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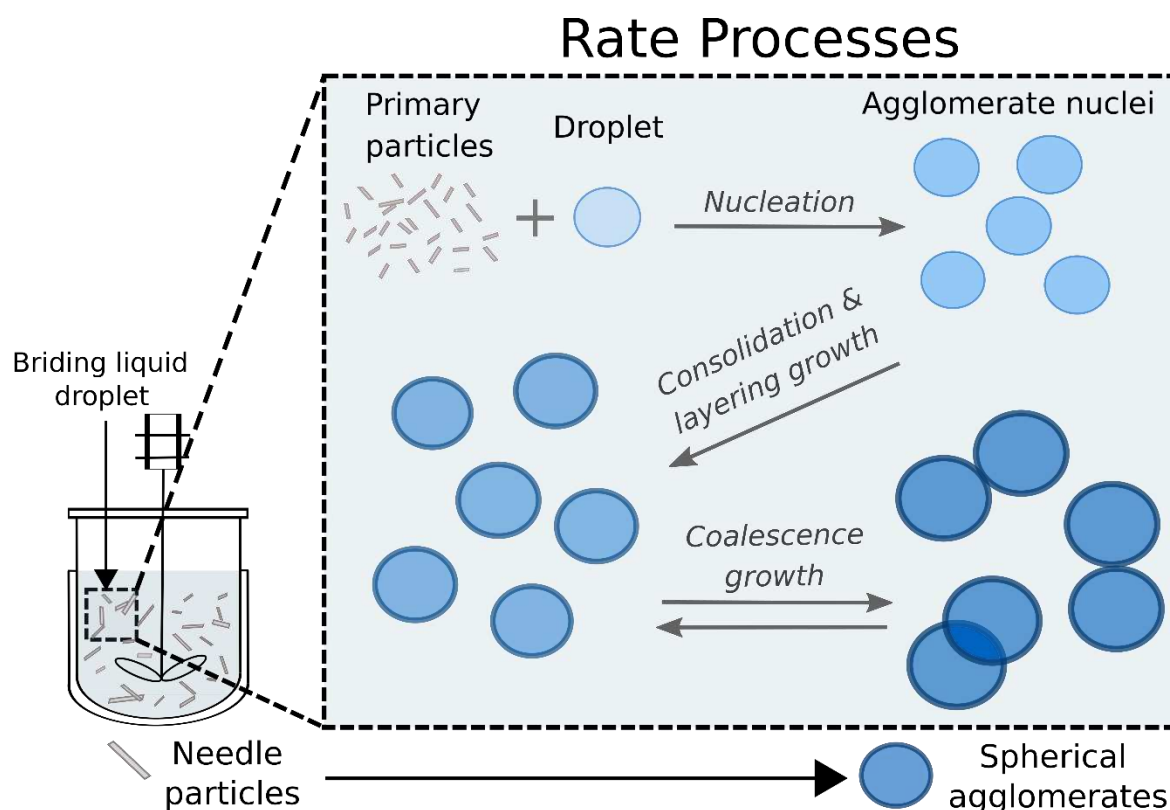
Mechanistic Modelling of Spherical Agglomeration Processes

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Graphical Abstract



Highlights

- Population balance model predicts spherical agglomeration behaviour
- Key rate process analysed for an immersion-driven mechanism
- Bridging liquid droplet size and bridging liquid to solid ratio parameters influence both agglomerate kinetics and attributes
- Primary particle size and mixing intensity only influence agglomeration kinetics

20 **Abstract**

21 Spherical agglomeration is emerging as an important unit process for pharmaceutical
22 manufacturing. However, at present, quantitative process design to control
23 agglomerate attributes is impossible. A new population balance model to predict
24 agglomerate attributes is presented where for the first time, all of the key rate
25 processes that control agglomerate properties are included. A parameter sensitivity
26 analysis is undertaken to study the effect of process parameters on agglomerate
27 attributes. Bridging liquid droplet size and bridging liquid to solids ratio (BSR) are
28 critical controlling parameters. Good quality agglomerates are formed over a relatively
29 narrow range of BSR. Within this range, bridging liquid droplet size can be used to
30 tune agglomerate size. Primary crystal size and process mixing intensity have only a
31 modest effect on equilibrium agglomerate attributes but do impact agglomerate
32 formation kinetics. This new model provides the basis for improved process
33 understanding and quantitative process design of spherical agglomeration.

34

35 **Keywords:** spherical agglomeration, population balance model, mechanistic
36 understanding, agglomerate size and size distribution, average liquid volume fraction

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61 **1. Introduction**

62 The manufacturing of active pharmaceutical ingredients (API) with suitable
63 characteristics for oral solid dosage applications requires tightly controlled particulate
64 properties from robust unit operations. In the pharmaceutical sector, traditional batch
65 manufacturing approaches have been the established practice. However, recent
66 advances in continuous manufacturing have demonstrated numerous advantages for
67 producing enhanced product properties. These range from ease of scale-up [1] to
68 reduced variability, processing times and costs [2-4]. To enable the adoption and
69 transition into fully integrated continuous unit operations, controlling API bulk powder
70 properties (size, shape, surface, flow *etc.*) with the required specifications is essential
71 and challenging [5]. For example, insufficient control during drug substance
72 manufacturing can lead to multiple issues with the bulk powder from poor flow,
73 inconsistent feeding, variable die-filling, and punch sticking which ultimately produces
74 unacceptable final tablet quality attributes [6].

75
76 Situated at the interface between drug substance and drug product manufacturing,
77 spherical agglomeration is an emerging particle engineering technique for challenging
78 APIs. The application of spherical agglomeration has already been investigated within
79 industries such as natural resources including coal [7], graphite [8] and sand [9] for
80 agglomerating a variety of products. It has also been used to agglomerate several
81 pharmaceutical drug compounds which exhibit poor characteristics such as needle-
82 like shapes when reliant on crystallization only [10-12] as well as poor solubility and
83 dissolution characteristics [13]. Across the numerous studies, a key benefit to
84 implementing spherical agglomeration is the ability to form dense and enlarged
85 spherical particles with high bulk densities and better flow properties. Furthermore,
86 spherical agglomerates which encapsulate and consolidate the crystal product during
87 formation, can be subjected to direct compression which offers the fastest and
88 simplest route to generate pharmaceutical dosage units. Currently there are four
89 common spherical agglomeration methods; (1) Spherical Agglomeration, (2) Quasi-
90 Emulsion Solvent Diffusion, (3) Ammonium Diffusion and (4) Crystal Co-
91 Agglomeration. The spherical agglomeration (1) method is the most favourable
92 approach which is performed either through the simultaneous crystal precipitation and
93 agglomeration in suspension (post-crystallization) in the same unit operation or

94 through agglomeration in isolation (separate to the crystallization) which is only
95 concerned with the agglomeration mechanisms [14]. To agglomerate directly
96 generated or a pre-suspension of crystals, controlled addition of an immiscible or
97 partially miscible solvent termed as the binder or bridging liquid is required and is a
98 critical step. Importantly, the bridging liquid should possess a high affinity for the
99 crystals in suspension to enable sufficient wetting and subsequent formation of
100 agglomerates.

101

102 Whilst numerous studies have reported on experimental methods for the preparation
103 of spherical agglomerates, there remains a lack of mechanistic understanding
104 concerning the fundamental rate processes and controlling parameters. Many of the
105 mechanisms are understood to occur through stages that are in parallel with wet
106 granulation: (i) wetting and nucleation of the particles by the bridging liquid; (ii)
107 consolidation and growth of agglomerate nuclei and; (iii) breakage and attrition
108 [15, 16]. The wetting of crystals by the bridging liquid droplets and the relative size
109 ratio between the two entities can direct the formation of agglomerate nuclei through
110 two separate mechanisms (distribution & immersion). If the bridging liquid droplets are
111 smaller than the suspended crystals (primary particles), a distribution mechanism will
112 occur. Here, the crystals become 'coated' by droplets over time which allows them to
113 aggregate to form an initial agglomerate nucleus. On the other hand, if the bridging
114 liquid droplets are larger than the suspended crystals, an immersion mechanism
115 occurs. Crystals will penetrate inside the droplets over time and form an initial
116 agglomerate nucleus. The immersion mechanism is preferred as the final
117 agglomerates display more uniform particle size distributions (PSD), higher sphericity,
118 and density [17]. The occurrence and interplay of these mechanisms can be found
119 from several reported studies [18-20].

120

121 Recently, two new agglomerate nucleation models were introduced to predict and
122 describe the wetting and nucleation kinetics during an immersion mechanism [21]. A
123 dimensionless number termed the *agglomerate nucleation number* was developed to
124 predict the kinetics of agglomerate nucleation by layering. The kinetics were identified
125 on the basis of three regimes: *immersion rate limited*; *collision rate limited* and;
126 *intermediate regime* which describes the system to be limited by both the immersion

127 and collision rate. The *immersion rate limited regime* assumes a packed layer of
128 stationary particles is always available on the surface of the bridging liquid droplets
129 where subsequent immersion is limited by the wetting (capillary) action of these
130 particles. In this case, the agglomerate size increases with the square root of time. For
131 the *collision rate limited regime*, immediate wetting and suction of particles inside the
132 bridging liquid droplet occur; however, the process is limited by the arrival of particles
133 to the surface of bridging liquid droplets. The agglomerate size, therefore, increases
134 linearly with time. Both models also assume the agglomerate nucleus grows by the
135 formation of a shell of a constant liquid volume fraction.

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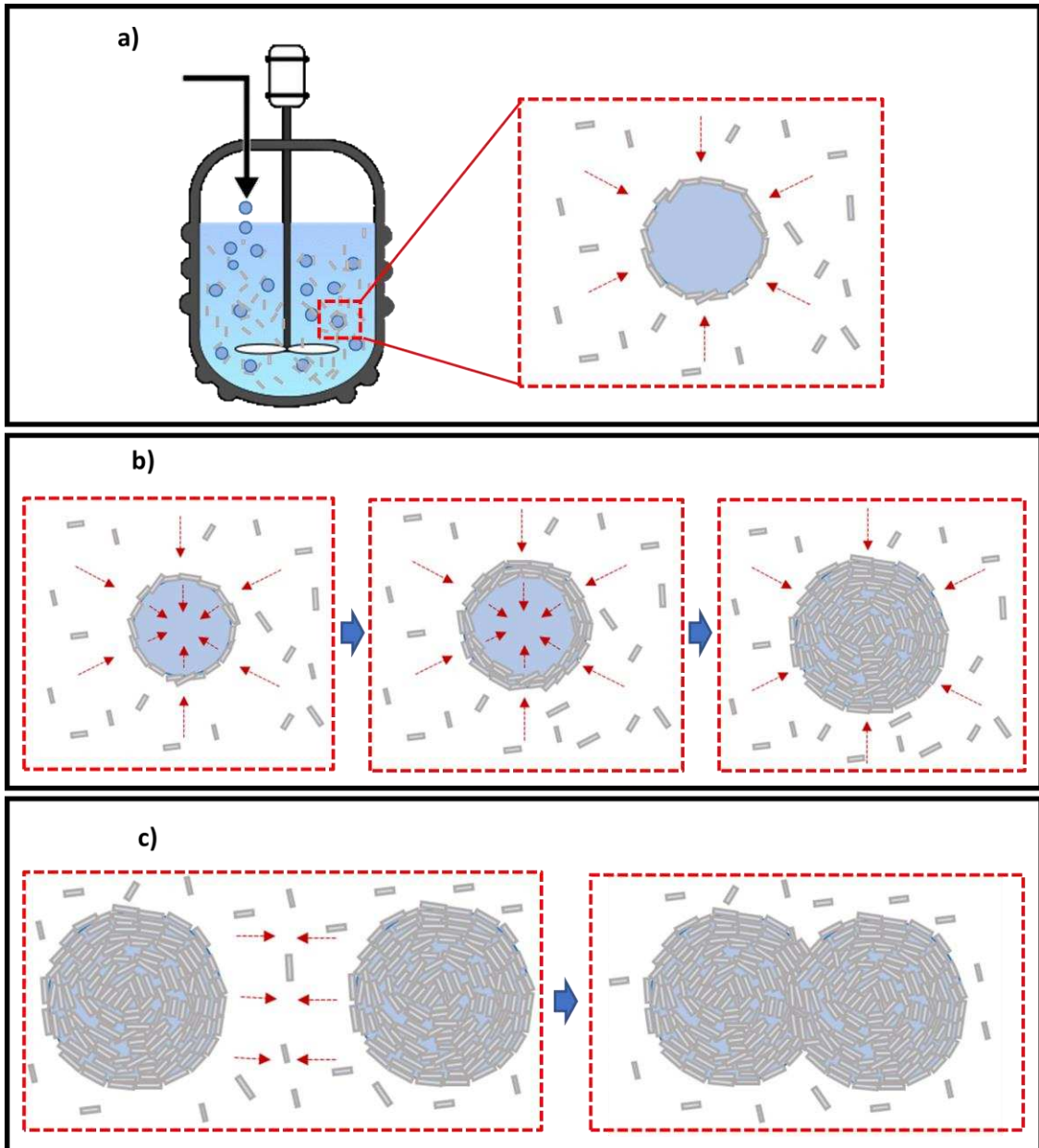
137 For consolidation and growth of agglomerates, certain studies have developed
138 agglomerate rate kernels to account for several particle-particle interactions:
139 *agglomerate-agglomerate collisions*; *crystal-crystal collisions*, and; *coalescence of*
140 *agglomerate nuclei* with a focus on the formation of liquid bridges between the
141 agglomerate nuclei or between crystal particles [17, 22-24]. One particular study
142 developed a coalescence rate kernel on the basis of a *meeting probability* term and
143 *coalescence efficiency* term for agglomerates in contact [25]. The *meeting probability*
144 is defined as the function of the target efficiency, agglomerate sizes and collision
145 velocity. As for the *coalescence efficiency* term, the model is a function of adhesion
146 and separation forces that act on the two deformed agglomerates upon their impact.
147 Overall, the model system displayed good agreement with experimental data (PSD &
148 porosity) which was validated for salicylic acid in an aqueous solution and chloroform
149 as the chosen bridging liquid.

150

151 Considering the approaches taken in literature to understand and describe a spherical
152 agglomeration process, a comprehensive model which incorporates all of the identified
153 key mechanistic rate phenomena is lacking. Population balance modelling is an
154 attractive tool for simulating agglomerate evolution over time and was previously
155 demonstrated for an antisolvent crystallization system of benzoic acid with
156 agglomeration [26]. However, to our knowledge there is no study to date which
157 includes the critical stages of wetting and nucleation as well as agglomeration through
158 a mechanistic-driven population balance model for an agglomeration in suspension
159 method.

160

161 In this work, a novel population balance model framework is developed and
162 investigated for mechanistic understanding and prediction of product properties for a
163 spherical agglomeration process. We specifically study the agglomeration in
164 suspension technique driven by the immersion mechanism and incorporate
165 customized layering and coalescence rate kernels for analysis of the concomitant rate
166 phenomena. This includes, wetting of the primary particles by the bridging liquid
167 droplets and subsequent agglomerate nuclei formation, consolidation and growth of
168 agglomerates due to layering and growth of agglomerates by coalescence (Figure 1).
169 Firstly, we outline the methodology used to integrate the mechanistically relevant rate
170 equations into the population balance model framework to characterize the
171 aforementioned stages. We then examine the influence of important formulation and
172 process parameters which consists of the starting primary particles size, bridging liquid
173 droplet size, true bridging liquid to solids ratio, and agitation rate on the agglomerate
174 size and size distribution and average liquid volume fraction over time.



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Figure 1. Schematic of the rate processes included within the population balance model: (a) bridging liquid addition and agglomerate nucleation; (b) consolidation and growth of agglomerates by layering; (c) growth of agglomerates by coalescence.

186 **2. Mathematical Modelling**

187 The governing 1-D population balance equation to simulate the evolution of
 188 agglomerates attributes over time is given by:

189

$$\begin{aligned} \frac{\partial V n_a(x, t)}{\partial t} + \frac{\partial V [G(x, t) n_a(x, t)]}{\partial x} &= \dot{Q}_{in} n_{a,in}(x, t) - \dot{Q}_{ex} n_{a,ex}(x, t) \\ &+ V [\dot{b}_{a,nuc}(x, t) + \dot{b}_{a,aggl}(x, t) - \dot{d}_{a,aggl}(x, t)] \end{aligned} \quad (1)$$

190

191 where, $n_a(x, t)$ is the number density (no/m⁴) representing the agglomerates of
 192 diameter x at time t . V is the suspension volume (m³). $G(x, t)$ is the growth rate of
 193 agglomerates (m/s) by layering. \dot{Q}_{in} and \dot{Q}_{ex} are the volumetric flows (m³/s) entering
 194 and leaving the system, and $n_{a,in}(x, t)$ and $n_{a,ex}(x, t)$ are the inlet and exit size
 195 distributions (no/m⁴). $\dot{b}_{a,nuc}(x, t)$ is the agglomerate nucleation rate (no/(m⁴.s)) due to
 196 bridging liquid addition into the suspension and wetting of crystals by the bridging liquid
 197 droplets. $\dot{b}_{a,aggl}(x, t)$ and $\dot{d}_{a,aggl}(x, t)$ are birth and death rates of agglomerates due
 198 to coalescence (no/(m⁴.s)). Breakage and attrition of the agglomerates is not
 199 considered due to a limited number of reported studies on the mechanisms involved
 200 [15].

201

202 gPROMS FormulatedProducts v2.2 (Siemens, Process Systems Enterprise, Ltd.) was
 203 used as the platform to develop and solve the population balance equation for
 204 spherical agglomeration. It is known that many of the mechanisms in a spherical
 205 agglomeration process are analogous to a high shear wet granulation process and
 206 therefore, the model flowsheet configured in gPROMS FormulatedProducts is adapted
 207 from the high wet shear granulation unit. Customized mechanistic rate kernels were
 208 then built within the model library which are selected and incorporated within the
 209 population balance framework. The rate processes and parameters of the model are
 210 described in the following sections.

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215 **2.1. Bridging Liquid Addition and Agglomerate Nucleation**

216

217 After the addition of bridging liquid droplets into the system, the formation of
218 agglomerate nuclei is assumed to occur based on the model of Barrasso and
219 Ramachandran [27]:

$$\dot{b}_{a,nuc}(x, t) = \frac{\dot{L}_{in,p} n_d(x, t)}{V_d} \quad (2)$$

220

221 Upon the addition of bridging liquid droplets with total a volumetric flow rate of \dot{L}_{in}
222 (m^3/s) and number density of $n_d(x, t)$ (no/m^4) into the vessel, they either wet the fine
223 crystals and form new agglomerate nuclei or they attach to the existing agglomerates
224 and increase their liquid content. The fraction of liquid added to the fine crystals and
225 forming new agglomerate nuclei ($\dot{L}_{in,p}/\dot{L}_{in}$), is assumed to be equal to the ratio of the
226 volume of the crystal to the total volume of particles (crystals+ agglomerates) in the
227 system. Here we also assume that the recently generated agglomerate nuclei have
228 the same size, D_d , and volume, V_d , as their constitutive bridging liquid droplets and the
229 initial liquid volume fraction of the agglomerate nuclei is one. This assumption will allow
230 us to differentiate the kinetics of bridging liquid addition and agglomerate nucleation
231 from the kinetics of consolidation and growth of agglomerates due to wetting of crystals
232 by bridging liquid droplets and subsequent immersion of crystals inside the droplets.

233

234 **2.2. Consolidation and Growth of Agglomerates by Layering**

235

236 The consolidation and growth rate of agglomerates in the suspension depend on the
237 wetting kinetics of crystals by bridging liquid droplets and subsequent immersion of
238 crystals inside the droplets (i.e. in an immersion mechanism in which the bridging liquid
239 droplets are larger than the particles to be agglomerated). In a recent publication [21],
240 we developed two new mathematical models for the kinetics of wetting of crystals and
241 their immersion inside the bridging liquid droplets: *immersion rate limited regime* and
242 *collision rate limited regime* where full derivation of the equations describing these
243 phenomena can be found. We will use these models to predict the kinetics of
244 consolidation and growth of agglomerate nuclei in the population balance framework
245 where we define the growth rate of an individual agglomerate as:

246

247

$$G(x, t) = \left(\frac{\partial x}{\partial t} \right)_x \quad (3)$$

248 According to Arjmandi-Tash et al. [21], the time evolution of agglomerate size in an
 249 agglomeration in suspension process is given by:

$$\left(\frac{\partial x}{\partial t} \right) = C_{growth} \frac{2\Psi D_p \gamma \cos \theta}{15\mu_d x} (1 - \varphi_{cp}) \varphi_{cp} \quad (4)$$

250 for an *immersion rate limited regime* or

$$\left(\frac{\partial x}{\partial t} \right) = C_{growth} 2\alpha [u(D_p)^2 + u(D_d)^2]^{\frac{1}{2}} \varphi_{P_b}(t) \quad (5)$$

251 for a *collision rate limited regime*.

252
 253 In Eqs. (4)-(5), D_p and Ψ are diameter and sphericity factor of crystal particles,
 254 respectively; γ is interfacial tension between bridging liquid and mother solution; θ is
 255 bridging liquid/solid contact angle at three-phase bridging liquid/mother solution/solid
 256 contact line; μ_d is the viscosity of the bridging liquid; φ_{cp} is critical-packing liquid volume
 257 fraction; α is target efficiency; $u(D_p)$ and $u(D_d)$ are the particle-mother solution and
 258 bridging liquid droplet-mother solution relative velocities, respectively; C_{growth} is a
 259 kinetic parameter to be determined by the agglomeration experiments; φ_{P_b} defines the
 260 crystal volume fraction in the bulk mother solution. φ_{P_b} remains constant in a
 261 continuous, well-mixed system at steady state (mixed-suspension, mixed-product
 262 removal, MSMPR) whereas, in a batch agglomeration system, it decreases due to
 263 immersion inside the bridging liquid droplets. The population balance in conjunction
 264 with a mass balance for the system in gPROMS FormulatedProducts enables us to
 265 account for any changes in the crystal volume fraction in the bulk mother solution
 266 during the agglomeration process.

267
 268 The agglomerate nucleation number, $AgNu$, predicts different regimes of
 269 agglomeration; *immersion rate limited* and *collision rate limited* and it determines
 270 which of the above correlations should be used to predict the growth rate of
 271 agglomerates in the population balance framework. For a system with an agglomerate
 272 nucleation number, $AgNu$, larger than one, the process of agglomerate nucleation is
 273 limited by the immersion rate. Thus, the growth rate can be found by

274 Eq. (4). On the other hand, if the agglomerate nucleation number, $AgNu$, is lower than
 275 one, the process is controlled by the collision and arrival of the particles at the bridging
 276 liquid droplet surfaces. The growth of agglomerates can be obtained by Eq. (5).

277

278 **2.3. Growth of Agglomerates by Coalescence**

279 The growth of larger agglomerates can also occur due to the possible coalescence
 280 during agglomerate-agglomerate impact. To account for this growth, a mechanistic
 281 coalescence kernel was implemented on the basis of Blandin *et al.* model [25], which
 282 is expressed as the product of the meeting probability and the coalescence efficiency.
 283 The main equations used for the birth and death rates of agglomerates due to
 284 coalescence in our population balance framework are listed:

285

$$\dot{b}_{a,aggl}(v, t) = \frac{1}{2} \int_0^v K(v', v - v', t) (n(v', t) n(v - v', t)) dv' \quad (6)$$

$$\dot{d}_{a,aggl}(v, t) = \int_0^\infty K(v, v', t) n(v, t) n(v', t) dv' \quad (7)$$

286

287 Where K is the coalescence kernel and v, v' represent the agglomerate volume. The
 288 coalescence kernel is defined as:

289

$$K(v, v', t) = K(i, j, t) = f(i, j, t) eff(i, j, t) \quad (8)$$

290

291 $f(i, j, t)$ determines the meeting probability of agglomerates and $eff(i, j, t)$ is the
 292 coalescence efficiency term. The meeting probability considers the encounter of
 293 agglomerates and is a function of the hydrodynamics of the system:

294

$$f(i, j, t) = \alpha(i, j, t) \frac{\pi}{4} (x_i + x_j)^2 [u(x_i)^2 + u(x_j)^2]^{1/2} \quad (9)$$

295

296 Here, $\alpha(i, j, t)$ is the target efficiency, x is the characteristic sizes of the agglomerates
 297 and $u(x)$ is the agglomerate-mother solution relative velocity which is calculated from
 298 the mean square of the particle-liquid relative velocity. The coalescence efficiency

299 term was introduced to correct for the meeting probability and to calculate the
 300 maximum size that agglomerates eventually reach:

301

If $f_{adh}(i, j, t) \geq f_{sep}(i, j, t)$:

$$\begin{aligned}
 eff(i, j, t) &= \frac{f_{adh}(i, j, t)}{f_{sep}(i, j, t)} - 1 \\
 &= C_{eff} \frac{\left[\frac{def^{max}(i, j, t)}{\frac{D_p}{2}} \right]^2 (1 - \varphi(t)) F_{bridge} \frac{x_i^2 + x_j^2}{x_i^3 + x_j^3}}{\rho_L [\varepsilon (x_i + x_j)]^{\frac{2}{3}} x_i^2} - 1
 \end{aligned} \tag{10}$$

If $f_{adh}(i, j, t) < f_{sep}(i, j, t)$: $eff(i, j, t) = 0$ (11)

302

303 $f_{adh}(i, j, t)$ is the adhesive force, $f_{sep}(i, j, t)$ is the shear-induced disruptive force,
 304 F_{bridge} is the bridging liquid bridge force between the two crystal particles,
 305 $def^{max}(i, j, t)$ is the radius of the contact surface, D_p is the mean size of the crystal
 306 particles, ρ_L the density of the mother solution, C_{eff} the coalescence efficiency
 307 coefficient, ε is the average energy dissipation. Expressions corresponding to the
 308 terms, $\alpha(i, j, t)$, $u(x)$, $f_{adh}(i, j, t)$, $f_{sep}(i, j, t)$, F_{bridge} and $def^{max}(i, j, t)$ can be found in detail [25].
 309 The average energy dissipation, ε , was estimated using a power number correlation
 310 as a function of suspension volume, V , agitation rate, n_r , and impeller diameter, d_{imp} .

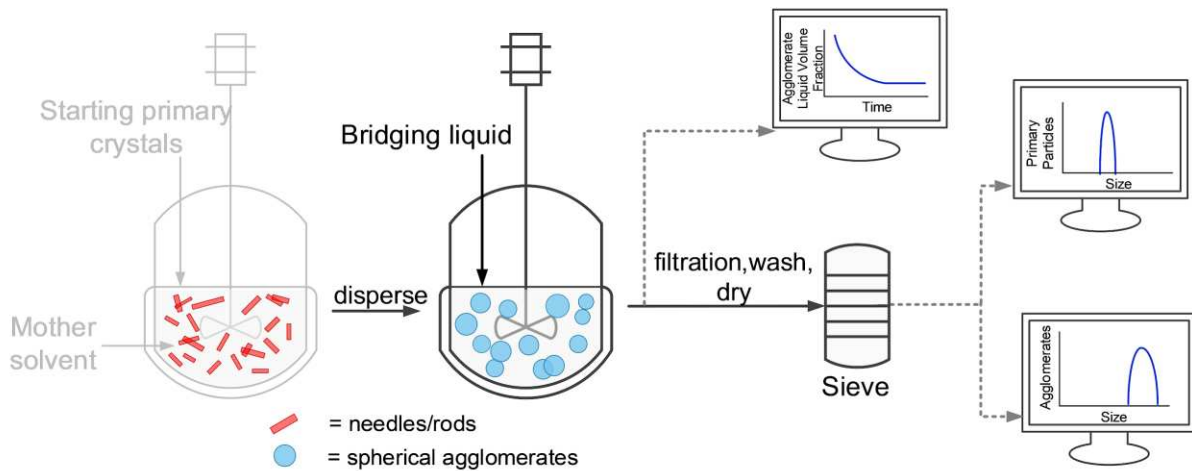
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312

313 **3. Model Parametrisation**

314 **3.1. Process Scheme**

315 The population balance model was set up and solved using the gPROMS process
 316 simulation platform. A sketch of the model process is shown in Figure 2 to depict a
 317 typical agglomeration in suspension technique.



318

319 **Figure 2.** Sketch of process flowsheet used to simulate the spherical agglomeration
 320 process (batch), mechanisms and the product attributes.

321

322 Before the addition of a bridging liquid, an assumed insoluble suspension of crystals
 323 is typically dispersed and held at equilibrium for some time. Incorporating the key
 324 constitutive rate equations as described in Section 2, the behaviour and performance
 325 of the model is then analysed upon immediate addition of the bridging liquid droplets.
 326 Whilst the governing 1-D population balance equation (Eqn. 1) presents the
 327 opportunity to model both a batch or continuous process, in this study a batch process
 328 was selected.

329

330 Product properties such as the particle size distributions are analysed and determined
 331 using a dry sieving unit consisting of 101 incremented sieves (non-linearly) with an
 332 aperture range from 0.01 to 3500 μm . The choice of the incremented sizes and
 333 aperture range were based on input measured data of the crystal particles. A
 334 logarithmic particle size distribution is then generated and reported as a volume %.
 335 The average liquid volume fraction inside the whole volume of the growing
 336 agglomerate nucleus was also examined over time from the following expression:

337

$$\varphi_{avg}(t) = \frac{(D_a/2)}{H_2(t)} \quad (12)$$

338

339 Where the size of the agglomerate nucleus, $H_2(t)$ can be found by:

340

$$H_2(t) = \frac{D_d}{2} + \left(\frac{\Psi D_p \gamma \cos \theta}{15 \mu_d} (1 - \varphi_{cp}) \varphi_{cp} t \right)^{1/2} \quad (13)$$

341

342 For an *immersion rate limited regime* or:

$$H_2(t) = \frac{D_d}{2} + \frac{D_d}{2TBSR} \left(1 - \exp \left(\frac{2\alpha [u(D_p)^2 + u(D_d)^2]^{1/2} \varphi_{P_{b0}} TBSR}{D_d} t \right) \right) \quad (14)$$

343 For a *collision rate limited regime*.

344

345 Therefore, at the start of the agglomeration process, $\varphi_{avg} = 1$ at $t = 0$ (bridging liquid
 346 only). The average liquid volume fraction was incorporated within the layering kernel
 347 in the gPROMS software which considers the density and inter-particle voidage.
 348 Considering the model assumptions, the unit operation is a well-mixed system and the
 349 dissolution of fine powder and agglomerate phases is negligible. The temperature of
 350 the process is constant and uniform at 25 °C. The bridging liquid droplet sizes have
 351 consistent uniformity at the specified mean size with a fixed standard deviation (20
 352 μm) and is immiscible with the mother solution. Bridging liquid to solids ratio (BSR) is
 353 therefore the same as the true bridging liquid to solids ratio (TBSR).

354

355 **3.2. Selection of Model Parameters and Operating Conditions**

356

357 A sensitivity analysis of selected model parameters and operating conditions (Table 1
 358 & Table 2) was investigated. Whilst numerous model parameters are included within
 359 the population balance model framework (Eqn. 1), studying the impact of each
 360 parameter would be unfeasible. Therefore, the selected parameters and chosen
 361 ranges are based upon reported literature values, several published experimental
 362 studies and reasonable estimations. The focus of this work was to study the bulk
 363 formation and behaviour of agglomerates and thus, high values were chosen for
 364 kinetic growth parameters. Additional parameters appearing in the different rate
 365 kernels, were based on already measured values for the agglomerating system,

366 Lovastatin in water as the mother solution and methyl isobutyl ketone (MIBK) as the
 367 bridging liquid which was studied as the system of interest [21, 28]. Lovastatin is an
 368 anti-cholesteremic BCS (Biopharmaceutical Classification System) class II drug used
 369 in the treatment for hypertension and displays poor solubility and dissolution
 370 properties. The API encompasses a complex chemical structure and is typically
 371 crystallised in a needle-like form making it desirable for a spherical agglomeration
 372 process.

373
 374

375 **Table 1.** Selection of formulation and material properties used in the simulations.

Stage	Parameter	Set point
All	Mother solution viscosity, μ_L (Pa.s)	8.9×10^{-4}
	Mother solution density, ρ_L (kg/m ³)	1000
	Bridging liquid-mother solution interfacial tension, γ (N/m)	1.01×10^{-2}
	Bridging liquid viscosity, μ_d (Pa.s)	5.8×10^{-4}
	Bridging liquid density, ρ_d (kg/m ³)	802
	Crystal skeletal density, ρ_p (kg/m ³)	1100
	Particle-bridging liquid contact angle in solvent, θ_z (°)	30
Consolidation & Layering	Sphericity factor for crystal particles, Ψ (-)	0.43
	Critical packing liquid volume fraction, ϕ_{cp} (-)	0.36
	C_Growth, (-)	0.69
Coalescence	Meeting probability, $f(i,j,t)$ (-)	1
	Coalescence efficiency, $eff(i,j,t)$ (-)	0.3×10^{-4}
	Separation distance, α (m)	0.1×10^{-5}
	Half-filling angle, β (°)	70
	BSR min, (m ³ /m ³)	0.01
	BSR max, (m ³ /m ³)	0.7

376
 377
 378

379 **Table 2.** Selection of operating conditions and ranges used in the simulations.

Process Parameters	Set point
Simulation duration (min)	22
Crystal loading, C_s (wt.%)	5
Temperature, (°C)	25
Suspension volume, $V_{suspension}$ (mL)	500
Impeller diameter, d_{imp} (m)	0.035
Bridging liquid addition rate, Q_d (g/min)	3
Mean initial particle size, D_p (μm)	40-120
Agitation rate, (RPM)	200-600
Bridging liquid addition time, t (min)	1-6
Bridging liquid droplet size, D_d (μm)	100-400

380

381 **3.3. Solution of the Population Balance Equation**

382

383 All simulations were run in gPROMS v2.2 (Siemens, Process Systems Enterprise Ltd.)
 384 The standard gPROMS solver for differential-algebraic equations is DAEBDF which
 385 was used as the numerical method to solve the population balance equations. A high
 386 resolution finite volume scheme with flux limiting function (HRFVS-FL) was used which
 387 includes the discrete rate processes (nucleation & coalescence) and was evaluated at
 388 the particle size midpoints whereas the continuous rate processes (consolidation &
 389 layering) are evaluated at the boundary conditions to determine the kinetics of growth.
 390 The size domain has been divided for the discretization of the population balance
 391 equation according to a geometrical grid (non-linear), giving smaller step sizes to
 392 contribute to a higher numerical accuracy of the solution and, improving the PSD
 393 resolution at initial times. A logarithmic grid was chosen with 64 bins for the
 394 agglomerate size distribution (1 – 3500 μm).

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400 4. Results & Discussion

401 4.1. Reference Conditions

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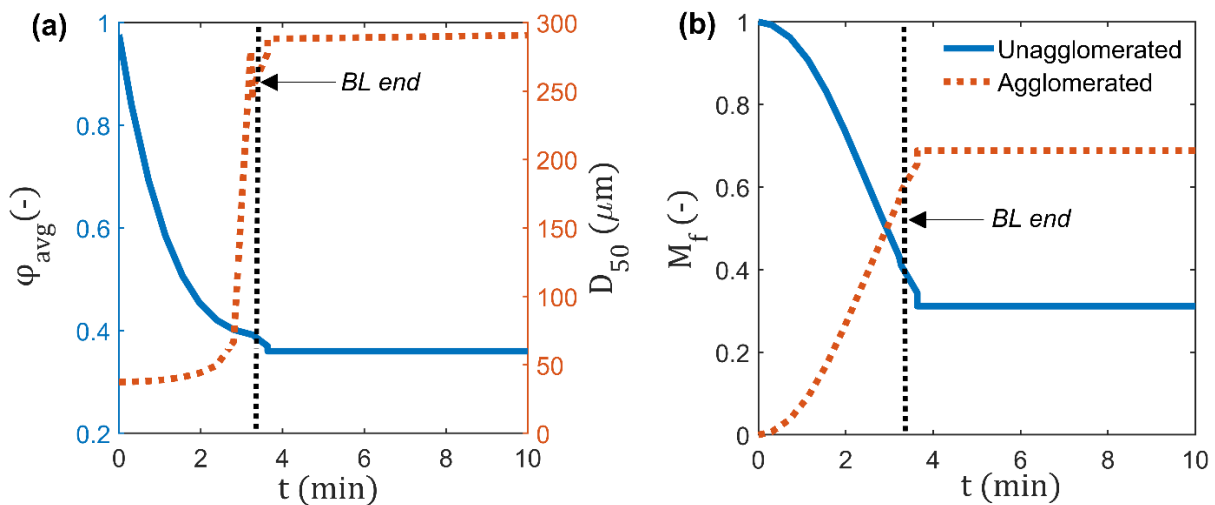
403 Prior to analysis of the selected formulation and process parameters within the
404 specified ranges, an example trend is shown (Figure 3) to demarcate the key features
405 and mechanisms during spherical agglomeration by the immersion mechanism.

406

407 Figure 3 displays the evolving average agglomerate liquid volume fraction, $\varphi_{avg}(-)$ and
408 median particle size, $D_{50}(\mu\text{m})$ for the total particle population over time (a) as well as
409 the fraction of non-agglomerated and agglomerated particles (b). The simulated
410 process trends are analysed upon immediate addition of the bridging liquid at 0 min
411 with a flow rate of 3 g/min. After 3.35 min, the bridging liquid addition is stopped and
412 the simulation continues for 22 min. In this analysis (Figure 3), the region between 0
413 to 10 min is closely examined as there is a minimal change from the predicted trends
414 during 10 to 22 min.

415

416



417

418

419 **Figure 3.** Simulated profiles showing the (a) average agglomerate liquid volume
420 fraction, φ_{avg} and median particle size, D_{50} over time; (b) the mass fraction, M_f for non-
421 agglomerated and agglomerated particles over time. Key parameter values prediction
422 were: bridging liquid (*BL*) droplet size, $D_d = 200 \mu\text{m}$; *BL* addition rate, $Q_d = 3 \text{ g/min}$, *BL*
423 addition time, $t = 2 \text{ min}$ ($\text{BSR} = 0.55$); agitation rate = 400 RPM
424 ($\varepsilon = 0.0023$) and; mean initial primary particle size, $D_p = 40 \mu\text{m}$. A simulation time of
425 22 min was selected for all conditions.

426 During the bridging liquid addition stage (0 to 3.35 min) with a fixed droplet size
427 ($D_d = 200 \mu\text{m}$) to the pre-suspended crystals ($D_p = 40 \mu\text{m}$) resulted in a rapid decline
428 of the φ_{avg} (1 to 0.39). A slow increase during initial wetting followed by a sharp incline
429 in the D_{50} profile (40 to 260 μm) during growth occurred until the final addition point
430 Figure 3, (a). Simultaneously, the fraction of unagglomerated (primary particles) in
431 suspension was reduced (60%) compared to the fraction of agglomerated particles
432 (Figure 3, b) which increased over time (0 to 3.35 min).

433

434 The results confirm wetting, agglomerate nucleation and growth by consolidation and
435 layering to be prevalent during the bridging liquid addition stage. Operating in the
436 *collision rate regime* (Eqn. 5) is predicted as the agglomeration nucleation number,
437 $AgNu = 4.56 \times 10^{-6}$ is less than 1. After the final addition of the bridging liquid droplets
438 (> 3.35 min), a minimal increase in the D_{50} and a small decrease in the φ_{avg} are
439 observed. Further growth to form larger agglomerates by coalescence mechanisms
440 can occur (Figure 1) however in this case, coalescence is negligible as the
441 agglomerate properties are unchanged after 4 min (Figure 3).

442

443 Decoupling the mechanisms in a spherical agglomeration process is challenging.
444 However, through population balance modelling one can begin to understand and
445 provide mechanistic insight into the concurrent wetting and nucleation, consolidation
446 and growth phenomena from the effect of selected formulation properties and process
447 conditions on the evolution of agglomerate properties.

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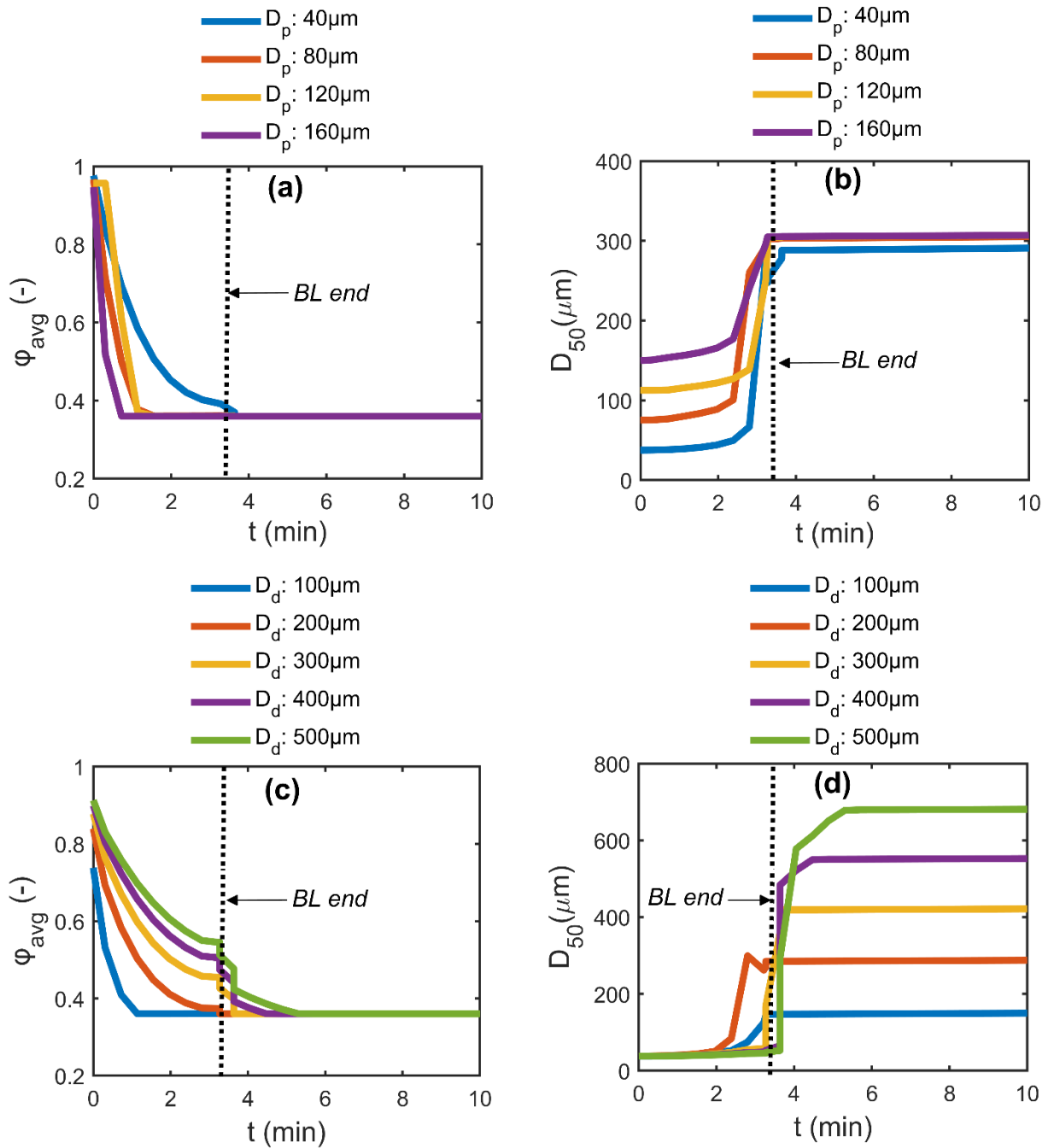
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4.2. Effect of Formulation and Process Parameters

The following section presents a local sensitivity analysis from the selected input variables: mean initial primary particle size, D_p (μm); mean droplet size, D_d (μm); bridging liquid to solids ratio (BSR); and the agitation rate (RPM). To ensure the immersion mechanism was maintained across all conditions, D_d was kept larger than D_p . Furthermore, under the given material system with fixed input parameters (Table 1 & Table 2), $AgNu$ remained below 0.01 and as a result, the system was always within the collision rate regime.

Figure 4 and Figure 5 show the effect of the selected formulation and process variables on the average liquid volume fraction, φ_{avg} , and median agglomerate size, D_{50} . Increasing the primary particle size (40 to 160 μm) increases the initial wetting and nucleation rate because the collision rate increases with particle size. The agglomeration process is complete within 6 min for 40 μm particles but reduces to 3.50 min for 160 μm particles (Figure 4, (a-b)). On the other hand, increasing the droplet size (100 to 500 μm) prolonged the timescale for immersion of crystals within the droplets when compared to varying the initial primary particle size. This is seen from the φ_{avg} trends (Figure 4, (c)) where $D_p = 100 \mu\text{m}$ produced a faster reduction in φ_{avg} than $D_p = 500 \mu\text{m}$ during the full wetting period (0 to 3.35 min). Selecting a $D_p > 300 \mu\text{m}$ lengthened the nucleation process during the wetting period and subsequent time to agglomerate completion. Increased growth rates with larger final sizes were achieved as observed from the median agglomerate size, D_{50} profiles (Figure 5, (d)).

The BSR value corresponded to different total bridging liquid addition times and so the final addition point varied from 2 to 5 min (Figure 5, (a-b)). Minimal differences in the overall φ_{avg} profiles were observed with a BSR range of 0.15 to 0.75 whereas the highest selected value of 2 had a substantial impact on φ_{avg} over time (Figure 5, (a)). This impact is also observed in the full D_{50} profile (Figure 5, (b)) indicating uncontrolled agglomeration. Operating within the BSR range from 0.15 to 0.75 increased the agglomerate median size. However, for $BSR < 0.35$ there is insufficient bridging liquid content available to promote agglomerate growth (Figure 5, (b)).



498

499 **Figure 4.** Sensitivity of time evolution of the average agglomerate liquid volume

500 fraction, ϕ_{avg} and median particle size, D_{50} to (a-b) initial mean primary particle size,

501 D_p (μm) and; (c-d) mean bridging liquid droplet size, D_d (μm).

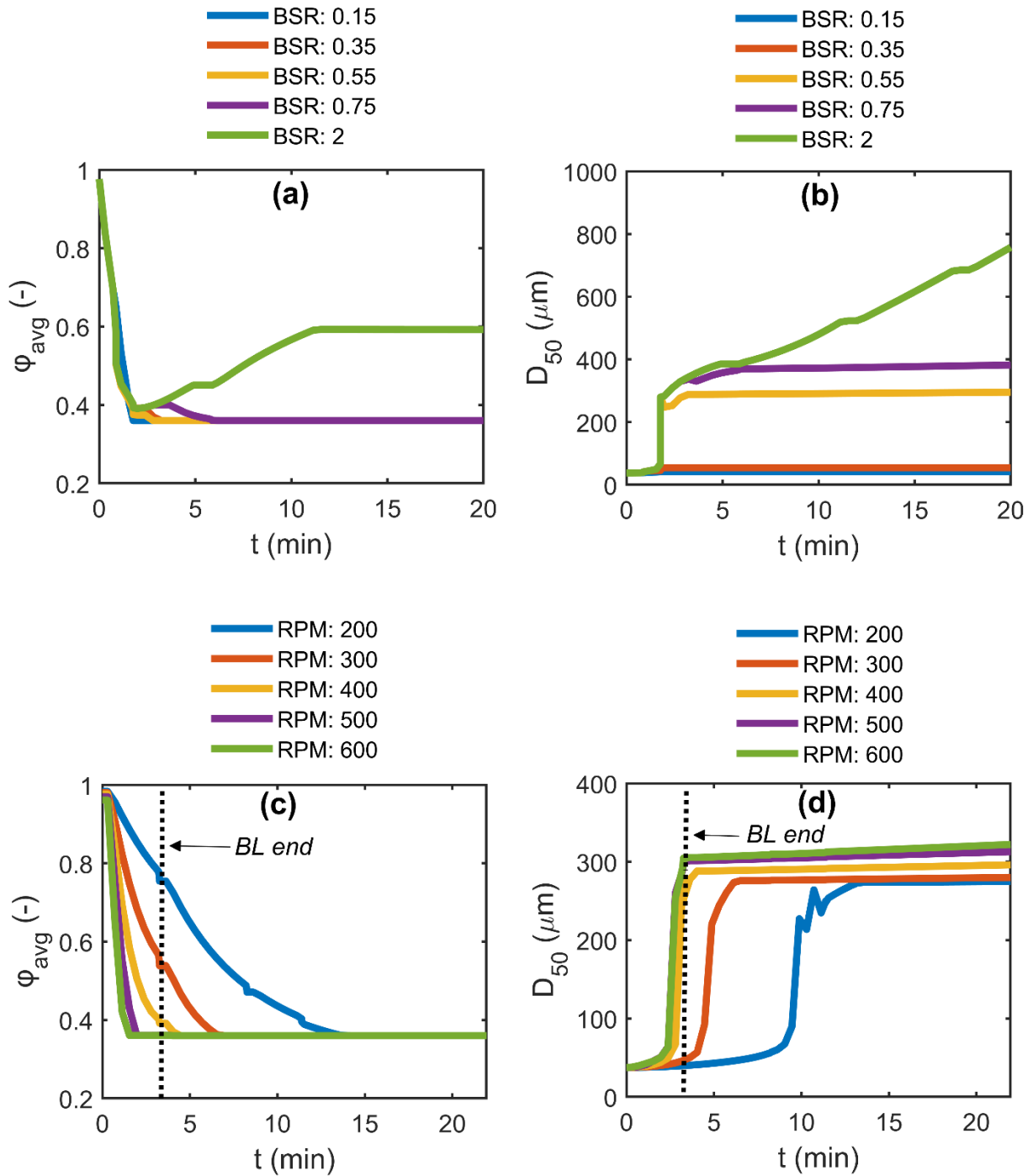
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508 **Figure 5.** Sensitivity of time evolution of the average agglomerate liquid volume
 509 fraction, ϕ_{avg} and median particle size, D_{50} to (a-b) bridging liquid to solids ratio (BSR)
 510 and (c-d) agitation rate (RPM).

511

512

513

514 Nucleation and agglomeration kinetics were highly sensitive to the agitation rate
515 parameter (Figure 5, (c-d)). For instance, the time to agglomerate completion at 200
516 RPM was 15 min whereas at 600 RPM, 3.50 min is required for agglomerate
517 completion (Figure 5, (c-d)). This substantial difference in time to agglomerate
518 completion is due to increased mixing intensity within the batch reactor which
519 increases the collision frequency between droplets and crystals, therefore,
520 accelerating the immersion process during the wetting stage.

521

522 Figure 6 and Figure 7 show how the full size distribution changes with time. Here, the
523 size distributions show both the primary particles (smallest size mode) and the
524 agglomerates (larger size mode). As growth by consolidation and particle layering
525 occurs, the first mode reduces in size as primary particles are captured by droplets.
526 The height of the second mode increases and agglomerate size also increases. In
527 addition to the selected conditions shown in Figure 4 and Figure 5, full PSDs for all
528 conditions are captured and displayed within the appendix.

529

530 Reduction in primary particles and growth of agglomerates from 0 to 22 min is shown
531 for both the mean initial primary particle size, D_p and the droplet size, D_d . Tuning the
532 droplet size had a clear impact on the final agglomerate size as shown from the PSD
533 evolution for $D_d = 500 \mu\text{m}$ and $200 \mu\text{m}$ in Figure 6, (d). A high BSR value (2) was shown
534 to have a significant impact on the mean agglomerate size. However, at low BSR
535 (0.15), the effect was negligible (see Figure 7 (a)-(d)). Although the primary particles
536 have been completely removed in Figure 7 (b), agglomeration is still ongoing (see
537 Figure 5, (b)). Agglomerate coalescence continues as a consequence of deformation
538 and compaction mechanisms throughout the growth-period which can lead to paste
539 formation. Similar to Figure 5 observations, varying the agitation rate had a minimal
540 impact on the final agglomerate size distributions as opposed to the time to
541 agglomerate completion kinetics (Figure 7, (c-d)).

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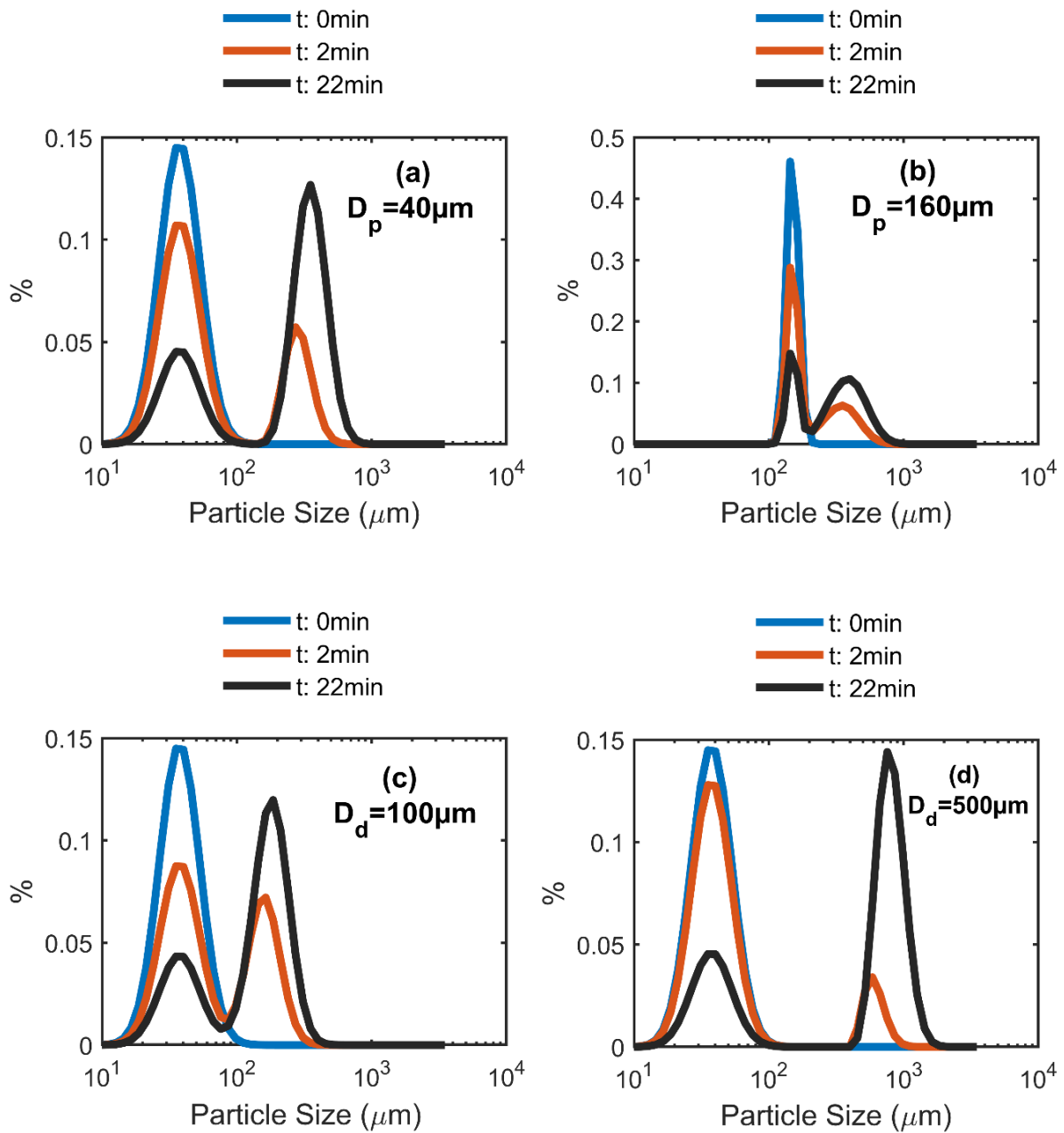
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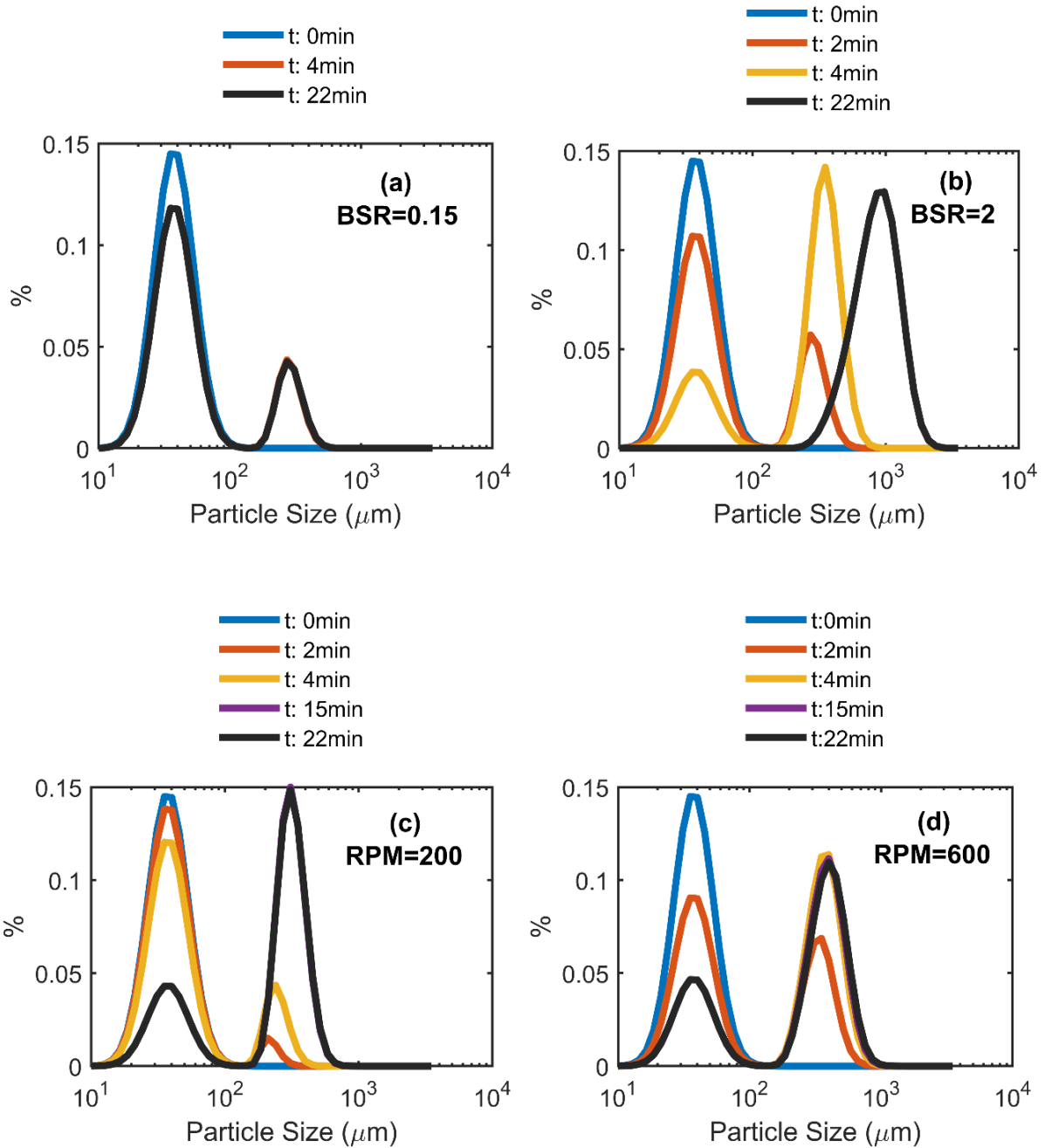
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550 **Figure 6.** Evolving agglomerate size distributions over time for an initial mean primary
 551 particle size, D_p (μm) of (a) 20 μm and (b) 120 μm as well as for mean bridging liquid
 552 droplet sizes, D_d (μm) of (c) 100 μm and (d) 500 μm .

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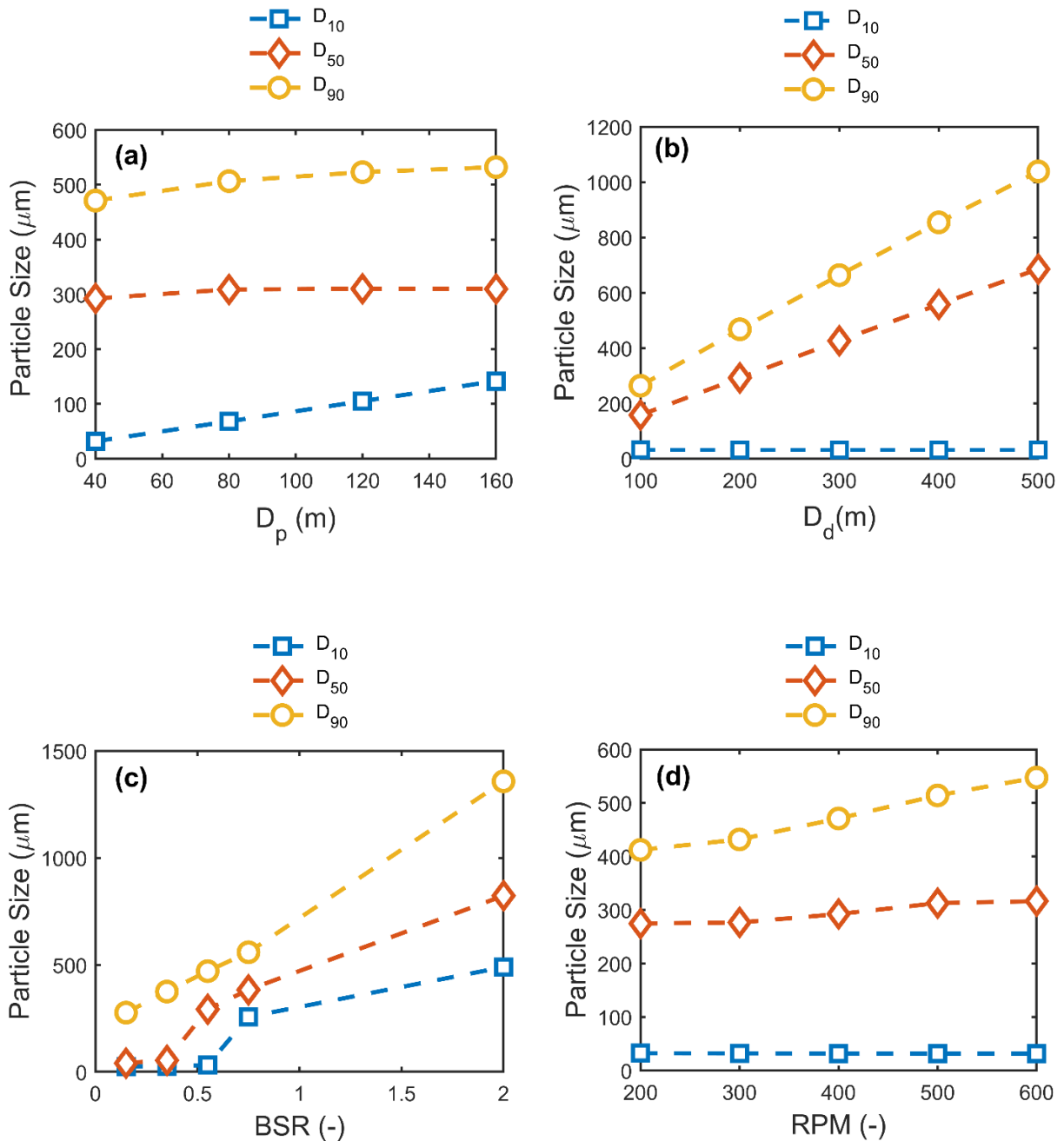
557 **Figure 7.** Evolving agglomerate size distributions over time for BSR of (a) 0.15 and (b)
 558 2 as well as for an agitation rate, (RPM) of (c) 200 and (d) 600.

559

560 The impact of the selected parameters on various particle size statistics (D_{10} , D_{50} and
 561 D_{90}) are shown in Figure 8. Bridging liquid droplet size and BSR have the most
 562 profound effect on the final agglomerate sizes achieved. Interestingly, when
 563 comparing the trends in Figure 8, (b & c), the median and larger sizes (D_{50} & D_{90}) show
 564 an increasing trend whilst the smaller sizes represented by D_{10} remains largely
 565 unchanged for changes in D_d as opposed to the BSR parameter and within the

566 selected parameter ranges. In contrast, there is minimal change in the particle size
 567 distribution statistics from varying the initial mean primary particle size and agitation
 568 rate.

569



570

571 **Figure 8.** Final agglomerate size values (D_{10} , D_{50} , D_{90}) plotted as a function of varying
 572 the (a) initial mean primary size, D_p (μm) (b) mean bridging liquid droplet size, D_d (μm)
 573 (c) bridging liquid to solids ratio (BSR) and (d) agitation rate (RPM).

574

575

576 **5. Conclusions**

577 A population balance model has been developed and was used to study a spherical
578 agglomeration process. The simulated results (agglomerate size and size distribution,
579 average liquid volume fraction) from the selected formulation and process parameters
580 (initial primary particle size, bridging liquid droplet size, true bridging liquid to solids
581 ratio, and agitation rate) revealed important mechanistic insights and tuneable
582 conditions to produce desirable agglomerates. Bridging liquid droplet size and BSR
583 had the most influence on both the nucleation and agglomeration kinetics, time to
584 completion, and the final equilibrium agglomerate attributes. This effect was most
585 noticeable when tuning the size of the bridging liquid droplets which generated a range
586 of final agglomerate size and size distributions. The model can also be used to set a
587 safe operating range for the BSR parameter to produce stable agglomerates which in
588 this case were from 0.35 to 0.75. Higher values of BSR led to uncontrolled
589 agglomeration that can produce paste-like material which is unsuitable for downstream
590 processing. On the other hand, the initial primary particle size and agitation rate
591 parameters had a significant impact on the wetting, nucleation and layering timescales
592 which affected the time to completion. However, the impact on the final equilibrium
593 agglomerate attributes such as the agglomerate size and size distribution were small.

594

595 To improve further mechanistic understanding and enable spherical agglomeration as
596 a key particle engineering technique for pharmaceutical manufacturing, validation of
597 the kinetic parameters within the population balance model is essential. The power of
598 the models is dependent on the quality of the model parameters and therefore, the
599 ability to measure these parameters through off line characterisation experiments will
600 be very helpful. Equally, sensitivity analysis of the model under various material
601 systems and different regimes i.e., immersion nucleation would be beneficial.

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714 data on the spherical agglomeration process. The authors would also like to thank Dr
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717 population balance model in gPROMS FormulatedProducts.

718

719

720 **8. CRediT Authorship Contribution Statement**

721 **Bilal Ahmed:** Writing – original draft, Methodology, Software, Data curation.

722 **Omid Arjmandi-Tash:** Writing – original draft, Methodology, Software, Formal
723 analysis.

724 **James D. Litster:** Conceptualization, Supervision, Writing – review & editing,
725 Funding acquisition.

726 **Rachel M. Smith:** Conceptualization, Supervision, Writing – review & editing,
727 Funding acquisition.

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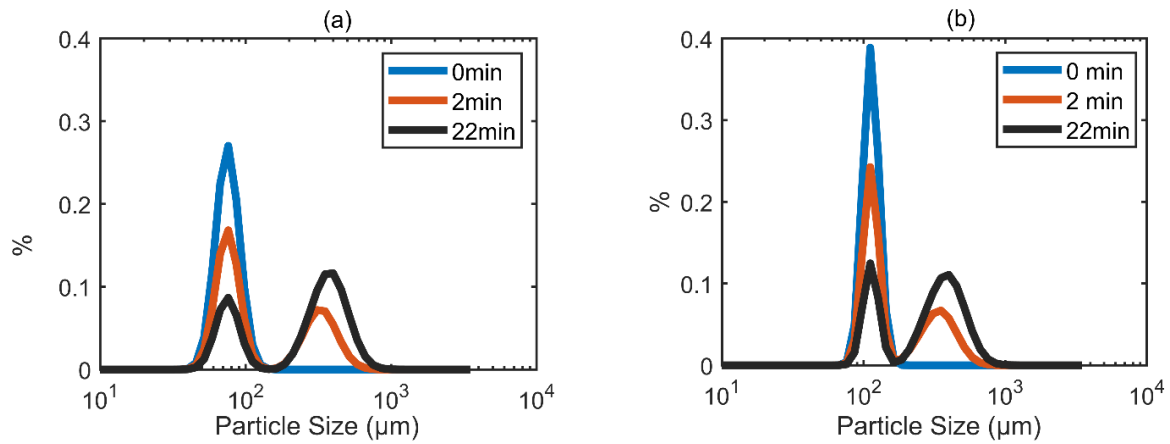
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744 **Appendix:**

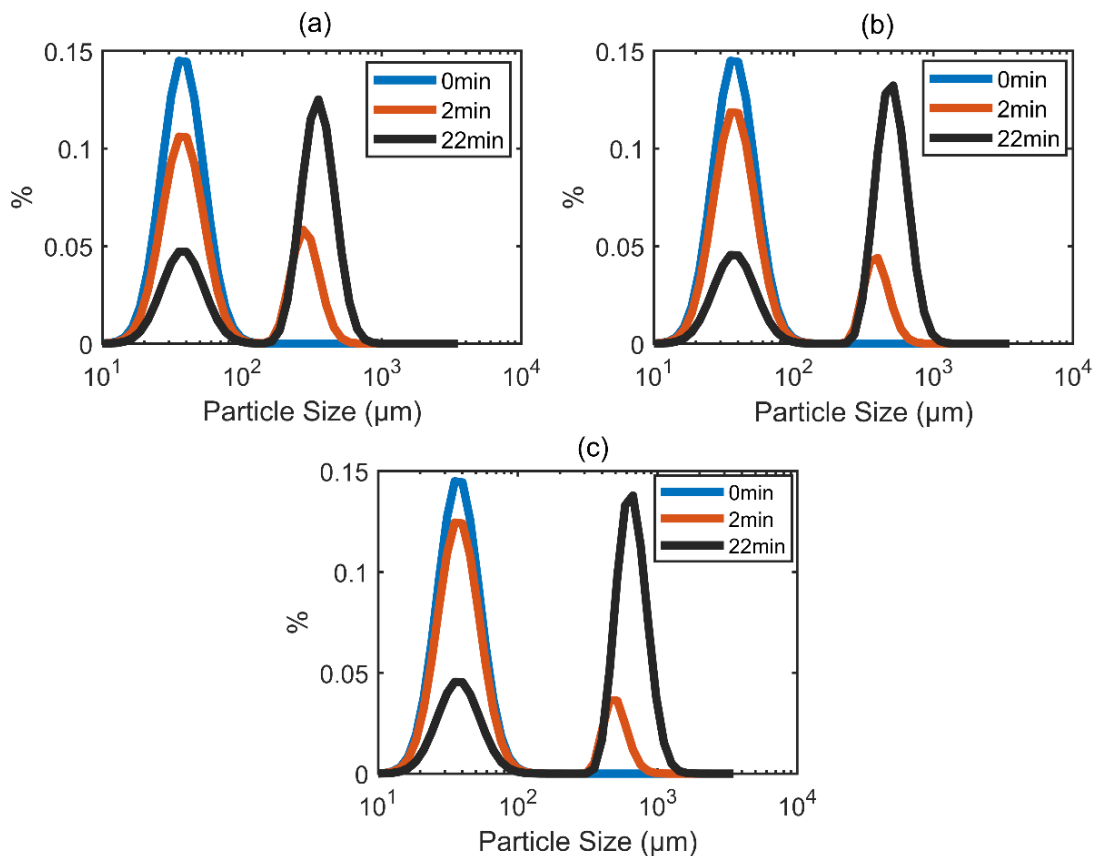


745

746 **Figure A 1.** Sensitivity of time evolution of agglomerate size for the initial mean primary
747 particle sizes, D_p of (a) $80 \mu\text{m}$ and (b) $120 \mu\text{m}$.

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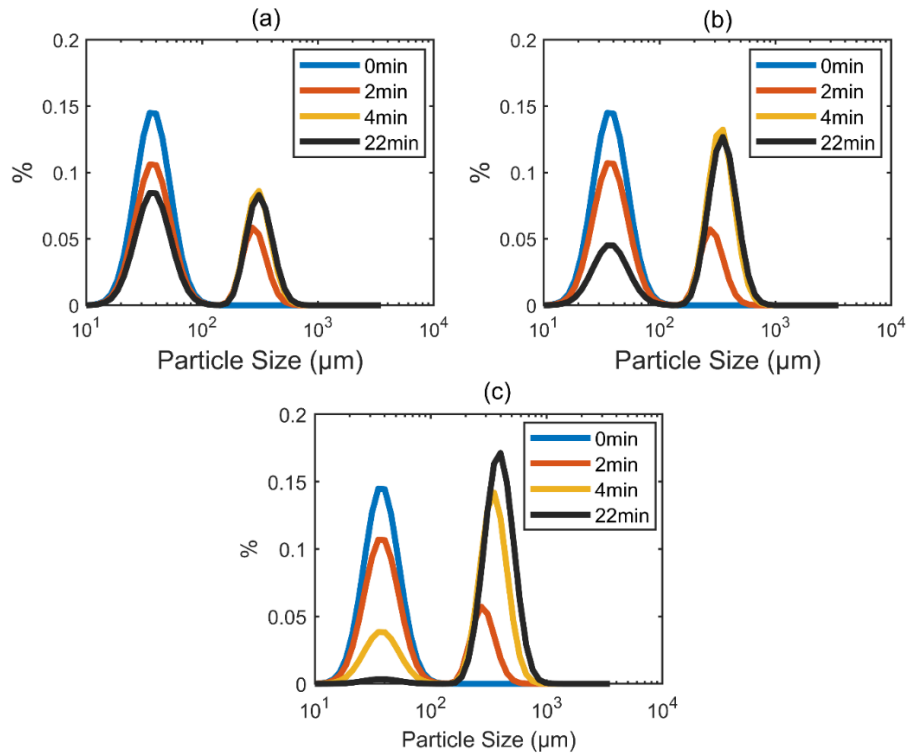
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751 **Figure A 2.** Sensitivity of time evolution of agglomerate size for the mean bridging
752 liquid droplet size, $D_d(\mu\text{m})$ of (a) $200 \mu\text{m}$ (b) $300 \mu\text{m}$ and (c) $400 \mu\text{m}$.

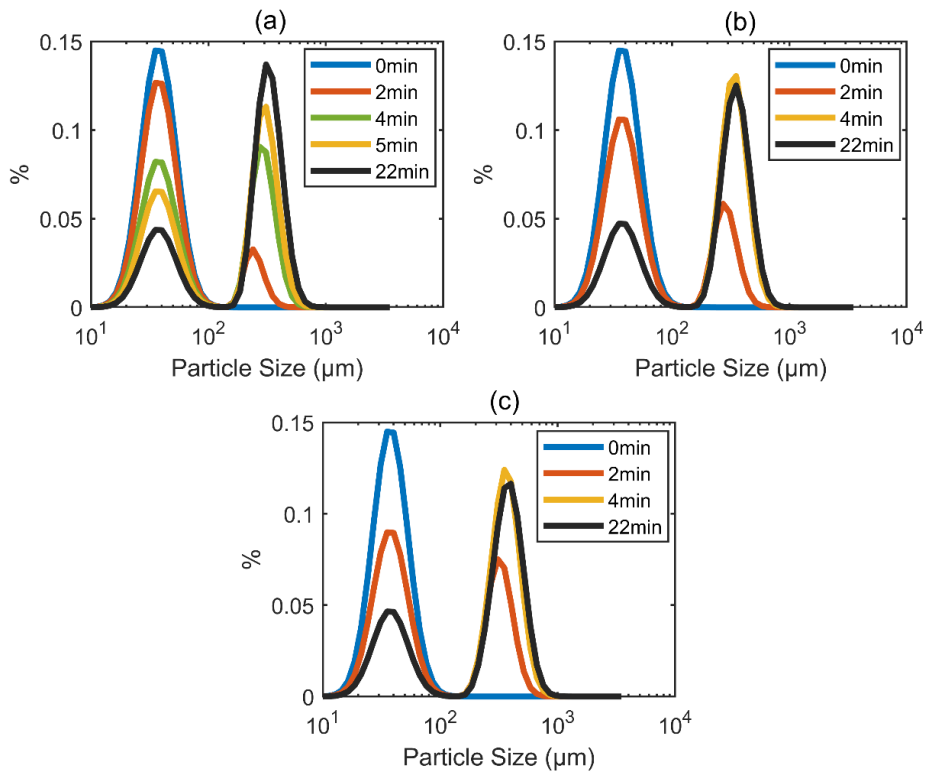
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755 **Figure A 3.** Sensitivity of time evolution of agglomerate size for the bridging liquid to
 756 solids ratio (BSR) of (a) 0.35 (b) 0.55 and (c) 0.75.

757



758

759 **Figure A 4.** Sensitivity of time evolution of agglomerate size for the agitation rate
 760 (RPM) of (a) 200 (b) 300 and (c) 400.