



Modelling Recrystallization of Amorphous Lactose

Master's Thesis in Engineering Mathematics and Computational Science

ELSA BJÖRLING

DEPARTMENT OF CHEMISTRY and CHEMICAL ENGINEERING

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Supervisors: Ronnie Andersson, Professor Dr. Ingela Niklasson Björn, AstraZeneca Dr. Julien Giovannini, Solid State Expert, AstraZeneca

Examiner: Ronnie Andersson, Department of Chemistry and Chemical Engineering

Master's Thesis 2021 Department of Chemistry and Chemical Engineering Chalmers University of Technology SE-412 96 Gothenburg Telephone +46 31 772 1000

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Abstract

When producing powders within the inhalable range, particles often need to be micronized to achieve a small enough size. During this process, amorphous content is introduced. The amorphous state is a higher energy state than the crystalline one, and therefore such content tends to recrystallize over time, especially if exposed to elevated temperature and/or humidity. During recrystallization of partly amorphous lactose, unwanted properties such as stickiness, caking and particle growth may occur.

This thesis sets up a model for simulating recrystallization of partly amorphous lactose at different conditions. To be able to compare results with experiments, the model is created as to simulate the conditions of an isothermal microcalorimetry, TAM. The driving force for recrystallization is the difference between the glass transition temperature (T_G) of the amorphous lactose and the operating temperature. In this work, the Gordon & Taylor equation is used to describe T_G . Glass transition temperature is directly connected to moisture content and temperature of the powder, and so moisture sorption isotherms of the crystalline and amorphous content is of the essence. Guggenheim–Anderson–de Boer (GAB) equations with parameters fitted for the different states of lactose are utilized in this project to estimate saturated moisture content at different humidity levels. The crystallization kinetics used are the ones proposed by Bronlund [1], namely Avrami-Bronlund.

The problem solved by the model is a set of partial differential equations for mass and energy balances. The results are compared with a series of TAM experiments, covering a range of $T - T_G$ at equilibrium.

The model manages to cover the main phenomena of the sorption and recrystallization processes, and, when changing factors such as weight or relative humidity (RH), answers well to what is expected. The exact results are highly dependent on many model and material parameters, where the precise value of some are unknown. The experimental data show variation even for identical setups, and it is therefore difficult to tune the model.

Whilst the general outcome of the model are good, it does not fully manage to capture the sorption and recrystallization behaviour. The sorption process appear differently in the simulations compared to the experiments, and the crystallization kinetics seem to be too slow at lower relative humidities (RH 53 and below).

Keywords: amorphous lactose, DPI, recrystallization, powder bed, microcalorimetry, conditioning, annealing, pharmaceutical.

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During these couple of years, the global pandemic of Covid-19 made studies quite different from the expectations. For me, it has been a curse, but in a weird way also a blessing. During this time, I made some friends who are now closer to me than I can imagine they would have been without the virus. Amongst these friends is Andrea, with whom I was randomly partnered up to do the project at AstraZeneca, which later turned into this thesis. Thank you for not understanding relative humidity together with me!

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Elsa Björling, Gothenburg, October 2021

Nomenclature

Latin letters	3
a_w	water activity, [-]
C	heat capacity, $[J kg^{-1}K^{-1}]$
C_1	constant in Avrami-Bronlund Model, [-]
C_2	constant in Avrami-Bronlund Model, [-]
C_3	constant in Avrami-Bronlund Model, [-]
С	constant in GAB equation, [-]
D	diffusivity, $[m^2 s^{-1}]$
D'	constant related to the rate of diffusion in amorphous lactose particles, [-]
d	height of powder bed in TAM ampoule, [m]
f	constant in GAB equation, [-]
H	moisture content/absolute humidity of air, [kg water kg^{-1} dry air]
H'	third stage sorption isotherm constant, [-]
H''	third stage sorption isotherm constant, [-]
ΔH	heat/enthalpy, [J kg ⁻¹]
h	third stage sorption isotherm constant, [-]
h_{fq}	latent heat of evaporation, $[J \text{ kg}^{-1}]$
j_{vs}	moisture sorption rate, $[kg m^{-3} s^{-1}]$
K_{AB}	rate constant in Avrami-Bronlund Model, [-]
k	rate constant in Avrami equation, [-]
L	liquid water content, [kg liquid water kg^{-1} dry lactose]
M	moisture content of lactose powder, $[kg kg^{-1} dry lactose]$
M_0	mono-layer moisture content in GAB equation, $[kg kg^{-1} dry lactose]$
n_{AB}	parameter in Avrami-Bronlund Model, [-]
n_A	parameter in Avrami equation, [-]
Q	heat, [J]
q	constant for Gordon and Taylor equation, [-]
R	universal gas constant, $[J \pmod{K}^{-1}]$
r	particle radius, [m]
RH	relative humidity, [%]
T	temperature, [K]
T_G	glass transition temperature, [K]
t	time, [s]
w	weight fraction, $[kg kg^{-1}]$
X	degree of amorphicity; 1 - Y , [kg kg ⁻¹]
Y	fraction unchanged material, $[kg kg^{-1}]$
Greek letter	s
δ	constrictivity, [-]
ε	porosity, [-]
au	tortuosity, [-]
Θ	time to crystallize all amorphous material, [s]
heta	temperature, [°C]
λ	conductivity, $[W m^{-1} K^{-1}]$
ho	density, $[kg m^{-3}]$

Subscripts

Avrami
crystallization
effective
fully amorphous
glass transition
gas
initial
combination of several substances
powder
solid particle
sorption
water

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1 Introduction

This thesis investigates the possibilities of mathematically modelling the process of recrystallization of lactose powder with amorphous content. Supervised recrystallization is desired, as some unwanted properties of the powder and particles might emerge during the process. At AstraZeneca, powder is micronized via jet-milling, creating amorphous content on the surface of the particles. As the amorphous form of lactose is at a higher energy state than the crystalline one, such particles tend to recrystallize over time. Today, a system is put in place for conditioning(/annealing) the partly amorphous powder, effectively recrystallizing particles. Surrounding temperature and humidity is precisely controlled, and outcome of the conditioning can be measured in several ways. As of today, there is, however, no modelling involved in the conditioning; everything happens with real materials in lab environment.

If the properties of amorphous and crystalline lactose, as well as the crystallization process, could be mathematically understood and described, it would be possible to eliminate some number of time- and resource consuming experiments, and instead simulate them in a computer program.

There have been many studies in literature aimed towards describing different aspects of crystalline and amorphous lactose, and the recrystallization process. Moisture sorption behaviour and glass transition temperatures have been thoroughly examined, the various crystalline forms of lactose have been mapped and different approaches to modeling crystallization kinetics have been attempted.

The goal of this work is combine these things into one model, so that sorption behaviour and recrystallization at different conditions of temperature and humidity can be investigated.

1. Introduction

2

Theory

In the following sections, the theory of recrystallization of amorphous lactose and its driving forces are discussed. Moreover, the glass transition temperature of lactose with some moisture content, moisture sorption isotherms for crystalline and amorphous lactose, mass and energy balances for a powder bed and different ways of modeling crystallization kinetics are presented. Microcalorimetric experiments and conditioning of amorphous powders are also explained.

2.1 Conditioning/Annealing of Lactose

One way of distributing drugs to the lungs is via dry powder inhalers (DPI). To achieve the best performance of the drug in such a system, allowing for it to easily reach the respiratory tract, the powder particles need to be small, often 1-5 μ m [2, 3]. The process of reducing particle size is called micronization, and one way of doing this is via jet milling.

During the jet milling process, existing particles are fractured with force to split them into smaller parts. As that happens, there can be some undesired consequences; the fractured particles may form agglomerates, the powder can become electrostatically charged, and amorphous regions can be introduced on the surface of the particles [2, 4]. The possible amorphous state of the newly micronized powder is not thermodynamically favorable, and so, over time, the material might recrystallize. This is especially true if the material is stored at elevated temperatures and/or levels of relative humidity; close to, or above, the glass transition temperature, $T_{\rm G}$. As such recrystallization would be unsupervised, unwanted effects could occur, and may lead to variability of the performance of the final drug. To prevent uncontrolled recrystallization, a supervised conditioning/annealing step can be added to the process, after the micronization of the particles. During such conditioning, the micronized powder is exposed to some, carefully controlled, temperatures and relative humidities, to enable the particles to recrystallize in a controlled environment. This way, the powder can reach a thermodynamically lower energy state without unexpected side effects. In the photos in figures 2.1a and 2.1b, magnified lactose particles before and after micronization can be observed, and the amorphicity is visible in the latter. Regardless of if the recrystallization is spontaneous, during storage, or happens in a controlled conditioning process, some unwanted properties can emerge as it takes place. Such properties include particle growth, aggregation, and reduction of specific surface area [2, 4]. To enable the micronized, amorphous, particles to recrystallize



(a) Before micronization.

(b) After micronization.

Figure 2.1: Magnified (x100) photos of lactose crystals before and after micronization.

in a desired way, it is necessary to thoroughly monitor the process. Parameters such as temperature and relative humidity must be controlled, and the finished product examined to ensure that a lower energy state was actually reached, without any critical changes to the particles.

2.2 Isothermal Microcalorimetry (TAM)

In order to measure the amount of amorphous content of a sample, as well as to investigate recrystallization behaviour, isothermal microcalorimetry can be used. A sample (of for example lactose powder) is placed in an air-tight ampoule together with a microhygrostat containing some saturated salt solution at a known relative humidity. The sample is put into the TAM, where the temperature has been set to some desired value. This way, the relative humidity and temperature surrounding the sample are kept constant during the experiment. The TAM then measures heat flow from the closed system, and outputs it, with a fine tolerance, at all times. This way any endo- or exothermic processes taking place within the system can be monitored. Before the measuring begins, there is an equilibrium time for the system of 15 minutes, where the reactions may have already begun, but are not registered. Therefore, rapid processes, taking place during those first 15 minutes, cannot be captured by this system.

In figures 2.2a and 2.2b, the vessels for the sample in the TAM can be seen. The hygrostat, supposed to contain the salt solution, is the leftmost in 2.2a, followed by the ampoule, to contain the powder sample, and the lid, to be crimped onto the ampoule to ensure airtightness. In 2.2b the parts are assembled, as they would be before placed into the TAM.

When studying a sample of a partly amorphous lactose in a TAM experiment, the exothermic process of recrystallization can be observed.



(a) Disassembled vessels for (b) Assembled vessels for TAM. TAM.

Figure 2.2: The vessels that go into the TAM machine: the hygrostat for the salt solution, the ampoule to contain the powder sample and the hygrostat, and the lid (to be sealed on), disassembled and assembled.

In a paper from 1994, Sebhatu et al. established that microcalorimetry is a good way of studying recrystallization of amorphous lactose, even at low levels of amorphicity (down to 2 %) [5]. The authors proposed the heat of crystallization for lactose to be 32 J/g. This value was found by a series of experiments at different levels of amorphicity and relative humidities, and had good accuracy throughout the tests.

Sebhatu et al. also present a typical microcalorimetric heat flow curve for 100%amorphous lactose (by spray-drying), as shown in figure 2.3. They state that the first phase (I) corresponds to sorption of moisture by the powder minus evaporation from the hygrostat; claiming that the moisture binds stronger to the lactose than to the salt solution, explaining the exothermic signal. The second phase (II) is said to represent recrystallization of the amorphous content. During this phase, moisture will be expelled from the amorphous matrix, resulting in a total endothermic response, reasonably of almost the same total size as the heat of sorption in phase I. The crystallization peak "hides" this endothermic desorption by its much larger exothermic peak. Therefore, increasing the temperature of the experiments will result in a larger crystallization integral: less water will be sorbed before the crystallization takes place, hence the endothermic desorption of moisture will be smaller, and the crystallization integral will appear bigger. In the same way, higher humidity conditions give a smaller crystallization integral; more water is expelled [5]. The third phase (III) is mostly left unexplained by Sebhatu et al., but mutarotation from β to α lactose is mentioned as a possible source.

In [6], Briggner et al. support microcalorimetry as a good way of determining amount of amorphous material in a sample. They also show microcalorimetric measurements for spray-dried (another micronization technique) versus jet-milled samples of amorphous lactose, shown in figure 2.4a and 2.4b. In the same article, a



Figure 2.3: Typical heat flow curve for a 31 mg sample of 100 % amorphous lactose (via spray-drying) at relative humidity 57 %, adopted from [5].

simple formula for computing the degree of amorphicity (X) is also proposed as:

$$X = (Q - \text{blank})/Q_{fa}.$$
(2.1)

Here, Q is the total heat output for the sample, and Q_{fa} is the same output for a fully amorphous sample. At AstraZeneca, the value of Q_{fa} is set to 100 J [4]. The subtraction of "blank" is the response of the calorimetric output of an empty ampoule; heat produced by friction or air disturbances when lowering the ampoule into its measuring position.



(a) Spray-dried lactose samples.

(b) Lactose samples jet-milled at different pressures.

Figure 2.4: Typical output from TAM experiments with samples of spray-dried and jet-milled lactose, adopted from [6].

2.3 Glass Transition Temperature

At some temperature, a solid, amorphous material transitions from behaving "glassy"; hard and brittle, into becoming soft and flexible, or "rubbery", due to increased molecular mobility in the material. The temperature where this happens is called the glass transition temperature, $T_{\rm G}$, of a material. A plasticiser is a substance that lowers the glass transition temperature of an amorphous material [7]. For amorphous lactose, water is a plasticiser, and the glass transition temperature varies strongly with moisture content.

In such a solution, containing a material (solute) and a plasticiser (solvent), $T_{\rm G}$ can be computed using the Gordon and Taylor equation [7, 8, 9]:

$$T_{\rm G,\ mix} = \frac{w_1 T_{\rm G,\ 1} + q w_2 T_{\rm G,\ 2}}{w_1 + q w_2},\tag{2.2}$$

where w_1 and $T_{G,1}$ are weight fractions and glass transition temperatures for solute, and w_2 and $T_{G,2}$ are the same parameters for solvent. For a solution of lactose and water, the constant q = 6.7, as determined by Jouppila and Roos [8]. They used a T_G of dry lactose of 101 °C, and T_G for water of -135 °C, to compute T_G of the solute as a function of moisture content of lactose. Other sources have later set the glass transition temperature of dry lactose to 114 °C [7, 10]. Plotting equation (2.2) with q = 6.7 and $T_G = 114$ °C of lactose results in figure 2.5. Here, it can be seen that T_G decreases significantly as moisture content in lactose increases.



Figure 2.5: Glass transition temperature of lactose at different moisture contents.

As the crystallization process of an amorphous material requires mobility of molecules, the rate of the crystallization depends strongly on the difference between operating temperature and glass transition temperature $(T - T_G)$. Lactose starts crystallizing at temperatures above the T_G [8, 11]. Higher operating temperature or relative humidity (bigger difference between operating temperature and glass transition temperature, $T - T_G$), causes more molecular movement and faster crystallization, why it is clear that the highly hygroscopic amorphous form of lactose is prone to recrystallization at elevated humidities.

2.4 The Crystallization Process

The kinetics of crystallization of a solution takes place in three steps: initiation of new crystals (nucleation), mass transfer of the solute to the crystal surface (adsorption), and solute being incorporated into the crystal structure (absorption), where the last two steps can be summarized into a single step called growth [12, 13]. The crystallization process will begin when a solution reaches a so-called supersaturated state.

A solution is considered saturated when crystals of a size visible to the naked eye do no longer dissolve in it. In this state, the solution and bigger crystals (visible by the naked eye) both exist in equilibrium. Smaller crystals may, however, still dissolve, as solubility increases with decreased size. When a solution contains more solute than possible according to the normal saturation limit, it is said to be supersaturated. Supersaturation has its own limit, where not even small crystals can dissolve any longer; the metastable limit. When a solution has a concentration of solute between the saturation limit and the metastable (supersaturation) limit, it is said to exist in a metastable region. Here, primary nucleation (spontaneous) can not occur, but only secondary nucleation; as a reaction to some impurities or some agitation. If some crystals are already present in the metastable region, growth occur. Above the concentration at the metastable limit, primary nucleation of small crystals is spontaneous. This kind of nucleation is called primary nucleation [12].

In the conditioning process and TAM experiments, the recrystallization of the lactose powder mainly includes the growth of crystals. The nuclei are already present to a high degree, they reshape and grow during the recrystallization.

2.4.1 Crystallization Kinetics of Lactose

There have been many attempts to model the kinetics of lactose recrystallization [1, 9, 10, 11, 14, 15, 16], where the Avrami, (2.3), and Williams-Landel-Ferry (WLF), (2.4), equations are frequently used. The models include both formation of nuclei and growth of crystals.

2.4.1.1 Avrami Equation

The Avrami equation models the kinetics as an exponential function of time as follows:

$$Y = 1 - \exp(-K_A t^{n_A}), \tag{2.3}$$

where Y is the unchanged fraction, or degree of crystallinity, K_A is the rate constant, t is time and n_A is the Avrami exponent [1, 9, 11, 14]. Experimental data is used to determine K_A and n_A , which are both related to nucleation and growth in different ways.

2.4.1.2 Williams-Landel-Ferry Equation (WLF)

The WLF equation accounts for the difference between operating temperature and glass transition temperature as [11, 14, 15]:

$$\log_{10}\left(\frac{\Theta_{cr}}{\Theta_G}\right) = \frac{-17.44(T - T_G)}{51.6 + (T - T_G)}$$
(2.4)

In the WLF equation, Θ_{cr} is the total time to fully crystallize the material at any given operating temperature, and Θ_G is the total time to fully crystallize the material at the glass transition temperature, and so some experimental data is required in order to utilize the equation in this form.

2.4.1.3 Avrami-Bronlund Equation

The differentiated Avrami equation is formulated as (2.5). In order to include the importance of temperature versus glass transition temperature, Bronlund (1997) proposed fitting the parameter K as a function of $T - T_G$ [1, 16, 17]. The resulting K, as proposed in the same paper, is defined by equation (2.6), where C_1, C_2 and C_3 are constants fitted to the data, and R is the universal gas constant.

$$\frac{d(1-Y)}{dt} = n_A K_A Y \left(\frac{-\log Y}{K_A}\right)^{\frac{n_A-1}{n_A}}$$
(2.5)

$$K_A = C_3 \left(\exp\left(\frac{-C_1}{R(C_2 + T - T_G)}\right) \right)^3$$
(2.6)

These two equations form the Avrami-Bronlund model. The constants were fitted as $C_1 = 3.54 \times 10^4$, $C_2 = 108.4$, and $C_3 = 3 \times 10^{27}$ by Bronlund [1]. Using these values, and plotting the parameter K as a function of difference between $T - T_G$, results in figure 2.6. It is clear that the speed of crystallization is highly non-linearly dependent on the difference between the temperatures.

This is further visualized in figure 2.7, from the Handbook of Food Engineering [18]. It is clear that a small change of water activity corresponds to a big change in crystallization times.



Figure 2.6: Logarithm of Avrami-Bronlund kinetics parameter K at different values of $T - T_G$.



Figure 2.7: Lactose crystallization times at 25 °C and different water activities, adopted from [18].

2.5 Equilibrium Moisture Contents of Crystalline versus Amorphous Lactose

Water can be present in a powder in a couple of different ways; it can be chemically bound in the crystal lattice of the solid particles, or it can be adsorbed on some parts of the particle surfaces, forming layers [1]. Water taken up by crystalline lactose is only by adsorption; on the surface. The moisture then forms some number of layers on the particle surface, increasing with relative humidity. This moisture uptake can be reversed by increasing temperature or lowering humidity [7].

In amorphous lactose, a significant part of water taken up is integrated into the solid structure: absorbed. Amorphous lactose is highly hygroscopic, but the crystalline form is not. In order to determine moisture uptake during conditioning, the different equilibrium moisture contents of amorphous and crystalline lactose at different relative humidities must therefore be considered. One well-established way of computing equilibrium moisture content of lactose at different humidities is by the Guggenheim, Anderson, de Boar equation (GAB), as described by (2.7), [19, 8].

$$M = \frac{M_0 c f a_w}{(1 - f a_w) \left(1 - (1 - c) f a_w\right)}$$
(2.7)

Where M is moisture content of lactose, M_0 is mono-layer moisture content as a fraction per dry solid, c and f are dimensionless constants, and a_w is water activity.

To describe the same relationship for crystalline lactose, the model needs to be expanded [19, 20]. Up until some level of relative humidity (around 90 %), crystalline lactose sorbs very low levels of water. At higher humidity levels however, the increase in water content is exponential, due to capillary condensation (where pore spaces become filled with condensed liquid from the vapor phase) [19]. To compensate for this, the isotherm model from (2.7) is extended as:

$$M = \frac{M_0 c H' f a_w H''}{(1 - f a_w) \left(1 + (c H' - 1) f a_w\right)}$$
(2.8)

$$H' = 1 + \frac{(1-f)(fa_w)^h}{f(1-a_w)}$$
(2.9)

$$H'' = 1 + \frac{(H'-1)(1-fa_w)}{H'(1-a_w)} \left(h + (1-h)a_w\right), \qquad (2.10)$$

where, for lower water activities, the sorption isotherm constants H' and H'', approach unity. These equations describe equilibrium relationships, and are applicable where no crystallization will occur (i. e. below the glass transition temperature). In [19], the authors fitted the parameters for the different forms of lactose, summarized in table 2.1.

Isotherm	Amorphous lactose	Milled, crystalline α -lactose
parameters	at 20-38 $^{\circ}\mathrm{C}$	monohydrate
M_0	0.0488	1.68e-4
f	1.16	0.878
c	3.23	8.8
h	-	30

It has been stated that the moisture sorption isotherms are not dependent on temperature, in the range of 15-40 °C [1, 19]. Plotting the different sorption isotherms for water activity levels ranging from 0 to 1 results in figure 2.8.

As previously discussed, the extended isotherm model for crystalline lactose is only necessary for high water activities, close to 0.9. Below that level, the simpler model, where H' = H'' = 1, is very similar to the extended one.

The sorption isotherm for amorphous lactose approaches an asymptote at water activities somewhere between 0.8 and 0.9, and is equal to 1 at water activities around 0.82, meaning that there would be 100 percent water at this point. This is clearly not accurate. The experiments performed in literature studying amorphous sorption isotherms are reported at water activity levels of 0-0.6, as this phenomena must be studied below the glass transition temperature [1, 19]. The model can therefore only be considered valid at water activities at and below 0.6. At higher water activities, crystallization will occur, even at low temperatures.

When a sample contains both amorphous and crystalline forms of lactose, the equilibrium moisture content can be described by a simple method based on fractions of each form:

$$M_{\rm mix} = (1 - X)M_{\rm cryst} + XM_{\rm am},$$
 (2.11)

where X is fractional amount of amorphous lactose [19].

When crystallization does occur, and a crystalline structure starts forming from amorphous lactose, some of the sorbed moisture will be expelled, as the crystalline structures of lactose do not contain nearly as much water as the amorphous one, at some relative humidity. If this expelled water is not transported away, it will be absorbed into the not yet crystallized material. This will lead to increased water content in the remaining material, actively lowering $T_{\rm G}$ and speeding up the kinetics of crystallization of the remaining amorphous material.



(a) Moisture sorption isotherms for crystalline lactose.



(b) Moisture sorption isotherms for amorphous (bottom) lactose.

Figure 2.8: Moisture sorption isotherms for crystalline and amorphous lactose. For the crystalline one, both the simpler and more complex model for higher water activities are plotted.

2.6 Energy Balance of Powder Bed

The energy transport in a powder bed of fully crystalline lactose depend on how moisture diffuses into it, and how heat conducts through it, as described by Bronlund et al. [20]. Each of the two phases; particle/solid and void/gas, can be described by their own enthalpy balances. The enthalpy in the gas is dependent on moisture diffusion, conduction and how moisture sorbs into the solid phase. This is described by equation (2.12). In a similar way, enthalpy in the solid phase is governed by conduction of heat and moisture sorbed by the particles, equation (2.13).

$$\varepsilon \frac{\partial (h_g \rho_g)}{\partial t} = \underbrace{D_{\text{eff}} \frac{\partial^2 (h_v H \rho_g)}{\partial x^2}}_{\text{diffusion}} \underbrace{+ \lambda_g \varepsilon \frac{\partial^2 \theta}{\partial x^2}}_{\text{conduction}} \underbrace{- j_{vs} h_{fg}}_{\text{sorption}}$$
(2.12)

$$(1-\varepsilon)\frac{\partial(h_s\rho_s)}{\partial t} = \underbrace{\lambda_s(1-\varepsilon)\frac{\partial^2\theta}{\partial x^2}}_{\text{conduction}} \underbrace{+j_{vs}h_{fg}}_{\text{sorption}}$$
(2.13)

Here, ε is porosity, ρ_g and ρ_s is density of the gas and solid particle respectively, h_g and h_s is enthalpy in gas and solid, D_{eff} is effective diffusivity, λ_g and λ_s is conductivity of gas and solid, θ is temperature, j_{vs} is amount of moisture sorbed and h_{fg} is latent heat of evaporation of the moisture (water).

As described by Bronlund et al. [20], the total energy balance of the powder bed can then be written as equation (2.14). Equations (2.15) and (2.16) describe the enthalpy in gas and solid respectively. From these three equations, the temperature can be found, according to equation (2.17). The c_{pg} , c_{ps} and c_{pw} are the heat capacities of gas, solid particle and water, respectively.

$$Q = h_g \varepsilon \rho_g + h_s (1 - \varepsilon) \rho_s \tag{2.14}$$

$$h_g = c_{pg}\theta + H(c_{pv}\theta + h_{fg}) \tag{2.15}$$

$$h_s = c_{ps}\theta + Mc_{pw}\theta \tag{2.16}$$

$$\Rightarrow \theta = \frac{Q - Hh_{fg}\varepsilon\rho_g}{\varepsilon\rho_g(c_{pa} + Hc_{pv}) + (1 - \varepsilon)\rho_s(c_{ps} + Mc_{pw})}$$
(2.17)

The differentiated form of the total energy can be derived by the differentiated forms of enthalpy in gas and particle phase, and by assuming local thermal equilibrium between gas and solid phase at all times:

$$\Rightarrow \frac{\partial Q}{\partial t} = D_{\text{eff}} \frac{\partial^2 (h_v H \rho_g)}{\partial x^2} + \lambda_{\text{eff}} \frac{\partial^2 \theta}{\partial x^2}, \qquad (2.18)$$

where λ_{eff} is the effective thermal conductivity for the powder bed, with a value estimated to 0.17 W/(m K) for lactose powder by Bronlund, [1].

2.7 Moisture Balance of Powder Bed

Similarly to the energy balances, the following model for moisture transport in gas and solid in a powder bed are also proposed by Bronlund et al. [20].

In the system, the only way for the total moisture of the powder bed to change is via diffusion between the surrounding environment and the gas phase of the powder. Within the powder, moisture can be sorbed or expelled by the solid particles, as described by the moisture sorption isotherms for amorphous and crystalline lactose, according to equations (2.7) and (2.8). The total moisture content is modeled by equation (2.11).

Each of the two phases has its own formula for moisture balance:

$$\varepsilon \frac{\partial (H\rho_g)}{\partial t} = \underbrace{D_{\text{eff}} \frac{\partial^2 (H\rho_g)}{\partial x^2}}_{\text{diffusion}} \underbrace{-j_{vs}}_{\text{sorption}}$$
(2.19)

$$(1-\varepsilon)\frac{\partial(M\rho_s)}{\partial t} = \underbrace{j_{vs}}_{\text{sorption}},$$
(2.20)

where j_{vs} is the amount of moisture sorbed per unit time. It is clear that the water sorbed by the powder is taken from the gas. If the sorption term was negative, moisture would be leaving the powder and entering the gas.

The total moisture concentration W in the powder bed is then computed and differentiated as:

$$W = \varepsilon H \rho_g + (1 - \varepsilon) M \rho_s \tag{2.21}$$

$$\frac{\partial W}{\partial t} = \varepsilon \frac{\partial (H\rho_g)}{\partial t} + (1-\varepsilon) \frac{\partial (M\rho_s)}{\partial t}.$$
(2.22)

Combining this with equations (2.19) and (2.20) results in:

$$\Rightarrow \frac{\partial W}{\partial t} = D_{\text{eff}} \frac{\partial^2 (H\rho_g)}{\partial x^2}.$$
(2.23)

From equation (2.21), the water activity a_w can be determined by iterating with moisture sorption isotherms, (2.7) and (2.8), in combination with the following relationships:

$$P_w = \exp\left(23.4795 - \frac{3990.56}{\theta + 233.833}\right) \tag{2.24}$$

$$P_v = a_w P_w \tag{2.25}$$

$$H = \frac{18P_v}{29(P_T - P_v)}.$$
(2.26)

Here, P_v is vapor pressure, P_w vapor pressure at saturation, and P_T is total, ambient pressure.

2.8 Effective Diffusivity

Within the particle bed, diffusion of moisture is hindered due to the solid particles. Bronlund [1] lists some different ways of computing effective diffusivity in a powder bed, where the simplest one is:

$$D_{\rm eff} = \varepsilon D,$$
 (2.27)

that is, computing effective diffusivity by porosity and unhindered moisture diffusivity only. This equation represents the maximum diffusivity possible through a bed, ignoring effects of tortuosity (geometric complexity of a porous medium) and constrictivity (dimensionless parameter, less than one, describing how constricted the movement of air in a powder is) in the powder. To handle the effects of tortuosity and constrictivity, Bronlund et al. [1, 20] propose an extension of equation (2.27) as:

$$D_{\rm eff} = \frac{\delta}{\tau^2} \varepsilon D, \qquad (2.28)$$

with different values of $\frac{\delta}{\tau^2}$ in the range from 0.5 to 1, depending on how hindered the diffusion is estimated to be. In [1], Bronlund states that lactose is relatively homogeneous, and as such the values of $\frac{\delta}{\tau^2}$ do not need to be in the lower spectra. In [20], the value is set to 0.7.

2.9 Assumptions of Equilibrium

In the above described energy and mass balances, local thermal and moisture equilibrium is assumed at all times. For this to be true for the energy balance, the rate of heat transfer between the air and the particles of the powder bed must be fast compared to the time it takes for the entire system to reach equilibrium, i. e. pseudo-steady-state.

In [1] and [20], Bronlund et al. show that the first order time constant for heat transfer between lactose and stagnant air in a powder bed (as is the case in the TAM experiments) is less than a second. The full model (in the case of this work) runs for at least some hours, making the assumption of local thermal equilibrium valid.

To have local moisture equilibrium between powder and air, the sorption process must be fast compared to diffusion of moisture into the bed. In the same articles as for energy equilibrium, the authors show a time constant of less than a second for the sorption process of adsorption onto the surface of lactose particles, proving that the assumption of local moisture equilibrium is valid when this is the main sorption process; as for crystalline lactose.

The sorption process for amorphous lactose is more complex and also slower. In [1] the sorption rates for the different structures of lactose are studied experimentally,

and it is established that pure adsorption onto a surface can not explain the sorption for amorphous lactose. The full process must be hindered in a way that adsorption onto surfaces is not. A possible mathematical model to explain absorption into the amorphous particles is proposed in the article. It has the difference between moisture content and equilibrium moisture content (with the moisture in the air, that is) as driving force, and uses a layer thickness of amorphous lactose computed from specific surface area, degree of amorphicity (in %) and densities of crystalline and amorphous particles. Using the proposed formula for layer thickness, Bronlund states that the different grades of lactose tested all have a somewhat consistent amorphous layer thickness of around 0.3 μ m, despite ranging from mesh # 300 to mesh # 100 (corresponding to about 43-140 μ m) in diameter. To finally determine diffusivity of moisture in the amorphous material, Bronlund uses equation 2.29:

$$D' = \frac{\pi^2 D}{r_s^2},$$
 (2.29)

where r is particle radius, D is diffusivity and D' is a constant experimentally decided to be 9×10^{-4} s⁻¹. For Bronlunds particle size of 32 µm, that gives a diffusivity in the amorphous matrix of $D = 2.33 \times 10^{-14}$.

Whilst the model formulated corresponds well to the experimental data shown in the article, Bronlund states that the process depends on temperature and humidity, and that more experiments are needed before the moisture sorption in amorphous lactose can be understood. The author further states that the so called diffusivity here actually consists of many different transport mechanisms, including molecular diffusion, mixing, closed pores, and so on. Furthermore, it should be noted that these findings regard spray-dried lactose, and may not apply to jet-milled amorphous lactose, with much smaller diameter.

In Bronlunds final model, local moisture equilibrium is assumed also for amorphous lactose content, as there are too many unknowns in the sorption of moisture into amorphous lactose.

2. Theory

Model Development

In the following part, it is explained how the theory described in chapter 2 has been applied to create the model of the recrystallization of partly amorphous lactose in the TAM-experiments. The experimental setup of the performed microcalorimetric measurements is also described.

3.1 Creation of Model

In order to describe the recrystallization of amorphous content in lactose powder during elevated temperature and humidity conditions, a physical model based on equations found in literature, and presented in chapter 2, was created. The first step was to set up energy and mass balances for the system. After that, crystallization kinetics were implemented. As crystallization is an exothermic reaction, during which some moisture is also expelled, some additional terms in the moisture and energy balances had to be added.

3.1.1 Energy and Mass Balances without Crystallization

As a first step, the energy and mass balances, as described in sections 2.6 and 2.7, were implemented. To solve the partial differential equations, the SciPy package for Python was utilized, specifically the **odeint** solver was used.

In the paper by Bronlund et al. [20], the powder material was fully crystalline lactose, and so the moisture sorption isotherm described by equation (2.8), with fitted values according to crystalline lactose in table 2.1, was used. In the case of this work, the powder is a combination of amorphous and crystalline lactose. To account for that, the GAB model for amorphous lactose, equation (2.7), with corresponding fitted parameters, was also utilized. The total moisture sorption term was then computed by the additive method in equation (2.11).

As the TAM is a closed system, the water that is sorbed by the powder must be resupplied by the hygrostat. Humidity is indeed constantly controlled by the hygrostat, but there is an energy cost to keep vaporizing water. This could be included in some different ways; here, it was chosen to add a source term in the energy balance. The term adds a cost for water introduced into the system, as follows:

$$\frac{\partial \Delta Q_{vap}}{\partial t} = -\frac{\partial W}{\partial t} h_{fg}.$$
(3.1)

In [20], Bronlund et al. assumes that the heat of evaporation equals the heat of sorption into the lactose. This is a simplification, as typical TAM curves clearly shows some heat generated during the sorption phase, see figures 2.3, 2.4b and 2.4a and section 2.2. In the work by Bronlund, the material modeled is fully crystalline, and so there are only small amounts of moisture sorbed. In this work, the sample is a combination of crystalline and amorphous lactose. Therefore, the heat of sorption should be included, as amorphous particles sorb much larger quantities of water than crystalline ones.

As the heat of sorption of lactose is not known, the value had to be determined by comparing experiments with simulations. When a value had been established, the heat of sorption was added to the model as:

$$\frac{\partial \Delta Q_{sp}}{\partial t} = (1 - \varepsilon) \frac{\partial M \rho_s}{\partial t} \Delta H_{sp}.$$
(3.2)

In each iteration of the odeint solver, total water weight and energy of the system is updated. To do this, the temperature and water activity, and corresponding moisture contents of the different parts of the powder (crystalline and amorphous), is needed. The temperature is computed by equation (2.17), but the water activity must be computed iteratively. The method used to find the water activity by iterating equations (2.7), (2.8), (2.21), (2.24), (2.25) and (2.26) is the minimize function included in scipy.optimize. The specific algorithm chosen is the one called "Sequential Least Squares Programming" (SLSQP) with bounds on water activity to be between 0 and 1.

3.1.2 Crystallization

In order to include crystallization in the model, the Avrami-Bronlund kinetics model, equation (2.5), was used. This was implemented as a third differential equation, so that the solver in the end solves for total energy, water weight and amorphicity. In the equation, Y is defined as fraction unchanged material by Bronlund. This could be interpreted in two different ways. One way is to consider that Y = 1 from the start, so that the initial amount amorphous material is the unchanged fraction. After some runs, it seemed more appropriate to consider $Y = X_{\text{initial}}$ from the start, treating it as if the crystallization is already ongoing. This is justified by the fact that the particles all are amorphous to some extent; it is not a mixture of fully crystalline and fully amorphous lactose.

Here, the difference between the operating temperature and the glass transition temperature is the driving force for crystallization, and the speed of the reaction increases with increased difference between the two, as shown in figure 2.6. The glass transition temperature is computed at all times by the Gordon and Taylor equation, (2.2), and used as input to the Avrami-Bronlund kinetics model. This way, crystallization of amorphous lactose can be computed, and amorphous content can be updated at all times. The exothermic crystallization liberates heat, which was included in the energy balance as:

$$\frac{\partial \Delta Q_{cr}}{\partial t} = \frac{\partial X}{\partial t} \Delta H_{cr}.$$
(3.3)

In the end, the energy balance equation for the system was set up as:

$$\frac{\partial Q}{\partial t} = \underbrace{D_{\text{eff}} \frac{\partial^2 (h_v H \rho_g)}{\partial x^2}}_{\text{diffusion}} \underbrace{+ \lambda_{\text{eff}} \frac{\partial^2 \theta}{\partial x^2}}_{\text{conduction}} \underbrace{- \frac{\partial X}{\partial t} \Delta H_{cr}}_{\text{crystallization}} \underbrace{- \frac{\partial W}{\partial t} h_{fg}}_{\text{evaporation}} \underbrace{+ (1 - \varepsilon) \frac{\partial M \rho_s}{\partial t} \Delta H_{sp}}_{\text{sorption}}.$$
 (3.4)

The total water weight differential is unchanged from previously described, and is used as (2.23), with moisture sorption isotherms combined as (2.11). As crystallization starts taking place, more moisture is made available to the remaining amorphous part of the powder as the previously amorphous, now crystalline, powder holds less water after the crystallization. As that happens, the glass transition temperature is further lowered, creating a bigger difference $T - T_G$, actively speeding up crystallization. This reaction quickly becomes fast in comparison to other phenomena of the model, and water activity increases drastically. For some common setups, the water activity reaches one as crystallization starts happening quickly.

At such high water activities, there will, at times, be more total water in the system than can be held by the different phases. When water activity becomes 1, both the air and the different parts of the powder can be saturated, and some moisture can still remain. This moisture needs to be included when computing the temperature, as its own source term. As the moisture expelled this way will collect at the surface of the particles, it was included in the enthalpy for the solid material in the temperature equation, as L in equations (3.7) and (3.8).

$$Q = h_g \varepsilon \rho_g + h_s (1 - \varepsilon) \rho_s \tag{3.5}$$

$$h_g = c_{pg}\theta + H(c_{pv}\theta + h_{fg}) \tag{3.6}$$

$$h_s = c_{ps}\theta + (M+L)c_{pw}\theta \tag{3.7}$$

$$\Rightarrow \theta = \frac{Q - Hh_{fg}\varepsilon\rho_g}{\varepsilon\rho_g(c_{pa} + Hc_{pv}) + (1 - \varepsilon)\rho_s(c_{ps} + (M + L)c_{pw})}$$
(3.8)

3.1.2.1 Kinetics Model

In order to visualize the time for crystallization at different values of $T - T_G$ for the model, a plot similar to figure 2.7 was created. The moisture sorption isotherm for amorphous lactose was used to compute the moisture content at different water activity levels, and Avrami-Bronlund kinetics was used to compute the time for crystallization. In the plot shown in figure 3.1, the times at different water activities are on the same scale as the ones proposed by [18] at water activities from 0.5 and upwards, but are faster for lower humidity levels.



Figure 3.1: Time until 99% of fully amorphous lactose has crystallized at 25 °C and different values of $T - T_G$, using Avrami-Bronlund kinetics and GAB moisture sorption isotherms.

3.1.3 Assumptions and Simplifications

Here, some simplifications made during the creation of the model are discussed.

3.1.3.1 Local Equilibrium

Thermal local equilibrium in each discretized section is assumed at all times, in accordance with what is explained in section 2.9. For the crystalline part of the powder, local moisture equilibrium is also assumed at all times. In the first setting, the same is applied to amorphous content. In order to try to understand the differences between experimental results and simulated TAM curves, a second version of the model is also tested, including resistance in sorption for amorphous lactose. As the only available attempt at modeling this is the one by Bronlund [1], equation (2.29) was used with the constant D' as fitted in the paper. Using a particle radius of 1 µm then gives diffusivity $D = 9.12 \times 10^{-17}$.

Whilst Bronlund does state that smaller particles have larger specific surface area and higher amorphous content, and that therefore the size of particles does not really affect the thickness of the amorphous layer (which is around 0.3 μ m for all particle diameters tested), the particle sizes he compares are between 43-140 μ m (diameter). In the case of this work, the particle diameters are much smaller, at around 2 μ m. Without any further knowledge about the thickness of the amorphous layer, some different values were tested. In the end, an amorphous layer thickness of 0.25 μ m was set, corresponding to one quarter of the radius.
3.1.3.2 Limited Water Activity for Amorphous Lactose

As explained in 2.5 and seen in figure 2.8, the GAB equation for moisture sorption isotherm for amorphous lactose has not been validated above a water activity of 0.6, and according to the equation reaches one at $a_w \approx 0.82$. It is clear that the model is not valid for water activities at, or higher than, 0.82, and probably not for values close to this either. The authors of [19] state that the model is only valid at operating temperatures below glass transition, where no crystallization occurs. When computing the sorption isotherm of amorphous lactose, water activity is therefore limited to 0.6 in the model. For all other purposes, water activity can rise to 1, but not when computing the GAB equation for the amorphous part of the powder.

This assumption will affect the simulations when water activities are higher, but at $a_w = 0.6$ and T = 25 °C, the value of $T - T_G \approx 42$ °C, gives a crystallization time of less than two minutes, according to figure 2.7 (which also agrees with simulations done in this work). As two minutes is considered fast in the overall process of some hours, it is deemed that this simplification will not affect the results in a significant way.

3.1.3.3 Simplified Sorption Isotherm for Crystalline Lactose

In the sorption isotherm for crystalline lactose, the equations become complicated when including the adjusted model for high water activities; equations (2.8), (2.9) and (2.10). In the interest of speeding up the program, it was deemed not important to include the adjusted model for the sorption isotherm for high water activities. The simpler model, with H' = H'' = 1, was used instead. Comparisons were made, and it was clear that whilst including the complex model did result in smoother graphs, the general results were the same, and the time for the simpler version was less than 1/5 of the complex one.

3.1.4 Discretization

In order to get a good, smooth result, the domain was discretized in one dimension. Since the moisture diffuses in from the top of the powder bed, it was deemed enough to discretize the height, and assume equal properties throughout the radius. The domain was limited to the volume of the actual powder bed, not including the full ampoule. The runtime of simulations strongly depends on the number of sections, as it directly influences the number of computations performed, but the results are also influenced. The thinner the layers, the faster moisture diffuses in and crystallization can start. It was decided that a good compromise between runtime and accuracy was to divide the powder bed into 3 sections.

3.1.5 Boundary Conditions

The system is interacting with its boundaries when computing the Laplacian for diffusion of moisture or heat conduction. This is how total energy and water in the system can change, so the definition of the boundary conditions is important. Many different ways of defining the boundary conditions were tested. The final choices are presented here.

3.1.5.1 Water Activity

In the TAM experiments, the microhygrostat is used to control relative humidity in the ampoule. As a starting point, the relative humidity was therefore set constant directly adjacent to the start of the powder bed at all times. After some initial runs, it became clear that this was not accurate, as diffusion could happen too quickly, making too much moisture available for sorption in the first discretized part of the powder bed. Instead, the air above the powder bed was also discretized in the same way as the powder bed itself, but with a bigger discretization step (corresponding to the actual distance from the top of the hygrostat to the beginning of the powder bed). The relative humidity, as set by the microhygrostat, was then used as boundary condition for the air at the topmost discretization, and the relative humidity of the first discretization of the powder bed was used as bottom boundary condition:

$$H_{\rm air} = a_{w, \text{ initial}} \qquad \text{for } x < 0 \qquad (3.9)$$

$$H_{\rm air} = H_1 \qquad \qquad \text{for } x > d_{amp}. \tag{3.10}$$

It could then be computed, by diffusion of water vapor, what the relative humidity of the air closest to the powder bed was at all times, and this was used as boundary condition for diffusion of moisture into the powder bed.

Since no diffusion can happen at the other end of the powder bed (bottom of glass ampoule), diffusion was set to zero flux there:

$$\frac{\partial^2 (h_v H \rho_g)}{\partial x^2} = 0 \qquad \qquad \text{for } x \ge d_{bed}. \tag{3.11}$$

3.1.5.2 Temperature

The operating temperature in the TAM experiments is a setting done on the machine. As temperature changes in the powder are relatively small, it was deemed realistic to set temperature directly above and below powder bed to be equal to the surrounding temperature. This is not completely accurate, as the air inside the ampoule will also change temperature when water evaporates from hygrostat and when the exothermic crystallization within the bed takes place, but after some initial runs it was decided to be good enough:

$$T = T_{\text{init}}$$
 for $x \le 0$ and $x \ge d$, (3.12)

where d is the total height of the powder bed.

3.1.6 Initial Conditions

In the lab environment, material is stored at a relative humidity of 20% and a temperature of 20 °C. At the start of the simulations, the moisture content of the gas in the ampoule and the solid particles and void in the powder are all computed according to these conditions.

3.1.7 Material Properties and Model Parameters

All the material properties are presented in Appendix A. For some properties, there are different values to be found in literature In such cases, the ones used are in bold text in the tables. Parameters for the various equations are as described for each equation in the Theory part, chapter 2, and are also summarized in the table B.1 in Appendix B.

3.2 Experimental Setup

In order to validate the model, a set of experiments were conducted. As the difference $T - T_G$ is believed to be the main driving factor for crystallization, some different values of this entity at equilibrium were of interest.

It was avoided to change the temperature of the TAM equipment, as the equilibrium time of the new setting is a couple of days. Therefore, to obtain different values of $T - T_G$, some different humidity levels were tested instead.

Two different batches, with different amorphicity, were prepared at AstraZeneca by micronization via jet-milling. The two batches had different original particle size, and were both milled to be about 2 μ m in diameter, resulting in higher amorphicity for the originally larger sized particles. The amorphicity of the samples was computed by averaging results from equation (2.1) for all the samples of the same batch.

Further, two different weights of samples were tested. Since the density and porosity of the powder are important parameters in the energy and mass balances, the density of the powder was measured at AstraZeneca. The density of fully crystalline lactose was known, and porosity could then be computed as:

$$\varepsilon = 1 - \frac{\rho_p}{\rho_s}.\tag{3.13}$$

3.2.1 Relative Humidity of Salt Solutions

The hygrostat in the microcalorimetry experiments ensures constant relative humidity during the experiments. To enable testing at different humidities, different salt solutions can be used. Relative humidity is highly dependent on temperature, and different salt solutions behave differently when temperature changes. Data for various salt solutions is summarized by Greenspan [21]. The available and significant solutions at AstraZeneca and their humidities at 25 °C are presented in table 3.1.

	Lithium	Sodium	Magnesium	Sodium	Sodium
	Chloride	Iodide	Nitrate	Bromide	Chloride
Temp $^{\circ}\mathrm{C}$	LiCl	NaI	Mg(NO3)2	NaBr	NaCl
25	11.3	38.17	52.89	57.57	74.25

Table 3.1: Relative humidity of various salt solutions at 25 °C, as established by Greenspan [21].

3.2.2 Experiment Plan

Experiments were done at three separate times. The experiment plans 2 and 3 were created after having seen previous results, as to ensure getting the most valuable information. The experiments took place with about a week in between each setting. The full experiment plan is presented in tables 3.2, 3.3 and 3.4. The conditions are further shown in figure 3.2.

During initial runs of the model, it became evident that the density and porosity of the powder is important, and that small changes in values lead to big differences in results. In order to validate that the handling of the samples does not affect these values, a sample was run where the ampoule was not tapped before insertion (experiment 30), and another one where it was tapped multiple times (experiment 31). The standard procedure is to tap once, and so that is what is done for all other tests.

Exp. $#$	13	14	15	16	17	18
Salt	MG(NO3)2	NaBr	NaCl	MG(NO3)2	NaBr	NaCl
RH	52.89	57.57	75.3	52.89	57.57	75.3
Batch no.	2	2	2	1	1	1
Weight, mg	150	150	150	150	150	150
$T - T_G$, °C	21	34	109	21	34	109

 Table 3.2:
 Summary of TAM experiments conducted in the first run.

Table 3.3: Summary of TAM experiments conducted in the second	run
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Exp. $\#$	19	20	21	22	23	24
Salt	NaI	MG(NO3)2	NaBr	NaI	MG(NO3)2	MgCl2
RH	38.17	52.89	57.57	38.17	52.89	32.78
Batch no.	2	2	2	1	1	1
Weight, mg	300	300	150	300	300	300
$T - T_G$, °C	-12	21	34	-12	21	-21

Exp. $#$	25	26	27	28	29	30	31	32
Salt	NaBr	NaBr	LiCl	MG(NO3)2	NaBr	NaBr	NaBr	NaBr
RH	57.57	57.57	11.3	52.89	57.57	57.57	57.57	57.57
Batch no.	2	2	2	Sample	Sample	2 un-	2 multi-	Blank
				from $#20$	from $#24$	tapped	tapped	
Weight, mg	150	150	150	300	300	150	150	-
$T - T_G$, °C	34	34	-62	34	34	34	34	-

Table 3.4: Summary of TAM experiments conducted in the third run.



Figure 3.2: Experimental plan on the $T - T_G$ map. The highest humidity (RH 75) is represented by the leftmost dot; the equilibrium state is high above the operating temperature $(T - T_G = 109 \text{ °C})$. The following dots are the equilibrium states for the other salt solutions, with decreasing RH the further right the dot is placed.

3. Model Development

4

Results

Here, the results of the experiments and simulations are presented and compared. Plots from TAM experiments and model simulations are shown, and each investigated factor is discussed separately. At the end, a sensitivity analyses is included, to investigate the affect of some uncertain model parameters.

4.1 TAM Experiments

In a typical TAM experiment with a sample of partly amorphous lactose, there are two main exothermic peaks [5, 7]. Firstly, the powder sorbs water vapor from the humid air. As the same amount of water will also be vaporized from the hygrostat in order to keep relative humidity constant, and the TAM only measures what heat is expelled to, or absorbed by, the surrounding environment, it is the difference between the heat of vaporization from the hygrostat and the heat of sorption from the powder that is registered by the TAM.

The second, bigger, heat generation registered by the TAM for a lactose sample with amorphous content will be (any) crystallization taking place. As the crystalline form of lactose is at a lower energy state, heat will be liberated during the exothermic crystallization process.

In tables 4.1, 4.2 and 4.3, some interesting features from the experiments are shown. From equation (2.1), amorphicity of batch 1 was estimated (by averaging) to be 14% and batch 2 about 21% for the samples in the first runs. For the second runs, the amorphicity computed was lower when using the same method (about 13 and 20% respectively), why it was assumed that some crystallization had occurred in the week of storage between the tests. The same was observed after the third run, where amorphicity was again somewhat lower than after the second run: 19% for batch 2. Batch 1 was not used in the third run.

In the following, some typical trends in the data are presented. The results that are not shown here can be found in Appendix C.

Exp. $#$	13	14	15	16	17	18
RH	53	58	75	53	58	75
$T - T_G$, °C	21	34	109	21	34	109
Batch	2	2	2	1	1	1
Peak time, min	188	176	105	143	130	79
Integral, J/g	20.4	21.2	21.7	13.3	14.8	14.2

Table 4.1: Summary of experimental results from TAM, first run: week 38.

Table 4.2: Summary of experimenta	l results from TAM, second	run: week 39.
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Exp. #	19	20	21	22	23	24
RH	38	53	58	38	53	33
$T - T_G$, °C	-12	21	34	-12	21	-21
Batch	2	2	2	1	1	1
Peak time, min	-	304	147	589	243	184
Integral, J/g	18.5	20.1	20.3	12.4	13.2	12.0

Table 4.3: Summary of experimental results from TAM, third run: week 40.

Exp. #	25	26	27	28	29	30	31	32
RH	58	58	11.3	53	58	58	58	58
$T - T_G$, °C	34	34	-62	34	34	34	34	-
Batch	2	2	2	#20	#24	2 untapped	2 multitapped	None
Peak time, min	152	136	Х	Х	Х	139	152	Х
Integral, J/g	18.9	19.4	-0.04	0.3	Х	19.2	19.5	-0.04

4.1.1 Repeated Experiments

As crystallization of lactose is known to be complicated, and the precision of the TAM equipment was uncertain, it was decided to do some duplicates of one run. The resulting plots from the TAM experiments can be seen in figure 4.1. The peak of crystallization differs with around 30 minutes between experiment 14 and 21, and the total integral differs about 1 J/g. Experiment 14 was performed one week before 21, and 25 and 26 were done about one week after that. Part of the differences in the curves and integrals might be due to that the sample can have slowly crystallized during the time of storage. Number 25 and 26 were done in the same run. The time between the peaks of crystallization are 16 minutes, and the integrals differ about 0.5 J/g.

4.1.2 Weight of Samples

Figure 4.2 shows experiment 13 and 20, where all conditions but the weight of the samples are the same. The weight is doubled for experiment 20, which results in a longer sorption time. As expected, the total integrals are about the same.



Figure 4.1: TAM measurement of replicates over three weeks: RH 58, weight 150 mg, batch 2. There was a week in between each run, and experiments 25 and 26 were both done in the third run.



Figure 4.2: TAM measurements of samples with different weights at RH 53, batch 2.

4.1.3 Amorphicity of Samples

To visualize the effect of different amorphicity, figure 4.3 shows experiments where everything but the degree of amorphicity is the same. Experiment 14 is from batch 2 (higher amorphicity), whilst experiment 17 originates from batch 1. As expected, lower amorphicity results in faster sorption and crystallization, and a lower integral. This is due to the fact that sorption will be faster with lower degree of amorphicity, since crystalline particles hold less water than amorphous ones.



Figure 4.3: TAM measurements of samples with different degree of amorphicity, RH 58, weight 150 mg.

4.1.4 Relative Humidity

Figure 4.4 shows how the speed of sorption and crystallization depend on the humidity levels. Since the gradient of the humidity through the bed will be larger for higher humidities, such conditions result in faster reactions. The integrals are approximately the same, which is as expected since the amount of amorphous material is the same.



Figure 4.4: Effect of humidity using: weight 150 mg, batch 1.

4.1.5 Negative $T - T_G$ Values

Figure 4.5 shows an experiment run at RH 38. The value of $T - T_G$ here is -12 °C (see table 4.2). Despite the low value, crystallization does occur.



Figure 4.5: TAM measurement at RH 38, weight 300 mg, batch 2.

Figure 4.6 shows experiments 24 and 29. The $T - T_G$ value of 24 is -21 °C. This integral is almost as large as for the other runs of batch 1, indicating that crystallization has occurred. Experiment 29 is a rerun of the sample from experiment 24, at higher humidity, to investigate remaining degree of amorphicity. There looks to be two peaks, indicating some residual crystallization, but the integral is small, so most of the material appears to be crystalline already.



Figure 4.6: A sample run at low humidity (RH 33) and then again at higher humidity (RH 58).

These results indicate that crystallization has taken place in both cases, despite the low relative humidity. For such low values of $T - T_G$, no crystallization is expected within the time frame (if at all). The peak of crystallization appear much later than in the other runs.

4.1.6 Tapped or Untapped Samples

The results from the tests with different degree of tapping, along with the duplicates from the third run, can be seen in figure 4.7.



Figure 4.7: Comparison of different degrees of tapping at: RH 58, weight 150 mg, batch 2.

4.1.7 Blank

It is mentioned in literature and also discussed at AstraZeneca that there is some signal taken up by the TAM when the sample is first lowered into position after the 15 minutes of equilibrium. This can be due to friction, air disturbances and/or temperature imbalance [6, 7]. According to Brignner et al., [6], these disturbances are insignificant about five minutes after the lowering of the sample. In order to study this, a blank ampoule was run, experiment 32. This is shown in figure 4.8. There is a big endothermic peak at the start, probably due to some temperature imbalance and perhaps also including evaporation of water from the hygrostat. As the diffusion of water vapor in air is fast, it is also possible that the ampoule is already saturated after the 15 minutes equilibrium time, and that it is only the effect of lowering the sample that is observed.



Figure 4.8: Empty ampoule at RH 58.

4.2 Simulations with Local Moisture Equilibrium

Here, the results of simulations of the same conditions as used in the experiments are presented. Local moisture equilibrium is assumed for both crystalline and amorphous lactose. As what is of interest here is mainly the heat generated within the samples, the results are shown mostly as heat flow plots, similar to the experimental ones. In order to better understand what the model is doing, some other simulated properties are shown in figure 4.9. This is the simulation of experiment 14, and represents typical results from the simulations. In 4.9a, the total water, W, in the powder bed is shown. At first, moisture diffuses into the system and is sorbed by the particles, constantly increasing W. As that happens, the water activity, figure 4.9c, and the $T - T_G$ value, figure 4.9b, of the amorphous phase also increase. When crystallization begins, figure 4.9d, moisture is expelled from the amorphous particles and diffuse out of the system again. After some time, the total water of the system equals the water content of fully crystalline particles. Since water activity of amorphous particles is limited to 0.6 (see 3.1.3) the $T - T_G$ stabilizes at about 42 °C when water activity exceeds that value. Water activity can obviously not be higher than 1, but does reach that during the crystallization process of this particular run, as seen in figure 4.9c.



(c) Water activity in the system over time.

(d) Degree of amorphicity in the system over time.

Figure 4.9: Typical simulation results, here for experiment 14: RH 58, 150 mg, batch 2.

4.2.1 Heat of Sorption

The heat of sorption was defined so that the total integrals would roughly match experimental values. The integrals were computed from 15 minutes and onward, as the first 15 minutes are not recorded by the TAM equipment. As the TAM only registers the difference between heat of vaporization and heat of sorption, the heat of sorption was expressed in terms of latent heat of vaporization for water. The value of heat of sorption was thusly established to be somewhere around $\Delta H_{sp} \approx h_{fg} \times 1.0025$. Since the integrals of the simulations are very large during the first (uncomputed) 15 minutes, and also vary a lot for different humidity levels, this was considered sufficiently precise.

4.2.2 Weight of Samples

Figure 4.10 shows simulations of experiment 13 and 20, where all conditions but the weight are the same. The weight is doubled for experiment 20, which results in a longer sorption time, approximately twice as long as for the lower weight. This is in agreement with experimental results, although the exact position of the peaks differ.



Figure 4.10: Simulation of samples with different weights at RH 53, batch 2.

4.2.3 Amorphicity of Samples

Figure 4.11 shows simulations of experiments where everything but the degree of amorphicity is the same. As expected, lower amorphicity results in faster sorption (less water content in crystalline particles) and crystallization, and a lower total integral (less material that needs to transform).

4.2.4 Relative Humidity

In figure 4.12, simulations of experiments at different humidities are shown. As expected, higher humidity results in faster reactions, since the differences in humidity throughout the powder bed will be larger.



Figure 4.11: Simulations of samples with different amorphicity using: RH 58, weight 150 mg.



Figure 4.12: Simulations at different humidity, weight 150 mg, batch 1.

4.2.5 Negative $T - T_G$ Values

Figure 4.13 shows simulation results with the conditions of experiment 19, where $T-T_G = -12$ °C. In the simulation, this low value of $T-T_G$ gives no recrystallization. The same holds for all simulations at RH 38 and below: no recrystallization.



Figure 4.13: Simulation of RH 38, weight 300 mg, batch 2.

4.2.6 Sensitivity Analysis

In this section, some important model parameters for which the exact value is uncertain are discussed.

4.2.6.1 Tortuosity and Constrictivity

The effective diffusion is computed by (2.28). From the equation, the parameter $\frac{\delta}{\tau^2}$ directly scales the diffusion rate. From [1], the value is in the range 0.5-1. Varying the parameter from 0.5 to 1 results in doubling the diffusivity. Hence, this parameter can be adjusted to move the whole process in time. Scaling the diffusivity affects the time for diffusion in a non-linear way, as the Laplacian includes the squared distance for diffusion.

As Bronlund states that the homogeneity of lactose powder is high and the parameter should be in the higher range, and he himself sets the the value of $\frac{\delta}{\tau^2}$ to be 0.7, this was also used in this work [1]. Different values were tested, but this was the best one in the compromise of not delaying the lower humidity processes too much and not having the higher humidity events happening too fast.

4.2.6.2 Glass Transition Temperature

There exists a few different values of glass transition temperature for dry lactose in literature, ranging between 97 and 114 °C (see table A.1). Using these different values of T_G lactose results in different speed of crystallization, which is shown in figure 4.14. It is clear from this figure that the value used for T_G of lactose is important, and it will affect the results of the model to a high degree. Changing the T_G of dry lactose affects the full model similarly though, meaning that all results are shifted in a similar way. If all results are erroneous in that all crystallization happens too fast or too slow, it could then indicate that the glass transition temperature is not defined correctly.



Figure 4.14: Crystallization times for different values of T_G lactose.

4.2.6.3 GAB Constants

In the moisture sorption isotherms for lactose, there are several model parameters. The values used in this work are the ones fitted by Bronlund [1]. Changing these parameters changes equilibrium moisture content at different levels of water activity, and therefore also the glass transition temperature of the moist lactose. As the parameter T_G influences the kinetics strongly, the GAB parameters are of high importance.

4.3 Simulations with Hindered Diffusion in Amorphous Matrix

All simulations except for the ones with higher weight resulted in much too short time until the crystallization peak, compared to experimental values. Furthermore, there was some undefined mechanism, with an always increasing signal, in the middle region in all experiments before the crystallization occurred. If that middle region is due to sorption with overlapping crystallization, as it is claimed in literature [6] and also internally at AstraZeneca, something in the model is not described accurately. If a large part of the middle region is crystallization, the value of heat of crystallization is clearly not correct, but should be much larger. If a large part is instead sorption, then the sorption is not correctly described. In an attempt to reproduce a more similar curve in the simulations, the sorption process was modeled with hindered diffusion in amorphous particles. Some results from this is shown in figures 4.15 and 4.16.

The sorption in these plots is a bit more similar to the experiments, where heat flow starts low and increases, but there is still a decrease before simulation starts. The delay in crystallization also corresponds better to experimental results, as well as the lower and less narrow peaks achieved here. These results are further discussed in section 5.6.



Figure 4.15: Simulations including hindered diffusion in the amorphous layer. Two different weights at RH 53, batch 2.



Figure 4.16: Simulations including hindered diffusion in the amorphous layer. Two degrees of amorphicity at RH 58, weight 150 mg.

4. Results

5

Discussion and Conclusions

It is clear that the model developed in this work captures the main phenomena of the real process to some extent. There are, however, many material parameters where the values are debated in literature, and many tunable parameters which have big impact on results. Even when tuning the parameters, there remain phenomena not captured by the model. Here, the experimental results will be compared with the simulations, and the differences (and similarities) will be discussed.

5.1 Mechanisms in the Middle Region

Looking at a typical experimental curve, it starts off at the lowest heat flow registered, increases slowly for a long time and then has a sharp peak. According to the model produced here, the sorption should be starting off at a high speed, which should then decrease as saturation is approached. Whilst the sharp crystallization peak is achieved by the model with some accuracy, the model fails to reproduce the slowly increasing middle region. This is believed to be due to one of three possible reasons (or some combination of them):

- 1. The kinetics model used fails to capture the real crystallization process. Possible the crystallization is starting earlier and overlaps the sorption to a larger extent, so that the total heat flow is indeed always increasing. If so, the heat of crystallization is probably higher than the value used in this work, as the peak height is fairly accurate in the simulations. However, this explanation fails to map the observed dip right before the sharp peak in some experiments (# 25 and # 26, for example).
- 2. The sorption process is more complex than thought. It can be said with some confidence that the sorption of the crystalline lactose is accurately described. It has been proved in literature that the sorption onto a surface is fast, and that local moisture equilibrium therefore can be assumed for this phase [1, 20]. It also seems clear that the sorption into the amorphous matrix is more complex. The attempt to capture this, modeling the amorphous layer separately and using a much lower diffusion of moisture in it, has to some extent produced better results; more similar to experimental curves. The numbers used are more guesses than based on facts, and the shape of the curves is still not matching.
- 3. There is some other, unknown, exothermic process going on.

5.1.1 Jet-milling versus Spray-drying

A lot of the literature cited in this work uses mixtures of spray-dried and fully crystalline lactose in order to produce mixtures with varying levels of amorphicity. At AstraZeneca, the amorphous content is introduced via jet-milling. In the figures from [6] (plot 2.4a and 2.4b), it is clear that there are differences in how the recrystallization happens. One theory here is that the 100% amorphous lactose created by spray-drying not only need crystal-growth, but also to form nuclei, whilst nuclei are already present to a higher degree in the jet-milled material. When growth of crystals is the main part of crystallization, the curve will most likely look differently from when nucleation also needs to happen. This could also explain the recrystallization observed in TAM-experiments at low relative humidities. At values far below T_G , nucleation is unlikely to occur, whilst growth of crystals might still happen (albeit slowly). Perhaps this is not captured by the kinetics model used.

5.2 Duplicates

When analyzing the results, consideration was taken to that the supposedly identical settings of experiments 25 and 26 differed in time for peak of crystallization with 16 minutes (figure 4.1). As only these two experiments could be considered identical, this difference might be bigger or smaller for further identical experiments. Therefore, variations in times of less than 20 minutes are considered to be negligible. The peak of crystallization between the identical experiments differed with 0.5 mW/g, and the integrals differ with 0.5 J/g. The same must therefore apply to variations in that size range: such variation is considered non-existent. Ideally, and since the repeated experiments of "identical" samples are quite different, even more experiments would be needed. Originally, it was aimed for four equal samples, but as the integrals showed that crystallization had occurred in the week between the runs, only experiment 25 and 26 (both from third run) can be considered identical.

5.3 Sample Weight

Whilst the relative placements of the peaks of crystallization in the simulations for the different weights are correct in that the higher weight takes longer, the time for the peak of crystallization for the sample with 300 mg is off with more than two hours in the simulation (figure 4.10), compared to the experiment (figure 4.2). The time is very accurate for the lower weight sample, however, with only 6 minutes difference.

In the experiments, the peak of the higher weight takes place after almost twice as long as as the sample with less weight. In the simulations, the corresponding higher weight peak occurs after a bit more than twice as long time as for the lower weight. The simulated height of the lower weight peak is higher than in the experiment: 0.0145 vs 0.0085, and the shape of the peak is narrower. This is more obvious in the simulation of the sample with higher weight: the simulated peak is almost as high as for the lower weight, and almost three times higher than the experimental value.

5.4 Effect of Amorphicity

The peaks of the simulations (figure 4.11) are again higher than the experimental values (figure 4.3), but the relation between the heights are better than for the different weights; the lower amorphicity peak values are both about 80% of the higher peak. The peaks occur at much earlier times in the simulations than in the experiments; but in both settings the simulated lower amorphicity peak takes place after about half the time of the higher one.

5.5 Effect of Humidity

Figure 4.12 shows an example of a model run with only humidities differing between samples. It should correspond to the experiments in figure 4.4. There is a big difference in the relative location of the peaks of the two lower humidities, experiments 16 and 17. In the experiments, these peaks happen with about 15 minutes in between, whilst this number is 70 minutes in the simulation. Meanwhile, the peaks of the two higher humidity happens with a shorter time in between in the simulations (44 minutes) compared to the experiments (51 minutes). This difference is within the error of identical samples, so it can be considered good, but the relation in time between the three peaks is not accurate.

In figure 4.5, a run of batch 2 at RH 38 is shown as the black curve. The same setup was used for the simulation in figure 4.13. This condition (in equilibrium) is below the glass transition temperature $(T - T_G < 0)$, even if adjusting all parameters so as to maximize T_G of lactose. As such, no crystallization is expected to occur within the time frame of the experiment, and it does not in the simulation. The idea of this experiment was to be able to observe the sorption behaviour of the sample. Since the experimental result showed a relatively large integral, indicating that crystallization had indeed occurred, it was decided to run the exact same sample again at a higher humidity (RH 58). This is shown as the red curve in the figure. It can be concluded that crystallization did occur at the low RH level. The reason for this is not fully understood, but there are some possible explanations:

- 1. The kinetics model used here was proposed by Bronlund [1]. This work used relatively high equilibrium values of $T-T_G$ only (RH above 60 and temperature around 20 °C). It is therefore possible that the model is not appropriate for use at lower $T - T_G$ values, but needs some adjustment. This could also explain why the crystallization peaks for all experiments at RH 53 are slower in the simulations than in the experiments, whilst for higher humidities the process rather happens too fast in the simulations.
- 2. The kinetics model might also not be able to describe the process without nucleation. The equation is considering both nucleation and growth, whilst in the jet-milled lactose the main process is thought to be growth of already present nuclei.

5.6 Hindered Diffusion

Considering the figures 4.16 and 4.15 where simulations rely on slower diffusion in the amorphous particles, some noteworthy things are observed. The sorption process does look different, with a delay in the sorption peak instead of being at its maximum from the start. The times for the peak of crystallization are delayed (as expected with hindered diffusion). The full crystallization peaks are also lower and a little bit broader, more in accordance with experimental curves. The top peak is actually too broad, where experimental peaks are quite spiky.

These results are not generally better than the moisture equilibrium ones, but they do show improvement in some areas. The way hindered transport has been implemented here is not well established and includes some liberal estimations, but it still shows potential and could be developed more.

5.7 Tapping of Samples

In figure 4.7, experiments with different levels of tapping is shown. Number 30 is a sample without tapping, and 31 is multitapped. Numbers 25 and 26 are tapped once (as all other samples), and are supposed to be identical. It is clear that the identical samples differ more than any difference observed between the different levels of tapping. From this, it seems that the handling of samples has not affected the results in a noticeable way.

5.8 Summary

To conclude:

- The main crystallization event is relatively well captured by the model.
- Adjusting different factors such as weight and amorphicity gives expected outcome in the simulations, with a somewhat correct difference in time of crystallization and peak height.
- All simulations of humidity levels of RH 53 and lower delays the crystallization, (or eliminates it completely in the case of RH 38) compared to experiments.
- The simulated crystallization peaks are typically higher and narrower than the experimental ones.
- The sorption modeled looks different than the experimental ones.
- It has not been possible to distinguish between sorption and crystallization in the undefined middle region.

6

Future Work

The aim of this project was to create a physics based model for recrystallization of amorphous lactose at different conditions. A lot of progress has been done, but the model is not perfect. There are some parts that are not yet understood, and some things were discovered during the work that opened up new possible paths forward, but which could not be included in the scope of this project due to time constraints. Main ideas on how to take this work forward are presented here.

6.1 Absorption in Amorphous Lactose

In this project, some experiments were set up at low humidities to investigate the sorption behaviour without crystallization. As it turned out that crystallization took place at lower humidities than expected, the sorption behaviour could not be decoupled from crystallization. It could therefore not be established what the constantly increasing middle region actually is; if it is due to sorption, crystallization, or a combination of the two. In order to better understand the process, this would be a main point of interest. One idea is to do gravimetric measurements: an experiment where mass change over time is studied at elevated humidity. When crystallization takes place, mass will decrease as moisture is expelled, and so such a test might also show overlap, but the results from the experiment could still help in the understanding.

Another related thing could be to investigate the parameters in the GAB equation for amorphous lactose. Measurements could be done on a sample of the same material as is used here, and the parameters could be fitted accordingly. If the values are different, that will change the $T - T_G$ values of the experiments, and this might explain some phenomena (the difference for low humidity runs compared to simulations, for example).

6.2 Differences between Spray-dried and Jet-milled Powders

Most literature referenced in this work has been dealing with spray-dried, fully amorphous, lactose, or mixtures of such spray-dried material with a fully crystalline sample, to achieve different levels of amorphicity. In the jet-milling process, all particles will instead be (somewhat) the same; amorphous on the surface. It has been shown that TAM curves look different depending on which method is used, see figures 2.4a and 2.4b, but not really been stated why. Theoretically, the jetmilled particles can be seen as having already begun the crystallization; nuclei are present and only growth occur, whilst for fully amorphous spray-dried particles the full process of nucleation and growth is necessary. This could be the explanation of the undefined, increasing middle region observed in all experiments but not present in the simulations. If this was clearer, it might be possible to create a better model by improving the way the kinetics of crystallization is described.

6.3 Hybrid Modeling

It could be possible to create a pure machine-learning model to predict the recrystallization behaviour, but the amount of data in this case is limited and probably not enough to train such a model. It is also desired, by AstraZeneca, to have some transparency in the model, and to understand the processes going on.

Whilst it is evident that there are some parts of the physics based model created in this thesis that do not work very well, the model still manages to capture the essence of the sorption and recrystallization processes. When a physical model can describe some phenomena but fails in capturing others, one way to achieve better results is to include data, to create what is called a hybrid model. The idea of hybrid models is to use what is known, or easy to describe, to create a physics based model, and to then integrate it with a model based on experimental data and statistics. There are several different ways in which said integration can be done, and the two main branches are called parallel and serial architecture.

6.3.1 Parallel Architecture

In a parallel hybrid model architecture, the physical model and the data driven one each give individual output. The output is then combined in some way, to give the output of the full model. This is typically a good choice when the physical model has been overly simplified, or when there are some effects that are not modelled at all due to lack of knowledge or computing times [22]. The data driven model can then compensate for such known differences between experimental results and physical model, to give better accuracy to the final result [23].

One way of doing this is having the models predict the same quantity, and then simply weighting the outputs. This would again require a lot of data, and is probably not applicable here.

Another strategy is to have the models compute different aspects, and add the results together. This could be an option for this project; as there are some uncertainties about the kinetics of recrystallization, that whole part of could be excluded from the physics based model, to instead be computed by, for example, a neural network. A third option for implementing a parallel hybrid model is to have the machine learning model estimate the errors, or residuals, of the physics based model. This could also be a viable way forward for this project. All simulation and experimental results could be compared at all times, and a neural network could be trained on the differences.

6.3.2 Serial Architecture

In a serial architecture, the output of one of the models (physical or data driven) is used as input for the other, where the second one in the arrangement gives the final output. This is typically used when the physical model is not capable of accurately describing the relationship between input and output [22]. This architecture is a bit more complex, as the models are more closely integrated in each other, but this might also be an option for future work.

Bibliography

- [1] John Bronlund. *The modelling of caking in bulk lactose*. PhD thesis, Massey University, Manawatu, New Zealand, October 1997.
- [2] Vibha Puri, Jagdeep Shur, and Ajit S. Narang. Elucidating Molecular- and Particle-Level Changes during the Annealing of a Micronized Crystalline Drug. *Molecular Pharmaceutics*, 16(10):4339–4351, October 2019.
- [3] Nivedita Shetty, David Cipolla, Heejun Park, and Qi Tony Zhou. Physical stability of dry powder inhaler formulations. *Expert Opinion on Drug Delivery*, 17(1):77–96, January 2020.
- [4] Suzana Adilovic. Small Scale Flow Conditioning Equipment an Optimization of Operational Parameters. Master's thesis, University of Gothenburg, Pharmacy, 2012.
- [5] Tesfai Sebhatu, Maria Angberg, and Claes Ahlneck. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. *International Journal of Pharmaceutics*, 104(2):135–144, April 1994.
- [6] Lars-Erik Briggner, Graham Buckton, Katarina Bystrom, and Patricia Darcy. The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders. *International Journal of Pharmaceutics*, 105(2):125–135, May 1994.
- [7] Sarah Hogan. Investigation of the amorphous and crystalline properties of lactose and raffinose. PhD thesis, University of London, London, January 2002.
- [8] K. Jouppila and Y. H. Roos. Glass Transitions and Crystallization in Milk Powders. Journal of Dairy Science, 77(10):2907–2915, October 1994.
- [9] K. Jouppila, J. Kansikas, and Y. H. Roos. Glass Transition, Water Plasticization, and Lactose Crystallization in Skim Milk Powder. *Journal of Dairy Science*, 80(12):3152–3160, December 1997.
- [10] Eric A. Schmitt, Devalina Law, and Geoff G. Z. Zhang. Nucleation and Crystallization Kinetics of Hydrated Amorphous Lactose Above the Glass Transition Temperature. *Journal of Pharmaceutical Sciences*, 88(3):291–296, March 1999.
- [11] Y. Rjö Roos and M. Arcus Karel. Crystallization of Amorphous Lactose. Journal of Food Science, 57(3):775–777, 1992.
- [12] J. D. Seader, Ernest J. Henley, and D. Keith Roper. Separation process principles: chemical and biochemical operations. Wiley, Hoboken, NJ, 3rd ed edition, 2011.
- [13] Marc Descamps and Emeline Dudognon. Crystallization from the Amorphous State: Nucleation–Growth Decoupling, Polymorphism Interplay, and the Role of Interfaces. *Journal of Pharmaceutical Sciences*, 103(9):2615–2628, September 2014.

- [14] T. A. G. Langrish. Assessing the rate of solid-phase crystallization for lactose: The effect of the difference between material and glass-transition temperatures. *Food Research International*, 41(6):630–636, July 2008.
- [15] Yrjö Roos and Marcus Karel. Plasticizing Effect of Water on Thermal Behavior and Crystallization of Amorphous Food Models. *Journal of Food Science*, 56(1):38–43, 1991.
- [16] Zachary Clark. AMORPHOUS LACTOSE CRYSTALLISATION KINETICS. Master's thesis, Massey University, Manawatu, New Zealand, 2012.
- [17] Nicholas Ibell-Pasley. Directional Amorphous Lactose Crystallization. Master's thesis, Massey University, Manawatu, New Zealand, 2018.
- [18] D.R. Heldman and D.B. Lund. Handbook of food engineering, second edition. CRC Press, 2nd edition, January 2006.
- [19] John Bronlund and Tony Paterson. Moisture sorption isotherms for crystalline, amorphous and predominantly crystalline lactose powders. *International Dairy Journal*, 14(3):247–254, March 2004.
- [20] John E. Bronlund and (AHJ) Tony Paterson. Mathematical modelling of temperature induced moisture migration in bulk powders. *Chemical Engineering Science*, 63(9):2330–2340, May 2008.
- [21] L. Greenspan. Humidity fixed points of binary saturated aqueous solutions. Journal of Research of the National Bureau of Standards, 1977.
- [22] Shu Yang, Pranesh Navarathna, Sambit Ghosh, and B. Bequette. Hybrid Modeling in the Era of Smart Manufacturing. *Computers & Chemical Engineering*, 140:106874, May 2020.
- [23] Dae Sung Lee, Che Ok Jeon, Jong Moon Park, and Kun Soo Chang. Hybrid neural network modeling of a full-scale industrial wastewater treatment process. *Biotechnology and Bioengineering*, 78(6):670–682, June 2002.
- [24] pharma DFE. Lactose: Some basic properties and characteristics, September 2021.

Appendix A: Material Properties

In this appendix, all material properties used in the model are presented.

A.1 Lactose, Solid Particle

For the solid lactose particles, the values in table A.1 were used. In the case with multiple entries for the same property (T_G) , all were tried and the one in bold text was the one finally used. References for where the values were taken from are also included.

Table A.1:	Properties	used for	or solid	lactose.
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Property	Notation	Value	Unit	Source
Glass transition temperature	T_G	374.15, 101	K, °C	[1]
Glass transition temperature	T_{G}	387.15,114	K, °C	[7, 10]
Glass transition temperature	T_G	370.15,97	K, °C	[9]
Density	$ ho_s$	1540	$\frac{kg}{m^3}$	[24]
Heat/enthalpy of crystallization	ΔH_{cr}	3.2×10^4	$\frac{J}{ka}$	[5]
Particle heat capacity	c_{ps}	1252	$\frac{J}{kgK}$	[1]

A.2 Water Vapor

These properties for water vapor are used in the model. The values are the ones typically found and may not be exact, but are good enough for the model.

 Table A.2: Properties used for water vapor.

Property	Notation	Value	Unit
Heat capacity	c_v	2000	$\frac{J}{kaK}$
Conductivity	λ_a	0.01	$\frac{W}{mK}$

A.3 Liquid Water

Most of these properties for liquid water are generally agreed upon. The glass transition temperature has been debated, and so the sources for the used value are included.

Property	Notation	Value	Unit	Source
Density	$ ho_w$	1000	$\frac{kg}{m^3}$	
Glass transition temperature	T_G	138.15, -135	K, °C	[8, 9, 1]
Heat capacity	c_w	4200	$\frac{J}{kaK}$	
Latent heat of evaporation	$h_{ m fg}$	2.5×10^6	$\frac{J}{kgK}$	

 Table A.3: Properties used for liquid water.

A.4 Lactose Powder Sample

The density of the used lactose powder, as well as the particle diameter after micronization, was measured at AstraZeneca. The other values were taken from literature, and for the value of $\frac{\delta}{\tau^2}$, a sensitivity analysis was also done (as this value is a bit uncertain), see 4.2.6.

Table A.4: Properties used for the lactose powder sample.

Property	Notation	Value	Unit	Source
Density	$ ho_p$	218	$\frac{kg}{m^3}$	-
Particle diameter, batch 1	2r	2.75×10^{-6}	m	-
Particle diameter, batch 2	2r	1.89×10^{-6}	m	-
Hindered diffusion	$\frac{\delta}{\tau^2}$	0.7	-	[20], [1]
Conductivity	λ_s	0.17	$\frac{W}{mK}$	[1]

Appendix B: Model Parameters

In the table B.1, all parameters used in the thesis are summarized, to get an overview of how the model works.

Table B.1:	Model	parameters.
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Equation	Notation	Value	Equation	Source
Gordon and Taylor, T_G	q	6.7	(2.2)	[7]
Avrami-Bronlund	C_1	3.54×10^4	(2.6)	[20]
Avrami-Bronlund	C_2	108.4	(2.6)	[20]
Avrami-Bronlund	C_3	3×10^{27}	(2.6)	[20]
GAB amorphous lactose	M_0	0.0488	(2.7)	[1]
GAB amorphous lactose	f	1.16	(2.7)	[1]
GAB amorphous lactose	С	3.23	(2.7)	[1]
GAB crystalline lactose	M_0	1.68×10^{-4}	(2.8)	[19]
GAB crystalline lactose	f	0.878	(2.8)	[19]
GAB crystalline lactose	c	8.8	(2.8)	[19]
GAB crystalline lactose	h	30	(2.8)	[19]

It could be interesting to be able to extend the model; to use it for materials other than lactose and water vapor. In order to apply the created model to other kinds of powders or gases, some work would be required.

- 1. First of all, the material properties for the chosen materials/vapor, according to the tables in Appendix A, must be established.
- 2. Secondly, the sorption isotherms must be properly defined. If GAB equations can be used, the different parameters must be decided. This can perhaps be done by studying literature, as in this work, or can else be determined experimentally.
- 3. Then, the kinetics of crystallization must be implemented. If they are similar to lactose, they can perhaps be kept as they are.

B. Model Parameters
Appendix C: Additional Experiments

Here, all experiments not discussed in the main report are shown. Some of them are discussed, whilst others are just shown.



Figure C.1: RH 75, weight 150 mg, batch 2.

C.1 Low Humidities

The experiments at RH 38 were done with the intent of studying the sorption process. As crystallization did (unexpectedly) occur, it was not possible to understand the sorption decoupled from crystallization from these runs.

As a complementary try, one experiment was also done at RH 11, essentially drying the powder.



Figure C.2: RH 53, weight 300 mg, batch 1.

C.2 Fully Crystalline Sample

When the idea of studying the sorption process by using low relative humidity (RH 33) failed, as it turned out that it did in fact recrystallize even at this low level, it was decided to rerun a previous (ideally fully crystallized) sample again, to observe only sorption. The result is shown in figure C.5. The sorption process does look more like what is seen in the experiments, but the values are as small as for the blank sample, although opposite. It can not be said with certainty that the observed signal is not just noise from lowering the sample into position. Also, as this is fully crystalline, the sorption is expected to be very fast, and according to the theories proposed here, most of it would already have happened during the first 15 minutes (equilibrium time). More tests would be needed in order to say something about the sorption here.



Figure C.3: RH 11, weight 150 mg, batch 2.



Figure C.4: RH 38, weight 300 mg, batch 1.



Figure C.5: RH 53, weight 300 mg, rerun of sample from experiment 20.

Department of Chemistry and Chemical Engineering CHALMERS UNIVERSITY OF TECHNOLOGY Gothenburg, Sweden www.chalmers.se

