Simulation of mixing and precipitation of nanoparticles for pharmaceutical applications with CFD and MD

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Abstract: We present a new approach to calculate the nucleation rate in solvent-displacement processes. The expression obtained from classic nucleation theory seems not to be adequate to describe this kind of process when macromolecules of polymer are used, due to the number of approximations involved. A new expression for the nucleation rate is derived and molecular dynamics simulations are used to obtain all the parameters involved. This expression is then implemented together with the classical one into computational fluid dynamics simulations and predictions compared.

Keywords: Solvent-displacement process, molecular dynamics, poly-ε-caprolactone, nucleation rate, computational fluid dynamics

1 Introduction

Interest in polymer nanoparticles has grown in recent years due to their unique properties as nanocarriers for controlled drug delivery. Polymer nanocarriers can incorporate hydrophobic, water-insoluble drugs [1] and reduce the side-effect associated with most medical treatment, especially for cancer treatment, thanks to their high specificity in the targeting the desired zone [2]. Among the processes used in nanoparticles production, solvent displacement in micro-mixers is one of the most employed. In solvent-displacement processes, fast mixing of solvent (containing the polymer and the drug) and anti-solvent (in which both the polymer and the drug are insoluble) induce particle formation. One of the most important operating conditions is the mixing rate of the solvent and the anti-solvent streams. In this work we focus on the confined impinged jets mixer (CIJM) [3] that allows the fine tuning of this latter parameter. In order to be used as carriers, polymer nanoparticles must have certain well-defined properties, notably particle size distribution (PSD) within a specific range and hydrophilic surface [4]. The PSD is strictly related to fluid dynamics and mixing inside the CIJM. The aim of this work is to develop a comprehensive model, based on computational fluid dynamics (CFD) and population balances, able to describe the precipitation process. Particular attention will be devoted to the reformulation of the nucleation rate via molecular dynamics (MD) simulations.
2 Overview on MD and CFD

Our CFD model couples the solution of the continuity and momentum balance equations with the population balance model (PBM). The turbulent velocity field is described through the Reynolds-averaged Navier-Stokes equations (RANS) approach, while the PBM is solved with the Quadrature Method of Moments (QMOM). The interaction between turbulence and particle formation is treated with the Direct Quadrature Method of Moments with the Interaction and Exchange with the Mean (DQ MOM-IEM) approach. Particle formation is described using the Classical Nucleation Theory (CNT). CNT is based on the assumption that there exists an energy barrier to nucleation of particles. The variation of free energy of formation of a cluster of \( n \) molecules \( \Delta G_n \) is given by:

\[
\Delta G_n = n\Delta G' + A_n\sigma
\]  

(1)

where \( n \) is the number of molecules inside the cluster, \( \Delta G' \) is the variation of free energy associated to one molecule in the new phase, \( A_n \) is the surface of a cluster and \( \sigma \) is the interface energy between the cluster and the mixture. It is assumed that \( \Delta G' \) and \( \sigma \) do not depend on the dimension of the cluster. In CNT many approximations are employed to obtain a simple formulation which produces reliable enough results for simple systems, but do not seem very suitable for more complex systems (such as polymer molecules interacting with drug molecules). Dirksen and Ring [5] proposed for the nucleation rate the following expression

\[
J(S) = 2D d^5 \exp \left( -\frac{\Delta G^*(S)}{k_B T} \right)
\]

(2)

in which \( D \) is the coefficient diffusion of the molecule in the solvent/anti-solvent mixture, \( d \) is the molecular diameter, \( k_B \) is the Boltzmann constant, \( T \) is the temperature, \( S \) is the super-saturation and \( \Delta G^* \) is the free energy of the cluster with critical dimension \( r^* \). We call the critical dimension of a cluster \( r^* \) the dimension of a cluster for which Eq. (1) is maximized. In obtaining this equation it is generally assumed that the limiting step is the diffusion from the bulk to the cluster. Kelton [6], obtained an exact equation for the nucleation rate

\[
J(x) \sum_{n=u}^{v} \frac{1}{N_n^e \gamma} \exp \left( -\frac{\Delta g_n}{2k_B T} \right) = 1
\]

(3)

where \( O_n = 4n^{\frac{5}{2}} \) represents the number of sites where one molecule can be included in a cluster (i.e. \( O_n \) represents the number of molecules that can be placed with their centre on the surface of a sphere that enclose all the molecules in the cluster), \( \gamma \) is the rate of molecules that enter in a cluster, \( \Delta g_n \) is the difference of free energy between a cluster of size \( n \) and a cluster of size \( n + 1 \), \( N_n^e \) is the equilibrium number of cluster of size \( n \), given by

\[
N_n^e = N_i \exp \left( -\frac{(\Delta G_n - \Delta G_1)}{k_B T} \right)
\]

(4)

where \( N_i \) is the number of molecules still in the initial phase and \( u \) and \( v \) represents a minimum and a maximum dimension for a cluster. In Eq. (4) \( \Delta G_1 \) is introduced to recover the self consistency (i.e. there is no energetic barrier for cluster composed by one molecule, that is to say, for a single molecule). Starting from Eq. (3) we can derive a suitable expression for the nucleation rate for the system under study. The first thing to notice is that to obtain an exact expression for \( J(x) \) all the possible values of the dimension of cluster must be considered in the summation. However, at the value of \( n^* \), the critical size of the nuclei, \( N_n^e \) has a maximum. Hence, elements around \( n^* \) should
dominate. That is to say that \( u \) and \( v \) can be identified quite arbitrarily as long as they are chosen far from \( n^* \). \( \Delta g_n \) is taken equal to zero and this approximation improves with the increasing of the dimension of the cluster. \( N_i(x) \) can be calculated as

\[
N_i(x) = \frac{c(x)}{M_w} N_A \tag{5}
\]

were \( c(x) \) is the composition of the mixture at point \( x \), \( M_w \) is the molecular weight of the polymer and \( N_A \) is the Avogadro number. \( \gamma(x) \) can be obtained from the diffusion coefficient \( D \) of polymer in liquid. Due to the fact that there are different environments in the reactor, in general \( D \) will be a function of space. Hence,

\[
\gamma(x) = \frac{6D(x)}{\lambda^2(x)} \tag{6}
\]

where \( \lambda \) can be taken equal to the diameter of the molecule in that particular mixture. \( \Delta G_n \) is set equal to Eq. (1). For spherical clusters, \( O_n = (36\pi \frac{1}{3}(v_{moln})^{\frac{2}{3}} \) and the free volume energy in the new phase can be written as

\[
\Delta G' = -k_B T \ln S(x) \tag{7}
\]

in which the supersaturation is defined as \( S(x) = c(x)/c_{eq}(x) \), and \( c_{eq} \) is the equilibrium concentration of the polymer at point \( x \). Finally, combining all the expressions, the following equation is obtained for the nucleation rate:

\[
J(x) \sum_{n=u}^{v} \left(4n^{\frac{2}{3}}\gamma(x)N_i(x) \exp \left(\frac{(n-1)k_B T \ln (S(x)) - 36\pi \frac{1}{3}(v_{mol}(n-1))^{\frac{2}{3}} \sigma(x)}{k_B T} \right) \right)^{-1} = 1 \tag{8}
\]

Some of the parameters appearing in this equation, such as \( c_{eq}(x) \), \( \sigma(x) \), can be found by independent experiments [7]. The problem stands in the estimation of quantities related to single molecules (e.g., \( v_{mol} \)). This parameter can however be conveniently evaluated via MD simulations.

As already highlighted most of these microscopic properties depend on the mixture composition and therefore on the physical location in the CIJM. For this reason in MD simulation different solvent/anti-solvent ratios (\( R_s \)) are considered. The molecular volume can be estimated from the radius of gyration of the macromolecules, which represents the dimension of the molecules and is defined as:

\[
\langle R_G^2 \rangle = \frac{1}{(N_b + 1)^2} \left\langle \sum_{i>j} R_{ij}^2 \right\rangle \tag{9}
\]

in which \( \langle \cdot \rangle \) denotes the ensemble average, \( N_b \) is the number of the bonded atoms in the polymer chain and \( R_{ij}^2 \) is the distance between the \( i \) – th and \( j \) – th atom. \( \langle R_G^2 \rangle \) depends upon the solvent in which the polymer is dissolved as stated by Flory: "the better the solvent the greater the swelling of the molecule. Conversely, the poorer the solvent the smaller the molecule" [8], and \( N_b \) which in turn depends on molecular weight. It is found that polymer obeys at a simple power law for the dependence from \( N_b \):

\[
\langle R_G^2 \rangle \propto N_b^{2\nu} \tag{10}
\]

in which \( \nu \) is an exponent which depends from the characteristics of the solvent and its
value is $\nu = 3/5$ in a good solvent and $\nu = 1/3$ in a poor solvent [8] However it can change slightly from one polymer to another as shown in [9] for poly-styrene.

3 Results and discussion

The system we propose to study is the precipitation of poly-$\varepsilon$-caprolactone (PCL) nanoparticles in a CIJM through the solvent displacement process in which acetone is the solvent and water is the anti-solvent. The water/acetone flow rate ratio considered is $R = 2$, whereas the initial concentration of PCL in acetone is 2.5mg/mL; the $M_w = 14000$ g/mol. In the first part we show and compare the results for nucleation rate and supersaturation calculated with Eqs. (2) and (8) in considering constant PCL molecular volume and then, after showing some results for the MD part, we complete our nucleation term with the results obtained from MD.

In Fig. 1 the nucleation rate and supersaturation in the CIJM resulting from the simulation carried out using the two different forms of $J(x)$ models are showed. While the magnitude and the profile of $S$ is quite similar in both cases, the resulting nucleation rates are not. In addition, while in the simulation of $J(x)$ with Eq. (2) contains some points of the domain in which the value of $J(x)$ is unreasonably higher than in the rest of the domain, in the other case we observe a smoother profile. Analyzing the results from a numerical point of view, Eq. (8) stabilizes the solution. It is important to highlight here that of course it is possible that some points are characterized by values of the nucleation
rate higher than the rest, but what seems not to be correct is that these points do not belong to the symmetry plane showed in Fig. (1).

With MD we simulate the polymer in pure water and pure acetone. The polymer and acetone are described using the OPLS (Optimized Potential for Liquid Simulation) with parameters and geometry reported in [10]. After a short period of equilibration (3 ns), in which the properties of the solvent was compared with data in literature [11], a molecule of PCL was inserted in the simulation box, as showed in Fig. 2. Simulation time in each case is 40 ns in order to calculate the diffusion coefficient. Results for the radius of gyration are reported in Tab. 1. The values obtained for $\nu$ are very close to the theory, both for a poor solvent ($\nu \approx 0.333$) and for a good solvent ($\nu \approx 0.6$). The molecular volume is not computed directly using $R_g$, resulting in its overestimation. This latter increases as the molecule is far from the spherical shape (i.e., when is completely uncoiled as in a good solvent) but through the radii of gyration about the $x$, $R_x$, $y$, $R_y$ and $z$, $R_z$, axes. To obtain a description of the variation of $R_x$, $R_y$, $R_z$ we define the shape factor $\langle S_x \rangle = \langle R_x^2 \rangle / \langle R_G^2 \rangle$, $\langle S_y \rangle = \langle R_y^2 \rangle / \langle R_G^2 \rangle$, $\langle S_z \rangle = \langle R_z^2 \rangle / \langle R_G^2 \rangle$ which can be considered independent from $M_w$ [12]. Results for PCL are reported in Tab. 2

<table>
<thead>
<tr>
<th>pure Water</th>
<th>pure Acetone</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCL 10</td>
<td>PCL 10</td>
</tr>
<tr>
<td>$\langle R_G^2 \rangle$</td>
<td>0.63 ± 0.04</td>
</tr>
<tr>
<td>PCL 30</td>
<td>PCL 30</td>
</tr>
<tr>
<td>$\langle R_G^2 \rangle$</td>
<td>1.15 ± 0.16</td>
</tr>
<tr>
<td>$\nu$</td>
<td>0.292</td>
</tr>
<tr>
<td></td>
<td>0.489</td>
</tr>
</tbody>
</table>

Table 1: $\langle R_G^2 \rangle$ in (nm$^2$) obtained from the MD simulation for PCL molecules (constituted by 10 and 30 monomers) in pure water and pure acetone.

<table>
<thead>
<tr>
<th>pure Water</th>
<th>pure Acetone</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\langle S_x \rangle$</td>
<td>0.497 ± 0.036</td>
</tr>
<tr>
<td>$\langle S_y \rangle$</td>
<td>0.300 ± 0.014</td>
</tr>
<tr>
<td>$\langle S_z \rangle$</td>
<td>0.196 ± 0.026</td>
</tr>
<tr>
<td>$\langle S_x \rangle$</td>
<td>0.717 ± 0.009</td>
</tr>
<tr>
<td>$\langle S_y \rangle$</td>
<td>0.204 ± 0.004</td>
</tr>
<tr>
<td>$\langle S_z \rangle$</td>
<td>0.062 ± 0.01</td>
</tr>
</tbody>
</table>

Table 2: Shape factors for PCL in pure water and pure acetone.

As one can expect, convolution of PCL is greater in water than in acetone, as it is possible to see from Tab. 2 in which results for acetone suggest that in this solvent PCL is uncoiled along the x-axis.
4 Conclusion

A new way of calculate the nucleation rate in the solvent-displacement process for nanoparticles precipitation is presented. This new approach does not need the approximations done in CNT and seems to be able to correctly describe the behavior observed. In the second part it is showed that MD is a very useful tool in order to characterize the properties of the polymer and therefore can be used to obtain the parameters needed by the precipitation model. This approach can be further extended to obtain a full description of the behaviour of the polymer (e.g. diffusion coefficient and mean-square-displacement) in the mixture.

References


