolds number cases, and large-eddy simulations (LES) using the Smagorinsky-Lilly subgrid model were performed for the higher Reynolds number cases. The 3-D flow simulations were performed using inlet conditions matching those measured in the experiments, and the predictions of the CFD models were found to be quite good for all Reynolds numbers investigated⁶. Fig. 3 shows a successful comparison of experimental data and simulations at 3 different heights within the MIV reactor.

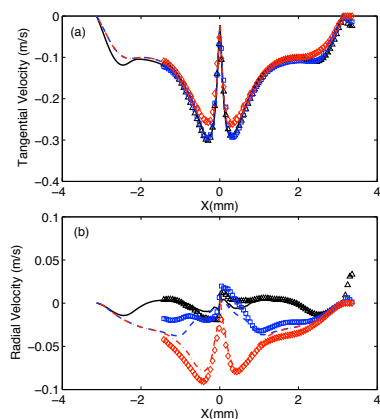


FIG 3. Velocity profile comparison of microPIV and CFD at $Re=93$. Symbols: experimental data; lines: simulations.

Kinetic Model for the Nanoprecipitation Process

To describe particle formation processes as functions of mixing time and physical properties of inlet streams, an aggregation model was developed using a population balance equation (PBE). The bi-variate number density function $n(p,q)$ in the PBE represents aggregates

containing p di-block copolymers and q organic molecules. In nanoprecipitation, nanoparticle aggregation is arrested by copolymer assembly on the particle surface. The di-block micelle unimer is in a chain shape composed of a hydrophobic block (A-block) and a hydrophilic block (B-block). When a unimer aggregates with organic particles, the A-block attaches to the organic particles and the B-block "deactivates" the attached area onto which no others can attach. The organic particles are then stabilized, encapsulated in star-like polymer micelles. Thus, as aggregation number of copolymers (p) increases, aggregation slows down and growth is eventually arrested. A bi-variate aggregation kernel has been developed to account for the aggregation kinetics. The kernel includes three different micellization cases: free coupling, unimer insertion, and large aggregate fusion⁷. A novel bi-variate form of the quadrature method of moments (QMOM) was developed to solve for the moments of the PBE, and validated against numerical solutions for $n(p,q)$. Due to its computational efficiency, the QMOM representation can be implemented in the CFD solver to study the role of mixing effects in the Flash Nanoprecipitation process. Using typical experimental conditions^{3,4}, the effect of varying the Reynolds number on the particle size distribution has been investigated, and the model results compared with available experimental data from Flash Nanoprecipitation.

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