UNIVERSITÀ DEGLI STUDI DI SALERNO

**Department of Industrial Engineering**
Master’s Degree in Chemical Engineering

# CFD-PBE MODELING OF NANOPARTICLE FORMATION IN A COAXIAL JET MIXER

Thesis in
**Modellistica Matematica e Controllo**
**per l’Industria di Processo**

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*Alla mia famiglia*

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# Abstract

Nanoparticles play a crucial role in drug delivery, sensing, and advanced materials, yet their performance depends on precise control of size and polydispersity during synthesis. Among bottom-up routes, nanoprecipitation offers simplicity and versatility, but batch processes suffer from poor mixing, while microfluidic systems trade control for scalability. Flash nanoprecipitation (FNP) in Coaxial Jet Mixers (CJMs) bridges this gap, providing millisecond mixing under continuous operation and tunable flow ratios, conditions transferable to large-scale manufacturing if described predictively. This thesis develops an experimentally grounded CFD-PBE framework for liposome formation by FNP, implemented in ANSYS Fluent. Hydrodynamics are modeled via RANS (RSM with Enhanced Wall Treatment) using composition-dependent mixture properties, while a discrete population balance (25 bins) captures nucleation and growth of liposomes driven by supersaturation derived from measured solubility data. The model reproduces key features of self-assembly: supersaturation and particle formation localize within the first 2-3 cm downstream of the injection point, where nucleation and growth dominate. Time-scale analysis indicates mixing-controlled formation (Da > 1), with nucleation slower than growth and large-eddy turnover governing homogenization. Model predictions qualitatively align with experimental observations, capturing the overall dependence of liposome size on flow conditions. The framework provides a mechanistic basis for predictive design and can be extended with micromixing-aware closures, secondary mechanisms (e.g., coalescence), and scale-resolving CFD (e.g., LES) to enhance reliability across operating conditions.

# Chapter Five

# Conclusions

*In this chapter, the conclusions of the thesis work will be discussed, along with potential future developments.*

This thesis developed and assessed a mechanistic CFD-PBE framework to describe liposome formation in a coaxial turbulent jet mixer. The modeling strategy was built in layers: hydrodynamics and ethanol-water mixing; introduction of phosphatidylcholine (PC) as precipitating solute; and fully coupled discrete PBEs for nucleation and growth. A comparative analysis of turbulence closures and near-wall options led to the selection of the Reynolds Stress Model (RSM) with Enhanced Wall Treatment (EWT) as the most reliable combination to capture anisotropy and near-wall shear in the jet shear layer, which then served as the backbone for all CFD-PBE simulations.

On the experimental side, three datasets underpinned model construction and validation. First, lipid extract quantification and compositional HPLC analysis confirmed PC as the representative species. Second, the PC density was estimated pycnometrically and used within the mixture property framework. Third, the PC solubility in ethanol/water exhibited a re-entrant trend with a pronounced maximum near $\omega_{etoh} \approx 0.6$ and was implemented as a piecewise correlation for the saturation function used by the CFD-PBE model. These data anchored the thermodynamic driving force for precipitation directly to experiment.

The calibrated model reproduces the main features of precipitation-driven self-assembly within the mixer. Supersaturation and the associated nucleation-growth activity are confined to the first few centimeters downstream of the needle; below $S = 1$, kinetics cease and particle properties stabilize. The model parameters were adjusted based on the experimental data to reproduce the observed stabilization of liposome size after approximately 2.5 cm, yielding a supersaturation decay ($S \approx 1$ at ~2.8 cm) consistent with the DLS measurements. Therefore, the simulated profiles reflect the experimentally observed axial extent of the active formation zone, where particle growth effectively freezes out.

Population-balance diagnostics clarify the respective roles of nucleation and growth. Nucleation is localized in the smallest class (bin 24), after which growth transports dispersed volume toward larger classes; the highest particle volume fractions reside in intermediate bins (≈19-15, corresponding to 31.7-80 nm) where growth slows and accumulation occurs, while the contribution of the largest bins is negligible. These features provide a mechanistic basis to interpret the measured and simulated PSDs under the reference operation.

The time-scale analysis identifies the controlling steps. Within the supersaturated region, the large-eddy turnover time is about an order of magnitude higher than the micromixing time, demonstrating that bulk turbulent turnover limits homogenization under the investigated conditions. Kinetically, nucleation is much slower than growth, making nucleation the intrinsic kinetic bottleneck. A local Damköhler number computed from the limiting kinetic time (nucleation) and the limiting turbulent time (large-eddy) indicates predominantly mixing-controlled conditions ($Da > 1$) over most of the active zone, particularly downstream as turbulence decays.

Across operating conditions, variations in hydrodynamics modulate both the residence time within the supersaturated region and the final liposome size. Longer residence times favor a more extended growth period and thus larger diameters, whereas shorter contact times lead to earlier freeze-out and smaller particles. The overall trends confirm that nucleation remains the rate-limiting step, while growth rapidly equilibrates once supersaturation begins to decay, establishing a direct link between mixing dynamics, residence time, and the stabilized particle size.

Model-to-experiment comparison against a DoE dataset shows that the framework captures the overall dependence of liposome size on flow conditions with a slight overestimation; the two highest-inner-flow cases deviate more markedly, plausibly due to pump-limited uncertainties and/or modeling simplifications (steady, axisymmetric flow; no explicit micromixing; no secondary particle processes).

The results indicate clear directions for advancement. Future work should focus on improving both the predictive reliability of the CFD-PBE framework and its ability to reproduce experimental trends more quantitatively. On the turbulence side, incorporating a micromixing model (e.g., IEM) consistently coupled to the discrete PBE would allow the model to track scalar variance at the Kolmogorov/Batchelor scales, precisely where nucleation is triggered. From the kinetic standpoint, refining the nucleation and growth parameters and extending the model to account for limited aggregation or coalescence phenomena, could help capture the experimental PSDs more faithfully. On the CFD side, exploring 3D or scale-resolving simulations (e.g., DES or LES localized in the near-jet region) for selected conditions would enhance the description of unsteady mixing and shear-layer intermittency, which strongly affect local supersaturation fields. Finally, at the experimental level, expanding the database of validation points by varying flow-rate ratios, total flow rate and PC feed concentration, would provide a broader basis for calibration and uncertainty quantification, thereby consolidating the model's generality and predictive robustness.

In summary, this thesis delivers a coherent CFD-PBE description of liposome formation in a coaxial turbulent jet mixer, identifies nucleation and large-eddy turnover as the rate-limiting phenomena, and shows that, under the tested conditions, liposome size is governed primarily by mixing-controlled supersaturation relaxation within the first ~2–3 cm downstream of injection. The framework provides a credible starting point for micromixing-aware, fully predictive simulations to guide design and scale-up of continuous nanoparticle manufacturing in coaxial jet platforms.

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