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Production of Inhaler Grade Lactose by Crystallization

A Thesis presented in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Process Engineering at Massey University

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Abstract

This work focused on producing Inhaler grade lactose (IGL) directly by crystallization. IGL is a high purity lactose excipient meeting a range of precise particle size distribution specifications. The 50 percent particle size ($d_{50}$) on a volume basis desired for this work was in the range of 50 to 90 $\mu$m, and a span less than 1. IGL is commonly used as a drug carrier in dry particle inhalers. Typical industrial lactose crystallization produces lactose with a $d_{50}$ greater than 200 $\mu$m and a span of around 2. The large span has been attributed to successive nucleation events during the growth phase and growth rate dispersion. Costly additional processing is currently required to produce IGL, generally in the form of sieving and milling.

Initially the crystallization literature was reviewed with a specific focus on alternative methods for producing a narrow particle size distribution. From this, three methods were mathematically modelled for their ability to produce IGL. Crystallization in droplets literature and model predictions showed great potential for targeting a particle size distribution with a very low span directly from crystallization; however issues arose with scalability and potential contamination if not using a lactose or water carrier phase. Subsequent crystallization product stream processing via a hydrocyclone or inclined settler also showed the ability, in theory, to produce IGL; however both these methods were deemed as additional processing and a novel crystallization process was desired. This led to the development of the continuous settling crystallizer (CSC).

The CSC consists of a vertical column, where a pre-nucleated feed stream enters near the bottom of the column and flows out the top, all under laminar conditions. Inside the column only growth occurs as additional nucleation is limited by the chosen column conditions. The CSC incorporates the key elements revealed from the literature for achieving a narrow span of a single nucleation event and a method to counteract growth rate dispersion. Slow growing crystals travel further up the column than fast growing crystals before growing to the terminal particle settling diameter, opposing flow, and settling out from the column and into the product stream. For a particular fluid velocity, the crystals settle out into the product stream at the same final particle size. Under laminar flow conditions a parabolic profile occurs across the column radius and the CSC theoretical model developed predicted a product $d_{50}$ of 73 $\mu$m and a span of 0.47 for the chosen column conditions.

Lab scale experiments were then carried out for the CSC. The resulting product $d_{50}$ was in the desired range of 50 to 90 $\mu$m, but the span ranged from 1.4 to 1.5. Column channelling, an area of high flow and subsequent low flow elsewhere, was suspected as the cause of the experimental deviations. The theoretical model was modified to include channelling and predictions matched the experimental product results well. Due to the high level of control required for the CSC it is recommended that a batch process is designed to efficiently produce IGL; this would incorporate a single nucleation event and a hydrocyclone cut.
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List of Figures

Figure 1 Typical batch lactose crystallization particle size distribution (PSD), span ~2, and this works desired inhaler grade lactose PSD, span less than 1 .............................................................. 1
Figure 2 Lactose molecular structure, showing the difference in α (a) and β (b) anomers; redrawn from Dincer (2000) ................................................................. 3
Figure 3 Lactose tomahawk crystal structure, including the miller indices; redrawn from van Kreveld and Michaels (1965) ........................................................................ 5
Figure 4 Causes of various types of interactions between fines and carrier particles; redrawn from Hickey et al., (2007) .................................................................................. 7
Figure 5 Process occurring when aerosol is used, fines are detached once static powder is dilated and aerosolised; redrawn from Hickey et al., (2007) ........................................................................ 7
Figure 6 Lactose solubility curve; using equations from McLeod (2007) ................................................................................................................................. 9
Figure 7 Crystal pathways for the classical nucleation model and two-step model: (a) supersaturated solution, (b) ordered subcritical cluster, (c) liquid-like cluster, (d) ordered crystalline nuclei, (e) solid crystal; redrawn from Erdemir et al., (2009) ............................................................... 11
Figure 8 Growth of common history seed plotted on a linear scale; redrawn from Butler (1998) ............... 20
Figure 9 Generalized industrial lactose crystallization process ........................................................................ 21
Figure 10 Number of crystals formed versus cavitation number for varying office diameters and constant relative supersaturation; reproduced with permission from McLeod (2007) .............................. 23
Figure 11 Schematic diagram of the ASES process; reproduced with permission (Foster et al., 2003) ....... 24
Figure 12 Single crystal growth within a drop, A: Change in particle size with time for fast and slow growing crystals, B&C: Rate change of size and concentration with time for fast and slow growing crystals ........................................................................................................ 25
Figure 13 Lactose crystals growing within a drop; reproduced with permission (R. D. Dombrowski, et al., 2007) .............................................................................................. 27
Figure 14 Main industry paths to solid-liquid separation; redrawn from Green and Perry (2008) .......... 30
Figure 15 Zones of batch sedimentation of binary mixture ........................................................................ 32
Figure 16 Inclined settler with overflow; reproduced with permission (Davis & Gecol, 1996) ............... 32
Figure 17 Continuous inclined settler for steady-state particle classification; reproduced with permission (Davis, et al., 1989) ............................................................................. 33
Figure 18 Semi-batch reflux classifier; reproduced with permission (Laskovski, et al., 2006) ................. 35
Figure 19 Principle parts of cyclone and flow patterns; reproduced with permission (Moir, 1985) ........... 37
Figure 20 Recovery and corrected recovery curves; reproduced with permission (Moir, 1985) ............ 38
Figure 21 Traditional (a) and new-type hydrocyclone (b) with volute chamber; reproduced with permission (Liu, et al., 2008) ............................................................................. 38
Figure 22 Growth time for a crystal to reach a specified diameter within a lactose drop ....................... 41
Figure 23 Automated drop on demand and imaging device ................................................................. 42
Figure 24 Simplified continuous process flow diagram (PFD) of an inclined settler setup; Appendix A.9 contains the same PFD with stream concentrations for each processing step ................................................................. 44
Figure 25 Simulated inclined settler cumulative PSD after 1st 100μm cut ............................................. 44
Figure 26 Simulated inclined settler cumulative PSD after 2nd 60μm cut ............................................. 45
Figure 27 Hydrocyclone cumulative PSD with a d50c of 69μm ................................................................ 47
Figure 28 Diagram of tomahawk shaped alpha-lactose crystal; redrawn from van Kreveld and Michaels (1965) ......................................................................................... 49
Figure 29 Initial sedimentation vessel consisting of a 500mL measuring cylinder .............................. 52
Figure 30 Gellan gum testing: (a) lactose crystals before gel extraction and (b) after viewed under a microscope ................................................................. 53
Figure 31 Low methoxyl pectin testing: (a) lactose crystals before gel extraction and (b) after viewed under a microscope .................................................................................................................... 54
Figure 32 κ-carrageenan testing: (a) lactose crystals before gel extraction and (b) after viewed under a microscope .................................................................................................................... 54
Figure 33 λ-carrageenan testing: (a) lactose crystals before gel extraction and (b) after viewed under a microscope .................................................................................................................... 54
Figure 34 Agar testing: (a) lactose crystals before gel extraction and (b) after ...................................................................................................................... .................................. 55
Figure 35 Elongation ratio values plotted against height for gel and plant grown tomahawk alpha lactose crystals ............................................................................................................................................................. 56
Figure 36 Stokes settling diameter versus measured height for gel and plant grown tomahawk alpha lactose crystals ............................................................................................................................................................. 57
Figure 37 Stokes spherical equivalent volume versus particle equivalent volume from measured mass of large gel-grown tomahawk alpha lactose crystals ............................................................................................................................................................. 57
Figure 38 Tomahawk alpha lactose crystals viewed under the microscope: (a) and (b) are gel-grown, and (c) is plant-grown ............................................................................................................................................................. 60
Figure 39 Pressure and velocity profiles through an orifice; reproduced with permission (Yan & Thorpe, 1990) ............................................................................................................................................................. 64
Figure 40 Flow regions at super cavitation: region A-super cavity; region B-white cloud region; region C-clear liquid; reproduced with permission (Yan & Thorpe, 1990) ............................................................................................................................................................. 65
Figure 41 Numbers of crystals formed versus Reynolds number for venturi flow of different diameters, constant relative supersaturation; reproduced with permission (McLeod, et al., 2010) ............................................................................................................................................................. 65
Figure 42 Continuous orifice nucleation experimental setup ............................................................................................................................................................. 68
Figure 43 Steady state values for number of crystals per mL for all conditions, Q46 and Q85 corresponds to the orifice flow rate in mL.min⁻¹, NW=no wait and W=wait ............................................................................................................................................................. 69
Figure 44 Steady state values for number of crystals per mL against absolute alpha lactose supersaturation for all conditions, Q46 and Q85 corresponds to the orifice flow rate in mL.min⁻¹, NW=no wait and W=wait ............................................................................................................................................................. 70
Figure 45 Steady state Malvern MasterSizer d₁₀ size values for all orifice conditions, Q46 and Q85 corresponds to the orifice flow rate in mL.min⁻¹, NW=no wait and W=wait ............................................................................................................................................................. 71
Figure 46 Steady state Malvern MasterSizer d₅₀ size values for all orifice conditions, Q46 and Q85 corresponds to the orifice flow rate in mL.min⁻¹, NW=no wait and W=wait ............................................................................................................................................................. 71
Figure 47 Steady state Malvern MasterSizer d₉₀ size values for all orifice conditions, Q46 and Q85 corresponds to the orifice flow rate in mL.min⁻¹, NW=no wait and W=wait ............................................................................................................................................................. 71
Figure 48 Averaged cumulative particle size distributions (volume basis) for all orifice conditions, Q46 and Q85 corresponds to the orifice flow rate in mL.min⁻¹, NW=no wait and W=wait ............................................................................................................................................................. 72
Figure 49 Basic schematic of a continuous settling crystallizer (CSC) ............................................................................................................................................................. 79
Figure 50 Schematic of theoretical CSC model fluid sections ............................................................................................................................................................. 88
Figure 51 Schematic of theoretical CSC model individual particle movement ............................................................................................................................................................. 89
Figure 52 Theoretical model particle height within the crystallizer column versus particle size at 16 hours of simulation time when single column fluid velocity is assumed ............................................................................................................................................................. 91
Figure 53 Model results for particle position within the crystallizer and particle size, crystallizer has a 10° cone angle starting at 40% of the total crystallizer height (0.35 m) ............................................................................................................................................................. 92
Figure 54 Parabolic velocity profile across a pipe cross section, redrawn from (Çengel & Cimbala, 2006) ............................................................................................................................................................. 92
Figure 55 Parabolic velocity profile showing fluid velocity against column radius ............................................................................................................................................................. 93
Figure 123 Combined theoretical column model showing fluid velocity against column radius, \( R_I = 18 \), \( m_s = 6 \) ................................................................................................................................. 153

Figure 124 Fast flow multiplication factor versus slow flow division factor for different radius interface boundaries ........................................................................................................................................ 155

Figure 125 Combined column theoretical model showing crystal diameter against column radius for \( R_I = 18 \) mm ........................................................................................................................................ 156

Figure 126 Product crystal diameter versus slow zone division factor for \( R_I = 18 \) mm .............................................. 156

Figure 127 Waste crystal diameter versus slow zone division factor for \( R_I = 18 \) mm ........................................ 157

Figure 128 Total crystal volume versus slow zone division factor for \( R_I = 18 \) mm .............................................. 158

Figure 129 PW crystal volume ratio versus slow zone division factor for \( R_I = 18 \) mm ........................................ 158

Figure 130 Span versus slow zone division factor for \( R_I = 18 \) mm ........................................................................ 159

Figure 131 \( m_s \) and \( m_t \) height transition, \( Z_t = 2 \), \( m_s = 37.5e(-Z*0.84) \), starting with \( m_s = 7 \) ...................... 162

Figure 132 Generalised CSC setup with a hydrocyclone ...................................................................................... 164

Figure 133 Generalised agitated batch setup with settling and hydrocyclone ...................................................... 166

Figure 134 Typical industrial batch growth setup ................................................................................................. 166

Figure 135 Hartel controlled growth crystallization setup ...................................................................................... 167

Figure 136 Recommended small scale batch crystallization setup........................................................................... 167
List of Equations

Equation 1 Lactose $\beta$ and $\alpha$ equilibrium ratio constant ................................................................. 4
Equation 2 Chemical potential dimensionless form (Myerson, 2002) .................................................... 9
Equation 3 Nucleation driving force equations (Kashchiev & van Rosmalen, 2003; McLeod, 2007; Myerson, 2002) ................................................................................................................ 11
Equation 4 Homogeneous primary nucleation equation (Kashchiev, 2000) ........................................... 12
Equation 5 Heterogeneous primary nucleation equation (Kashchiev, 2000) ........................................... 12
Equation 6 Total primary nucleation (Kashchiev, 2000) .................................................................... 12
Equation 7 Induction time .................................................................................................................. 12
Equation 8 Critical nucleus size (Kashchiev, 2000) ........................................................................... 13
Equation 9 Spiral growth model ........................................................................................................ 15
Equation 10 Mononuclear growth model ............................................................................................ 15
Equation 11 Polynuclear growth model ............................................................................................... 15
Equation 12 Birth and spread growth model ...................................................................................... 15
Equation 13 Supersaturation ratio (Visser, 1982) .............................................................................. 16
Equation 14 Relative supersaturation (Zumstein & Rousseau, 1987) .................................................. 16
Equation 15 Linear growth rate expressed as a power law function of supersaturation .................. 16
Equation 16 Supersaturation ............................................................................................................. 16
Equation 17 Burton-Cabrera-Frank growth theory ............................................................................. 18
Equation 18 Growth rate power law expression ................................................................................. 18
Equation 19 Mean time averaged crystal growth rate ...................................................................... 18
Equation 20 Variance of crystal growth rate ..................................................................................... 18
Equation 21 Growth rate related by supersaturation ........................................................................ 19
Equation 22 Growth rate variance .................................................................................................... 19
Equation 23 Growth rate variance at low supersaturation .................................................................. 19
Equation 24 Coefficient of variation (spread of size distribution) ..................................................... 26
Equation 25 Upward interstitial liquid velocity ................................................................................... 31
Equation 26 Large particles fall velocity relative to tube wall ............................................................ 31
Equation 27 Small particles fall velocity relative to tube wall ............................................................ 31
Equation 28 Large particle fall velocity ............................................................................................. 32
Equation 29 Reflux classifier segregation efficiency .......................................................................... 34
Equation 30 Sharpness Index ........................................................................................................... 36
Equation 31 Maximum crystal size in a drop (R. D. Dombrowski, et al., 2007) .................................. 41
Equation 32 Normalized probability size density function for the overflow condition 1 .................. 43
Equation 33 Normalized probability size density function for overflow condition 2 ....................... 43
Equation 34 Normalized probability size density function for underflow ........................................ 43
Equation 35 Volumetric inclined settling rate ..................................................................................... 43
Equation 36 Settling velocity related using Stokes law ..................................................................... 43
Equation 37 The corrected cut/classification size .............................................................................. 45
Equation 38 The classification index ............................................................................................... 45
Equation 39 The pressure drop ........................................................................................................... 46
Equation 40 Volumetric flow split (volumetric flow in underflow/volumetric flow in overflow) .......... 46
Equation 41 Classification function .................................................................................................... 46
Equation 42 Recovery of water to underflow ..................................................................................... 46
Equation 43 Selectivity function ........................................................................................................ 46
Equation 44 Overflow and underflow PSD, O(d) and U(d) respectively ............................................. 46
Equation 45 Crystal terminal settling velocity ..................................................................................... 50
Equation 46 Stokes shape factor ........................................................................................................ 50
Equation 47 Stokes shape factor in terms of particle volume ............................................................. 50
Equation 48 Stokes equivalent spherical volume ................................................................................. 58
Equation 49 Lactose empirical Stokes spherical volume relationship for gel grown crystals .......... 58
Equation 50 Cavitation number (Yan & Thorpe, 1990) .................................................................... 64
Equation 51 Particle growth rate incorporating specific crystal growth rate and fluid section m concentration ................................................................. 82
Equation 52 Initial growth rate constant prediction ........................................................................... 82
Equation 53 Alpha lactose concentration of fluid section ................................................................. 82
Equation 54 Alpha lactose solubility concentration of fluid section ................................................... 82
Equation 55 Total lactose solubility concentration (McLeod, et al., 2007) .......................................... 83
Equation 56 Correction factor for alpha lactose depression ............................................................ 83
Equation 57 Temperature effect of equilibrium constant ............................................................... 83
Equation 58 Total lactose concentration ............................................................................................ 83
Equation 59 Particle movement, difference in fluid velocity and crystal terminal settling velocity .... 83
Equation 60 Average column fluid velocity ....................................................................................... 83
Equation 61 Crystal terminal settling velocity relative to spherical particle diameter ...................... 84
Equation 62 Fluid density ................................................................................................................. 84
Equation 63 Fluid viscosity ............................................................................................................... 84
Equation 64 Effective volume fraction ............................................................................................. 84
Equation 65 Solvent viscosity ......................................................................................................... 84
Equation 66 Effective specific volume ............................................................................................. 84
Equation 67 Mass of soluble lactose in fluid section m .................................................................. 85
Equation 68 Soluble lactose mass used during crystal growth ......................................................... 85
Equation 69 Particle volume (includes particle longest length conversion to spherical diameter) ...... 85
Equation 70 Mass of water in fluid section m ..................................................................................... 85
Equation 71 Water mass used during crystal growth ......................................................................... 85
Equation 72 Fluid section height movement ..................................................................................... 86
Equation 73 Vertical length of an individual fluid section m ............................................................ 86
Equation 74 Volume of fluid section ................................................................................................ 86
Equation 75 Column area for a cylinder ............................................................................................ 86
Equation 76 Column area for a cylinder with a cone attached to the top ........................................ 86
Equation 77 Water mass for fluid sections entering the CSC column ............................................. 87
Equation 78 Soluble lactose mass for fluid sections entering the CSC column ......................................... 87
Equation 79 Solid lactose mass for fluid sections entering the CSC column ............................................. 87
Equation 80 Parabolic laminar flow radius velocity profile across a cylinder ........................................... 92
Equation 81 Agglomeration radius criterion (for both AGG1 and AGG2) .................................................. 144
Equation 82 Agglomeration 1 (AGG1) height criterion ............................................................................. 144
Equation 83 Agglomeration 2 (AGG2) modified height criterion ............................................................. 144
Equation 84 Column total area.................................................................................................................. 149
Equation 85 Column total flowrate ......................................................................................................... 149
Equation 86 Slow column average fluid velocity ..................................................................................... 149
Equation 87 Fast column average fluid velocity ...................................................................................... 149
Equation 88 Slow column laminar fluid profile ........................................................................................ 149
Equation 89 Fast column laminar fluid profile ........................................................................................ 150
Equation 90 Combined column model fast zone velocity ....................................................................... 153
Equation 91 Combined column model slow zone velocity ....................................................................... 154
Equation 92 Combined column model fast zone modified outer radius .................................................... 154
Equation 93 Combined column model fast zone flow rate ..................................................................... 154
Equation 94 Combined column model slow zone flow rate .................................................................... 154
Equation 95 Combined column model slow zone flow factor ................................................................ 154
Equation 96 Combined column model fast zone flow factor .................................................................. 154
Equation 97 Transition flow net Particle radial movement .................................................................... 161