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Effect of Different Good Solvents in Flash Nano-Precipitation via Multi-scale Population Balance Modeling-CFD coupling approach

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Abstract

A computational and modeling approach is used to highlight the key factors that affect the polymer nanoparticles (NP) size in flash nano-precipitation (FNP), when the good solvent, e.g., acetone, is replaced by acetonitrile, tetrahydrofuran and tert-butanol. A population balance model is coupled with computational fluid dynamics to study the kinetics effects on FNP. The mean NP size is predicted in terms of mean radius of gyration via the Flory law of real polymers. The effect of different good solvents is modeled in terms of solute-solvent interactions, using the Flory-Huggins theory and Hansen solubility parameters. Promising results show how the proposed methodology is

Abbreviations: ACT, acetone; ACN, acetonitrile; CMD, cluster mass distribution; CFD, computational fluid dynamics; CIJM, confined impinging jets mixer; DQMOM-IEM, direct quadrature method of moments coupled with the interaction and exchange with the mean; FNP, flash nano-precipitation; HSP, Hansen solubility parameters; NP, Nanoparticles; PCL, poly- ϵ -caprolactone; PBM, population balance model; PDF, probability density function; QMOM, quadrature method of moments; TBA, tert-butanol; THF, tetrahydrofuran.

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able to investigate the role played by different good solvents, analyzing single factors at the time. A deep insight into both the dynamics of mixing and the dynamics of aggregation is therefore reached and the main mechanisms involved are pointed out, showing a good agreement with experimental data.

Keywords: Flash Nano-Precipitation, Hansen Solubility Parameters, Flory-Huggins Theory, Population Balance Model, CFD

1. Introduction

Nanoparticles (NP) production has been widely investigated in the last decade, due to the wide range of its applications such as cosmetics, pharmaceuticals, textiles, agriculture, and food science (Das et al., 2009; Demetzos, 2016; Nelson, 2002; Prasad et al., 2014; Wu and Guy, 2009). The control of the final NP size and particle size distribution is of paramount importance, especially in controlled drug delivery systems applications, in which a threshold dimension must not be exceeded to guarantee the correct drug release at the targeted area inside the blood stream (Hans and Lowman, 2002; Petitti et al., 2008). In particular, polymer NP formation received a lot of attention from both experimental and modeling approaches, in order to determine the key parameters that govern the final NP targeted size (Celasco et al., 2014; Valente et al., 2012a,b; Zelenková et al., 2018). Due to their biological applications, polymers must be biocompatible and non-toxic; here, poly- ϵ -caprolactone (PCL) is used, since it has been considered one of the best candidates for this purpose (Who et al., 2000). One of the most used techniques for NP production is represented by the so-called flash nano-precipitation (FNP). It consists in the mixing of a ‘good solvent’ in which the

19 polymer is dissolved and a ‘bad solvent’ (also named as anti- or non-solvent),
20 which is miscible with the good solvent but not compatible with the polymer.
21 The anti-solvent destabilizes the mixture inducing polymer aggregation and
22 precipitation of the formed NP. The phenomenon that governs NP forma-
23 tion just described above is also labelled as solvent displacement (Saad and
24 Prud’homme, 2016).

25 Several studies have been already carried out to understand fluid dynam-
26 ics effects at macro- and micro-scales (Johnson and Prud’homme, 2003b;
27 Liu and Fox, 2006) for the confined impinging jets mixer (Johnson and
28 Prud’homme, 2003a) (CIJM) and also for different geometries, such as the
29 vortex mixer (VM) (Marchisio et al., 2009, 2008), the multi-inlet vortex mixer
30 (MIVM) (Liu et al., 2008), the T-mixer (Gradl et al., 2006) and the Y-mixer
31 (Choi et al., 2005). Other experimental (Lince et al., 2008) and modeling
32 (Cheng et al., 2010; Di Pasquale et al., 2012; Lavino et al., 2015, 2017) at-
33 tempts also showed the importance of accounting for the kinetics besides
34 the thermodynamics for FNP. However, numerous are still the open topics
35 under debate that need to be addressed. One of them is represented by the
36 effect of different good solvents in NP formation via FNP and has become
37 a crucial aspect of the industrial NP production. Here, the interesting case
38 of NP formation in CIJM is considered, with PCL as solute and water as
39 anti-solvent. Four different good solvents are investigated: acetone (ACT),
40 acetonitrile (ACN), tetrahydrofuran (THF) and tert-butanol (TBA).

41 The experimental procedure for polymeric NP production through solvent
42 displacement has been extensively applied throughout the years, testing dif-
43 ferent polymers; in particular, it was validated for PCL, obtaining also good

incorporation efficiency with different loading substances (Barresi et al., 2015; Celasco et al., 2014; Ferri et al., 2017; Lavino et al., 2019; Lince et al., 2008, 2009, 2011; Massella et al., 2018; Valente et al., 2012a,b; Zelenková et al., 2015, 2014). In experiments, water quenching (i.e. sudden dilution with distilled water) is employed as stabilization technique over time of the precipitated NP (Barresi et al., 2015; Ferri et al., 2017; Zelenková et al., 2015, 2014), preventing further aggregation in the reactor outlet (Barresi et al., 2015; Saad, 2007) and preserving the particle distribution. This is implicitly taken into account in our modeling approach by ‘freezing’ the predicted NP sizes at the outlet of the mixer (Lavino et al., 2017, 2019; Lince et al., 2009) allowing a consistent comparison with the experimental data, as it will be explained more clearly in the theoretical and modeling section of this work.

Experiments showed how different NP size and size distribution may be reached by just changing the good solvent (Ferri et al., 2017; Zelenková et al., 2015), a crucial aspect in several industrial contexts. At this level of description, from the experiments side, it is hard to fully understand the parameters that play a key role in determining different mean NP size at the outlet of the process. Hence, modeling and simulations are here employed to further examine those aspects and, eventually, to analyze them separately. A population balance model (PBM) which uses molecules as building blocks coupled with computational fluid dynamics (CFD) approach is used, already proposed and validated in an our previous work (Lavino et al., 2017), where the presence of the drug is neglected, as also in this present work. The main novelty of the proposed methodology consists in the incorporation of the thermodynamics theory of Flory-Huggins interaction parameter (Hansen, 2007) inside the ki-

69 netic model (PBM-CFD) to study the different good solvent effects on the
 70 final predicted NP size. Recent efforts also showed at the molecular scale
 71 the importance of accounting for the thermodynamics on the polymer con-
 72 formation in mixtures (Gartner and Jayaraman, 2018; Lavino et al., 2018,
 73 2020; Martin and Jayaraman, 2016). More specifically, the Flory-Huggins
 74 interaction parameter χ is here correlated to the mean radius of gyration,
 75 expressed, in turn, in terms of Flory law (Flory, 1953). The solubility of PCL
 76 is accounted for by using the Hansen solubility parameters (HSP) for the dif-
 77 ferent solvents investigated in this work. This modeling approach brings the
 78 advantage of considering thermodynamic quantities inside the kinetic model,
 79 such as the Flory-Huggins χ parameter and the HSP, extensively reported in
 80 literature for a wide range of solvents and, more importantly, shows how to
 81 correlate them to the prediction of the final mean NP size. In this way, it is
 82 possible to readily obtain a transferable model, when different good solvents
 83 are used in FNP. Kinetics and thermodynamics are therefore intertwined in
 84 a unique modeling tool and used to investigate the effect of different good
 85 solvents on NP precipitation. Another very important advantage is the pos-
 86 sibility to analyze single factors at a time, unlike experiments, getting a
 87 deeper insight into the main phenomena. In this way, the dynamics of mix-
 88 ing is studied separately from the dynamics of aggregation, highlighting the
 89 physical and modeling properties that mainly influence polymer aggregation,
 90 when different good solvents are used.

91 The paper is structured as follows: modeling and theoretical backgrounds
 92 are presented in section 2, with particular attention to the multi-scale kinetic
 93 model (CFD and population balance model) together with the thermodynam-

94 ics of NP formation by solvent displacement; then, operating conditions and
95 numerical details are reported in section 3. The main results are discussed
96 in section 4 and, finally, conclusions and future developments are presented
97 in section 5.

98 **2. Theoretical Background**

99 This section is dedicated to the theoretical background and the modeling
100 strategy adopted in this work. The theory presented here is divided into
101 two main subsections: *i.* the kinetic model, in which the main equations
102 of the population balance model (PBM) and computational fluid dynamics
103 (CFD) are presented; *ii.* the thermodynamic model, used to study the solute-
104 solvent interactions, with a particular focus on the theory of real polymers
105 in solution.

106 The PBM-CFD coupling approach is able to describe the effect of kinetics
107 on NP precipitation by accounting for the interplay of many factors, such as
108 the inlet flow rate, the turbulent mixing and the particles-collision dynamics
109 (details thereof will be presented in section 2.1), which have been proven to
110 strongly affect the final NP size at certain operating conditions (Lavino et al.,
111 2017). More specifically, the PBM predicts the mean particles size at the
112 outlet of the mixer, as well as the evolution of the particles size distribution,
113 also named cluster mass distribution (CMD), as it will be labelled from now
114 on. On the other hand, the thermodynamics of real polymers is used to build
115 up a modeling bridge, able to embrace the different good solvent effects, and
116 strictly interconnected to the PBM, as it will be explained in section 2.2.

117 Regarding the flow field, the steady-state Favre-averaged continuity and

Navier–Stokes equations are solved in the CFD code, together with the equations for the turbulent kinetic energy, k , and the turbulent dissipation rate, ε , in line with the standard $k - \varepsilon$ turbulence model (Andersson et al., 2012). As these equations are very well known and already implemented in the CFD code, they are omitted here for a sake of brevity and the readers can refer to our previous work Di Pasquale et al. (2012) for further details. The Favre-average approach (Favre, 1965) is necessary, since two fluids with different densities are involved. The fluid can still be considered incompressible, but density fluctuations are taken into account in this way.

The effect of turbulent fluctuations on NP formation is modeled by the direct quadrature method of moments, coupled with the interaction-by-exchange-with-the-mean (DQMOM-IEM) method (Marchisio and Fox, 2005), in which two nodes/environments are employed for the quadrature procedure. Below, two subsections are dedicated respectively to the PBM (aggregation dynamics and micro-mixing models) and the thermodynamics of real polymers in solution, presenting the main modeling details employed in this work.

2.1. Population Balance Model for FNP

A population balance model (PBM) is employed to describe the evolution of the cluster mass distribution (CMD). Being this model extensively presented in our previous work, here we report only the definition of the CMD and the kinetic equation in which the moments of the CMD are transported. For a complete detailed description of the PBM, please refer to Lavino et al. (2017). The CMD is modeled with a number density function, $f(\mathbf{x}, n)$, defined in such a way that the quantity $f(\mathbf{x}, n)dn$ represents the number density of NP, or molecular clusters, containing n macromolecules at position \mathbf{x} .

143 The term ‘macromolecule’ is here referred to as PCL molecule of molecular
 144 weight $M_W = 14000 \text{ g mol}^{-1}$. The variable n is labelled as dimensionless
 145 cluster mass or aggregation number and it can be treated as a continuous
 146 variable, since it varies from one to very large numbers. In the pure good sol-
 147 vent stream the PCL is completely dissolved and no aggregation takes place.
 148 Therefore, the CMD corresponds to a Dirac delta function centred in $n = 1$.
 149 By normalising the CMD with the Avogadro number (necessary to keep the
 150 simulations numerically stable), the CMD in the good solvent stream (initial
 151 conditions) corresponds to the initial polymer molar concentration.

152 The PBM is here solved with the quadrature method of moments (QMOM)
 153 approach (Marchisio and Fox, 2013). Let us recall the definition of the generic
 154 j^{th} -order moment:

$$m^{(j)} = \int_0^\infty f(n)n^j \mathrm{d}n. \quad (1)$$

155 The advantage is twofold: on one hand, the computational cost is heavily
 156 reduced, compared to other discretized methods (Marchisio and Fox, 2013);
 157 on the other hand, the moments of the CMD represent physical measur-
 158 able quantities. Indeed, $m^{(0)}$ is the total cluster number density, $m^{(1)}$ is a
 159 conserved quantity and corresponds to the total number density of macro-
 160 molecules, whereas the ratio between $m^{(1)}$ and $m^{(0)}$ results in the average
 161 number of macromolecules per NP or molecular cluster.

162 By applying the moment transform and the Favre average $\langle \cdot \rangle$, the steady-
 163 state transport equation for the j^{th} -order moment of the CMD $f(n)$ reads as
 164 follows:

$$\begin{aligned} \frac{\partial}{\partial \mathbf{x}} \cdot (\bar{\rho} \langle \mathbf{U} \rangle \langle m^{(j)} \rangle) - \frac{\partial}{\partial \mathbf{x}} \cdot \left(\bar{\rho} \Gamma_t \frac{\partial \langle m^{(j)} \rangle}{\partial \mathbf{x}} \right) = \\ = \frac{\bar{\rho}}{2} \left\langle \int_0^\infty \int_0^\infty \left[(n + n')^j - n^j - n'^j \right] \beta(n, n') f(n) f(n') dn dn' \right\rangle, \quad (2) \end{aligned}$$

165 where $\Gamma_t \approx \nu_t/0.7$, is the turbulent diffusivity which is much larger than the
 166 Brownian diffusivity and is calculated from the turbulent viscosity, ν_t , by
 167 assuming a turbulent Schmidt number of 0.7 (Andersson et al., 2012), $\bar{\rho}$ is
 168 the time-averaged fluid density and $\langle \mathbf{U} \rangle$ is the Favre-averaged fluid velocity,
 169 as the particle Stokes number is much less than unity (Baldyga and Orciuch,
 170 2001). The aggregation kernel, $\beta(n, n')$, that appears in the source term on
 171 the right hand side of Eq. (2) represents the rate with which two clusters
 172 (or, equally, nanoparticles) collide and aggregate (second order point process
 173 Marchisio and Fox (2013)). The source term consists of two contributions:
 174 a negative term that states the disappearance of two clusters containing
 175 respectively n and n' polymer macromolecules, and the appearance of the
 176 aggregate cluster (positive term) formed by $n + n'$ macromolecules. It is
 177 noteworthy to stress that molecular dynamics investigations (Di Pasquale
 178 et al., 2014) have shown that the freely-jointed chain model (Rubinstein
 179 and Colby, 2003) can be applied in this mathematical formulation, so that
 180 a cluster made by n molecules of molecular weight M_w will behave as a
 181 cluster made by one single PCL molecule of molecular weight $n \cdot M_w$. This
 182 assumption affects the formula used for the mean clusters size, in terms of
 183 Flory law, as it will be shown in section 2.2.

184 The aggregation kernel accounts for two mechanisms: Brownian motions

185 and turbulent fluctuations. Here, the assumption is that these two contri-
 186 butions are simply additive, and it holds on the physical evidence that at
 187 low initial polymer concentration in good solvent stream, Brownian aggrega-
 188 tion dominates over the turbulent one, and vice versa at high initial polymer
 189 concentration. Applying the Stokes-Einstein formulation (Elimelech et al.,
 190 1998), the aggregation kernel in function of the mean radius of gyration of
 191 the two NP, or molecular clusters, that are self-assembling or aggregating
 192 assumes the following expression (Cheng et al., 2010):

$$\begin{aligned} \beta(n, n') = \eta \frac{2k_B T}{3\mu} \frac{(\llbracket R_g(n, x_s) \rrbracket + \llbracket R_g(n', x_s) \rrbracket)^2}{\llbracket R_g(n, x_s) \rrbracket \llbracket R_g(n', x_s) \rrbracket} + \\ + 1.2944\eta \sqrt{\frac{\varepsilon}{\nu}} (\llbracket R_g(n, x_s) \rrbracket + \llbracket R_g(n', x_s) \rrbracket)^3, \quad (3) \end{aligned}$$

193 where μ is the molecular viscosity of the suspending liquid (i.e. mixture
 194 of the good and bad solvents and therefore function of the good solvent
 195 molar fraction x_s (Lavino et al., 2017)), k_B is the Boltzmann constant, ε is
 196 the turbulent dissipation rate, ν is the mixture kinematic viscosity and $\llbracket \cdot \rrbracket$
 197 represents the ensemble-average.

198 The term η stands for an aggregation efficiency, only dependent on the
 199 initial supersaturation ratio. It is represented by a stepwise function: zero for
 200 undersaturated solutions and one for supersaturated solutions. The super-
 201 saturation ratio is defined as the ratio between the local PCL concentration
 202 and its equilibrium one. Their expressions are reported in our previous work
 203 (Lavino et al., 2017). When the supersaturation ratio is locally greater than
 204 unity, or in other words when the local PCL concentration is greater than its

205 local solubility (i.e., equilibrium concentration), which in turn depends on
 206 the local solvent composition, self-assembly and aggregation are triggered;
 207 namely PCL molecular self-assemble forming NP that then further aggre-
 208 gate forming the final NP. The main assumption is that molecules are more
 209 stable when in a molecular cluster and therefore they self-assemble or aggre-
 210 gate irreversibly. This implies that the energy barrier for particle formation
 211 is null and therefore particle formation, under these conditions, can be in-
 212 terpreted as spinodal decomposition rather than nucleation. In line with the
 213 classical nucleation theory this model is applicable only when the initial su-
 214 persaturation is very large, as also found out in our previous work, where the
 215 model was originally validated by Lavino et al. (2017). An accurate quantifi-
 216 cation of the precipitated PCL with respect to what is left in solution during
 217 FNP still remains an unsolved issue; when the supersaturation ratio is much
 218 larger than unity, it is reasonable to assume that most of PCL precipitates
 219 out with the operating conditions investigated in this work.

220 $\llbracket R_g(n, x_s) \rrbracket$ represents the ensemble-averaged radius of gyration, depen-
 221 dent on the aggregation number n and on the good solvent molar fraction
 222 x_s . It is expressed in terms of the Flory law, as explained in subsection 2.2.

223 Moreover, the dynamics of mixing is also considered, as turbulence fluc-
 224 tuations and local mixing gradients (supersaturation) affect PCL aggrega-
 225 tion. More specifically, the solvent mixture fraction is described in terms of
 226 probability density function (PDF) for the good solvent mass fraction, ξ , in
 227 the good solvent-water mixture. As anticipated above in the text, mixing is
 228 treated with the DQMOM-IEM approach with only two nodes/environments.
 229 This turns out to be a strategic approach in modeling a binary mixture when

no reaction occurs (Di Pasquale et al., 2012; Gavi et al., 2007). In line with the DQMOM-IEM, the weights and weighted abscissas in the two environments 1 and 2 are directly solved through suitable transport equations:

$$\frac{\partial}{\partial \mathbf{x}} (\bar{\rho} \langle \mathbf{U} \rangle p_1) - \frac{\partial}{\partial \mathbf{x}} \left(\bar{\rho} \Gamma_t \frac{\partial p_1}{\partial \mathbf{x}} \right) = 0, \quad (4)$$

and $p_2 = 1 - p_1$ (the PDF integrates to unity), together with:

$$\begin{aligned} \frac{\partial}{\partial \mathbf{x}} (\bar{\rho} \langle \mathbf{U} \rangle p_1 \xi_1) - \frac{\partial}{\partial \mathbf{x}} \left(\bar{\rho} \Gamma_t \frac{\partial}{\partial \mathbf{x}} (p_1 \xi_1) \right) = \\ = \bar{\rho} \gamma_M p_1 p_2 (\xi_2 - \xi_1) + \frac{\bar{\rho} \Gamma_t}{\xi_1 - \xi_2} \left(p_1 \frac{\partial \xi_1}{\partial \mathbf{x}} \frac{\partial \xi_1}{\partial \mathbf{x}} + p_2 \frac{\partial \xi_2}{\partial \mathbf{x}} \frac{\partial \xi_2}{\partial \mathbf{x}} \right). \end{aligned} \quad (5)$$

The right-hand side of Equation (5) represents the molecular mixing, also referred to as micro-mixing term, mathematically closed with the IEM approach (Fox, 2003); $\gamma_M = \frac{C_\phi}{2} \frac{\varepsilon}{k}$ is the micro-mixing rate, where C_ϕ is a parameter that depends on the local Reynolds number (Fox, 2003) and ε and k are respectively the turbulence dissipation rate and the turbulent kinetic energy. More details can be found in Gavi et al. (2007). By inverting the subscripts 1 and 2, the transport equation related to $p_2 \xi_2$ can be obtained. ξ_1 and ξ_2 can be interpreted as local good solvent mass fractions in the two "environments", representing turbulent composition fluctuations. The Favre-averaged mass fraction can be calculated as follows:

$$\langle \xi \rangle = \int_0^1 p(\xi) \xi d\xi \approx p_1 \xi_1 + p_2 \xi_2, \quad (6)$$

where $p(\xi)$ is the PDF related to the mixture fraction ξ . According to Equa-

tion (6), also the good solvent volume fraction can be defined as:

$$\langle \xi_v \rangle = p_1 \xi_{1,v} + p_2 \xi_{2,v}, \quad (7)$$

where $\xi_{i,v}$ is the volume fraction in the environment $i = 1, 2$, function of the mass fraction through the relation $\xi_{i,v} = [1 + (1/\xi_i - 1) \cdot \rho_s/\rho_w]^{-1}$, with ρ_s and ρ_w the good solvent and water densities, respectively.

2.2. Thermodynamics of real polymers in solution

This section is referred to the thermodynamic model that is incorporated into the PBM-CFD model. Let us recall the Flory theory of real polymers in solution (Flory, 1953). The polymer conformation in a given mixture is the balance between attractive and repulsive forces among the repeated units, taken into account through the so called excluded volume v . The polymer conformation is strictly related to the nature of the solvent and, more specifically, the polymer mean squared radius of gyration, appearing in Eq. (3), can be expressed via the Flory law, that can in turn be extended to molecular clusters or NP containing n polymer molecules, as shown in our previous work:

$$\llbracket R_g^2(n, x_s) \rrbracket = k_s(x_s)(nM_w)^{2\nu_s(x_s)}, \quad (8)$$

where, as mentioned, the freely-jointed chain hypothesis is applied for a molecular cluster containing n PCL molecules, M_w is the molecular weight of a single PCL molecule and $k_s(x_s)$ and $\nu_s(x_s)$ are the Flory parameters, dependent, in turn, on the good solvent molar fraction x_s and on the nature of the solvent, as indicated by the subscript s . As far as the acetone is

265 concerned as good solvent, molecular dynamics calculations have been per-
 266 formed and interpolated and the corresponding functional forms determined
 267 in a previous work (Di Pasquale et al., 2014):

$$k_s(x_s) = k_{ref}(x_{ref}) = 0.0064 \exp(-3.15x_{ref}), \quad (9)$$

$$\nu_s(x_s) = \nu_{ref}(x_{ref}) = 0.30 + 0.45x_{ref} - 0.15x_{ref}^2, \quad (10)$$

268 where the subscript '*ref*' is introduced and from now on it will refer to as the
 269 reference solvent, namely the solvent for which all the necessary information
 270 is already provided from previous studies (acetone in this case).

271 When the repulsive forces dominate on the attractive ones among the
 272 monomers, the excluded volume v assumes a positive value and the polymer
 273 shows a more stretched (coil) conformation, corresponding to a good solvent
 274 condition, and the Flory exponent is equal to $3/5$. On the contrary, when
 275 the monomer attractive forces prevail, the excluded volume v is negative and
 276 the polymer exhibits a globule conformation. The latter case corresponds to
 277 a bad solvent condition and the Flory exponent is equal to $1/3$. When the
 278 two forces counterbalance each other, the excluded volume is null and the
 279 polymer assumes an ideal conformation, related to the so called ' θ -condition'.
 280 At the θ -condition, the Flory exponent is equal to $1/2$. The close proximity to
 281 the bad solvent condition is crucial to be locally reached in FNP, in order to
 282 induce the spontaneous self-assembly of the polymer molecules in molecular
 283 cluster or NP.

284 As a matter of fact, then, the polymer conformation is strictly depen-

285 dent on the nature of the surrounding solvent; therefore, the Flory-Huggins
 286 interaction parameter, $\chi_{s,p}$, is introduced in this modeling framework, being
 287 this one a direct measure of the energetic interaction of two components, e.g,
 288 a solute p and a solvent s , in turn, strictly correlated to the solubility of
 289 the solute in that specific solvent. The solubility is here taken into account
 290 by using the Hansen solubility parameters (HSP). The model presented in
 291 this work correlates the radius of gyration with the interaction parameter χ
 292 and the HSP, in order to be able to properly define the Flory parameters
 293 ($k_s(x_s)$ and $\nu_s(x_s)$) functional forms in Eq. (8), when different good solvents
 294 are employed.

295 Before getting into the HSP theory, a brief mention to the Hildebrand
 296 approach is mandatory. The Hildebrand solubility parameter (Hildebrand
 297 and Scott, 1950) of a substance corresponds to the cohesive energy per unit
 298 volume (it quantifies the work necessary to keep molecules close to each
 299 other) and reads as follows:

$$\delta = \left(\frac{\Delta H_v - RT}{V} \right)^{1/2}, \quad (11)$$

300 where ΔH_v is the vaporization enthalpy, R is the gas constant, T is the
 301 absolute temperature and V is the molar volume.

302 Hansen (2007) proposed a decomposition of the Hildebrand parameter
 303 into three different contributions, leading to the so-called Hansen solubility
 304 parameters (HSP):

$$\delta = (\delta_D^2 + \delta_P^2 + \delta_H^2)^{1/2}, \quad (12)$$

305 where δ_D considers the dispersion attractive forces (non-polar), δ_P accounts
 306 for the permanent dipole-permanent dipole interactions and δ_H for the hy-
 307 drogen bonds. The main advantage of the HSP approach is that polar effects
 308 are explicitly considered, differently from the Hildebrand parameter that is
 309 more suitable for apolar systems. The ability of a given solvent to solubilize
 310 a solute (e.g., polymer) is expressed in terms of solubility ‘distance’ from the
 311 solute itself and takes the form of the radius of a sphere in Hansen solubility
 312 space $\{\delta_D, \delta_P, \delta_H\}$ (Hansen, 2007):

$$Ra^2(\delta) = 4(\delta_{D,s} - \delta_{D,p})^2 + (\delta_{P,s} - \delta_{P,p})^2 + (\delta_{H,s} - \delta_{H,p})^2, \quad (13)$$

313 where $Ra(\delta)$ is the solubility ‘distance’, in terms of sphere radius in the
 314 Hansen space, and the subscripts s and p refer respectively to the solvent
 315 and the polymer. The term ‘4’ is added in order to make the shape of this
 316 functional form more spherical and less elliptical. The whole derivation can
 317 be found in Hansen (2007). The Flory-Huggins parameter relative to the
 318 interaction between the solvent and the polymer $\chi_{s,p}$ can be expressed as a
 319 function of the HSP through:

$$\chi_{s,p} = \frac{1}{2} \cdot \left(\frac{Ra(\delta)}{2R_m} \right)^2, \quad (14)$$

320 where $Ra(\delta)$ is the solubility distance, function of the HSP, as reported in
 321 Eq. (13) and R_m represents the radius of the solubility sphere, namely the
 322 maximum solubility distance (in Hansen solubility space) that allows the sol-
 323 vent to dissolve the solute. It is worthwhile to stress again that in Hansen
 324 phase space the coordinates are square roots of energies per unit volume;

therefore, talking about ‘solubility distances’ refers implicitly to ‘energetic distances’ contributions between two components. The parameter R_m is defined in such a way that the dependence of the solubility parameters on the polymer molecular weight is accounted for, thanks to the following expression:

$$R_m^2 = 0.5(1 + 1/r^{1/2})RT/V_m, \quad (15)$$

where V_m is the molar volume of the solvent and r is the degree of polymerization, which can be calculated as the ratio between the total PCL macromolecule and the single repeated unit molecular weights.

Solvents characterized by $Ra > 2R_m$ are classified as non-solvents (or bad solvents) with respect to that specific solute. On the contrary, all the solvents that belong to the Hansen solubility sphere ($Ra/2R_m$ smaller than unity) are classified as good solvents for that solute. In terms of $\chi_{s,p}$ interacting parameter, what stated above is equivalent to infer that when $\chi_{s,p} < 1/2$ the system is in good solvent condition, namely the solute molecule shows a more stretched conformation because the solvent-solute interactions are preferred over the solute-solute ones; $\chi_{s,p} > 1/2$ corresponds to bad solvent condition, namely the solute molecule shows a more globule conformation because the solute-solute interactions are preferred over the solvent-solute ones; $\chi_{sp} = 1/2$ is the θ -condition, corresponding to ideal conformation of the solute molecule occurring when the solute-solvent and solute-solute interactions are energetically equivalent.

As stated above, it is the local close proximity to bad solvent condition that energetically (and also entropically) drives the spontaneous PCL self-

assembly. Under these conditions, the radius of gyration of a single polymer molecule, R_g , can be expressed as a function of the Flory-Huggins parameter, $\chi_{s,p}$ (Rubinstein and Colby, 2003):

$$R_g \approx \frac{b^2}{|v|^{1/3}} N^{1/3} = \frac{bN^{1/3}}{(2\chi_{s,p} - 1)^{1/3}}, \quad (16)$$

where b is the Kuhn length (representative of the monomer length) and N is the number of repeated units that form the polymer chain. The expression reported in Eq. (16) is for real polymers in solution, since the negative excluded volume v is taken into account, as well as the Flory exponent $1/3$ appears, meaning that the single polymer molecule is surrounded by a bad solvent.

Starting from the relationship reported in Eq. (14), combined with Eq. (16), the whole procedure to find the Flory parameters functional forms for an unknown good solvent is developed and extensively explained in the following section.

3. Operating conditions and numerical details

3.1. Experimental background

Details about the experimental set-up which this modeling work is based on are here reported. As already stated, PCL is the polymer employed as solute in the FNP process investigated in this work. It is especially suitable for NP production in the pharmaceutical field and for biological applications, since PCL is bio-compatible and non-toxic (Who et al., 2000); among the other advantages, it is also permeable to low molecular weight drugs and can therefore be used for diffusion controlled delivery systems (Le Roy Boehm

370 et al., 2000). The experimental procedure for PCL NP production has been
 371 extensively validated throughout the years (Barresi et al., 2015; Celasco et al.,
 372 2014; Ferri et al., 2017; Lavino et al., 2019; Lince et al., 2008, 2009, 2011;
 373 Massella et al., 2018; Valente et al., 2012a,b; Zelenková et al., 2015, 2014).
 374 In the experimental context, the NP stabilization over time is of paramount
 375 importance and, in order to prevent further aggregation at the mixer outlet
 376 (Barresi et al., 2015; Saad, 2007) and to preserve the particle size distribu-
 377 tion, the outlet CIJM stream is usually quickly diluted in ultra-pure water
 378 and gently stirred to stabilize the NP suspension. Dilution, also labelled as
 379 ‘quench’, avoids the size increase due to Ostwald ripening effects (Barresi
 380 et al., 2015; Ferri et al., 2017; Zelenková et al., 2015, 2014) and keeps the
 381 precipitated NP stable up to 20 days (Le Roy Boehm et al., 2000). The
 382 water quench volume can have an effect of the final NP size (Barresi et al.,
 383 2015; Ferri et al., 2017), therefore all the experimental data shown here are
 384 obtained by quenching with the same water amount.

385 Although several polymers have been tested for NP production via FNP
 386 (Saad, 2007), very little experimental data are available in literature - to the
 387 best of the authors knowledge - showing the effect of different good solvents
 388 for the same specific type of polymer. As this represents the aim of this
 389 work, only experimental studies using PCL as polymer solute have produced
 390 enough data to guarantee a consistent comparison with our modeling results.

391 The experimental measurements were conducted via Dynamic Light Scat-
 392 tering (DLS) in diluted samples. By means of this technique the hydrody-
 393 namic radius, R_H , is estimated as the ratio between the 7th- and the 6th-order
 394 moments of the NP distribution. However, from our modeling point of view,

those quantities can be determined only with a numerical regression since the highest order moment we solve numerically is of order three (only two nodes in the aggregation model solved via QMOM). Therefore, it turns out to be more reasonable to express the mean particle size in terms of ratio between 1^{st} - and 0^{th} -order moments of the radius of gyration, R_g , distribution. Despite the hydrodynamic radius is generally greater than the radius of gyration (Bhattacharjee, 2016), we made the approximation: $R_H \approx R_g$ which holds particularly for spherical NP. Ultimately, it is an acceptable assumption for narrow CMD characterized by small poly-dispersity indexes (Barresi et al., 2015; Ferri et al., 2017).

3.2. Experimental set up

Four different good solvents are investigated in this work: acetone (ACT), acetonitrile (ACN), tetrahydrofuran (THF) and tert-butanol (TBA). As stated above, the acetone is labelled as the reference solvent, since a full modeling description thereof was already provided from previous molecular dynamics (Di Pasquale et al., 2014) and CFD simulations (Di Pasquale et al., 2012; Lavino et al., 2017). The geometrical dimensions of CIJM are: inlet and outlet diameters respectively equal to 1 and 2 mm. The width of the chamber is equal to 4.76 mm and its height is two times the width, in line with our previous work (Di Pasquale et al., 2012; Lavino et al., 2017).

3.3. Numerical details

According to the quadrature-based moments method employed in this work, the mean radius of gyration of a population of NP is calculated by means of nodes and weights of the quadrature procedure, as reported in

419 Lavino et al. (2017). The comparison with experiments is done in terms of
 420 this value exiting the CIJM. As stated above, during experiments the aggre-
 421 gation is limited and the particles are stabilized by quench water immediately
 422 after precipitation, preventing in this way further aggregation. It is reason-
 423 able to conclude, therefore, that measuring an average property at the outlet
 424 of the mixer from our simulations is totally equivalent to measure experi-
 425 mentally the given property immediately after quenching, via dynamic light
 426 scattering. However, it is worthwhile to mention that uncertainties present in
 427 the current work and the derivation of the models (Flory parameters, aggre-
 428 gation kernel, etc.) keep the predicted NP dimensions always included into
 429 the uncertainty range of the experimental results (Ferri et al., 2017; Lavino
 430 et al., 2017).

431 It is important to stress here that the choice of the good solvent has
 432 multiple effects on the FNP process. Indeed, by changing the good solvent
 433 we simultaneously change the thermodynamics of the interaction between the
 434 polymer chains and the good solvent and bad solvent mixture, the kinetics of
 435 polymer molecule self-assembly and the dynamics of mixing of the two feed
 436 streams (i.e., good and bad solvent). As mentioned in the introduction, the
 437 main objective of this work is to quantify each of these effects (on the final
 438 NP size and CMD) separately.

439 Density, viscosity and molar volume of the good solvents represent the
 440 physical-chemical properties that are expected to play a role in the FNP pro-
 441 cess. The density of the good solvent affects the fluid dynamics in the CIJM
 442 and the position of the impinging plane. The viscosity of the good solvent
 443 determines, via the Stokes-Einstein law already included in the aggregation

444 kernel reported in Eq. (3), the kinetics of molecules and molecular cluster
 445 self-assembly/aggregation. The molar volume of the good solvent defines the
 446 final good solvent molar fraction (for a given volume ratio between good and
 447 bad solvents). They are schematically listed in Table 1.

Table 1: Physical-chemical properties of the good solvents and Reynolds number, Re_s , range investigated in this work. Re_s refers to the good solvent inlet jet stream (see Eq. (17)).

Good solvent	Density, $kg\ m^{-3}$	Viscosity, $Pa\cdot s$	Molar volume, $cm^3 mol^{-1}$	Re_s range
ACT	780.85	3.10×10^{-4}	74.38	1069 – 6414
ACN	771.45	3.26×10^{-4}	53.21	1004 – 6026
THF	874.78	4.34×10^{-4}	82.43	855 – 5133
TBA	777.89	3.46×10^{-3}	95.29	95 – 573

448 As it can be seen in Table 1, acetone and acetonitrile have similar values
 449 of density and viscosity; instead, acetonitrile has a smaller molar volume;
 450 this may become a crucial factor that affects the mean NP size, as it will
 451 be shown in section 4. On the contrary, THF has higher density, viscosity
 452 and molar volume with respect to acetone and acetonitrile. More generally,
 453 despite all the solvents investigated here present similar physical properties,
 454 it is noteworthy to stress that TBA exhibits one order of magnitude higher
 455 viscosity. The way in which the density fluctuations are taken into account,
 456 as well as the local viscosity and molar fraction dependence on molar volumes,
 457 are reported in an our previous work (Lavino et al., 2017), and therefore here
 458 omitted for the sake of brevity.

459 Although experiments and simulations are conducted by varying the inlet
 460 flow rate, the mean radius of gyration of the NP exiting the CIJM is evaluated
 461 as a function of Reynolds number, Re_s , referred to the good solvent inlet jet

stream and its definition reads as follows:

$$\text{Re}_s = \frac{\rho_s d_{in} u_j}{\mu_s} \quad (17)$$

where d_{in} is the CIJM inlet diameter, u_j is the mean inlet jet velocity, ρ_s and μ_s are the good solvent density and viscosity respectively, as reported in Table 1. When comparing the dynamics of aggregation for different good solvents, the Reynolds number includes the inlet operating conditions as well as the physical properties of the good solvent to make the outcome of this work a general discussion, as it will be clearer in section 4.

Solvents and polymer Hansen solubility parameters (HSP), as well as the corresponding distances from PCL, Ra , are listed in Table 2.

Table 2: Hansen solubility parameters (HSP) and distances, Ra , from PCL (Eq. (13)) for all the components of the investigated system.

	δ_D , MPa ^{1/2}	δ_P , MPa ^{1/2}	δ_H , MPa ^{1/2}	Ra , MPa ^{1/2}
PCL	17.0	4.8	8.3	-
THF	16.8	5.7	8.0	1.0
ACT	15.5	10.4	7.0	6.5
TBA	15.2	5.1	14.7	7.4
ACN	15.3	18.0	6.1	13.8
Water	15.6	16.0	42.3	35.9

The distances from PCL are representative of the solvent affinity with the polymer. More specifically, the lower is the distance (last column in Table 2), the higher is the solvent-solute affinity. As expected, the water solubility distance is the highest value, much higher than the Hansen solubility sphere radius for PCL, $R_m \approx 9.8$ MPa^{1/2} (calculated by means of swelling tests Bordes et al. (2010)), proving therefore to behave as bad solvent. In

477 the Hansen phase space, acetone, THF and TBA belong to the Hansen sol-
 478 ubility sphere, behaving as good solvents. In the case of acetonitrile, the
 479 distance from PCL is shown to be slightly higher than the sphere radius.
 480 It is worthwhile mentioning that Bordes et al. (2010) obtained this value of
 481 R_m by performing swelling tests in which PCL initial concentration was two
 482 orders of magnitude higher than the one employed in this work. It is there-
 483 fore reasonable to assume that R_m would be much higher in this context,
 484 so that also acetonitrile leads to a full PCL solubilization, as seen in our
 485 experiments (Ferri et al., 2017), and consequently behaving as good solvent
 486 in these operating conditions.

487 In this analysis, the solute is the PCL and the solvent is the ‘good solvent-
 488 water’ mixture. Being the second phase made by a binary mixture, all the
 489 solubility parameters (e.g., HSP) and physical properties (e.g., molar volume)
 490 involved in the following calculations are weighted on the good-bad solvents
 491 volume and molar fractions. The binary mixture phase will be therefore
 492 generically labelled as ‘solvent’ from now on. The single PCL macro-molecule
 493 molecular weight $M_w = 14000 \text{ g mol}^{-1}$ and the repeated unit molecular
 494 weight $M_o = 114 \text{ g mol}^{-1}$. The term r appearing in Eq. (13) corresponds to
 495 the degree of polymerization, here simply evaluated as M_w/M_o .

496 Let us recall that in FNP the PCL solubility limit is overcome and the
 497 self-assembly induced only thanks to the presence of the bad solvent, which
 498 is a local effect. Furthermore, the mixing is generally very fast and efficient,
 499 leading to a well micro-mixed system in almost all the domain of the CIJM
 500 (Gavi et al., 2007). Hence, the assumption of considering the polymer chain
 501 at the mean good solvent molar fraction \bar{x}_s holds, after mixing occurs, in

the range $\bar{x}_s \in [0.15, 0.25]$ for all the good solvents, since the good solvent-to-water ratio in volume is constant and equal to unity. Consequently, the three-components phase diagram (water, good solvent and PCL) can be approximated as a two-components one (the polymer as solute and the binary mixture as solvent) (Flory, 1953). In these conditions, the single PCL radius of gyration dependence on $\chi_{s,p}$ can be expressed by means of Eq. (16), since the binary mixture behaves as a bad solvent, leading the single macromolecules to self-assemble. This concept will be confirmed by looking at the $\chi_{s,p}$ values, reported in Table 3 later on.

By using the relation reported in Eq. (16) for two different solvents $s1$ and $s2$ (e.g., $s1$ = acetonitrile-water and $s2$ = acetone-water), and assuming that the Kuhn length b (mainly a solute property) does not change too much for any solvent used, the following ratio can be readily obtained:

$$\frac{\llbracket R_g(n=1) \rrbracket_{s1}}{\llbracket R_g(n=1) \rrbracket_{s2}} \approx \frac{(2\chi_{s2,p} - 1)^{1/3}}{(2\chi_{s1,p} - 1)^{1/3}} = S_f, \quad (18)$$

where S_f is a scaling ratio, function of the solely Flory-Huggins parameters $\chi_{s1,p}$ and $\chi_{s2,p}$, calculated starting from the HSP through Eq. (14). The adopted strategy consists in setting $s2$ as the reference solvent, i.e., acetone-water in this case, for which the functional forms of Flory parameters are known from MD (Di Pasquale et al., 2014). By rearranging Eq. (18) as a function of the reference solvent, the following equality holds:

$$\sqrt{k_{s1}(x_{s1})M_w^{2\nu_{s1}(x_{s1})}} = S_f \cdot \sqrt{k_{ref}(x_{ref})M_w^{2\nu_{ref}(x_{ref})}}, \quad (19)$$

where, as stated above, the subscript *ref* refers to the acetone-water mix-

522 ture. Scaling factors S_f and Flory-Huggins parameters $\chi_{s,p}$ referred to the
 523 solvent-polymer systems investigated in this work, namely acetone-water,
 524 acetonitrile-water, THF-water and TBA-water, evaluated at mean good sol-
 525 vent molar fraction \bar{x}_s , are reported in Table 3.

Table 3: Flory-Huggins parameter, $\chi_{s,p}$, for acetone, acetonitrile, THF and TBA as good solvents with the relative scaling factors obtained from Eq. (18), at mean good solvent molar fraction, \bar{x}_s .

Solvent	\bar{x}_s	Flory-Huggins parameter, $\chi_{s,p}$	Scaling factor, S_f
ACT-water	0.20	0.926	1.00
ACN-water	0.25	1.007	0.94
THF-water	0.18	0.873	1.05
TBA-water	0.16	1.251	0.83

526 By looking at Table 3, the Flory-Huggins parameter is always greater than
 527 $1/2$ (θ -condition) for each solvent investigated here. This confirms what was
 528 already stated above: the systems are in bad solvent conditions and the single
 529 PCL macromolecules are spontaneously led to aggregate.

530 At this point, an iterative procedure can be carried out, based on Eq. (19)
 531 and on the values reported in Table 3. More specifically, Eq. (19) still presents
 532 two degrees of freedom, that are the Flory constant and exponent functional
 533 forms. By putting $\nu_{s1}(x_{s1}) = \nu_{ref}(x_{s1})$ as starting value, $k_{s1}(x_{s1})$ is univo-
 534 cally determined and with this new set of Flory parameters, say $k_{s1}^*(x_{s1})$ and
 535 $\nu_{s1}^*(x_{s1})$, simulations can be performed and the deviation against the experi-
 536 mental data is detected. Based on the deviation with respect to experiments,
 537 the Flory exponent is suitably adjusted to a new functional form, say $\nu_{s1}^{**}(x_{s1})$
 538 and, by means of Eq. (19), a new functional form for $k_{s1}^{**}(x_{s1})$ is obtained.
 539 With this new set of Flory parameters, simulations are performed until this

540 iterative procedure leads to an acceptable accordance against experiments.

541 This corresponds to the Flory parameters reported in Table 4.

Table 4: Flory parameters functional forms for acetone (reported in Eq. (9) and (10)), acetonitrile, THF and TBA.

Good solvent	$k_s(x_s)$	$\nu_s(x_s)$
ACT	$0.0064 \exp(-3.15x_s)$	$0.30 + 0.45x_s - 0.15x_s^2$
ACN	$0.0055 \exp(-3.15x_s)$	$0.30 + 0.40x_s - 0.10x_s^2$
THF	$0.0047 \exp(-3.15x_s)$	$0.30 + 0.62x_s - 0.32x_s^2$
TBA	$0.0056 \exp(-3.15x_s)$	$0.30 + 0.42x_s - 0.12x_s^2$

542 The adjustment of the Flory parameters functional forms deserves further
543 explanations. Regarding the Flory constant, $k_s(x_s)$, only the proportionality
544 constant of the exponential is adjusted with respect to the function referred
545 to acetone, Eq. (9). As far as the Flory exponent $\nu_s(x_s)$ is concerned, it
546 corresponds to a parabolic profile (Eq. (10)); therefore, three conditions are
547 needed: two of them are represented by the exponent value in pure good
548 and pure bad solvent, that are respectively 3/5 and 1/3, in line with the
549 Flory theory. The third condition is the only degree of freedom that the
550 user needs to fulfill and it might correspond to its value at the mean good
551 solvent molar fraction, $\nu_s(\bar{x}_s)$, that is suitably adjusted during the iterative
552 procedure presented above.

553 4. Results

554 First, only the dynamics of mixing is shown in order to assess the im-
555 portance of changes in physical properties when different good solvents are
556 used in FNP. In Figure 1 two quantities related respectively to macro- and
557 micro-mixing are reported for all the four solvents investigated here and for

558 two feeding flow rates. The first one is represented by the good solvent vol-
 559 ume fraction, $\langle \xi_v \rangle$ (see Eq. (7)). It is clear how in general the macro-mixing
 560 is very efficient for all the solvents since in almost the whole domain $\langle \xi_v \rangle$
 561 approaches to 0.5, as expected by using an inlet volume flow rate ratio equal
 562 to unity. Two different flow rates are here considered: 40 mL/min and 100
 563 mL/min. Further mathematical details about the macro-mixing are reported
 564 in Appendix A.

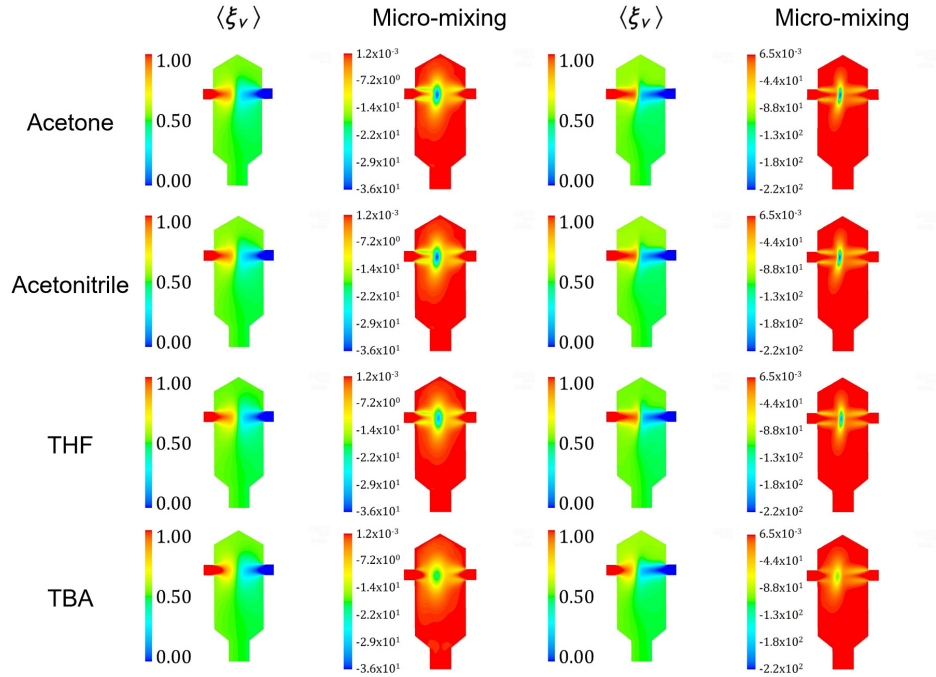


Figure 1: Good solvent volume fraction, $\langle \xi_v \rangle$ (Eq. (7)), and micro-mixing term, $\gamma_{MP_1P_2} (\xi_2 - \xi_1)$ (Eq. (A.4)), for which a further mathematical and physical analysis is reported in section 2.1 and in Appendix A. Two inlet flow rates are here reported: 40 mL min⁻¹ (left side) and 100 mL min⁻¹ (right side).

Besides macro-mixing, it is worthwhile to evaluate also the micro-mixing,
 being this one a fundamental aspect of FNP (Di Pasquale et al., 2012). As
 already mentioned, the mixture fraction is modeled via the DQMOM-IEM
 for which the corresponding transport equation is reported in section 2.1. A
 particular focus is given now to the micro-mixing term of that transport equation
 which corresponds to $\gamma_M p_1 p_2 (\xi_2 - \xi_1)$, where γ_M is the micro-mixing
 rate, namely expressing the rate with which good solvent and bad solvent
 mix at the molecular level. p_i and ξ_i correspond respectively to the weights
 and abscissas (or nodes, or environments) of the quadrature formula, in the
 two environments $i = 1, 2$, in line with the DQMOM approach (Marchisio
 and Fox, 2005). The whole micro-mixing term describes how fast the micro-
 mixing variance is dissipated by turbulence (Fox, 2003; Liu and Fox, 2006).
 The entire mathematical framework is here omitted, being already presented
 in our previous works (Di Pasquale et al., 2012; Lavino et al., 2017) and a
 further mathematical elaboration is provided in Appendix A, in which the
 relationship between micro-mixing term and micro-mixing variance is clearly
 stated.

At this level of description, Figure 1 points out that the micro-mixing term
 is very similar for acetone, acetonitrile and THF; a different trend is detected
 for TBA, for which micro-mixing turns out to be less efficient compared with
 the other good solvents. It is noteworthy to stress here that the numerical
 values in the contour plots must be interpreted as absolute values, since
 negative terms may come out from the local value of the abscissas in the
 two environments of the quadrature. Indeed, this is proven by looking at
 the region in which the turbulence is created and dissipated, which is where

590 molecular-mixing or micro-mixing occurs. It is clearly less shrunk around
 591 the impinging plane than in other solvents, showing wider spatial gradients
 592 in the mixer domain. This might be induced by the viscosity that in the
 593 case of TBA is shown to be much larger (one order of magnitude) than in
 594 the other solvents. These results, by just looking at the mixing dynamics of
 595 the system, already allows us to predict a different scenario for TBA with
 596 respect to acetone, acetonitrile and THF.

597 Let us move now on the dynamics of aggregation. In the case of the first
 598 three solvents (i.e., acetone, acetonitrile, THF), whose dynamics of mixing,
 599 only depending on their physical properties, is shown to be the same, it is
 600 worthwhile to conduct the following analysis. For the sake of brevity, let us
 601 consider only acetone and a ‘virtual’ solvent, characterized by the acetonitrile
 602 physical properties (Table 1) and by acetone functional forms of Flory
 603 parameters, namely Eq. (9) and (10). By simulating these two solvents with
 604 the solely Brownian aggregation kernel active, we can quantify the dynamics
 605 of self-assembly of polymer molecules into clusters and of small clusters into
 606 larger clusters (before turbulent aggregation takes over). Although the same
 607 functional forms of the acetone Flory parameters are considered here also
 608 for the ‘virtual’ solvent, the results show a very different profile, in terms of
 609 mean radius of gyration of the NP at the outlet of the mixer. This result
 610 is depicted in Figure 2 and tells us that, although the dynamics of mix-
 611 ing is identical between acetone and the ‘virtual’ solvent, the aggregation
 612 behaves in a very different way. The only physical explanation of that is
 613 attributable to one physical property and, more specifically, lies on the dif-
 614 ferent molar volumes of the two solvents (look at Table 1), because the other

615 physical properties (density and viscosity) are very similar to each other, as
 616 also demonstrated by looking at the respective Reynolds number values (see
 617 Table 1). The molar volumes affect the molar fraction of the mixture, x_s , as
 618 reported in Table 3 concerning its mean value, after mixing takes place. The
 619 Flory parameters functional forms are, in turn, function of molar mixture
 620 fraction. This analysis demonstrates that the differences between good sol-
 621 vents about the dynamics of aggregation only depend on Flory parameters.
 622 Furthermore, it is shown how the modeling approach presented in this work
 623 can be suitably employed to quantify the relative importance of the different
 624 mechanisms involved in particles formation.

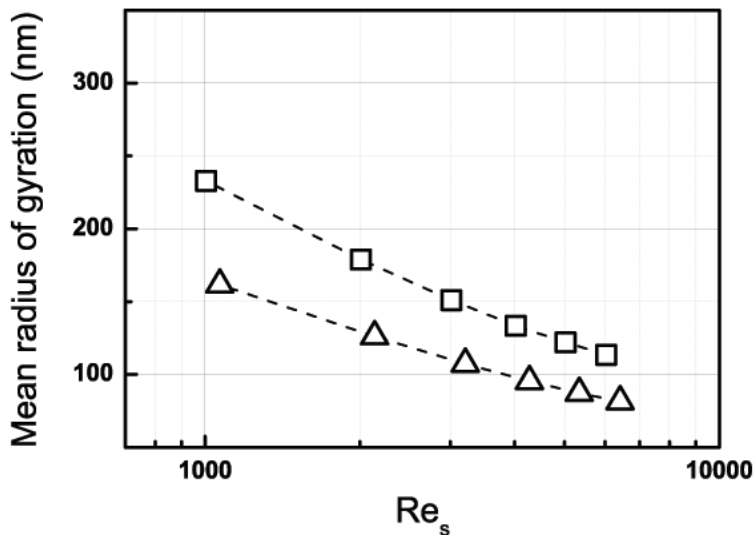


Figure 2: Mean radius of gyration as a function of Reynolds number referred to the good solvent inlet jet stream, with only Brownian aggregation for PCL initial concentrations equal to 6.0 mg/mL in acetone (triangles) and the ‘virtual’ solvent (squares), characterized by the acetonitrile physical properties and by the acetone functional forms of Flory parameters.

At this point of the current analysis, it is straightforward that the gap against experiments must be bridged by suitably adjusting the functional forms for $k_s(x_s)$ and $\nu_s(x_s)$ for all the solvents investigated here. As outcome of the iterative procedure presented in section 3 (see Eqs. (18) and (19) and Table 3), the final functional forms of the Flory parameters are determined and listed in Table 4. These new functional forms are able to guarantee a good agreement with experiments, as depicted in Figure 3 (TBA- and THF-water systems) and Figure 4 (acetone- and acetonitrile-water systems). The range of PCL initial concentrations in the good solvent stream spans from 3.0 to 9.0 mg mL⁻¹. The experimental error bars are also included.

Note that the accordance of the current model with experiments is in line with the results found out in our previous work (Lavino et al., 2017). As far as acetone, acetonitrile and THF are concerned, the agreement is excellent starting from medium PCL initial concentration in good solvent stream of about 5 mg/mL, namely the predicted NP dimensions are included into the uncertainty range of the experimental results. In the case of TBA, where the mixing dynamics is less efficient than in the other three good solvents, the model shows to be transferable, by means of the Flory-Huggins solubility theory. The experimental profile is qualitatively caught by this purely-aggregative model, reproducing the negligible effect of the kinetics on the final mean radius of gyration (flat profile of NP size as function of the inlet good solvent Reynolds number) (Johnson and Prud'homme, 2003b; Zelenková et al., 2015). This behaviour is also explained by looking at the Re_s range experienced by TBA in FNP with respect to the other systems, as clearly shown in Figures 3 and 4. Indeed, Re_s ranges of acetone, acetonitrile,

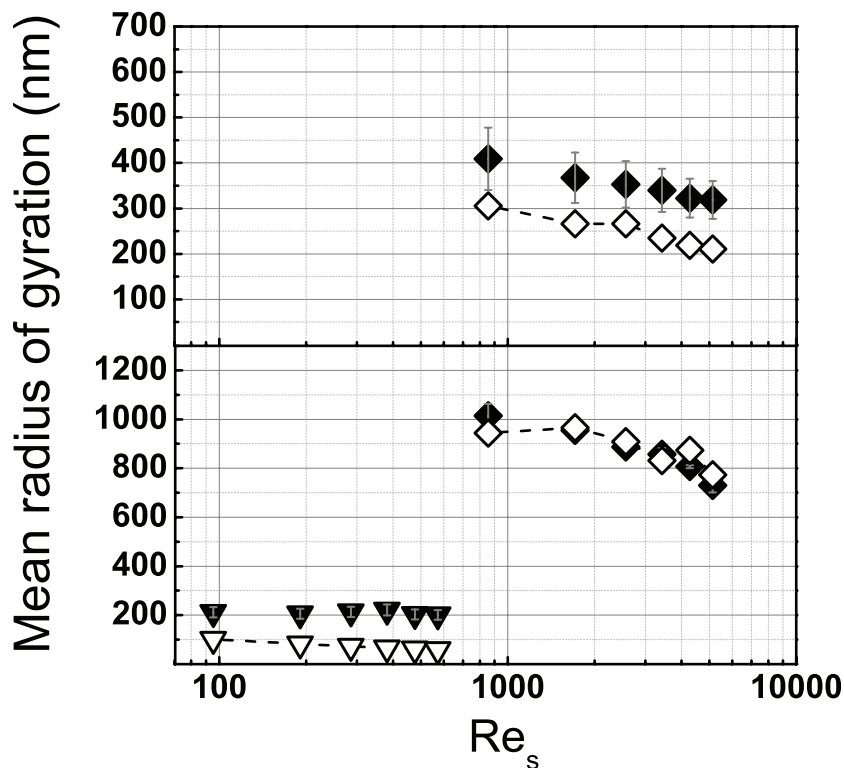


Figure 3: Mean radius of gyration of the NP exiting the CIJM versus the Reynolds number referred to the good solvent inlet jet stream as measured in experiments (black symbols) and as predicted by the purely-aggregative model (dashed line, empty symbols) for PCL-14000 initial concentrations equal to 3.0 (top panel) and 5.0 (bottom panel) mg/mL in THF (diamonds) and TBA (inverted triangles).

650 and THF are almost the same as well as one order of magnitude higher
651 than TBA inlet Reynolds number, mainly due to the TBA viscosity (see
652 Table 1). In the case of TBA, Re_s value presumes that the turbulence is
653 not completely developed inside the CIJM leading to less efficient mixing
654 dynamics - as already stated - and, therefore, to a less important effect of fluid
655 dynamics on the final mean NP size with respect to the other good solvent
656 systems, as reproduced by both experiments and simulations. Results show,

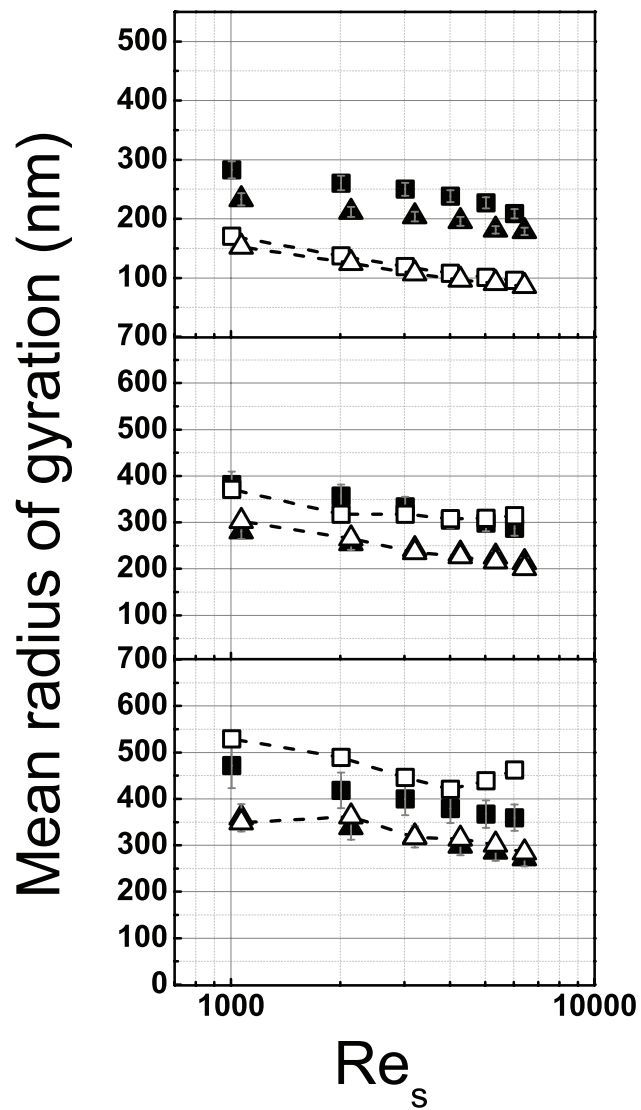


Figure 4: Mean radius of gyration of the NP exiting the CIJM versus the Reynolds number referred to the good solvent inlet jet stream as measured in experiments (black symbols) and as predicted by the purely-aggregative model (dashed line, empty symbols) for PCL-14000 initial concentrations equal to 3.0 (top), 6.0 (middle) and 9.0 (bottom) mg/mL in acetone (triangles) and acetonitrile (squares) as the good solvents.

657 however, a quantitative gap against experiments, which, on the contrary, is
 658 not observed in the case of THF (bottom panel in Figure 3) at the same
 659 PCL initial concentration (5 mg/mL). It is worthwhile to stress that this
 660 gap cannot be numerically overcome by using the proposed computational
 661 tuning (described in section 3, in order not to break the physics of the system,
 662 namely having higher values of Flory parameters for TBA than in acetone
 663 (look at Figure 5) which, instead, is shown to have a better affinity with PCL
 664 (lower solubility distance in Hansen phase space). This gap must be therefore
 665 related to another phenomenon, as for example the role of nucleation, here
 666 neglected (Lavino et al., 2017)). At constant PCL inlet concentration (around
 667 5 mg/mL), nucleation might be more important for TBA than in the other
 668 systems, in which turbulence is demonstrated to play a secondary role in
 669 the aggregation for PCL inlet concentration under 5 mg/mL by our previous
 670 CFD analysis (Lavino et al., 2017).

671 The Flory exponent profiles (Table 4) are depicted in Figure 5. The
 672 inset shows the ν_s values corresponding to the different mean good solvent
 673 molar fractions \bar{x}_s (discrete symbols), assuming the perfect mixing between
 674 the good and the bad solvent streams, already mentioned in the section 3.
 675 This perfect mixing condition corresponds to a single good solvent volume
 676 fraction value of 0.5 but different molar fractions, due to the different molar
 677 volumes of the good solvents. It is important to point out here that, from
 678 a qualitative point of view, the effect of the good solvent on the final mean
 679 NP size can be predicted looking at the Flory exponent evaluated at the
 680 mean good solvent molar fraction $\nu_s(\bar{x}_s)$. At the mean good solvent molar
 681 fraction \bar{x}_s , the inset shows the following relation for different good solvents:

682 $\nu_{\text{THF}}(\bar{x}_{\text{THF}}) > \nu_{\text{ACN}}(\bar{x}_{\text{ACN}}) > \nu_{\text{ACT}}(\bar{x}_{\text{ACT}}) > \nu_{\text{TBA}}(\bar{x}_{\text{TBA}})$. This justifies,
 683 indeed, the fact that PCL aggregates more in THF than in acetonitrile, in
 684 acetone and finally in TBA at constant PCL initial concentration, in line
 685 with experiments (Ferri et al., 2017; Zelenková et al., 2015). Therefore,
 686 the approach described here is able to reproduce the experimental evidences
 687 highlighting the fundamental role played by the good solvent molar fraction.
 688 Note that the $\nu_s(\bar{x}_s)$ values are very close to each other, denoting the high
 689 sensitivity of the Flory exponent on final mean NP size.

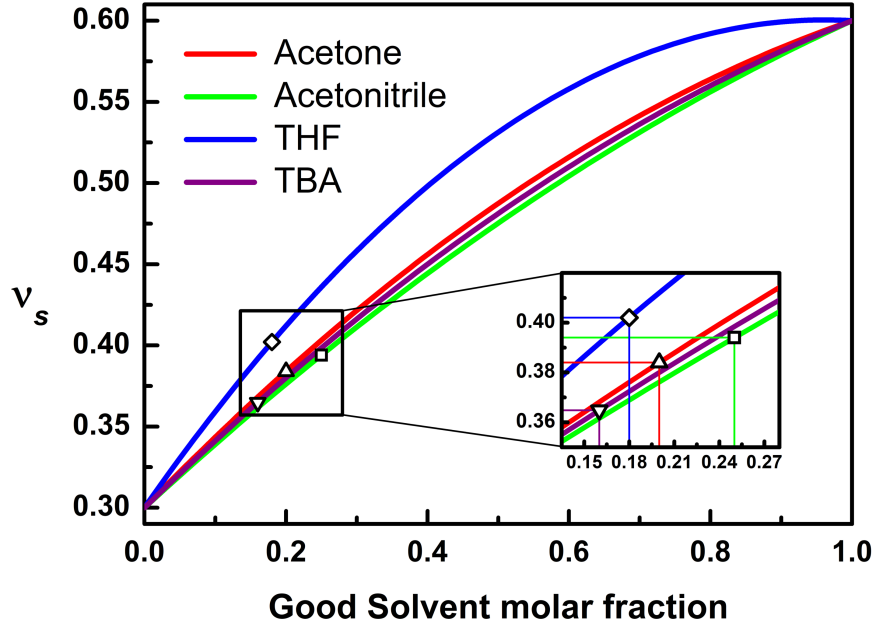


Figure 5: Flory exponent ν_s profiles in function of good solvent molar fraction for acetone (red), acetonitrile (green), THF (blue) and TBA (purple) (Table 4). The discrete symbols correspond to the Flory exponent at the outlet mean good solvent molar fraction $\nu_s(\bar{x}_s)$ (inset).

Figure 5 also depicts the affinity order found out in terms of HSP and solubility distance from PCL shown in Table 2, namely THF > ACT > TBA > ACN for which the solubility distances from PCL are respectively 1.0, 6.5, 7.4 and 13.8 MPa^{1/2}. Hence, at constant molar fraction, ν_s is directly proportional to the good solvent affinity with PCL (in terms of solubility distance). This implies that the polymer chain increases in size and assumes a more stretched conformation, according to the thermodynamics of real polymers in solution. However, operating at constant good-solvent-to-water ratio in volume leads to a mean good solvent molar fraction in the order: $\bar{x}_{\text{ACN}} > \bar{x}_{\text{ACT}} > \bar{x}_{\text{THF}} > \bar{x}_{\text{TBA}}$, because of the different molar volumes of the good solvents. This affects the Flory parameters and, consequently, aggregation, the final NP size and CMD.

In Figure 6 the mean-squared radius of gyration of a NP is reported for acetone (red), acetonitrile (green), THF (blue) and TBA (purple) in function of the aggregation number. The crossover between the red and green profiles (acetone and acetonitrile) shows the two different tendencies and contributions in case of single PCL molecule ($\llbracket R_g(n=1) \rrbracket$ higher in acetone) and at high aggregation number, n , in which $\llbracket R_g(n) \rrbracket$ is higher in acetonitrile than in acetone. This means that, despite the single PCL macromolecule occupies a smaller volume in acetonitrile, the PCL NP is bigger in acetonitrile, namely more PCL macromolecules form the same cluster (or NP) in acetonitrile ($m^{(1)}/m^{(0)}$ is therefore greater than in acetone). Therefore, the Flory theory combined together with the solubility affinity with PCL implies the following order of the single PCL macromolecule dimension: THF > ACT > ACN > TBA, as also indicated by

the S_f values in Table 3. However, the combination of good solvent mo-
lar volume (leading to different molar fractions) and the aggregation kernels
(dependent on Flory parameters) produces the following aggregation order:
THF > ACN > ACT > TBA.

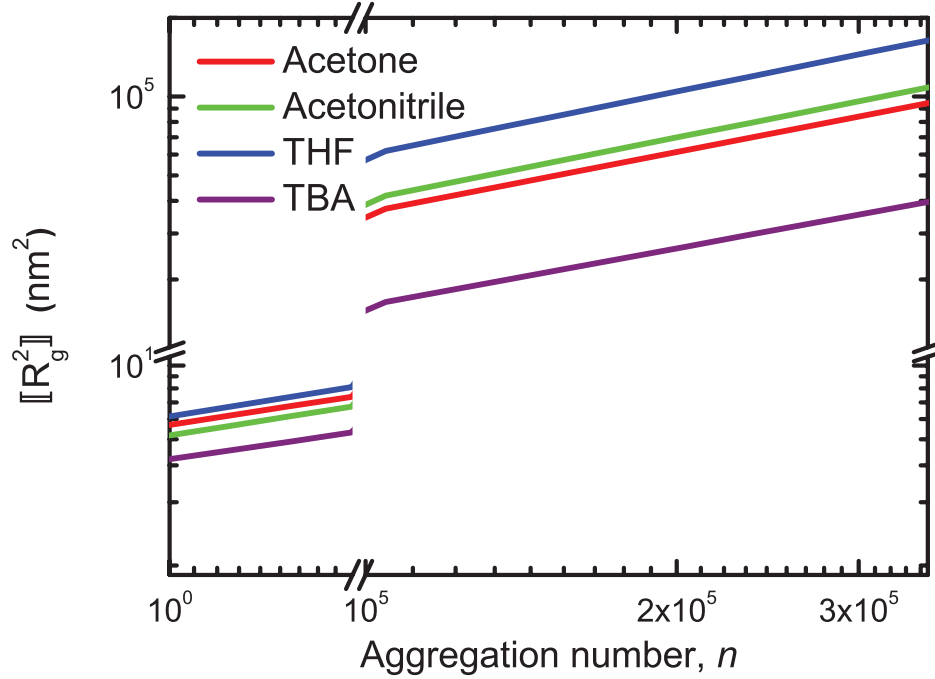


Figure 6: Mean squared radius of gyration, $[R_g^2]$, as a function of the number of molecules (Eq. (8)) that form a cluster (aggregation number, n) for acetone (red), acetonitrile (green), THF (blue) and TBA (purple) at the respective outlet mean good solvent molar fraction \bar{x}_s .

5. Conclusions

In this work the effect of different good solvents in flash nano-precipitation (FNP) is studied, from a modeling point of view. A population balance model (PBM) based on molecules as building blocks is coupled with computational

fluid dynamics (CFD) and implemented in a commercial CFD code. Moments of the cluster mass distribution (CMD) are transported and closed by using the quadrature method of moments (QMOM) (Marchisio and Fox, 2013). The CMD is defined in such a way that it represents the number of polymer molecules inside a cluster/NP. The turbulent mixing effects on NP formation are accounted for with the direct quadrature method of moments coupled with the interaction and exchange with the mean (DQMOM-IEM) method, in line with our reference work, in which this modeling approach was tested and validated (Lavino et al., 2017).

The novelty of the current approach consists in coupling PBM and CFD with thermodynamics of polymers in solution. More specifically, the Flory-Huggins interaction parameter χ is considered, taking into account therefore the energetic contribution related to the polymer in the mixture, and is here correlated to the prediction of the mean radius of gyration of the NP. All this is done by taking advantage of the solubility theory in mixtures, in terms of Hansen solubility parameters (HSP). In this way, different good solvents are studied, with water as anti-solvent and poly- ϵ -caprolactone (PCL) as solute, in confined impinging jets mixer (CIJM). Four different good solvents are considered: acetone (ACT), acetonitrile (ACN), tetrahydrofuran (THF) and tert-butanol (TBA), taking the acetone as the reference solvent, being this one already investigated at the molecular scale with molecular dynamics in a previous work (Di Pasquale et al., 2014).

Thanks to the proposed approach, kinetics and thermodynamics are intertwined in a unique modeling tool used to investigate separately the dynamics of mixing from the dynamics of aggregation, addressing the main

748 factors that play a key role in such a complex process. CFD simulations
749 demonstrate that acetone, acetonitrile and THF are characterized by the
750 same macro- and micro-mixing dynamics, whereas TBA shows a different
751 micro-mixing behaviour, strongly dependent on its viscosity, that is one or-
752 der of magnitude higher than the other solvents and water. Results also show
753 that the molar volume, combined together with the HSP, provides a good
754 prediction of the final mean NP size when different good solvents are em-
755 ployed in FNP. Furthermore, functional forms for the Flory parameters are
756 determined, by combining the Flory-Huggins solubility theory with a suitable
757 computational tuning. In this way, it is shown that the proposed modeling
758 approach is transferable and adaptable to different scenarios, leading to a
759 good prediction of the experimental results from quantitative and qualita-
760 tive points of view. This is valid also in the case of TBA which presents a
761 different mixing dynamics that, in turn, affects the final NP profile in func-
762 tion of the inlet Reynolds number. The detected limitations, in terms of
763 accordance with experiments, might be overcome by introducing nucleative
764 effects in the aggregation source term of the PBM. In conclusion, although
765 the phenomena involved are very complex and this is not indeed the ultimate
766 model for FNP, this model is able to capture the main effects experimentally
767 observed since both kinetics and thermodynamics are considered.

768 Future work may be done by investigating these good solvent-water sys-
769 tems at the molecular scale with full-atom and coarse-grained molecular dy-
770 namics simulations, aiming at confirming or refining the results obtained in
771 this work, with more detailed molecular models.

772 Appendix

773 Appendix A. Mixing modeling and micro-mixing variance

774 In this appendix, further mathematical details concerning the mixing
775 modeling are provided. More specifically, it will be shown how the micro-
776 mixing variance can be related to the mixing transport equation, in particular
777 to one of its terms: the micro-mixing term. In this modeling framework, as
778 reported in the main text, the mixture fraction is transported by means of
779 the direct quadrature method of moment coupled with the interaction and
780 exchange with the mean method (DQMOM-IEM) (Marchisio and Fox, 2013).

781 Besides the micro-mixing model introduced in the main text in section
782 2.1, a large-scale or macro-scale variance $\langle \xi'^2 \rangle_{macro}$ is defined as follows:

$$\langle \xi'^2 \rangle_{macro} = (\langle \xi \rangle - \bar{\xi})^2, \quad (A.1)$$

783 quantifying how different the local mean mixture fraction $\langle \xi \rangle$ is from the ideal
784 value $\bar{\xi}$ that it would assume if the mixing were perfect. In the analyzed case,
785 for instance, $\bar{\xi}_v = 0.5$ in volume. For the analyzed cases, this tells us that
786 the macro-mixing is very efficient, leading the macro-mixing variance to zero
787 in almost all the CIJM, as shown in Figure 1.

788 The micro-mixing variance is defined as (Liu and Fox, 2006):

$$\langle \xi'^2 \rangle = \langle \xi^2 \rangle - \langle \xi \rangle^2. \quad (A.2)$$

789 We can rearrange the last expression as follows:

$$\begin{aligned}
\langle \xi'^2 \rangle &= \langle \xi^2 \rangle - \langle \xi \rangle^2 = p_1 \xi_1^2 + p_2 \xi_2^2 - (p_1 \xi_1 + p_2 \xi_2)^2 = \\
&= p_1 \xi_1^2 (1 - p_1) + p_2 \xi_2^2 (1 - p_2) - 2p_1 p_2 \xi_1 \xi_2 = \\
&= p_1 p_2 (\xi_1^2 + \xi_2^2 - 2\xi_1 \xi_2) = p_1 p_2 (\xi_2 - \xi_1)^2, \quad (\text{A.3})
\end{aligned}$$

790 where the property $p_1 = 1 - p_2$ is applied. By using the results shown in
791 Eq. (A.3), the first term on right hand side of Eq. (5) that contains the micro-
792 mixing rate can be expressed as follows (the fluid density $\bar{\rho}$ is here omitted
793 for simplicity of notation):

$$\gamma_M p_1 p_2 (\xi_2 - \xi_1) = \frac{\gamma_M}{(\xi_2 - \xi_1)} \langle \xi'^2 \rangle, \quad (\text{A.4})$$

794 strictly dependent on the micro-mixing variance $\langle \xi'^2 \rangle$. The quantity ex-
795 pressed in Eq. (A.4) is the one reported in the contour plots in Figure 1
796 and can be thought of as a measure of how the micro-mixing variance is dis-
797 sipated by turbulence (included in the definition of γ_M) at the micro-scale.

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806 References

- 807 Andersson, B., Andersson, R., Hakansson, L., Mortensen, M., Sudiyo, R.,
808 van Wachem, B., 2012. Computational Fluid Dynamics for Engineering.
809 Cambridge: Cambridge University Press.
- 810 Baldyga, J., Orciuch, W., 2001. Some hydrodynamic aspects of precipi-
811 tation. Powder Technology 121, 9–19. doi:[https://doi.org/10.1016/](https://doi.org/10.1016/S0032-5910(01)00368-0)
812 [S0032-5910\(01\)00368-0](https://doi.org/10.1016/S0032-5910(01)00368-0).
- 813 Barresi, A.A., Vanni, M., Fissore, D., Zelenková, T., 2015. Thakur VK,
814 Thaku MK. Handbook of Polymers for Pharmaceutical Technologies.
815 Hoboken: John Wiley & Sons, Ltd. chapter Synthesis and preservation
816 of polymer nanoparticles for pharmaceutical applications. pp. 229–280.
817 doi:<https://doi.org/10.1002/9781119041412.ch9>.
- 818 Bhattacharjee, S., 2016. Dls and zeta potential – what they are and what
819 they are not? Journal of Controlled Release 235, 337 – 351. doi:<https://doi.org/10.1016/j.jconrel.2016.06.017>.
820

- 821 Bordes, C., Fréville, V., Ruffin, E., Marote, P., Gauvrit, J.Y., Briançon,
822 S., Lantéri, P., 2010. Determination of poly(ϵ -caprolactone) solubil-
823 ity parameters: Application to solvent substitution in a microencapsu-
824 lation process. *International Journal of Pharmaceutics* 383, 236–243.
825 doi:<https://doi.org/10.1016/j.ijpharm.2009.09.023>.
- 826 Celasco, E., Valente, I., Marchisio, D.L., Barresi, A.A., 2014. Dynamic light
827 scattering and x-ray photoelectron spectroscopy characterization of pe-
828 gylated polymer nanocarriers: Internal structure and surface properties.
829 *Langmuir* 30, 8326–8335. doi:<https://doi.org/10.1021/la501198v>.
- 830 Cheng, J.C., Vigil, R.D., Fox, R.O., 2010. A competitive aggregation model
831 for flash nanoprecipitation. *Journal of Colloid and Interface Science* 351,
832 330–342. doi:<https://doi.org/10.1016/j.jcis.2010.07.066>.
- 833 Choi, Y.J., Chung, S.T., Oh, M., Kim, H.S., 2005. Investigation of cristalliza-
834 tion in a jet y-mixer by a hybrid computational fluid dynamics and process
835 simulation approach. *Cristal Growth & Design* 5, 959–968. doi:<https://doi.org/10.1021/cg049670x>.
- 837 Das, M., Saxena, N., Dwivedi, P.D., 2009. Emerging trends of nanoparticles
838 application in food technology: Safety paradigms. *Nanotoxicology* 3, 10–
839 18. doi:<https://doi.org/10.1080/17435390802504237>.
- 840 Demetzos, C., 2016. *Pharmaceutical Nanotechnology*. Singapore: Adis.
- 841 Di Pasquale, N., Marchisio, D.L., Barresi, A.A., 2012. Model validation for
842 precipitation in solvent-displacement processes. *Chemical Engineering Sci-*
843 *ence* 84, 671–683. doi:<https://doi.org/10.1016/j.ces.2012.08.043>.

- 844 Di Pasquale, N., Marchisio, D.L., Barresi, A.A., Carbone, P., 2014. Sol-
845 vent structuring and its effect on the polymer structure and processabil-
846 ity: the case of water-acetone poly- ϵ -caprolactone mixtures. *Journal of*
847 *Physical Chemistry B* 118, 13258–13267. doi:[https://doi.org/10.1021/](https://doi.org/10.1021/jp505348t)
848 [jp505348t](https://doi.org/10.1021/jp505348t).
- 849 Elimelech, M., Gregory, J., Jia, X., Williams, R., 1998. *Particle Deposi-*
850 *tion and Aggregation: Measurement, Modelling and Simulation*. Woburn:
851 Butterworth-Heinemann.
- 852 Favre, A., 1965. Equations des gaz turbulents compressibles i. formes
853 générales. *Journal de Mecanique* 4, 361–390.
- 854 Ferri, A., Kumari, N., Peila, R., Barresi, A.A., 2017. Production of menthol-
855 loaded nanoparticles by solvent displacement. *The Canadian Journal of*
856 *Chemical Engineering* 95, 1690–1706. doi:[https://doi.org/10.1002/](https://doi.org/10.1002/cjce.22867)
857 [cjce.22867](https://doi.org/10.1002/cjce.22867).
- 858 Flory, P., 1953. *Principles of Polymer Chemistry*. Ithaca: Cornell University
859 Press.
- 860 Fox, R.O., 2003. *Computational Models for Turbulent Reacting Flows*. Cam-
861 bridge: Cambridge University Press. doi:[10.1017/CB09780511610103](https://doi.org/10.1017/CB09780511610103).
- 862 Gartner, T.E., Jayaraman, A., 2018. Macromolecular ‘size’ and ‘hard-
863 ness’ drives structure in solvent-swollen blends of linear, cyclic, and star
864 polymers. *Soft Matter* 14, 411–423. doi:[https://doi.org/10.1039/](https://doi.org/10.1039/C7SM02199B)
865 [C7SM02199B](https://doi.org/10.1039/C7SM02199B).

- 866 Gavi, E., Marchisio, D.L., Barresi, A.A., 2007. Cfd modelling and scale-
867 up of confined impinging jet reactors. *Chemical Engineering Science* 62,
868 2228–2241. doi:<https://doi.org/10.1016/j.ces.2006.12.077>.
- 869 Gradl, J., Schwarzer, H.C., Schwertfirm, F., Manhart, M., Peukert, W., 2006.
870 Precipitation of nanoparticles in a t-mixer: coupling the particle popula-
871 tion dynamics with hydrodynamics through direct numerical simulation.
872 *Chemical Engineering and Processing: Process Intensification* 45, 908–916.
873 doi:<https://doi.org/10.1016/j.cep.2005.11.012>.
- 874 Hans, M.L., Lowman, A.M., 2002. Biodegradable nanoparticles for drug de-
875 livery and targeting. *Current Opinion in Solid State and Materials Science*
876 6, 319–327. doi:[https://doi.org/10.1016/S1359-0286\(02\)00117-1](https://doi.org/10.1016/S1359-0286(02)00117-1).
- 877 Hansen, C.M., 2007. Hansen Solubility Parameters: A User’s Handbook (2nd
878 edition). Boca Raton: CRC Press.
- 879 Hildebrand, J., Scott, R.L., 1950. Solubility of Nonelectrolytes (3rd edition).
880 New York: Reinhold.
- 881 Johnson, B.K., Prud’homme, R.K., 2003a. Chemical processing and micro-
882 mixing in confined impinging jets. *AIChE Journal* 49, 2264–2282.
883 doi:<https://doi.org/10.1002/aic.690490905>.
- 884 Johnson, B.K., Prud’homme, R.K., 2003b. Flash nano-precipitation of or-
885 ganic actives and block copolymers using a confined impinging jets mixer.
886 *Australian Journal of Chemistry* 56, 1021–1024. doi:<https://doi.org/10.1071/CH03115>.
887

- 888 Lavino, A.D., Banetta, L., Carbone, P., Marchisio, D.L., 2018. Ex-
889 tended charge-on-particle optimized potentials for liquid simulation ace-
890 tone model: The case of acetone–water mixtures. *The Journal of Physical*
891 *Chemistry B* 122, 5234–5241. doi:[https://doi.org/10.1021/acs.jpcc.](https://doi.org/10.1021/acs.jpcc.8b01293)
892 8b01293.
- 893 Lavino, A.D., Carbone, P., Marchisio, D.L., 2020. Martini coarse-grained
894 model for poly- ϵ -caprolactone in acetone-water mixtures. *The Canadian*
895 *Journal of Chemical Engineering* 98, 1868–1879. doi:[https://doi.org/](https://doi.org/10.1002/cjce.23761)
896 10.1002/cjce.23761.
- 897 Lavino, A.D., Di Pasquale, N., Carbone, P., Barresi, A.A., Marchisio, D.L.,
898 2015. Simulation of macromolecule self-assembly in solution: A multiscale
899 approach. *AIP Conference Proceedings* 1695, 020036. doi:[https://doi.](https://doi.org/10.1063/1.4937314)
900 [org/10.1063/1.4937314](https://doi.org/10.1063/1.4937314).
- 901 Lavino, A.D., Di Pasquale, N., Carbone, P., Marchisio, D.L., 2017. A novel
902 multiscale model for the simulation of polymer flash nano-precipitation.
903 *Chemical Engineering Science* 171, 485–494. doi:[https://doi.org/10.](https://doi.org/10.1016/j.ces.2017.04.047)
904 1016/j.ces.2017.04.047.
- 905 Lavino, A.D., Marchisio, D.L., Vanni, M., Ferri, A., Barresi, A.A., 2019.
906 Nanoparticles production in continuous flow devices - modelling and ex-
907 perimental insights into continuous flow-based processes. *Chimica Oggi -*
908 *Chemistry Today* 37, 8–11.
- 909 Le Roy Boehm, A.L., Zerrouk, R., Fessi, H., 2000. Poly epsilon-caprolactone
910 nanoparticles containing a poorly soluble pesticide: formulation and sta-

911 bility study. *Journal of Microencapsulation* 17, 195–205. doi:<https://doi.org/10.1080/026520400288436>.

912

913 Lince, F., Marchisio, D.L., Barresi, A.A., 2008. Strategies to control the par-
 914 ticle size distribution of poly- ϵ -caprolactone nanoparticles for pharmaceu-
 915 tical applications. *Journal of Colloid and Interface Science* 322, 505–515.
 916 doi:<https://doi.org/10.1016/j.jcis.2008.03.033>.

917 Lince, F., Marchisio, D.L., Barresi, A.A., 2009. Smart mixers and reac-
 918 tors for the production of pharmaceutical nanoparticles: Proof of con-
 919 cept. *Chemical Engineering Research and Design* 87, 543–549. doi:<https://doi.org/10.1016/j.cherd.2008.11.009>.

920

921 Lince, F., Marchisio, D.L., Barresi, A.A., 2011. A comparative study for
 922 nanoparticle production with passive mixers via solvent-displacement: Use
 923 of cfd models for optimization and design. *Chemical Engineering and*
 924 *Processing: Process Intensification* 50, 356–368. doi:<https://doi.org/10.1016/j.cep.2011.02.015>.

925

926 Liu, Y., Cheng, C., Prud'homme, R.K., Fox, R.O., 2008. Mixing in a multi-
 927 inlet vortex mixer (mivm) for flash nano-precipitation. *Chemical Engineer-*
 928 *ing Science* 63, 2829–2842. doi:[https://doi.org/10.1016/j.ces.2007.](https://doi.org/10.1016/j.ces.2007.10.020)
 929 [10.020](https://doi.org/10.1016/j.ces.2007.10.020).

930 Liu, Y., Fox, R.O., 2006. Cfd predictions for chemical processing in a confined
 931 impinging-jets reactor. *AIChE Journal* 52, 731–744. doi:[https://doi.](https://doi.org/10.1002/aic.10633)
 932 [org/10.1002/aic.10633](https://doi.org/10.1002/aic.10633).

- 933 Marchisio, D.L., Fox, R.O., 2005. Solution of population balance equations
934 using the direct quadrature method of moments. *Journal of Aerosol Science*
935 36, 43–73. doi:<https://doi.org/10.1016/j.jaerosci.2004.07.009>.
- 936 Marchisio, D.L., Fox, R.O., 2013. *Computational Models for Polydisperse*
937 *Particulate and Multiphase Flows*. Cambridge: Cambridge University
938 Press.
- 939 Marchisio, D.L., Omegna, F., Barresi, A.A., 2009. Production of tio2
940 nanoparticles with controlled characteristics by means of a vortex reac-
941 tor. *Chemical Engineering Journal* 146, 456–465. doi:[https://doi.org/](https://doi.org/10.1016/j.cej.2008.10.031)
942 [10.1016/j.cej.2008.10.031](https://doi.org/10.1016/j.cej.2008.10.031).
- 943 Marchisio, D.L., Omegna, F., Barresi, A.A., Bowen, P., 2008. Effect of
944 mixing and other operating parameters in sol-gel processes. *Industrial &*
945 *Engineering Chemistry Research* 47, 7202–7210. doi:[https://doi.org/](https://doi.org/10.1021/ie800217b)
946 [10.1021/ie800217b](https://doi.org/10.1021/ie800217b).
- 947 Martin, T.B., Jayaraman, A., 2016. Using theory and simulations to calcu-
948 late effective interactions in polymer nanocomposites with polymer-grafted
949 nanoparticles. *Macromolecules* 49, 9684–9692. doi:[https://doi.org/10.](https://doi.org/10.1021/acs.macromol.6b01920)
950 [1021/acs.macromol.6b01920](https://doi.org/10.1021/acs.macromol.6b01920).
- 951 Massella, D., Celasco, E., Salaün, F., Ferri, A., Barresi, A.A., 2018. Overcom-
952 ing the limits of flash nanoprecipitation: effective loading of hydrophilic
953 drug into polymeric nanoparticles with controlled structure. *Polymers* 10,
954 1092. doi:<https://doi.org/10.3390/polym10101092>.

- 955 Nelson, G., 2002. Application of microencapsulation in textiles. *International*
 956 *Journal of Pharmaceutics* 242, 55–62. doi:[https://doi.org/10.1016/](https://doi.org/10.1016/S0378-5173(02)00141-2)
 957 [S0378-5173\(02\)00141-2](https://doi.org/10.1016/S0378-5173(02)00141-2).
- 958 Petitti, M., Vanni, M., Barresi, A.A., 2008. Controlled release of drug en-
 959 capsulated as a solid core: Theoretical model and sensitivity analysis.
 960 *Chemical Engineering Research and Design* 86, 1294–1300. doi:[https:](https://doi.org/10.1016/j.cherd.2008.05.008)
 961 [//doi.org/10.1016/j.cherd.2008.05.008](https://doi.org/10.1016/j.cherd.2008.05.008).
- 962 Prasad, R., Kumar, V., Prasad, K.S., 2014. Nanotechnology in sustain-
 963 able agriculture: Present concerns and future aspects. *African Journal*
 964 *of Biotechnology* 13, 705–713. doi:[https://doi.org/10.5897/AJBX2013.](https://doi.org/10.5897/AJBX2013.13554)
 965 [13554](https://doi.org/10.5897/AJBX2013.13554).
- 966 Rubinstein, M., Colby, R.H., 2003. *Polymer Physics*. Oxford: Oxford Uni-
 967 versity Press.
- 968 Saad, W.S., 2007. Drug nanoparticle formation via flash nanoprecipitation:
 969 Conjugation to encapsulate and control the release of paclitaxel. Ph.D.
 970 thesis. Princeton University.
- 971 Saad, W.S., Prud’homme, R.K., 2016. Principles of nanoparticle formation
 972 by flash nanoprecipitation. *Nano Today* 11, 212–227. doi:[https://doi.](https://doi.org/10.1016/j.nantod.2016.04.006)
 973 [org/10.1016/j.nantod.2016.04.006](https://doi.org/10.1016/j.nantod.2016.04.006).
- 974 Valente, I., Celasco, E., Marchisio, D.L., Barresi, A.A., 2012a. Nanopre-
 975 cipitation in confined impinging jets mixers: Production, characteriza-
 976 tion and scale-up of pegylated nanospheres and nanocapsules for phar-

977 maceutical use. Chemical Engineering Science 77, 217–227. doi:[https:](https://doi.org/10.1016/j.ces.2012.02.050)
978 [//doi.org/10.1016/j.ces.2012.02.050](https://doi.org/10.1016/j.ces.2012.02.050).

979 Valente, I., Stella, B., Marchisio, D.L., Dosio, F., Barresi, A.A., 2012b. Pro-
980 duction of pegylated nanocapsules through solvent-displacement in con-
981 fined impinging jets mixers. Journal of Pharmaceutical Sciences 101, 2490–
982 2501. doi:<https://doi.org/10.1002/jps.23167>.

983 Who, C., Jim, T., Gan, Z., Zhao, Y., Wang, S., 2000. A heterogeneous
984 catalytic kinetics for enzymatic biodegradation of poly(ϵ -caprolactone)
985 nanoparticles in aqueous solution. Polymer 41, 3593–3597. doi:[https:](https://doi.org/10.1016/S0032-3861(99)00586-8)
986 [//doi.org/10.1016/S0032-3861\(99\)00586-8](https://doi.org/10.1016/S0032-3861(99)00586-8).

987 Wu, X., Guy, R.H., 2009. Applications of nanoparticles in topical drug
988 delivery and in cosmetics. Journal of Drug Delivery Science and Technology
989 19, 371–384. doi:[https://doi.org/10.1016/S1773-2247\(09\)50080-9](https://doi.org/10.1016/S1773-2247(09)50080-9).

990 Zelenková, T., Barresi, A.A., Fissore, D., 2015. On the use of *tert*-
991 butanol/water cosolvent systems in production and freeze-drying of poly- ϵ -
992 caprolactone nanoparticles. Journal of Pharmaceutical Sciences 104, 178–
993 190. doi:<https://doi.org/10.1002/jps.24271>.

994 Zelenková, T., Fissore, D., Marchisio, D.L., Barresi, A.A., 2014. Size
995 control in production and freeze-drying of poly- ϵ -caprolactone nanopar-
996 ticles. Journal of Pharmaceutical Sciences 103, 1839–1850. doi:[https:](https://doi.org/10.1002/jps.23960)
997 [//doi.org/10.1002/jps.23960](https://doi.org/10.1002/jps.23960).

998 Zelenková, T., Mora, M.J., Barresi, A.A., Granero, G.E., Fissore, D., 2018.
999 On the production of chitosan-coated polycaprolactone nanoparticles in a

1000 confined impinging jet reactor. Journal of Pharmaceutical Sciences 107,
1001 1157–1166. doi:<https://doi.org/10.1016/j.xphs.2017.11.020>.