

Numerical analysis of in-flight freezing droplets: Application to novel particle engineering technology

Author names and affiliations

Andrew Tait^a, Jonathan G. M. Lee^a, Bruce R. Williams^b and Gary A. Montague^c

^a Biopharmaceutical Bioprocessing Technology Centre, School of Chemical Engineering and Advanced Materials, Newcastle University, Newcastle upon Tyne, Tyne and Wear, NE1 7RU

^b Accelyo Limited, 35 Gypsy Lane, Nunthorpe, Middlesbrough, Tees Valley, TS7 0DU

^c School of Science, Engineering and Design, Teesside University, Middlesbrough, Tees Valley, TS1 3BX

Corresponding author

Andrew Tait

a.tait@ncl.ac.uk

Biopharmaceutical Bioprocessing Technology Centre,
School of Chemical Engineering and Advanced Materials,
Newcastle University,
Newcastle upon Tyne,
Tyne and Wear,
NE1 7RU
United Kingdom
+44 (0) 7841656281

22 **Abstract**

23 The freezing of a stream of free-falling monodispersed droplets was simulated through the
24 development of numerical models in this work. Prediction of the freezing time and
25 temperature transition of a single droplet is beneficial for optimisation of novel continuous
26 spray freeze drying (cSFD) processes. Estimations of the vertical free-falling distance of the
27 droplets in a slip stream and predictions of the chances of droplet coalescence greatly
28 enhance process understanding and can be leveraged to direct equipment design and process
29 development. A design space of droplet diameters in the range from 100 μm to 400 μm and
30 ambient temperatures from -120°C to -40°C was explored. The rate of supercooling within
31 the design space was predicted to range from 48 to $830^{\circ}\text{C s}^{-1}$ depending on the ambient
32 temperature and droplet size. A comparison of the vertical free-falling distances of solitary
33 droplets and streams of droplets at different temperatures showed that the terminal velocity of
34 a vertically falling stream of droplets is always in excess of the terminal velocity of a solitary
35 droplet of the same size. A difference of 1.35 m was predicted for the free-falling distance of
36 a 400 μm droplet compared to a stream of droplets at -42°C . A comparison between flow
37 rates for consecutively generated 100 μm droplets showed that droplet coalescence was
38 predicted at 0.05 Lh^{-1} , whilst at 0.02 Lh^{-1} a separation distance of 23 μm was maintained thus
39 preventing coalescence.

40 **Keywords**

41 Continuous Spray Freeze Drying; Freeze Drying; Lyophilisation; Freezing Transitions;
42 Freezing; Numerical Modelling; Spray Freezing

43 **Abbreviations**

44 cSFD, continuous spray-freeze-drying

45 ICH, International Council for Harmonisation of Technical Requirements for

46 Pharmaceuticals for Human Use

47 NDF, numerical differentiation formula

48 NDS, new drug substances

49 NMR, nuclear magnetic resonance

50 VSVO, variable-step variable-order

51 **Introduction**

52 Freeze-drying is both a time-consuming and energy-intensive process with cycles typically

53 taking days or even weeks ¹. A shorter cycle has the advantage of higher throughput for a

54 given freeze dryer, enabling the use of fewer freeze dryers for a given amount of product ².

55 The risk of product contamination or batch failure increases with lengthy cycle times, and

56 manufacturing under sterile conditions is cost intensive. Scalability from lab- to production-

57 scale is complex and requires characterisation of the equipment for robust scale-up ³⁻⁶, such

58 as shelf temperature characterisation and surface mapping ⁷. Batch non-uniformity is an

59 ongoing concern, as the vials may exhibit different time evolutions due to radiation from the

60 wall of the chamber, temperature gradients on the heating shelf, vapour fluid dynamics, and

61 non-uniform inert distribution ^{8,9}.

62 Continuous processing is becoming established in the food industry to address these issues

63 with processes that combine frozen microsphere production by spray dispersion with

64 dynamic bulk freeze-drying. Process intensification by reducing the volume scale from

65 millilitre filled vials to nanolitre monodispersed droplets increases the achievable heat and

66 mass transfer capabilities. The increase in surface area to volume ratio results in rapid

67 freezing and drying. This continuous spray-freeze-drying (cSFD) process is a novel particle

68 engineering technology for the production of powders, as the freezing rate can be controlled

69 to determine the internal structure of the particles. The cSFD process uses liquid nitrogen
70 vapour as the ambient gas.

71 The aim of this study was to develop numerical models that would simulate the freezing of a
72 stream of monodispersed droplets in a cSFD process. The numerical models were extended
73 from the foundation works of Hindmarsh et al. to accommodate the differences in processing
74 conditions¹⁰⁻¹². Droplet vertical free-falling distance and droplet coalescence predictions
75 were incorporated into the numerical models to enhance process understanding, guide
76 equipment design, size and scale, and establish product processing boundaries.

77 **Background**

78 The temperature transition of a freezing aqueous solution droplet is important in determining
79 the morphology of the final dry product¹⁰⁻¹². The governing equations for the four stages of
80 the freezing process are discontinuous and can be defined as:

- 81 – Supercooling: The solution is cooled from the initial state to a temperature below the
82 equilibrium freezing point T_f until nucleation occurs.
- 83 – Nucleation and recalescence: Sufficient supercooling has occurred for spontaneous
84 nucleation at T_n . The supercooling drives rapid kinetic crystal growth from the nuclei,
85 where an abrupt temperature rise is apparent as this growth liberates the latent heat of
86 fusion. Recalescence terminates when the supercooling is exhausted and the
87 equilibrium freezing temperature T_f is reached.
- 88 – Freezing: Further growth of the solid phase is governed by the rate of heat transfer to
89 the environment. Freezing continues until the solution has completely solidified.
- 90 – Tempering: The temperature of the frozen solution reduces to a steady-state value
91 near that of the ambient temperature T_a .

92 The ability to predict the freezing process is important as changes to the product formulation
93 can affect the ice nucleation temperature¹³; freezing point depression and freeze

94 concentration of solutes ¹⁴; and the crystal growth rate during recalescence ¹⁵. Understanding
95 of how these changes affect the stages of freezing can lead to greater process control and
96 reduce the risk of unfrozen product accumulation in equipment or non-uniform product
97 within a batch.

98 Numerical modelling of the solidification of droplets has been well investigated in the
99 literature for droplets of water ¹⁶⁻¹⁸, food solutions ¹⁹, and metals ²⁰⁻²⁵. A key limitation of
100 these studies was the lack of experimental data to validate the model performance. However,
101 works by ^{10,11} addressed this issue by obtaining empirical data for suspended single droplets
102 on the junction of a thermocouple for both pure water and sucrose solutions. The application
103 of nuclear magnetic resonance (NMR) by Hindmarsh et al. also proved advantageous for the
104 verification of theoretical solidification models ¹².

105 It was found that the addition of sucrose significantly influenced the mass transfer rates from
106 unfrozen and frozen droplets ¹¹. Higher sucrose concentrations resulted in lower mass transfer
107 rates from both the unfrozen and frozen droplets, and significantly lower rates when
108 compared to water for frozen droplets. The mass transfer rate was also found to be lower at
109 reduced temperature for frozen droplets. The experimental data demonstrated a total droplet
110 mass reduction of up to 5% within the first minute but there was negligible observable
111 change within the timescale of this numerical study. Around 1.2% of the total heat transfer
112 was attributed to mass transfer during numerical modelling of the supercooling, freezing and
113 tempering stages of a 1% w/v sucrose solution droplet with a diameter of 100 μm . Based on
114 this numerical prediction and the experimental observations of Hindmarsh et al. ¹¹, it was
115 assumed that mass transfer could be neglected as there was limited potential to improve
116 model accuracy from increased complexity. Collection of further experimental data to
117 account for the reduced droplet size, temperature and ambient gas composition was beyond
118 the scope of this work. Experimental validation of the mass transfer rates was limited by the

119 sensitivity of measurement equipment. A droplet suspended on the junction of a
120 thermocouple would demand a rapid response time and a very small wire diameter to
121 minimise the impact on the droplet. The inclusion of a thermocouple into the droplet would
122 act as a nucleation site, which would affect the temperature transition profile compared with a
123 stream of free-falling droplets. Thus, an improved experimental method is required for
124 determining the mass transfer within the temperature and droplet size ranges explored within
125 this numerical model.

126 The numerical analyses were performed under conditions described by small Biot numbers
127 ($Bi < 0.1$), so that a lumped model for the droplet temperature could be used that did not
128 account for heat conduction in the interior of the droplet and assumed that there was a
129 uniform temperature distribution within the droplet during cooling and freezing^{11,12}. The Biot
130 number is defined as $Bi = hL_c/k_d$ where h is the heat transfer coefficient, $L_c = V_d/S_d$ is the
131 characteristic length, and k_d is the thermal conductivity of the droplet, as given in Table 1
132 where w_{per} is the weight fraction of the solution and the temperature T is in Kelvin. The
133 correlation factor k_d for thermal conductivity calculations²⁶ were consistent with the
134 experimental results within ± 0.012 ²⁷.

135 The freezing stage can be solved most simply by balancing the rate of heat transfer from the
136 droplet with the internal heat transfer. The external heat fluxes govern the freezing of the
137 remaining liquid following the formation of the initial solid volume during recalescence. The
138 heat transfer within the droplet is dependent on the assumed form of the initial solid volume
139 produced following nucleation with the possibilities being:

- 140 – Inward moving boundary: A solid shell on the surface which grows inwardly towards
141 the centre of the droplet. External heat fluxes conduct heat through the solid shell to
142 the droplet surface.

143 – Outward moving boundary: A solid core at the centre of the droplet which grows
144 outwardly to the surface. External heat fluxes conduct heat through the undercooled
145 liquid to the droplet centre.

146 – Heat balance: The solid volume fraction is uniformly dispersed within the droplet.
147 The solid fraction increases uniformly throughout the droplet as the latent heat of
148 fusion is removed by external heat transfer.

149 The inward moving boundary, outward moving boundary, and heat balance numerical models
150 were found to result in reasonable predictions of the experimental freezing times¹⁰. The
151 internal heat balance of the droplet was accurately solved within the experimental uncertainty
152 by employing a simple heat balance model for each of the liquid cooling, freezing, and solid
153 cooling stages.

154 The scanning electron microscopy images presented in Figure 1 further support the freezing
155 process assumption, as the thin shell and lack of visible dendrite growth in the internal
156 structure of the fractured particles demonstrates minimal freeze concentration, which is a
157 result of rapid ice growth speeds inhibiting solute diffusion²⁸. The purity of ice crystals
158 formed in ice crystallisation is dependent on growth rate. If the ice growth rate is low enough
159 for the solute to diffuse away from the advancing ice front, then pure ice is formed, and the
160 solution becomes more concentrated until the eutectic point is reached. Conversely, if the
161 growth rate is so high that all solutes are entrapped in the ice then this leads to impure ice
162 crystals and no enrichment of the solution²⁹. This phenomenon explains the increase in
163 primary drying times experienced for freezing at faster rates, as the impure ice crystals
164 impede vapour flow during sublimation, thus reducing the driving force behind primary
165 drying.

166 *Figure 1. Scanning electron micrographs of skimmed milk (10% w/w) particles produced by spray freezing into*
167 *vapour over liquid: (a) particle size distribution, (b) single particle, (c) particle surface, and (d) fractured*
168 *particle.*

169 Numerical models

170 The temperature transition of the droplet can be solved by balancing the internal energy with
171 the energy removed by convective heat transfer q_h and thermal radiation q_r from the droplet
172 surface. The governing equations of the freezing process describing the internal heat balance
173 of the droplet and the physical properties are discontinuous for the four stages. Separate
174 models were formulated for the supercooling, nucleation and recalescence, freezing, and
175 tempering stages. Model parameters are presented in Table 1.

176 Surface heat fluxes

177 The convective heat flux q_h from the droplet surface and the thermal radiation heat flux q_r are
178 respectively described by $q_h = h(T_d - T_a)$ and $q_r = \varepsilon\sigma(T_d^4 - T_a^4)$ where T_d is the droplet
179 temperature, T_a is the ambient temperature, and ε and σ are the emissivity for thermal
180 radiation and the Stefan Boltzmann constant, respectively ³⁰. The ambient temperature for
181 radiation is assumed to be the liquid nitrogen vapour temperature as the surrounding surfaces
182 for the cSFD equipment are thermally conductive and well insulated. The correlation for the
183 Nusselt number Nu was rearranged to estimate the heat transfer coefficient ³¹ as h , where r is
184 the droplet radius and the thermal conductivity of nitrogen gas is k . For flow past a sphere,
185 the Reynolds number is given by $Re = 2r\rho_a v/\mu_a$ where v is the relative velocity, μ_a is the
186 ambient viscosity, and ρ_a is the ambient density ³⁰, where P_a is the ambient pressure, $M(N_2)$
187 is the molar mass of nitrogen, and R is the universal gas constant. The ambient viscosity μ_a is
188 determined from the Sutherland's formula ³², as follows:

$$189 \mu_a = \mu_{a,0} \left(\frac{T_{a,0} + S_N}{T_a + S_N} \right) \left(\frac{T_a}{T_{a,0}} \right)^{3/2}$$

190

Equation 1

191 where $\mu_{a,0}$ is the reference viscosity, $T_{a,0}$ is the reference temperature, and S_N is the
 192 Sutherland constant for nitrogen gas. The Sutherland formula, Equation 1, is valid in the
 193 region from 100 K to 1900 K.

194 The relative velocity v was taken with respect to the terminal velocity of the droplet v_t ,
 195 which was determined from the Galileo number³³, as follows:

$$196 \quad Ga = \begin{cases} 18Re, & Ga_0 \leq 3.6 \\ 18Re + 2.7Re^{1.687}, & 3.6 < Ga_0 \leq 10^5 \\ \frac{1}{3}Re^2, & Ga_0 > 10^5 \end{cases}$$

197 Equation 2

198 where the initial Galileo number is defined as:

$$199 \quad Ga_0 = \frac{(2r)^3 \rho_a (\rho_l - \rho_a) g}{\mu_a^2}$$

200 Equation 3

201 Balancing the initial Galileo number (Equation 3) with the Galileo number (Equation 2),
 202 substituting in the Reynolds number, and rearranging with respect to the terminal velocity v_t
 203 enables the Reynolds number to be regressed. The density of supercooled water ρ_l ³⁴ is
 204 determined from:

$$205 \quad \rho_l = \left(\sum_{n=0}^6 A_n T_{r,l}^n \right) \times 10^3$$

206 Equation 4

207 where A_0 to A_6 are fitting parameters, as given in Table 1, and $T_{r,l}$ is the relative temperature.

208 The Prandtl number Pr used in determining the heat transfer coefficient is given by $Pr =$
 209 $c_{p,a} \mu_a / k$ where the ambient specific heat capacity $c_{p,a}$ is determined from $c_{p,a} = B_1 e^{B_2 T_a} +$
 210 $B_3 e^{B_4 T_a}$ where B_1, B_2, B_3 and B_4 are fitting parameters³⁵, as given in Table 1. The thermal
 211 conductivity k of nitrogen gas can be evaluated using the method for pure non-polar gases
 212 (linear molecules) at low pressure³⁶, as follows:

$$k = \frac{c_{v,a}\mu_a}{M_N} \left[1.30 + \left(\frac{R}{c_{v,a}} \right) \left(1.7614 - \frac{0.3523}{T_{r,a}} \right) \right]$$

214 Equation 5

215 The reduced ambient temperature $T_{r,a} = T_a/T_c$ where T_c is the critical temperature³⁷. The
 216 ideal gas isochoric heat capacity $c_{v,a}$ is given by $c_{v,a} = c_p^0 - R$. The ideal gas isobaric heat
 217 capacity c_p^0 for nitrogen is determined from:

$$c_p^0 = R \left(\frac{C_1}{T_a^3} + \frac{C_2}{T_a^2} + \frac{C_3}{T_a} + C_4 + C_5 T_a + C_6 T_a^2 + C_7 T_a^3 + \frac{C_8 (C_9/T_a)^2 e^{C_9/T_a}}{(e^{C_9/T_a} - 1)^2} \right)$$

219 Equation 6

220 where C_1 to C_9 are fitting parameters³⁸, as given in Table 1.

221 Supercooling

222 The temperature transition for the liquid cooling and supercooling of the liquid droplet is
 223 determined by the heat balance:

$$\frac{dT_d}{dt} = \frac{S_d}{c_{p,l}\rho_l V_d} (q_h + q_r)$$

225 Equation 7

226 where S_d and V_d are the surface area and volume of the droplet, respectively. The specific
 227 heat capacity of supercooled water $c_{p,l}$ ³⁹, used in Equation 7, is given by $c_{p,l} =$
 228 $(D_1 e^{D_2 T_d} + D_3 e^{D_4 T_d})/M(H_2O)$ where D_1, D_2, D_3 and D_4 are fitting parameters, as given in
 229 Table 1, and $M(H_2O)$ is the molar mass of water.

230 Nucleation and recalescence

231 The temperature transition for a droplet with a high degree of supercooling occurs extremely
 232 rapidly at the time of nucleation until the equilibrium freezing temperature is reached. The
 233 initial frozen volume V_{s_0} produced during the recalescence stage can be estimated using the
 234 experimentally validated Stefan number Ste ⁴⁰.

235 The Stefan number is a dimensionless representation of the latent to sensible heat in a system.
 236 Assuming that the liquid instantaneously rises to the equilibrium freezing temperature, the
 237 Stefan number will represent the solid fraction formed during recalescence. The Stefan
 238 number can be adjusted to compensate for the density difference between the solid and liquid
 239 phases. The solid fraction V_{s_0} formed from recalescence is given by:

$$240 \quad V_{s_0} = V_d \frac{c_{p,l} \rho_l (T_f - T_n)}{\rho_s L_f}$$

241 *Equation 8*

242 where L_f is the latent heat of fusion³⁰, the nucleation temperature T_n is assumed to be the
 243 homogeneous nucleation temperature of water, 235 K⁴¹, and T_f is the equilibrium freezing
 244 temperature $T_f = 273.15 - \Delta T_f$. The freezing point depression, ΔT_f , is defined as the
 245 difference between the equilibrium freezing point of the pure solvent and the freezing point
 246 of the solution, which is calculated from Blagden's Law for ideal solutions $\Delta T_f = K_f \cdot b \cdot i$
 247 where b is the molality, and i is the van't Hoff factor, which must be equal to 1 for diluted
 248 solutions, as this simple relationship does not include the nature of the solution. The
 249 cryoscopic constant for water K_f is dependent on the properties of the solvent, not the solute.
 250 The molality is given by $b = (\rho_s V_s) / M_s \rho_l V_l$ where M_s is the solute molar mass and V_s is the
 251 solute volume. The solid phase density ρ_s was evaluated from the density of ice below
 252 273.15 K, and is defined as:

$$253 \quad \rho_s = \sum_{n=1}^5 E_n T_d^{(5-n)}$$

254 *Equation 9*

255 where E_1 to E_5 are fitting parameters³⁵, as given in Table 1. The solid phase density used
 256 was that of ice due to the insolubility of common bulk excipients in ice on a micro-scale¹¹.

257 When the nucleation temperature T_n is reached, the droplet is assumed to instantly change to
258 the equilibrium freezing temperature T_f and have partially frozen volume V_{s_0} .

259 **Freezing**

260 The freezing stage can be modelled most simply with an energy balance, assuming a uniform
261 temperature within the droplet, by balancing the external heat transfer with the amount of
262 latent heat required to be removed in order to completely freeze the mass of water in the
263 droplet¹⁶:

$$264 \quad \frac{dV_s}{dt} = \frac{S_d}{L_f \rho_s} (q_h + q_r)$$

265 *Equation 10*

266 The heat balance equation was solved with a forward difference time step. For the time
267 period $t + dt$, the change in the solid volume fraction dV_s was calculated from the total heat
268 flux from the droplet for the time step dt . Blagden's Law was employed at each iteration to
269 calculate the freezing point depression with the increased solute concentration within the
270 liquid phase. The solvent mass is given by $m_s = \rho_{solvent} V_l$ where the liquid volume fraction
271 $V_l = V_d - V_{sf} - V_s$ was adjusted with the change in the solid volume fraction V_{sf} to calculate
272 the molality required to evaluate the equilibrium freezing temperature at each time step. The
273 phase change calculations were terminated when the droplet was fully frozen at $V_l = 0$.

274 **Tempering**

275 The temperature transition in the solid cooling or tempering stage of the solid frozen droplet
276 is determined by a heat balance similar to Equation 7 for the supercooling stage:

$$277 \quad \frac{dT_d}{dt} = \frac{S_d}{c_{p,s} \rho_s V_d} (q_h + q_r)$$

278 *Equation 11*

279 where the solid phase parameters replace the liquid phase specific heat capacity and density.
 280 The specific heat capacity of ice $c_{p,s}$ ³⁵ is given by $c_{p,s} = F_1 T_d^3 + F_2 T_d^2 + F_3 T_d + F_4$ where F_1
 281 to F_4 are fitting parameters, as given in Table 1.

282 **Droplet vertical free-falling distance**

283 Extension of the single droplet numerical model to a system of monodispersed droplets gives
 284 rise to directly applicable solutions in cSFD processes. Study of solitary droplets alone is
 285 beneficial to enhance understanding of the product, such as morphology, and processing
 286 conditions, such as the temperature transition of a freezing droplet. Numerical evaluation of
 287 the vertical free-falling distance travelled by monodispersed droplets is valuable in equipment
 288 design and determining processing boundaries. The total droplet vertical free-falling distance
 289 d_d is defined as:

$$290 \quad d_d = \sum_i v_{t,i} \Delta t_i$$

291 *Equation 12*

292 The iterative time step Δt_i is determined from the solutions of the supercooling, freezing and
 293 tempering stages. The terminal droplet stream velocity $v_{t,i}$ ⁴² is evaluated as:

$$294 \quad v_t = \frac{1}{2} \left[s_t + (s_t^2 + 4A)^{\frac{1}{2}} \right]$$

295 *Equation 13*

296 The droplet and ambient nitrogen streams approach a terminal condition where the drop
 297 velocity and peak average nitrogen velocity have constant values. In the terminal state:

$$298 \quad A = \frac{\dot{m}g}{\pi\mu_a a} \left(1 - \frac{(k_2 - k_3/2)}{k_1} \right) \left(1 - \frac{\rho_a}{\rho_d} \right)$$

299 *Equation 14*

300 where $k_1 = 0.52034$, $k_2 = 0.20992$, $k_3 = 0.31934$ and $a = \ln(2)$ are constants⁴², and \dot{m} is
 301 the mass flow rate of droplets. The standard terminal velocity s_t of a solitary falling sphere is
 302 given by:

303 $s_t = \frac{2(\rho_d - \rho_a)}{9\mu_a} g \left(\frac{D_d}{2}\right)^2$

304 *Equation 15*

305 where μ_a is the ambient viscosity.

306 **Droplet coalescence**

307 The velocity of a stream of vertically free-falling monodispersed droplets generated with jet
 308 velocity will adjust to the terminal droplet stream velocity during flight. It was assumed that
 309 the jet velocity is within the Rayleigh jet breakup regime and is equal to the initial droplet
 310 velocity. If the droplet jet velocity v_j is greater than the terminal droplet stream velocity, v_t
 311 then there is a possibility that the droplets will coalesce before reaching terminal velocity.

312 Droplet coalescence is assumed to occur when the separation distance between two
 313 consecutively generated droplets is equal to zero. The separation distance S between two
 314 vertically free-falling droplets d_1 and d_2 is defined as the pitch less the droplet diameter,
 315 where $D_d = D_{d_1} = D_{d_2}$.

316 The droplet vertical free-falling distance is denoted by δ_d . The separation distance S at time t
 317 can then be derived from the cumulative free-falling distances $\sum \delta_{d_1}$ and $\sum \delta_{d_2}$ travelled by
 318 droplets d_1 and d_2 , respectively:

319
$$S(t) = \sum_{i=0}^t \delta_{d_1,i} - \sum_{i=0}^t \delta_{d_2,i} - D_d$$

320 *Equation 16*

321 where $\sum \delta_{d_1} - \sum \delta_{d_2}$ is the pitch between droplets d_1 and d_2 . If monodispersed droplets are
 322 generated at a frequency of F_d then droplet d_2 will be generated $1/F_d$ s after droplet d_1 ,
 323 which is termed the fixed time step Δt_{F_d} . Applying this fixed time step to Equation 16 and
 324 eliminating the cumulative free-falling distance results in $S(t) = \delta_d(t) - D_d$.

325 When $S(t) = 0$ then it is assumed that the droplets begin to coalesce. The droplet vertical
 326 free-falling distance is defined as $\delta_d(t) = v_d(t)\Delta t_{F_d}$. The droplet velocity $v_d(t)$ is
 327 calculated from the preceding droplet velocity, acceleration and free-falling distance at time
 328 $t - \Delta t_{F_d}$. Therefore, the droplet velocity is given by $v_d(t) = [v_d^2(t - \Delta t_{F_d}) +$
 329 $2a_d\delta_d(t - \Delta t_{F_d})]^{1/2}$.

330 The initial droplet velocity $v_d(0)$ is defined as the jet velocity v_j and the initial free-falling
 331 distance is evaluated as $\delta_d(0) = \lambda$ where λ is the spatial disturbance wavelength. The
 332 acceleration of the free-falling droplet is $a_d(t) = [w_d - R(t)]/m_d$ where w_d is the droplet
 333 weight and m_d is the droplet mass. The aerodynamic resistance $R(t) = \frac{1}{2}A_X\rho_a v_d^2(t)C_D(t)$
 334 where ρ_a is the ambient density, $A_X = \pi(D_d/2)^2$ is the cross-sectional area of the droplet,
 335 and $C_D(t)$ is the drag coefficient:

$$336 \quad C_D(t) = \frac{8}{Re} \left(\frac{2 + 3\kappa}{1 + \kappa} \right)$$

337 *Equation 17*

338 where $\kappa = \mu_a/\mu$ is the viscosity ratio of the dispersed phase to the continuous phase ⁴³.

339 *Table 1. Fitting parameters.*

340 **Numerical solutions**

341 The numerical model was programmed in MATLAB R2015b (The MathWorks Inc., USA).
 342 The user inputs to the numerical model are displayed in Table 2. The stiff differential
 343 equations were evaluated with the ode15s multistep solver, which is a variable-step variable-
 344 order (VSVO) solver based on the numerical differentiation formulas (NDFs) of orders 1 to 5
 345 and requires the solutions at several preceding time points to compute the solution.

346

Table 2. Numerical model: user inputs.

347 **Results**

348 **Biot number**

349 The Biot numbers for droplet diameters ranging from 100 μm to 400 μm explored in this
350 study for the extremes of the ambient temperature range from 153 K to 233 K were evaluated
351 to be below the $Bi < 0.1$ condition. The 400 μm droplet at the coldest ambient temperature
352 approaches the limit of the assumption of uniform temperature distribution. Larger droplets at
353 colder ambient temperatures would exceed the small Biot number assumption and
354 incorporation of heat conduction within the droplet would be required for prediction under
355 these conditions.

356 **Temperature transition**

357 The temperature transition of a freezing droplet is one of the outputs of the numerical model.
358 The temperature transition from an initial temperature of 293 K to a final temperature of 253
359 K, with a homogeneous nucleation temperature of 235 K and an equilibrium freezing
360 temperature of 273 K was studied. The results showed clearly defined liquid (supercooling)
361 and solid (tempering) cooling stages.

362 The recalescence stage following nucleation differed from the general case, as the deeply
363 supercooled liquid droplet temperature instantaneously rose from the homogeneous
364 nucleation temperature of water to the equilibrium freezing point when the latent heat of
365 supercooling was released. The assumption of an instantaneous temperature rise in the
366 numerical model is attributed to the deep supercooling which drives the rapid temperature
367 transition.

368 The freezing stage was solved with an adjusted heat balance model which accommodated the
369 freezing point depression as the solute concentration increased in the unfrozen solution.

370 During rapid ice crystal growth, the solute is entrapped in the ice matrix, as solute diffusion

371 away from the water/ice interface is inhibited, which significantly reduces the effects of
372 freeze concentration.
373 A sensitivity analysis was conducted to assess the assumption of homogeneous nucleation at
374 253 K. The total time taken to completely freeze and temper a droplet with a diameter of 200
375 μm was considered. Two ambient nitrogen temperatures of 123 K and 223 K, which
376 represent a typical operating range of cSFD equipment, were used in the numerical analysis.
377 The final tempered droplet temperature was taken at 0.5 K above the ambient temperature in
378 each instance. The time and percentage variation at 123 K was $0.78 \text{ s} \pm 1.5\%$, and at 223 K
379 was $1.00 \text{ s} \pm 3.1\%$.

380 The effect of nucleation temperature on the freezing time was shown for two different
381 ambient temperatures¹⁰, and the experimental results demonstrated that the freezing time was
382 only significantly influenced by the nucleation temperature if the ambient temperature was
383 close to the minimum nucleation temperature. These results are in agreement with the results
384 of the sensitivity analysis, as the freezing time variation increases as the ambient temperature
385 approached the homogeneous nucleation temperature.

386 **Rate of supercooling**

387 The predicted rates of supercooling were calculated for a range of ambient liquid nitrogen
388 vapour temperatures for four droplet sizes. The results of the numerical analysis are presented
389 in Figure 2. As can be seen, the rate of supercooling is affected by both the ambient
390 temperature and droplet size, which emphasises the potential for improved process control
391 compared to batch lyophilisation, where only the supercooling rate can be controlled within a
392 much more limited range. Rapid supercooling at pilot-scale for batch processes is relatively
393 easy to achieve with pre-cooled shelves. However, at industrial scale, freezing at the same
394 rates is unrealistic due to issues with product preparation, such as filling and loading times.
395 The product morphology is dependent on the structure formed during the freezing stage.

396 Typical batch freeze-drying cycles are cooled at a rate of 0.5 K min⁻¹ to maximise the ice
397 crystal size upon nucleation. This reduces the primary drying time due to increased mass
398 transfer through the pores as the ice is sublimed.

399 *Figure 2. Rate of supercooling for droplet diameters of 100 μm (—), 200 μm (- - -), 300 μm (···), and*
400 *400 μm (- · -).*

401 A comparison can be made between the intensified freeze-drying process with rapid liquid
402 nitrogen freezing of droplets and the traditional batch freeze-drying process in vials using a
403 metric of mass transfer. The limit to mass transfer is described by the dry layer resistance
404 $R_p = A_p(P_i - P_c)/(dm/dt)$ where P_i is the vapour pressure of the sublimating ice, P_c is the
405 chamber pressure, A_p is the cross-sectional area of the vial, and dm/dt is the sublimation
406 rate of ice, which is experimentally determined⁴⁴. Assuming that the processing conditions
407 are the same, then a large reduction in the area from the cross-section of a vial to the surface
408 area of a droplet, would result in a much lower dry layer resistance. However, the
409 sublimation rate is dependent on the ice crystal structure of the product.

410 The sublimation rate for a 7.5% (w/w) trehalose solution frozen by ramped cooling on a shelf
411 at both slow (0.1 K min⁻¹) and moderate (1.67 K min⁻¹) rates, and by liquid nitrogen
412 quenching at a rapid rate (108 K min⁻¹) was compared⁴⁵. The results show little difference in
413 the sublimation rate for the slow and moderate freezing, however, the rapid freezing
414 demonstrated a significantly longer primary drying time. The mass transfer is limited due to
415 the small pores formed from the ice crystal structure during rapid freezing, which is reflected
416 in the reduced sublimation rate seen in the results. Applying these observations to the
417 sublimation rate would result in an increased dry layer resistance for a rapidly frozen product.
418 The surface area to volume ratio for the droplet sizes studied was in the range from 15000 m⁻¹
419 to 60000 m⁻¹ and for a 20 mL filled vial was 141 m⁻¹. Even with the increased dry layer
420 resistance due to the product morphology, the overall 1000-fold surface area reduction from

421 the cross-sectional area of a vial to the surface area of a droplet would significantly reduce
422 the dry layer resistance, thereby reducing the overall drying time.

423 **Droplet vertical free-falling distance**

424 The free-falling distances were calculated based on five ambient liquid nitrogen vapour
425 temperatures. The capacity to predict the free-falling distance travelled by droplets provides
426 an indication as to whether the droplets will be sufficiently solidified within the equipment
427 limits to prevent accumulation of unfrozen product.

428 It was found that if the droplet frequency and jet velocity are low, then the motion of a
429 droplet stream is an approximation of a solitary droplet ⁴². Conversely, if the droplet
430 frequency and jet velocity are high, then the droplet stream accelerates, and the solitary
431 droplet decelerates. Experimental results demonstrated that the entrainment of air by a stream
432 of droplets provides a sheath, in the form of an air jet, through which the droplet stream can
433 slip relative to the surrounding medium ⁴². The terminal velocity of a vertically falling stream
434 of droplets is always in excess of the terminal velocity of a solitary droplet of the same size.
435 These findings support the results shown in Figure 3, which presents a comparison between
436 the vertical free-falling distances of solitary droplets and streams of droplets at different
437 ambient temperatures. Figure 3 demonstrates that colder ambient temperatures result in
438 smaller vertical free-falling distances before droplets are sufficiently solidified.

439 *Figure 3. Vertical free-falling distance for sufficient droplet solidification evaluated for a solitary droplet*
440 *at ambient temperatures of 153 K (- - -) and 233 K (- · -) and a droplet stream at ambient temperatures*
441 *of 153 K (—) and 233 K (· · ·) with droplet diameters in the range from 100 μm to 400 μm.*

442 **Droplet coalescence**

443 Droplet separation distance will increase as droplet velocity increases from jet velocity v_j to
444 terminal droplet stream velocity v_t . If $v_j < v_t$ then the vertical free-falling distance D_1 , at
445 which point the droplet velocity becomes terminal, must not exceed the vertical free-falling

446 distance D_2 , where the separation distance equals zero and the droplets coalesce. Droplets
447 with diameters in the range of 200 μm to 400 μm were shown not to coalesce for a flow rate
448 of 0.05 Lh^{-1} , as the terminal droplet stream velocity v_t exceeded the jet velocity v_j . At the
449 same flow rate, 100 μm droplets were shown to have a higher initial jet velocity, which
450 would result in the droplets slowing to the terminal droplet stream velocity during flight and
451 potentially causing coalescence. Since D_1 (11.61 mm) was greater than D_2 (8.61 mm), it was
452 predicted that the droplets would coalesce. Reducing the flow rate for the 100 μm droplets to
453 0.02 Lh^{-1} was shown to slightly increase the vertical free-falling distance D_2 (8.92 mm) but
454 significantly reduce the vertical free-falling distance where the terminal droplet stream
455 velocity is reached (6.77 mm). This resulted in the estimation that the droplets would not
456 coalesce.

457 A comparison between the two flow rates of 0.02 Lh^{-1} and 0.05 Lh^{-1} for consecutively
458 generated 100 μm droplets is shown in Figure 4. The separation distance S is equal to zero
459 for the 0.05 Lh^{-1} flow rate of droplets at a vertical free-falling distance of 8.61 mm, at which
460 point the droplets coalesce. For the 0.02 Lh^{-1} flow rate of droplets, the terminal droplet
461 stream velocity is reached at a vertical free-falling distance of 6.77 mm thus preventing
462 coalescence by maintaining a separation distance of 22.85 μm .

463 *Figure 4. Separation distance S between two consecutively generated 100 μm droplets at flow rates of 0.02 Lh^{-1}
464 (—) and 0.05 Lh^{-1} (- - -). When $S = 0$ then it is assumed that the droplets begin to coalesce. Terminal drop
465 stream velocity is reached (···) for the 0.02 Lh^{-1} droplets before coalescence occurs.*

466 **Discussion**

467 Coupling the intensified freezing process with an ability to adjust the ambient temperature
468 and droplet size to achieve the desired product morphology is beneficial to produce novel
469 powders and for making improvements to existing products. Spray-freezing has been applied
470 as a novel particle engineering technology to enhance aqueous dissolution of poorly water

471 soluble drugs ⁴⁶⁻⁴⁸. Novel particle engineering overcomes the limitations of conventional size
472 reduction techniques, such as milling, which exhibits impeded control of particle size, shape,
473 morphology, surface properties and electrostatic charge. Conventional methods of size
474 reduction are less efficient due to high energy demands, risk of thermal or chemical
475 degradation of the product, and non-uniform particle size distribution.

476 Low water solubility of a high percentage of biopharmaceuticals is a big issue for
477 pharmaceutical applications due to the resulting low absorption and hence limited therapeutic
478 efficacy ⁴⁹. Overcoming this issue is important as about 40 % of the compounds being
479 developed by the pharmaceutical industry are poorly water soluble ^{50,51}. Various efforts have
480 been made to address the problem by delivery in nanocarriers and by nanoparticles
481 engineering. Drug nanoparticles can be produced by a range of top-down and bottom-up
482 approaches. The size of large drug nanoparticles can be reduced by high pressure
483 homogenisation, milling, or microfluidisation for the top-down approach, or for the bottom-
484 up approach, the drug nanoparticles are formed from molecules in an aqueous, organic, or
485 aqueous-organic co-solvent solutions, aqueous-organic emulsions, or suspensions ⁴⁹.

486 Nanoparticle engineering enables manufacturing of poorly water-soluble drugs into
487 nanoparticles alone, or incorporation with a combination of pharmaceutical excipients. The
488 use of these processes has dramatically improved in vitro dissolution rates and in vivo
489 bioavailabilities of many poorly water-soluble drugs ⁵².

490 The dissolution of poorly water-soluble APIs is the rate-limiting step to absorption, it is
491 important to improve the wetting and dissolution properties to thereby enhance absorption
492 and bioavailability ⁴⁸. cSFD processes can be employed to produce nanoparticles with an
493 amorphous structure, high surface area, and enhanced wettability to greatly improve
494 dissolution. The feed solution for a cSFD process can be produced by dissolving a
495 hydrophobic API and/or hydrophilic excipients in a solution. Some poorly water-soluble

496 APIs have relatively low solubility in aqueous-organic co-solvent solutions, however,
497 resulting in low solution loading ⁴⁸. The use of organic solvents, such as acetonitrile, ethanol,
498 acetone, methanol, and methylene chloride, can greatly increase the solubility of hydrophobic
499 APIs, which results in enhanced drug loading in the feed solution.

500 The benefits of freeze-drying droplets with diameters in the < 400 µm range are not just
501 purely processing-related, as a number of product-specific applications have been identified
502 within the literature. From a regulatory perspective, the ICH Q6A guidance demonstrates the
503 criticality that particle size may have to dissolution, solubility, or bioavailability of certain
504 drug products. The ability to process a drug product and the stability, content uniformity, and
505 product appearance are also all affected by particle size. For some new drug substances
506 (NDS) intended for use in solid or suspension drug products, particle size can have a
507 significant effect on dissolution rates, bioavailability, and stability.

508 **Conclusions**

509 This work has presented numerical models to simulate the freezing of a stream of free-falling
510 monodispersed droplets for application in a cSFD process. It was demonstrated that being
511 able to predict the freezing times and temperature transition of a single droplet is essential for
512 optimisation of spray-freezing processes ¹². Estimating the vertical free-falling distances of
513 monodispersed droplets in a slip stream and predicting the chances of droplet coalescence can
514 greatly enhance process understanding and guide equipment development. A design space of
515 droplet diameters in the range from 100 µm to 400 µm and ambient temperatures from 153 K
516 to 233 K was explored. Further experimental work is required to verify the validity of the
517 vertical free-falling distance and droplet coalescence numerical models. Simulation of hail
518 formation has been the focus of previous studies ⁵³ which has application for the freezing of
519 in-flight droplets. A subject of future study would be to combine the numerical models for
520 freezing of a stream of free-falling droplets presented in this work with droplet generation

521 models in a computational fluid dynamics (CFD) simulation within the design space
522 described above for droplet diameters and ambient temperatures.

523 The small Biot number condition was satisfied for the experimental design space. Therefore,
524 a uniform temperature distribution was assumed within the droplet during supercooling and
525 freezing, which did not account for heat conduction within the interior of the droplet. It was
526 found that the assumption of a uniform temperature profile within a droplet was empirically
527 justified and accurate for droplets with small Biot numbers^{10,11}.

528 The temperature transitions of freezing droplets were evaluated for 1% lactose solutions
529 within the experimental design space from an initial temperature of 293 K to a final droplet
530 temperature of 253 K, with a homogeneous nucleation temperature of 235 K. An adjusted
531 heat balance model was used to solve the freezing stage, which accommodated the freezing
532 point depression as the solute concentration increased in the unfrozen solution. The effects of
533 freeze concentration were significantly reduced as solute diffusion away from the water/ice
534 interface is inhibited during rapid ice crystal growth. The solute is entrapped in an ice matrix
535 and no solute shell is formed, as demonstrated by the scanning electron microscopy (SEM)
536 images presented in Figure 1. It was illustrated that the surface morphology of droplets can
537 be controlled with the addition of excipients and/or changing the freezing conditions⁵⁴. Most
538 significantly, the rate of supercooling offers a means of controlling the surface properties of a
539 powder produced by cSFD. It was noted that if the formulation contains a sugar, then an
540 outer surface layer may be formed which can affect the quality of the powder. It was
541 demonstrated that a high freezing rate with high supercooling inhibited the formation of a
542 sucrose layer on the outer surface of the droplets, which could reduce the stickiness and
543 increase the flowability of the powder⁵⁴.

544 The assumption of homogeneous nucleation resulted from the rapid rates of supercooling
545 experienced by small droplets in cSFD processes and the minimal heterogeneous nucleation

546 sites present in the filtered precursor solutions. The reduced variability from homogeneous
547 nucleation compared to heterogeneous nucleation is beneficial for cGMP processes and
548 minimising batch to batch variation. A sensitivity analysis concluded that an approximate
549 $\pm 3\%$ variation in total freezing time is experienced for ambient temperatures close to the
550 nucleation temperature, which is well within the computational error.

551 The rates of supercooling were determined within the experimental design space for a 1%
552 lactose solution. Superior process control is afforded to cSFD processes compared to batch
553 freeze-drying, as the rate of supercooling is affected by both the ambient temperature and the
554 droplet size. The supercooling rate is determined by the temperature alone for batch
555 lyophilisation processes within a much more limited range. Issues with rapid freezing in
556 batch lyophilisation processes become more prevalent at industrial scale, where product
557 preparation becomes a limiting factor. The product morphology is dependent on the structure
558 formed during the freezing stage. Further studies would be necessary to determine the
559 relationship between the degree of supercooling and the ice crystal structure formed at rapid
560 freezing rates.

561 The design of equipment for cSFD processes can be guided by the estimation of droplet
562 vertical free-falling distances. The slip stream effect and phase changes within the droplets
563 during freezing result in droplet velocity fluctuations during flight. Ensuring that droplets are
564 sufficiently frozen within the equipment limits can prevent the accumulation of unfrozen
565 product leading to downstream blockages. Estimation of vertical free-falling distances
566 evaluated from solitary droplet calculations alone were shown to under predict the total
567 distance travelled. Entrainment of the surrounding medium by a stream of droplets provides a
568 sheath, in the form of a jet, through which the droplet stream can slip. Therefore, the terminal
569 velocity of a vertically falling stream of droplets is always more than the terminal velocity of
570 a solitary droplet of the same diameter. The numerical results could influence equipment

571 design and process control by increasing the height to accommodate larger droplet diameters,
572 reducing the ambient temperature when processing larger droplet diameters, or focusing on
573 smaller droplet diameters. Consideration of the vertical free-falling distance alone is not
574 sufficient to prevent unfrozen product accumulation, as droplet velocity changes, from the
575 initial jet velocity to the terminal droplet stream velocity, can lead to coalescence. For the 100
576 μm diameter droplets, coalescence was predicted for a droplet mass flow rate of 0.05 Lh^{-1} .
577 Reducing the flow rate to 0.02 Lh^{-1} resulted in a droplet separation distance of $22.85 \mu\text{m}$,
578 which would prevent coalescence.

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