CFD modeling of precipitation of nanoparticles in Confined Impinging Jet Reactors

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Motivation and goals

• Organic actives are often dispersed in polymer structures forming nano-spheres and nano-capsules

• The main advantages of these particulate systems are:
  • Possibility of release of actives insoluble in water
  • Controlled drug-delivery
  • Passive and active targeting
  • Increased lifetime in bloodstream

• The polymer usually has to be hydrophilic, flexible and non-ionic
Motivation and goals

• Very often block co-polymers are used: poly(MePEGCA-co-HDCA) poly (methoxypolyethylene glycol cyanoacrylate – co – hexadecyl cyanoacrylate)

• HDCA chains (hydrophobic) are inserted in the organic active core

• PEG chains (hydrophilic) are oriented towards the water phase, forming a flexible protective layer that reduces the absorption of plasmatic proteins
Preparation

• Nano-particles are produced by precipitation (solvent displacement)
Effect of mixing

- Mixing controls nucleation, molecular growth (and aggregation) rates and therefore controls the particle size distribution.
- Mixing (and cohesion forces) control the mass ratio of organic active/polymer in each particle.
- Generally speaking good product quality is obtained with very high mixing rates.
Aim of this work

• Design, optimization and scale-up of a continuous process to produce significant amounts of particles with a certain size range (≈200 nm) and with a specific active-to-polymer ratio

• CFD is used to simulate the precipitation process and its interaction with turbulent mixing

• Reactor configuration: confined impinging jet reactor (CIJR)

• Reacting systems:
  • parallel reaction scheme
  • barium sulphate precipitation

• Real system: acetone-PEG-doxorubicine + water
Confined Impinging Jet Reactor

- The flow regimes in the reactor are characterized by the jet Reynolds number.
- In this work we investigated $300 < \text{Re} < 3000$ for $d=1\text{mm}/D=4.76\text{ mm}$.
- Flow field simulations were run with LES and RANS approaches in Fluent 6.1.22.
- Different three dimensional unstructured grids were tested in order to find a grid independent solution.
- LES: $\approx 500,000$ cells for the full geometry.
- RANS: $\approx 100,000$ cells (with finer resolution near the walls).

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Large Eddy Simulation

- Fluent: box filter with bandwidth $\Delta$ equal to the cell size

$$\frac{\partial \overline{U}_i}{\partial t} + \frac{\partial \overline{U}_i \overline{U}_j}{\partial x_j} = \nu \frac{\partial^2 \overline{U}_i}{\partial x_i \partial x_i} - \frac{1}{\rho} \frac{\partial p}{\partial x_i} - \frac{\partial \tau_{ij}^r}{\partial x_j}$$

- The residual stresses are closed by using the Smagorinsky model

$$\tau_{ij}^r = -2\nu S_{ij}$$ filtered Strain rate

$$\nu_r = (C_s\Delta)^2 \bar{S} \quad C_s = 0.08 - 0.10 - 0.12$$

- Next steps: implementation of a dynamic SGS model

- Cluster: 6 Xeon bi-processors 2400 (MHz)
Large Eddy Simulation

- Laminar inlet conditions (parabolic profile)
- Instantaneous velocity magnitude for Re= 704 and Re=2696
Large Eddy Simulation

- Velocity magnitude for Re=3000
(RANS)

- Different turbulence models have been tested: $k-\varepsilon$, RNG $k-\varepsilon$, relizable $k-\varepsilon$, $k-\omega$, RSM

- Different near wall treatments have been tested: standard wall function, non-equilibrium wall function, enhanced wall treatment

- Results show that RSM with enhanced wall treatment gives the best agreement with time-averaged LES velocities

- Further analysis needs experimental data or DNS data (Alfredo Soldati, University of Udine)
Step 1: Parallel chemical reaction

- In order to test mixing efficiency in the confined impinging jet reactor a parallel reaction has been used

\[ A + B \rightarrow R \quad A + C \rightarrow S + (A) \]

- The system can be described with mixture fraction and progress reaction variables

\[
\begin{align*}
\frac{c_A}{c_{Ao}} &= \xi - \xi_{s1} Y_1 \\
\frac{c_B}{c_{Bo}} &= 1 - \xi - (1 - \xi_{s1}) Y_1 \\
\frac{c_C}{c_{Co}} &= 1 - \xi - (1 - \xi_{s2}) Y_2 \\
\xi_{s1} &= \frac{c_{Bo}}{c_{Ao} + c_{Bo}} \\
\xi_{s2} &= \frac{c_{Co}}{c_{Ao} + c_{Co}}
\end{align*}
\]
Step 1: Parallel chemical reaction

- Micro-mixing is modeled with the DQMOM-IEM model
- Functional form of the Probability Density Function:

\[ f(\xi; x, t) = \sum_{\alpha=1}^{N} p_{\alpha}(x, t) \delta[\xi - \xi_{\alpha}(x, t)] \]

- ... where weights \( w_{\alpha} \) and weighted abscissas \( w_{\alpha}\xi_{\alpha} \) are calculated by solving their corresponding transport equations and forcing the moments of the PDF to be correctly predicted

- With two nodes (\( N=2 \))

\[
\begin{align*}
m_0(x, t) &= p_1 + p_2 \\
m_1(x, t) &= p_1\xi_1 + p_2\xi_2 \\
m_2(x, t) &= p_1\xi_1^2 + p_2\xi_2^2 \\
m_3(x, t) &= p_1\xi_1^3 + p_2\xi_2^3
\end{align*}
\]
Step 1: Parallel chemical reaction

B+C → Mixture fraction
A → Mixture fraction variance
Step 1: Parallel chemical reaction

- Comparison between DQMOM-IEM and beta-PDF for the mixture fraction PDF
Step 1: Parallel chemical reaction

- Transport equations for weights and weighted abscissas

\[
\frac{\partial p_1}{\partial t} + \langle u_i \rangle \frac{\partial p_1}{\partial x_i} - \frac{\partial}{\partial x_i} \left[ (\Gamma + \Gamma_t) \frac{\partial p_1}{\partial x_i} \right] = 0
\]
\[
p_2 = 1 - p_1
\]

\[
\frac{\partial (p_1 \xi_1)}{\partial t} + \langle u_i \rangle \frac{\partial (p_1 \xi_1)}{\partial x_i} - \frac{\partial}{\partial x_i} \left[ (\Gamma + \Gamma_t) \frac{\partial (p_1 \xi_1)}{\partial x_i} \right] = \gamma p_1 p_2 (\xi_2 - \xi_1) + \frac{p_1 c_1 + p_2 c_2}{\xi_1 - \xi_2}
\]

\[
\gamma = \frac{C_\phi k}{2 \varepsilon}
\]

\[
c_1 = \Gamma_t \left( \frac{\partial \xi_1}{\partial x_i} \frac{\partial \xi_1}{\partial x_i} \right)
\]

\[
c_2 = \Gamma_t \left( \frac{\partial \xi_2}{\partial x_i} \frac{\partial \xi_2}{\partial x_i} \right)
\]
**Step 1: Parallel chemical reaction**

- The reacting system is described by transport equations for:
  \[ p_1 \quad p_1 \xi_1 \quad p_2 \xi_2 \quad p_1 Y_{2,1} \quad p_2 Y_{2,2} \]

- ... and algebraic equations for:
  \[ p_2 = 1 - p_1 \quad Y_{1,1} \quad Y_{1,2} \]

Selectivity of the second reaction

No micromixing limit

\[ \gamma = \frac{C_\phi k}{2 \varepsilon} \]
Step 1: Parallel chemical reaction

- Comparison with experimental data from Johnson & Prud’homme (2003) for the CIJR

$$C_\phi = f(Re_1)$$

Step 2: barium sulphate precipitation

- Different jet Reynolds numbers (80<Re<2500)
- Different reactant concentration (Ba\(^{++}\), SO\(_4^{-}\))
- Different reactant concentration ratio (Ba\(^{++}\)/SO\(_4^{-}\))

\[ Ba^{++} + SO_4^- \rightarrow BaSO_4 \]

- The reaction is very fast and mixing sensitive
- Relevant phenomena involved: nucleation, molecular growth and aggregation
Step 2: barium sulphate precipitation

- Effect of Reynolds number $\text{Ba}^{++}$:800 $\text{SO}_4^-$:100 mol/m$^3$
Step 2: barium sulphate precipitation

- The CFD model uses the DQMOM-IEM ($N=2$) for micromixing
- Standard kinetic expressions for nucleation and growth

$$B_{\text{hom}} = 1.5 D_{AB} \left( \sqrt{k_{ps} S N_A} \right)^{7/3} \sqrt{\frac{\gamma_{CL}}{k_B T}} V_m \exp \left( -\frac{16\pi}{3} \left( \frac{\gamma_{CL}}{k_B T} \right)^3 \frac{V_m^2}{(\nu \ln S)^2} \right)$$

$$G = 2 \frac{ShD_{AB} \sqrt{k_{ps} M}}{\rho} \frac{S - 1}{L}$$

- Brownian aggregation kernel

$$\beta = \frac{2k_B T}{3\mu} \left( L_1 + L_2 \right) \left( \frac{1}{L_1} + \frac{1}{L_2} \right) \alpha$$

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Step 2: barium sulphate precipitation

- The population balance equation is solved by using the QMOM (for the two reacting environments)

- The Particle Size Distribution is computed through the moments of the distribution \((k=0,\ldots,3)\)

\[
m_k (x,t) = \int_{0}^{+\infty} n(L;x,t)L^k dL \approx \sum_{i=1}^{N} w_i L_i^k
\]

\[
\frac{\partial m_k (x,t)}{\partial t} + \frac{\partial}{\partial x_i} (\langle u_i \rangle m_k (x,t)) - \frac{\partial}{\partial x_i} \left( \Gamma_t \frac{\partial m_k (x,t)}{\partial x_i} \right) = 0^k J(x,t)
\]

\[
+ k \sum_{i=1}^{N} G(L_i) w_i L_i^{k-1} + \sum_{i=1}^{N} w_i \sum_{j=1}^{N} w_j \left( L_i^3 + L_j^3 \right)^{k/3} \beta(L_i, L_j) - \sum_{i=1}^{N} w_i L_i^k \sum_{j=1}^{N} w_j \beta(L_i, L_j).
\]
Step 2: barium sulphate precipitation

Re=2696

$c_{A0} = c_{B0} = 100 \text{ mol/m}^3$

Supersaturation  Nucleation rate (1/m$^3$s)  Growth rate (m/s)
Step 2: barium sulphate precipitation

- Effect of the aggregation efficiency on the final mean particle size
- Crystallite size from X-ray measurements \( \approx 20-40 \text{ nm} \)
Step 3: acetone-PEG-doxorubicine/water

- Thermodynamics data concerning polymer and active solubility
- Bivariate population balance equation: DQMOM
- Validation by comparison with Monte Carlo simulations
Step 3: acetone-PEG-doxorubicine/water

- Validation by comparison with Monte Carlo simulations

\[
m_{k,l} = \int_{0}^{\infty} \int_{0}^{\infty} n(\xi_1, \xi_2) \xi_1^k \xi_2^l \, d\xi_1 \, d\xi_2
\]

- Coalescence
- Aggregation and restructuring

\[
\tau = t \beta(0)m_{00}(0)
\]
Conclusions and next steps

• The flow field in the confined impinging jet reactor has been modeled with RANS and LES (further validation with DNS data)

• Micromixing is taken into account with the DQMOM-IEM model and validation is carried out by comparison with experimental data from literature

• The population balance is described with QMOM (monovariate) and DQMOM (bivariate) resulting in a small number of additional scalars (4-8)

• Simulation of the real process will be carried out when thermodynamic and kinetic expressions will be available
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