An Integrated Computational and Experimental Approach to Study and Scale-Up Vacuum Drying of Pharmaceutical Products

Aditya G. Dodda
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AN INTEGRATED COMPUTATIONAL AND EXPERIMENTAL APPROACH TO STUDY AND SCALE-UP VACUUM DRYING OF PHARMACEUTICAL PRODUCTS

A Dissertation Presented
By
ADITYA G. DODDA

Submitted to the Graduate School of the University of Massachusetts Amherst in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

February 2016

Chemical Engineering
AN INTEGRATED COMPUTATIONAL AND EXPERIMENTAL APPROACH TO STUDY AND SCALE-UP VACUUM DRYING OF PHARMACEUTICAL PRODUCTS

A Dissertation Presented
By
ADITYA G. DODDA

Approved as to style and content by:

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Department of Chemical Engineering
DEDICATION

To my family
ACKNOWLEDGMENT

I thank my advisor, Michael A. Henson, for giving me the opportunity to work on this project and for encouraging me to do my best at all times; Kostas Saranteas, my committee member and mentor for his insights on key attributes of this work, and for the motivation he provided throughout the project; T.J. Mountziaris for serving as my committee member and for being a very encouraging teacher from the beginning of the graduate program; and D.P. Schmidt, for serving as my committee member and for the short yet, insightful and motivational conversations.

I wish to acknowledge Sunovion Pharmaceuticals for funding this research and for providing facilities to perform the drying experiments. I thank the following individuals for their assistance: John Barck (Sunovion) for custom building the vacuum oven and for other miscellaneous improvements to the laboratory-scale drying system; Bob Prytko (Sunovion) for all the help on a daily basis; Haitao Zhang, Vitaly Nivorozhkin, Mike Sizensky, Robert Bujalski, and Mike Filios (Sunovion) for help with experiments.

I am grateful to my friends at Boston and Amherst for making my experience through this journey filled with fun. I also thank my group members, classmates and others members of the Department of Chemical Engineering for their support.

I wish to express utmost gratitude to my parents without whom none of this would be possible. I am grateful to my brother for always inspiring me to do better. I thank the love of my life, Srivani, for being there whenever I needed help. I dedicate my thesis to my family.
ABSTRACT

AN INTEGRATED COMPUTATIONAL AND EXPERIMENTAL APPROACH TO STUDY AND SCALE-UP VACUUM DRYING OF PHARMACEUTICAL PRODUCTS

FEBRUARY 2016

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Drying of Active Pharmaceutical Ingredients (APIs) is an energy intensive process that is often a manufacturing bottleneck due to its relatively long processing times. A key objective is the ability to determine the drying end point, the time at which all solvent has been evaporated from the solid cake. A novel method for determining the end point of pharmaceutical dryers, based on on-line mass spectrometry is developed and tested. The proposed method offers several advantages over existing spectrometric methods, including the ability to detect when the cake is dry from vapor phase measurements and a very simple implementation that does not require chemometric models. The drying end point was determined as the time at which the gas phase solvent concentration measurement from the mass spectrometer converged to a predicted value computed from a solvent mass balance on the oven assuming zero flow
rate from the cake. The method was tested on a laboratory scale vacuum dryer over a range of temperatures and pressures using glass beads with three different particle sizes. The method was validated by performing Loss On Drying (LOD) experiments for one combination of pressure, temperature and bead size.

The mass spectrometer (MS) was used as a Quality by Design (QbD) tool along with thermocouples to understand dynamics in vacuum tray drying. The data indicated that boiling was the dominant mechanism. A multiphase transport model to predict drying performance was developed. It was found that a two phase transport model with the vapor and solid considered as one phase and the liquid treated as the second phase was capable of qualitatively reproducing the drying dynamics. Adjustable model parameters estimated from experimental data collected over a range of operating conditions exhibited trends that provided further insight into drying behavior.

The understanding of drying from a vacuum tray dryer was extended to an Agitated Filter Drier (AFD) using the MS. Further, one of the most challenging issues with the use of an AFD, particle size change, was investigated. The change in particle size of API during drying at different RPMs was studied. The experiments indicated that the process was dominated by breakage of API which showed strong correlation with LOD. Population balance models were used to estimate parameters and derive empirical relations to LOD levels.
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1.1 Fundamentals of Drying

Drying may be defined as the vaporization and removal of water or other liquids from a solution, suspension, or other solid-liquid mixture to form a dry solid. This includes drying pharmaceuticals, clay, wood, coatings, etc. Drying is a complex process that involves simultaneous heat and mass transfer which can lead to physical and chemical transformations. Based on the mechanism of heat transfer, drying is categorized into direct (convection), indirect or contact (conduction), radiant (radiation) and dielectric or microwave (radio frequency) drying.

A typical graph of moisture content versus drying rate and moisture content versus time are shown in Figure 1.1. In the figure, Section AB represents the constant-

![Figure 1.1: Regimes of drying showing constant rate period AB, first falling rate period BC and second falling rate period CD.](image)
rate period. In that zone, moisture is considered to be vaporizing from a saturated surface. The rate of mass transfer balances the rate of heat transfer, and the temperature of the saturated surface remains constant [7]. The constant rate period is succeeded by two falling rate periods, namely, first falling rate period (section BC in Figure 1.1) and second falling rate period (section CD in Figure 1.1). The first falling rate is the zone of unsaturated surface drying, that is the entire vaporization surface can no longer be maintained and saturated by moisture movement within the solid. Vaporization can be in the form of boiling or evaporation. In the case of boiling, which is observed in vacuum dryers, the temperature of the liquid is equal to the saturation temperature. This is not true in the case of evaporation, where the temperature can be below boiling point. The second falling rate is the zone of where internal moisture movement controls drying. Movement of liquid may occur by diffusion under the concentration gradient created by the depletion of liquid at the surface. The gradient can be caused by evaporation, or as a result of capillary forces, or through a cycle of vaporization and condensation, or by osmotic effects.

1.2 Drying in pharmaceutical industry

The major steps involved in downstream processing of active pharmaceutical ingredients (APIs) are crystallization, filtration, drying and milling. Drying operation is many times the rate limiting step in the overall manufacturing cycle [27]. Moreover, drying is by far the most energy intensive unit operation [16]. Drying can adversely impact API properties if operating conditions are not carefully selected and controlled. More specifically, improper combinations of temperature, pressure and mixing can lead to API degradation that affects drug efficacy and particle agglomeration/attrition that alters the particle size distribution and therefore drug availability [14]. As a result, the implementation of simple strategies such as increasing the
drying temperature driving force to reduce processing times not only increase energy costs but also have the potential to alter key product quality attributes. Therefore, the development of more systematic methods to simulate and optimize drying operations that ensure product quality and minimize operating time are needed.

1.2.1 Dryer types

Vacuum tray dryer is the more common form of contact dryer used in the industry. A vacuum tray dryer consists of shelves with hot fluid running through them. Trays containing API to be dried are placed on the shelves. The heat travels through the shelves and to the wet cake via conduction. The purpose of the vacuum is to lower boiling point of the solvent which enables the operation to be carried out at low temperatures. This is necessary in most cases as API could degrade at higher temperatures. An image of the lab filter dryer is seen in Figure 1.2.

![Vacuum tray dryer at Sunovion Pharmaceutical Inc.](image)

Figure 1.2: Vacuum tray dryer at Sunovion Pharmaceutical Inc.

Traditionally, the unit operations of filtration and drying are carried out in different equipment. Consequently, there are transfer losses, additional cleaning re-
quirements and other issues that come along with product transfer like increase in production time. A single unit having the ability to carry out both the unit operations can avoid all the mentioned drawbacks. This idea has lead to the migration towards Agitated Filter Dryers (AFDs) from an older setup, which had a filtration unit followed mostly by a vacuum tray dryer. Figure 1.3 is an example of agitated filter dryer on a lab scale.

In addition to the two types of dryer mentioned, other dryers include tumble dryers, drum type dryers, centrifugal filter dryers, spray dryers (for amorphous API), radiation (microwave) based dryers, and many more [54].
1.2.2 Drying end point

There are a number of approaches to determine the end of the drying process. The most common one is to construct a drying curve by taking samples during different stages of the drying cycle against the drying time and establish a drying curve. Karl Fischer titration and loss on drying (LOD) moisture analyzers are also routinely used in batch processes. For LOD measurements, the sample is dried until no solvent is left behind. This is ensured by drying the sample at reasonably high temperatures and/or for a long time. LOD measurement involves periodic removal and weighing of the drying cake until continued drying offers negligible improvement. While standardized throughout the pharmaceutical industry, the LOD method is highly intrusive, manpower intensive and further slows the drying process.

Recently, the development of Quality by Design (QbD) methods enabled by Process Analytical Technology (PAT) has received intense interest in the pharmaceutical industry [50]. While many QbD techniques are under development for other downstream processing steps such as crystallization [29], the drying step has been largely neglected despite its importance. In principle, recent advances in PAT allow the development of less intrusive and more effective QbD methods. However, technologies currently being studied suffer from a number of disadvantages. Off-line analysis methods such as Magnetic Resonance Imaging (MRI) and X-ray Tomography (XRT) are very useful for obtaining detailed information on the cake internal structure. However, MRI is expensive and studies are limited to water [51, p. 91–182], while XRT has limited resolution and can have difficulty detecting multiple compounds without the addition of dopants [51, p. 91-182].

An ideal PAT tool would provide noninvasive, real-time measurements of solvent concentrations within the drying cake. While such a tool does not currently exist, Near Infrared (NIR) spectroscopy has been shown to be capable of providing
realtime solvent concentration measurements of the head space gas [31]. However, NIR relies on part of the spectrum that contains weak overtones and combination spectral frequencies that can be better observed as intense, fundamental vibrations in the Midinfrared (MIR) range [50]. Both NIR and MIR necessitate the development of multivariate models that require considerable data, time and expertise. By contrast, mole fraction measurements of multiple components in a gas sample are readily obtained using Mass Spectrometry (MS). The mole fractions are calculated from measured intensities of fragments with different mass to charge ratios. Because every chemical component produces different fragments in different amounts, various species are easily differentiated and their mole fractions are readily quantified. More importantly and as emphasized in this thesis, the head space gas does not capture the current state of the drying cake but instead is impacted by mixing effects in the dryer headspace. With the introduction of portable and relatively inexpensive mass spectrometers into the pharmaceutical industry, MS is an attractive technology for developing QbD tools aimed at improving the performance of drying operations.

1.3 Modeling drying

A promising approach for process improvement is to use a mathematical model to predict and optimize dryer performance. A wide variety of drying models exist [44] and can be conveniently classified as: a) vaporization front models, b) pore network models, c) population balance models, d) discrete element models and, e) transport models. Vaporization front and population balance models typically contain numerous unknown parameters that must be estimated from dryer data [44]. Furthermore, the extensibility of these models to new operating condition as needed for process optimization has not been well studied. Pore network models are most useful for developing fundamental understanding of the impact of the cake pore structure on
drying behavior. However, these models require substantial information about the cake structure and do not account for many important transport effects including non-isothermal operation. While they do not suffer from the limitations of the other drying models, discrete element models are highly computationally intensive as individual particles must be simulated [44]. Consequently, these models are not well suited for process simulation and optimization. Whitaker developed a general theory of drying based on coupled heat and mass transfer [56]. A number of drying models with applications to pharmaceutical products [13], [27] as well as in other industries [47], [28] have been based on the Whitaker model. For example, variants of the Whitaker model have been developed for three-dimensional simulation of wood drying [33] and clay drying [49]. These models have the ability to generate qualitatively accurate predictions with reasonable computational effort.

In 1980s, a lot of work was done on parametric study of mechanically agitated vacuum drying using penetration models ([52, 53, 48, 6]). These studies investigated heat transfer into the material, effect of mixing times and correlated mixing time to Froude number and mixing number. The effect of intermittent stirring on drying performance was looked into in [25]. A parametric study of the process using the classic vapor front model is in [26]. Very recently [30], the penetration model was extended to study the performance and to optimize the filter drying process. In addition, general guidelines were proposed to operate filter dryers for efficient drying. Thermal DEM was used to study agitated drying as well [18, 19]. These studies demonstrated how thermal DEM could be very useful as it can provide temperature distribution at the particle level. There has been a good amount of effort on the DEM front [38, 39, 40] to understand the effect of RPM and load during agitation. DEM models have also been used to parametrically study drying by comparing with experiments [44, 42, 45].

On the contrary, the scenario is very different on the agitated filter drying
front when considering changes in morphology of API or other crystals. The impact of agitated drying on the crystal size distribution and morphology of KCl and L-threonine (needle-like) was studied in [22, 21]. Further work with agitated filter dryer includes [11]. The focus in the work was primarily on DEM models to predict attrition. Another study [10] very recently published looks into the breakage of paracetamol and aspirin at very low stresses. The impact of agitation on bulk density, specific surface area, particle size and millability of fibrous needle morphology was studied in [15]. A systematic experimental and modeling study of agitated drying with glass beads and lactose monohydrate was performed in [43] looking into the effect of temperature, load and RPM on particle morphology. Recently efforts have been directed towards developing and applying laboratory tools to predict particle properties on scale-up in AFDs [2, 58]. Following these, the effect of shear stress and hydrostatic pressure on API powder properties keeping in mind scale-up was studied in [41]. Although, there has been a great interest in studying particle size changes of API crystals due to attrition, agglomeration and other factors during drying, very limited work exists in the front of modeling particle size change during vacuum agitated filter drying.

1.4 Organization of the Thesis

In Chapter 2, I described the development and application of a mass spectrometer (MS) based QbD tool for monitoring pharmaceutical drying processes. The QbD method was applied to a laboratory-scale vacuum contract dryer with glass beads of different particle sizes, with single and multiple solvents, and over a range of operating temperatures and pressures. In Chapter 3, I described experiments with a vacuum tray dryer using a MS and thermocouples. I developed a multiphase transport model to capture the dynamics of the process. In Chapter 4, I demonstrated the effects of agitation speed (RPM) and solvent concentration (dry basis) on breakage of active
pharmaceutical ingredient (API) during agitated vacuum drying. I used a population balance model with a power law breakage function and generalized Hill-Ng daughter distribution to model the evolution of particle size.
CHAPTER 2

USING ONLINE MASS SPECTROMETRY TO PREDICT
THE END POINT DURING DRYING OF
PHARMACEUTICAL PRODUCTS

2.1 Introduction

This chapter describes the development and application of a mass spectrometer (MS) based QbD tool for monitoring pharmaceutical drying processes. As MS provides mole fraction measurements of solvents in the head space gas, solvent concentrations in the drying cake are not easily predicted due to mixing dynamics in the dryer headspace. Therefore, the proposed method is based on detecting the drying end point, the time at which all solvents have been completely evaporated from the cake. As the gas phase measurement alone is not sufficient to determine this time, the drying end point for each solvent is determined as the time at which the gas phase solvent concentration measurement converges to a predicted value computed from a solvent mass balance on the dryer headspace assuming zero flow rate from the cake. The QbD method was applied to a laboratory-scale vacuum contract dryer with glass beads of different particle sizes, with single and multiple solvents, and over a range of operating temperatures and pressures. LOD experiments were performed to validate the end point prediction for a particular case. To demonstrate industrial relevance, the method was also applied to vacuum drying of a representative API. While the
present study is focused on vacuum contact dryers, the method is equally applicable to other types of pharmaceutical dryers, assuming the necessary solvent balances can be derived.

2.2 Materials and Methods

2.2.1 Materials

The solids used for experiments were either spherical glass beads or a representative API. The glass beads were manufactured by Corpuscular Inc. (Cold Spring, NY) and consisted of three size ranges: a) 10-25 µm, b) 70-110 µm and c) 150-250 µm. Particle Size Distributions (PSDs) were measured with a HORIBA LA-920 (Albany, New York) static laser scattering analyzer. Figure 2.1 shows the measured PSDs as well as the volume weighted arithmetic mean diameters for the three bed samples and the API. While the glass beads produced unimodal PSDs, the API PSD had a strong bimodal characteristic. Interestingly, the measured mean diameter for the 10-25 µm bead sample was 9.38 µm, which was outside the range claimed by the manufacturer. Additional details about the API cannot be provided due to proprietary concerns. Solvents used in different experiments included acetone, methanol and methyl tert-butyl ether (MtBE). Important properties of these solvents with respect to their drying behavior are listed in Table 2.1. The enthalpy of vaporization of methanol is an order of magnitude larger than that of acetone and MtBE, and methanol has a high boiling point compared to both the other solvents. For all three solvents, the enthalpy of vaporization does not change significantly over the range of operating pressures considered in this work. Methanol and MtBE are known to form a minimum boiling point azeotropic mixture [1]. Due to the solvent concentrations used, azeotrope formation was not an issue in my experiments.
Figure 2.1: Particle size distributions for glass bead samples: 10–25 µm, 70–110 µm, and 150–250 µm and for the API. The dashed line indicates the volume-weighted mean diameter.

Table 2.1: Properties of solvents at different operating pressures

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Pressure (mmHg)</th>
<th>Boiling point [°C]</th>
<th>Enthalpy of vaporization (J kg⁻¹)</th>
<th>MW (g mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>30</td>
<td>−15.39</td>
<td>5.67 × 10⁵</td>
<td>58.08</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>−10.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>−6.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>−0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methanol</td>
<td>40</td>
<td>4.53</td>
<td>1.23 × 10⁶</td>
<td>32.04</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>8.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>−18.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MtBE</td>
<td>40</td>
<td>−13.15</td>
<td>3.62 × 10⁵</td>
<td>88.15</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>−9.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2.2 Laboratory-scale vacuum dryer

I designed and constructed a customized vacuum contact dryer system to perform laboratory experiments (Figure 2.2). The oven was specially designed for efficient heat transfer to the cake and insulated to avoid heat loss. Rather than use electrical heaters on the walls of the oven, the cake was heated with a hot fluid that
circulated through the tray upon which the sample dish was placed. The fluid temperature was regulated by a Lauda Model Proline RP 845 temperature controller (Delran, NJ) with an accuracy of ± 0.01°C. Nitrogen (purity 99.998%) was pumped into the oven as the carrier gas at a volumetric flow rate of 5 L min\(^{-1}\) \((2.98 \cdot 10^{-3} \text{ m}^3 \text{s}^{-1})\). The nitrogen flow rate was regulated by a Cole Parmer Model 32907-69 flow controller (Vernon Hills, IL) with an accuracy of 0.1%. Oven gas consisting of evaporated solvents, nitrogen, and residual oxygen and carbon dioxide was continuously removed to maintain the oven pressure at the setpoint value. The exit gas flow rate was measured with an Omega Model FMA-1610A-VOL flow meter (Stamford, CT) with a maximum flow rate of 100 L min\(^{-1}\) \((0.0595 \text{ m}^3 \text{s}^{-1})\) and an accuracy of 1%. The flow meter used the Hagen-Poiseuille equation to calculate the flow rate and was calibrated using pure nitrogen. Data from the flow controller and flow meter were logged using PuTTY (open source software under the MIT license). To enhance mixing of gases, the inlet and outlet gas ports were placed at the lower bottom right corner and the top of the oven, respectively. At the inlet flow rate of 5 L min\(^{-1}\) \((2.98 \cdot 10^{-3} \text{ m}^3 \text{s}^{-1})\), the oven residence time \((\tau)\) was calculated to be 512 seconds by performing a nitrogen step experiment and fitting the nitrogen mass fraction data to the first-order differential equation (eq A.5).

The oven pressure was regulated with a BUCHI Model V-850 pressure controller (New Castle, DE) that manipulated a control valve on the exit gas stream. The pressure controller operated as an on-off type controller with a specified tolerance of 1 mmHg \((0.1333 \text{ kPa})\). Pressure data was logged using Distillation Record software provided by BUCHI. The exist gas was passed through a FTS Systems Model Titan Trap vapor trap (Warminster, PA) and then was pumped out of the system with an Edwards Model XDS10 A72601906 pump (Sanborn, NY). Three Oakton Model 073098B-K-G-12 type K thermocouples (Vernon Hills, IL) were available for direct placement inside the drying cake to measure spatial temperature gradients.
The adjustable thermocouples were placed at 0 cm, 0.6 cm and 1.9 cm from the base of the sample dish, and temperature data was recorded with a Cole-Parmer Model USB-5201 data logger (Vernon Hills, IL) using Tracer DAQ software provided by Cole-Palmer. Gas exiting the top of the oven through a tube wrapped in heat tape to avoid condensation of solvents was passed to an Extrel CMS Model Max LG 300 mass spectrometer (Pittsburgh, PA) for composition analysis. The MS was capable of achieving accuracies of 100 ppb ($10^{-7}$ mole fraction) in the absence of interference between the components. Due to the presence of very small interference, an accuracy of $10^{-5}$ mole fraction was attainable for my experiments. Mole fraction measurements were generated every 3–4 seconds and processed using Questor 5 software provided by Extrel.

### 2.2.3 Experimental Procedure

The solid material was placed inside a glass dish with an inner diameter of 8.6 cm (OD: 9 cm) such that the cake thickness was 2.3 cm. The solid was saturated
with the solvent(s), placed in the oven and outfitted with the three thermocouples. The vapor trap, pump, flow meter, flow controller and the thermocouple data loggers were turned on and data recording was initiated. The oven was closed securely and pressure reduction was commenced by opening the exit gas control valve using the pressure controller. This point represented time zero and was used to synchronize all data. Drying operation was stopped by venting the oven with air when the MS displayed a value of 0.5% mole fraction of the least volatile component.

2.2.4 Theory

A representative set of data obtained from the MS for the drying of glass beads with acetone solvent is shown in Figure 2.3. The mole fraction profile for acetone suggests that drying was complete at approximately 70 min. However, the MS analyzes gas from the head space and therefore provides composition measurements that trail those in the actual cake due to the residence time of the oven. In actuality, the cake is dry well before 70 min and the MS was simply measuring flow driven depletion of acetone from the headspace. Therefore, the MS measurements are not sufficient to determine solvent compositions in the cake and must be combined with appropriate mathematical analysis to extract more useful information for monitoring drying performance.

Determining solvent compositions within the cake from gas phase composition measurements is difficult due to dryer headspace dynamics. The problem is simplified considerably by using the available composition measurements to determine the drying end point for each solvent as the time at which all the solvent is evaporated from the cake. At the end point for a particular solvent, the evaporation rate of the solvent from the cake becomes essentially zero and the only source of solvent is that contained in the head space of the oven. Under the simplifying assumption that gas
in the head space is well mixed, the mass fraction of each component \( i \) in the gas phase will satisfy the following equation derived in the Appendix:

\[
\frac{dx_i}{dt} = - \frac{q_{\text{purge}} M_{\text{purge}}}{V M_g} x_i
\]  

(2.1)

where \( x_i \) is the mass fraction of component \( i \) in the gas phase, \( M_g \) is the average molecular weight of the gas phase, \( q_{\text{purge}} \) and \( M_{\text{purge}} \) are the volumetric flow rate and molecular weight of the purge gas, respectively, and \( V \) is the volume of the head space. The following equation was used to convert the mole fractions provided by the MS into mass fractions:

\[
x_i = \frac{M_i y_i}{M_g}
\]  

(2.2)

where \( y_i \) is the mole fraction of component \( i \). An algorithm was developed to automatically and robustly determine the drying end points from gas phase composition measurements. At any given time, composition data over the last 60 seconds were collected in a vector \( \alpha \). An analogous vector was formed from data collected over the last 120 seconds and then smoothed by moving average to account for fluc-
tuations in the MS signal caused by frequent switching of the pressure control valve. The last 60 seconds of this smoothed data was collected into a vector $\beta$. Equation 2.1 was integrated to yield:

$$x_i = x_{i,o} \exp \left( -\frac{M_{\text{purge}}}{M_g} \frac{t}{\tau} \right) \text{ where } \tau = \frac{V}{q_{\text{purge}}} \quad (2.3)$$

This equation was fit to the measured composition data by adjusting $x_{i,o}$ such that $x_i(t)$ passed through the mid-point of the vector $\alpha$ where $t = 0$ corresponds to the first point in $\alpha$. The last 60 seconds of predicted $x_i(t)$ values were collected into a vector $\gamma$ (Figure 2.4). The root mean square (RMS) error between $\beta$ and $\alpha$ was denoted $\epsilon_1$, and the RMS error between $\beta$ and $\gamma$ was denoted $\epsilon_2$. A drying end measure was defined as $\Omega = \epsilon_2 / \epsilon_1$, such that $\Omega < 1$ indicated that the convergence error $\epsilon_2$ between the model and the smoothed data was less than the error in the data due to noise. Therefore, I considered the first time where $\Omega < 1$ as the tentative drying end point for the solvent. To further validate this conclusion, this condition was checked at each time point over a span of 120 seconds before declaring drying complete for the solvent. This analysis was done simultaneously for all the solvents in the mixture. The cake was assumed to be completely dry when the end point was reached for the least volatile solvent. While all analyses in this paper were performed off-line following data collection, the proposed algorithm can easily be implemented in real time.


Figure 2.4: Representation experiment showing the vectors $\alpha$, $\beta$, and $\gamma$ used to determine the drying end point.

### 2.3 Results and Discussion

#### 2.3.1 Pure Solvents

##### 2.3.1.1 Acetone

Drying experiments with acetone as the solvent were performed for three different glass bead size (10-25, 70-110 & 150-250 µm), three temperatures (30, 40 and 50 °C) and three pressures (30 mmHg, 40 mmHg and 50 mmHg). The nominal case was chosen as 150-250 µm beads, 50 °C (323.15 K) and 50 mmHg (6.665 kPa), and six other experiments were performed by changing one variable at a time. Mole fraction data obtained from the mass spectrometer for the seven experiments are shown in Figure 2.5. The data for varying bead sizes followed the expected trend, with larger particles drying more rapidly. However, the data for varying temperature and pressure did not appear to follow the expected trends. The 40 and 50 °C experiments produced very similar mole fraction profiles, while the 30 mmHg (3.999 kPa) experi-
ment produced slower drying dynamics than the two higher pressures. As mentioned in the Section 2.2, the cake thickness was fixed for all experiments even though the three bead sizes had different void fractions. Consequently, the initial amount of liquid in every experiment was different and the results should be reinterpreted according to the amount of drying per unit mass of liquid. This issue is revisited below.

Figure 2.5: Acetone mole fractions measured by mass spectroscopy for drying of glass beads (a) glass bead size 150-250 μm, temperature 50°C and pressure 30, 40 and 50 mmHg; (b) glass bead size 150-250 μm, pressure 50 mmHg and temperature 30, 40 and 50°C (c) temperature 50°C, pressure 50 mmHg and glass bead sizes 10-25, 70-110 & 150-250 μm.

Figure 2.6 illustrates the application of the drying end point detection algorithm to the data collected for the nominal case of 150-250 μm beads, 50°C (323.15 K) and 50 mmHg (6.665 kPa). The light gray color denotes the region where the drying end measure Ω > 1 and the cake was deemed to be drying. The dark gray color denotes the region where Ω < 1 and the cake was deemed to be dry subject to 120 s of continued validation as discussed in Section 2.2.4. The red line marks the completion of the validation process and the corresponding time was taken as the drying end point of 36.9 min. It is important to note that drying was complete
long before the measured gas phase mole fraction reached a very low value at approximately 80 min, as shown by the blue line in Figure 2.6. This example shows the power of the proposed QbD tool, as a plant operator monitoring the end point detection plot would be able to conclude that drying was complete in less than half the time indicated by the unprocessed MS signal.

![Figure 2.6: Drying end point detection algorithm with acetone solvent, glass beads of size 150-250 \( \mu m \), temperature of 50\(^{\circ}\)C, and pressure of 50 mmHg.](image)

The drying end point times determined with the proposed algorithm for the seven experiments shown in Figure 2.5 are listed in Table 2.2. Also shown for each case are the initial mass of acetone and the drying time per gram of acetone (scaled drying time) that accounts for initial amount of liquid. As expected, the scaled drying time decreased with increasing temperature due to the larger driving force for heat transfer and with increasing bead size because smaller particles offer a higher resistance to mass transfer. However, pressure did not have the expected effect on the scaled drying time as 40 mmHg (5.332 kPa) produced a shorter drying time than did 30 mmHg (3.999 kPa). These results can be rationalized by noting that the flow controller could not maintain the inlet nitrogen flow rate at the target 5 L min\(^{-1}\) (2.98 \( \cdot \) 10\(^{-3}\) m\(^3\) s\(^{-1}\)) at 30 mmHg (3.999 kPa). During the experiment, the flow rate
fell to 4.32 mmHg (0.5759 kPa) and the residence time of gas in the head space was increased accordingly. This discrepancy caused the 30 mmHg (3.999 kPa) experiment to exhibit slower drying dynamics than expected.

Table 2.2: Comparison of drying times for seven experiments with acetone as the solvent and different bead sizes, temperatures and pressures

<table>
<thead>
<tr>
<th>Exp #</th>
<th>Temperature °C</th>
<th>Pressure mmHg</th>
<th>Particle size µm</th>
<th>Drying time g</th>
<th>Mass of liquid g</th>
<th>Time per gram min g⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>40</td>
<td>150 to 250</td>
<td>37.04</td>
<td>0.86</td>
<td>31.70</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>30</td>
<td>150 to 250</td>
<td>34.7</td>
<td>36.72</td>
<td>0.94</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>50</td>
<td>150 to 250</td>
<td>36.9</td>
<td>35.93</td>
<td>1.03</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>50</td>
<td>150 to 250</td>
<td>39.1</td>
<td>36.65</td>
<td>1.07</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>50</td>
<td>150 to 250</td>
<td>45.6</td>
<td>36.85</td>
<td>1.24</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>50</td>
<td>70 to 110</td>
<td>48.1</td>
<td>36.01</td>
<td>1.34</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>50</td>
<td>10 to 25</td>
<td>73.6</td>
<td>51.15</td>
<td>1.44</td>
</tr>
</tbody>
</table>

In an attempt to validate the end point dying predictions for acetone, LOD experiments were performed at the nominal conditions: glass beads of size 150 µm to 250 µm, temperature of 50 °C (323.15 K) and pressure of 50 mmHg (6.665 kPa). Rather than reinsert the sample back into the oven following weighing, a separate drying experiment was performed for each measurement time. A total of six experiments of different durations were performed, and each experiment was terminated once the sample was removed from the oven so as to eliminate the unmodeled disturbance that would occur if the sample was reinserted. The solid and solvent masses were determined before the start of the experiment. The final mass of material was weighed at the end of each experiment to determine the dry basis moisture content. This procedure was based on the assumption that the six experiments were identical until sample removal, which seemed to be approximately validated by the results in Figure 2.7 where the abrupt decrease in the mole fraction measurement indicated termination of the experiment. The results of these LOD experiments are summarized in Table 2.3 along with the value of the end point drying measure Ω calculated at the end of each experiment. According to this analysis, the sample was dry by the end of experiment 5, suggesting that drying was complete between 33 and 38 min. This
time range agreed with the results of experiment 3 in Table 2.2, which indicated that
drying was complete at 36.9 min. The moisture content values determined from the
LOD experiments indicated that the sample was not completely dry until the end of
experiment 6.

Figure 2.7: Loss of drying experiments for glass beads of size 150-250 µm, acetone
as the solvent, temperature of 50 °C, and pressure of 50 mmHg. The duration of each
experiment is listed in Table 2.3.

Table 2.3: Comparison of the cake moisture content determined from the loss on
drying experiments in Figure 2.7 and the end point drying measure calculated by the
QbD method

<table>
<thead>
<tr>
<th>Exp #</th>
<th>Stop time</th>
<th>Liquid in cake</th>
<th>Moisture content dry basis</th>
<th>Drying measure Ω at end of run</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.75</td>
<td>7.524</td>
<td>3.552</td>
<td>44.70</td>
</tr>
<tr>
<td>2</td>
<td>20.00</td>
<td>2.408</td>
<td>1.136</td>
<td>7.01</td>
</tr>
<tr>
<td>3</td>
<td>26.00</td>
<td>0.718</td>
<td>0.339</td>
<td>4.22</td>
</tr>
<tr>
<td>4</td>
<td>33.00</td>
<td>0.118</td>
<td>0.056</td>
<td>4.37</td>
</tr>
<tr>
<td>5</td>
<td>38.00</td>
<td>0.025</td>
<td>0.012</td>
<td>0.56</td>
</tr>
<tr>
<td>6</td>
<td>42.00</td>
<td>0.000</td>
<td>0.000</td>
<td>0.38</td>
</tr>
</tbody>
</table>

However, acetone is a class 3 solvent [8] and the acceptable residual solvent
concentration is 0.5 % (5,000 ppm) moisture content dry basis. The moisture content
calculated at the end of experiment 5 was 0.012 % (120 ppm), which is well below 0.5 %
Therefore, I can conclude that the proposed QbD method satisfactorily predicted the drying end point under these conditions.

2.3.1.2 Methanol

Drying experiments with methanol as the solvent were performed at a temperature of 40°C (313.15 K) and pressure of 50 mmHg (6.665 kPa) for the three different glass bead sizes. Mole fraction data obtained for the three experiments followed the expected trend with cakes comprised of larger particles drying more rapidly (Figure 2.8). Application of the QbD method to the mole fraction data obtained for the 150 to 250 µm beads is illustrated in Figure 2.9. The sample was predicted to be completely dry at 88.7 min, while the measured gas phase mole fraction reached a very low value at approximately 110 min. The benefit of QbD analysis was not as large as for acetone (Figure 2.6) because methanol has a higher enthalpy of vaporization (Table 2.1). QbD analysis of the drying data for the three experiments with different bead sizes summarized in Figure 2.10 reconfirmed the conclusion that cakes with larger particles dried more rapidly. As compared to results with acetone as the solvent (Table 2.2), the effect of particle size was more pronounced with methanol due to the larger enthalpy of vaporization.
Figure 2.8: Methanol mole fractions measured by mass spectroscopy for drying of glass beads of different sizes (1025 µm, 70110 µm, 150250 µm) at a temperature of 40°C and pressure of 50 mmHg.

Figure 2.9: Drying end point detection algorithm with methanol solvent, glass beads of size 150250 µm, temperature of 40°C, pressure of 50 mmHg.
Figure 2.10: Comparison of drying times for three experiments with methanol solvent, temperature of 40 °C and pressure of 50 mmHg, and different glass bead sizes.

2.3.2 Multiple Solvents

2.3.2.1 Glass Beads with Methanol-MtBE

Drying experiments with methanol:MtBE mixture (2:1 volume ratio) as the solvent were performed at a temperature of 50 °C (323.15 K) and pressure of 50 mmHg (6.665 kPa) for different glass bead sizes. Figure 2.11 shows methanol and MtBE mole fraction data for the three experiments. Despite having a lower initial concentration in the cake, methanol evaporated much more slowly due to its higher heat of vaporization (Table 2.1). As observed with single solvents, cakes with larger particles dried more rapidly because smaller particles offered a higher resistance to mass transfer.
Figure 2.11: MTBE and methanol mole fractions measured by mass spectroscopy for drying of glass beads of different sizes (1025 µm, 70110 µm, 150250 µm) at a temperature of 50°C, and pressure of 50 mmHg.

Application of the QbD method to the mole fraction data obtained for 150 to 250 µm beads is illustrated in Figure 2.12. In this case, a separate plot was generated for each solvent to determine which solvent was evaporated last from the cake, as this time represented the drying end point. MtBE was predicted to be evaporator first, while the drying end point was determined as the time methanol was evaporated at 51.9 min. By contrast, the unprocessed gas phase measurements suggested a methanol drying time of approximately 75 min. QbD results obtained for the three bead sizes are summarized in Table 2.4. Methanol exhibited the expected trend in drying time with particle size.

Table 2.4: Comparison of drying times for three experiments with methanol and MtBE as solvents, glass beads and API as solids, temperature of 50°C, and pressure of 50 mmHg

<table>
<thead>
<tr>
<th>Solid</th>
<th>Particle size (µm)</th>
<th>Drying time (min)</th>
<th>Mass of liquid (g)</th>
<th>Time per gram (ψ) (min g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass beads</td>
<td>150 to 250</td>
<td>51.9</td>
<td>36.818</td>
<td>1.41</td>
</tr>
<tr>
<td>Glass beads</td>
<td>70 to 110</td>
<td>64.2</td>
<td>35.675</td>
<td>1.80</td>
</tr>
<tr>
<td>Glass beads</td>
<td>10 to 25</td>
<td>92.6</td>
<td>41.152</td>
<td>2.25</td>
</tr>
<tr>
<td>API</td>
<td>≈ 5 to 220</td>
<td>51.5</td>
<td>12.346</td>
<td>4.17</td>
</tr>
</tbody>
</table>
2.3.2.2 API with Methanol-MtBE

To demonstrate industrial potential of the proposed QbD method, drying experiments were performed with a proprietary API. As in the glass bead experiments, the solvent was a 2:1 methanol:MtBE mixture, the temperature was 50 °C (323.15 K) and the pressure was 50 mmHg (6.665 kPa). The solvent mole fractions generated by the mass spectrometer (Figure 2.13) were qualitatively similar to those obtained for glass beads (Figure 2.11) despite the API having a broad, biomodal particle size distribution (Figure 2.1). The end point detection algorithm indicated that methanol evaporated first and that methanol was completely evaporated by 51.5 min. The unprocessed gas phase measurements indicated a drying time of 75 min (Figure 2.14). This relative improvement was consistent with that obtained for glass beads (Table 2.4). The lower API drying rates may have been caused by a strong shielding effect due to the bimodal particle size distribution [34] and/or by hydrogen bonding between the API and the solvents.
Figure 2.13: MtBE and methanol mole fractions measured by mass spectroscopy for drying of a proprietary API at a temperature of 50°C and pressure of 50 mmHg.

Figure 2.14: Drying end point detection algorithm for drying of a proprietary API with methanol (top) and MtBE (bottom) solvents, temperature of 50°C, and pressure of 50 mmHg.

2.4 Conclusions

I have presented a novel Quality-by-Design (QbD) method for determining the end point of drying for pharmaceutical dryers based on on-line mass spectroscopy. The drying end point was determined algorithmically as the time at which the gas phase
solvent concentration measurement of the least volatile component converged to a predicted value computed from a solvent mass balance on the oven assuming zero flow rate from the drying cake. As compared to alternative dryer monitoring techniques based on spectroscopic methods, the proposed method offers several key advantages including the ability to detect when the cake is dry from vapor phase measurements, applicability to multiple solvents, and simple off-line and real-time implementation that does not require chemometric models. On the other hand, the method only predicts when drying is complete and does not generate predictions of solvent concentrations in the cake with time. Although not observed in my experiments, it is possible that low solvent concentrations could be established in the cake for an extended period and the method would lead to excessive drying. Further studies will be required to investigate this issue. To demonstrate application of the QbD tool, drying experiments were performed with a custom built, laboratory-scale vacuum dryer over a range of temperatures and pressures using glass beads with three different particle sizes as the solid phase. Drying end points were automatically detected for acetone, methanol and methanol-MTBE solvents well before the unprocessed gas phase solvent concentration measurements suggested that drying was complete. As expected, I found that the drying time per gram of solvent ($\Psi$) increased with increasing temperature, decreasing pressure and increasing glass bead size. Furthermore, I found that the ratio of $\Psi$ for two solvents was approximately equal to the ratio of their enthalpies of vaporization. At operating conditions of 40°C (313.15 K) and 50 mmHg (6.665 kPa) with glass beads of size 150–250µm, the $\Psi$ ratio of acetone to methanol was 0.453 while the ratio of their enthalpies of vaporization was 0.460. Figure 2.15 shows a similar trend for the other two bead sizes.
The QbD method was validated by performing loss on drying experiments for one combination of pressure, temperature and bead size. I found that the method could successfully detect moisture content on a dry basis down to 0.012% (120 ppm). Application of the method to an API with methanol-MTBE solvents produced a substantially reduced drying rate compared to comparably sized glass beads, most likely due to the API bimodal particle size distribution and hydrogen bonding with the solvent. The initial studies reported here suggest that the proposed method represents a powerful QbD approach for pharmaceutical drying processes. The benefit achievable with the method will depend on the relative magnitudes of the drying rate and gas residence time in the dryer headspace. The greatest benefit will be realized for fast evaporating solvents and large residence times because gas phase composition measurements do not represent the current state of the cake under these conditions.
CHAPTER 3
MULTIPHASE TRANSPORT MODELING FOR VACUUM DRYING OF PHARMACEUTICAL PRODUCTS

3.1 Introduction

This chapter describes the development of a multiphase transport model that can capture the dynamics observed in vacuum drying accurately. I also based the development of my vacuum drying model on the Whitaker model [56]. The model has the ability to generate qualitatively accurate predictions with reasonable computational effort. I observed from my experiments that the thermodynamics during vacuum drying were very similar to that of simple boiling. The same behavior was observed in another study on vacuum drying of pharmaceutical products with multiple solvents [20]. However, existing drying models including the Whitaker model do not account the thermodynamics of boiling. Therefore, the goal of this study was to develop a novel multiphase drying model that captured the boiling mechanism. To avoid the complexities of a full three phase model, I considered the system to comprise of two phases: the liquid phase and a combined solid-vapor phase. As opposed to drying models in which the rate of liquid vaporization was calculated from empirical relationships, I used the liquid phase energy balance to rigorously compute the mass loss due to boiling. Cake temperature and solvent composition data collected over a range of temperatures, pressures and glass bead sizes were used to identify parameter
trends and obtain further insights into drying behavior. While I focused on vacuum tray drying, the proposed model can be extended to other vacuum drying processes such as agitated Nutsche dryers.

3.2 Materials and Methods

3.2.1 Experiments

3.2.1.1 Materials

The solids used for experiments were spherical glass beads (Corpuscular Inc., Cold Spring, NY) of three size ranges: a) 10-25 µm, b) 70-110 µm and c) 150-250 µm. Particle Size Distributions (PSDs) were measured with a HORIBA LA-920 static laser scattering analyzer (Albany, NY). Only this method was used to measure the particle size as it provides a good estimate for volume based particle size distribution. In addition, the method also provides sufficient information to characterize the glass bead samples. Figure 3.1 shows the measured PSDs as well as the volume weighted arithmetic mean diameters of the three bead samples. All the samples produced unimodal PSDs. Interestingly, the measured mean diameter of the 10-25 µm bead sample was 9.38 µm, which was outside the range claimed by the manufacturer.

Acetone was used the solvent in all experiments. Important properties of acetone with respect to its vaporization behavior are listed in Table 3.1. The enthalpy of vaporization does not change significantly over the range of operating pressures considered in this work.
Table 3.1: Properties of acetone at different operating pressures.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Pressure (Torr)</th>
<th>Boiling Point (°C)</th>
<th>Enthalpy of vaporization ( \frac{J}{kg} )</th>
<th>Molecular weight ( \frac{g}{mol} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>30</td>
<td>-15.39</td>
<td>5.67 ( \times 10^5 )</td>
<td>58.08</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>-10.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>-6.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2.1.2 Laboratory-scale vacuum drying system

![Diagram of laboratory-scale vacuum contact dryer](image)

Figure 3.2: Laboratory-scale vacuum contact dryer connected to a portable mass spectrometer for real-time analysis of drying performance.

I designed and constructed a customized vacuum contact dryer system to perform my laboratory experiments (Figure 3.2). The oven was specially designed for efficient heat transfer to the cake and insulated to avoid heat loss. Rather than use electrical heaters on the walls of the oven, the cake was heated with a hot fluid that circulated through the tray upon which the sample dish was placed. The fluid temperature was regulated by a Lauda Model Proline RP 845 temperature controller...
Figure 3.1: Particle size distributions of the glass bead samples: (a) 10–25 μm, (b) 70–110 μm, and (c) 150–250 μm. The dashed line indicates the volume-weighted mean diameter ($d_p$).
(Delran, NJ) with an accuracy of 0.01 °C. Nitrogen (purity 99.998%) was pumped into the oven as the carrier gas at a volumetric flow rate of 5 LPM ($8.33 \times 10^{-5} \text{ m}^3\text{s}^{-1}$). The nitrogen flow rate was regulated by a Cole Parmer Model 32907-69 flow controller (Vernon Hills, IL) with an accuracy of 0.1%. Gas in the oven head space consisting of evaporated solvents, nitrogen, and residual oxygen and carbon dioxide was continuously removed to maintain the oven pressure at the setpoint value. The exit gas flow rate was measured with an Omega Model FMA-1610A-VOL flow meter (Stamford, CT) with a maximum flow rate of 100 LPM ($1.67 \times 10^{-3} \text{ m}^3\text{s}^{-1}$) and an accuracy of 1%. The flow meter used the Hagen-Poiseuille equation to calculate the flow rate and was calibrated using pure nitrogen. Data from the flow controller and flow meter were logged using PuTTY (open source software under the MIT license).

To enhance mixing of gases, the inlet and outlet gas ports were placed at the lower bottom right corner and the top of the oven, respectively. At the inlet flow rate of 5 LPM ($8.33 \times 10^{-5} \text{ m}^3\text{s}^{-1}$), the oven residence time ($\tau$) was calculated to be 512 seconds by performing a nitrogen step experiment and fitting the nitrogen mass fraction data to the first-order differential equation ([4]).

The oven pressure was regulated with a BUCHI Model V-850 pressure controller (New Castle, DE) that manipulated a control valve on the exit gas stream. The pressure controller operated as an on-off type controller with a specified tolerance of 1 Torr. Pressure data was logged using Distillation Record software provided by BUCHI. The exist gas was passed through a FTS Systems Model Titan Trap vapor trap (Warminster, PA) and then was removed from the system with an Edwards Model XDS10 A72601906 pump (Sanborn, NY). Three Oakton Model 073098B-K-G-12 type K thermocouples (Vernon Hills, IL) were available for direct placement inside the drying cake to measure spatial temperature gradients. The adjustable thermocouples were placed at 0 cm, 0.8 cm, and 1.8 cm from the base of the sample dish, and temperature data was recorded with a Cole-Parmer Model USB-5201 data
logger (Vernon Hills, IL) using Tracer DAQ software provided by Cole-Palmer. Gas exiting the top of the oven through a tube wrapped in heat tape to avoid condensation of solvents was passed to an Extrel CMS Model Max LG 300 mass spectrometer (MS, Pittsburgh, PA) for composition analysis. The MS was capable of achieving an accuracy of 100 ppb \((10^{-7} \text{ mole fraction})\) in the absence of interference between the components. Due to the presence of some interference, an accuracy of \(10^{-5}\) was attainable after calibration. Mole fraction measurements were generated every 3-4 seconds and processed using Questor5 software provided by Extrel.

### 3.2.1.3 Procedure

The solid material was placed inside a glass dish with an inner diameter of 8.6 cm (OD: 9 cm) such that the cake thickness was 2.3 cm. The solid was saturated with the solvent, placed in the oven and outfitted with the three thermocouples. The vapor trap, pump, flow meter, flow controller and thermocouple data loggers were turned on and data recording was initiated. The oven was closed securely and pressure reduction was commenced by opening the exit gas control valve using the pressure controller. This point represented time zero and was used to synchronize all data. Drying operation was stopped by venting the oven with air when the MS displayed a mole fraction of 0.5% or less of the least volatile component.
3.2.2 Multiphase Transport Model

3.2.2.1 Information Flow Diagram

Figure 3.3: Information flow diagram for transport modeling and parameter estimation. The dashed lines represent flow of data used by the optimizer for parameter estimation.

Figure 3.3 shows the flow of information as the model was executed. The main components were the multiphase transport model (MPTM), grid generation module, oven model, drying time endpoint module and optimizer module. The MPTM was supplied solid properties and liquid and vapor phase properties of the solvent. Grid generation was a simple module that generated a spatial grid for numerical solution given the thickness of the cake and the specified number of nodes. The partial differential equations (PDEs) were discretized in space along this grid. The time dependent ordinary differential equations (ODEs) obtained from this discretization procedure were solved in the MPTM. The Clausius-Clapeyron equation was used to calculate the enthalpy of vaporization for use in the MPTM module using pressure and boiling point data [57]. A drying time module[4] was used to detect the endpoint of drying, at which time the simulation was terminated. Under assumption that the gas head space
was well mixed, the oven model received the solvent vaporization rate from MPTM and calculated the gas compositions leaving the oven. Both the MPTM and the oven module were supplied with system properties such as the sample container dimensions, the oven headspace volume, etc. Following one or more simulations, outputs from both the MPTM and the oven model were sent to the optimizer where measured and predicted variables were compared based on a specified least-squares objective function. Updated values of selected model parameters for future simulations were generated by minimizing the objective function.

3.2.2.2 Governing equations for cake drying model

In this analysis, the macroscopic continuum approach was adopted. The model accounted for two phases, the liquid phase and a combined solid-vapor phase. I assumed that the vapor phase would very rapidly track the temperature of the solid phase. The characteristic time for temperature to reach equilibrium between the vapor and solid phases was approximated as the time constant for heat transfer in the vapor phase. This time constant was of the order $10^{-3}$ seconds for the system under consideration. As the drying time was many orders of magnitude larger, the lumping of the solid and vapor phase for the heat balance was valid. When conditions were favorable for boiling, the temperature of the liquid phase was constrained to be equal to the saturation temperature as observed in my experiments. However, this constraint was not imposed on the solid-vapor phase. All variables in the model varied in time and only in the z-direction spatially (Figure 3.4). Variables were volume averaged using the approach described by Whitaker [56]. For example, in a control volume $V$ containing solid, liquid and vapor, the average concentration of solvent in the liquid was $C_l = \frac{1}{V} \int C_{l,local} dV$. Thus $C_{l,local}$ is treated as the solvent concentration in the liquid at any point in the control volume $V$. 

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The model was derived based on the following assumptions,

1. Mass transfer in the liquid phase occurred via diffusion, and the diffusion coefficient varied linearly with the moisture content as shown in Eq. 3.2. The resulting diffusion equation was of the form of the Richard’s equation.

2. All material properties were treated as constants including $k_s, k_l, k_v, c_p_s, c_p_l, c_p_v, c_p_b, \Delta H, \rho_l, \rho_s, \& \rho_b$ (see Nomenclature).

3. Mass transfer resistance for vapor flow from the point of vaporization to the head space of the oven was negligible.

4. The vapor behaved like an ideal gas under the vacuum conditions used. Hence, the density of the vapor was calculated from the ideal gas equation.

5. Boiling was the only form of vaporization considered in the model, with evaporation assumed to be negligible. When the temperature of the liquid phase was equal to or greater than the saturation temperature, the liquid was considered to be boiling.

6. The solid was impermeable to the liquid and vapor and any form of adsorption on the solid particles was neglected.
7. The liquid phase was considered to be incompressible.

8. The effect of the size of the solid particles on drying behavior could be captured with the mean particle diameter independent of the particle size distribution.

9. Deformation of the porous medium was considered to be negligible.

10. The sides of the cake were considered to be perfectly insulated (Figure 3.4). Hence, heat transfer in the radial direction was omitted.

11. Diffusion of gas from the oven head space into the cake was considered to be negligible. This assumption was based on the fact that boiling leads to high volumes of vapor being generated. Because the cake was initially saturated with solvent, this assumption was the potential to introduce significant error only at the very end of the drying cycle. However, the ppm concentration of the solvent at this point was much lower than the acceptable residual solvent concentration (e.g. see [9] for acetone). Therefore, the simulation was typically stopped before this point was reached.

Table 3.2: Volume fraction, concentrations and thermal conductivities of the different phases.

<table>
<thead>
<tr>
<th>Component</th>
<th>Volume fraction</th>
<th>Concentration</th>
<th>Thermal conductivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid</td>
<td>$\epsilon_s = 1 - \epsilon_{\text{void}}$</td>
<td>$C_s = \rho_s \epsilon_s$</td>
<td>$k_s = k_s \epsilon_s$</td>
</tr>
<tr>
<td>Liquid</td>
<td>$\epsilon_l = \epsilon_{\text{void}} - \epsilon_v$</td>
<td>$C_l = \rho_l \epsilon_l$</td>
<td>$k_l = k_l \epsilon_l$</td>
</tr>
<tr>
<td>Vapor</td>
<td>$\epsilon_v$</td>
<td>$C_v = \rho_v \epsilon_v = \frac{P \rho_v}{R_g T_v} \epsilon_v$</td>
<td>$\bar{k}_v = k_v \epsilon_v$</td>
</tr>
<tr>
<td>Total</td>
<td>$\epsilon_s + \epsilon_l + \epsilon_v = 1$</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Mass balance on the liquid phase

Based on the assumptions above, the mass balance on the liquid phase had the form in Eq. (3.1). The diffusion coefficient varied linearly with the liquid volume fraction, denoted by $\epsilon_l$, as shown in Eq. 3.2. Here $D_o$ is the diffusion coefficient when the void space was saturated with liquid. As the equations were volume averaged, the linear reduction in the diffusion coefficient $D$ with volume fraction $\epsilon_l$ represented a
reduction in the cross-sectional area available for diffusion. In Eq. (3.1), \( \dot{\Gamma} \) denotes the rate of liquid mass vaporizing per unit volume. For the case of drying by evaporation, this rate has been replaced with various empirical forms (e.g. see [27]). In this work, I rigorously calculated the rate from an energy balance on the liquid phase.

\[
\frac{\partial C_l}{\partial t} = \frac{\partial}{\partial z} \left( D \frac{\partial C_l}{\partial z} \right) - \dot{\Gamma} \tag{3.1}
\]

\[
D = D_0 \epsilon_l \tag{3.2}
\]

**Mass balance on the solid-vapor phase**

The concentration of solid was assumed to be constant in time and space. Hence,

\[
\frac{\partial C_s}{\partial t} = 0 \tag{3.3}
\]

Furthermore, newly created vapor was assumed to have a free path from its point of origin within the cake to the oven head space. Exploiting this assumption to simplify the calculations, I used the fact that \( \epsilon_v = 1 - (\epsilon_s + \epsilon_l) \) as listed in Table 3.2.

**Energy balance on the liquid phase**

Four distinct mechanisms were considered to affect the rate of change of enthalpy in the liquid phase. As shown in Eq. 3.4 these mechanisms were heat transfer by conduction, heat transfer due to diffusion, heat transferred from the solid-vapor phase and enthalpy lost due to vaporization.

\[
\frac{\partial (C_l h_l)}{\partial t} = \frac{\partial}{\partial z} \left( \bar{k}_l \frac{\partial T_l}{\partial z} \right) + \frac{\partial}{\partial z} \left( D \frac{\partial C_l}{\partial z} h_l \right) + h_{int} (T_{sv} - T_l) - \dot{\Gamma} h_v \tag{3.4}
\]
Using Eq. 3.1, the energy balance Eq. 3.4 can be simplified as,

\[(C_l c_{pl}) \frac{\partial T_l}{\partial t} = \frac{\partial}{\partial z} \left( k_l \frac{\partial T_l}{\partial z} \right) + h_{int} (T_{sv} - T_l) - \dot{\Gamma} \Delta H + D c_{pl} \frac{\partial C_l}{\partial z} \frac{\partial T_l}{\partial z} \] (3.5)

When conditions were favorable for boiling, I attempted to mimic my experimental results by constraining the liquid temperature \(T_l\) to track the saturation temperature \(T_{sat}\) calculated at the current pressure. Hence, Eq. 3.5 was rearranged to obtain an explicit equation for \(\dot{\Gamma}\) as shown in Eq. 3.6.

\[\dot{\Gamma} = \frac{\partial}{\partial z} \left( k_l \frac{\partial T_l}{\partial z} \right) + h_{int} (T_{sv} - T_l) - (C_l c_{pl}) \frac{\partial T_{sat}}{\partial t} \] (3.6)

The term \(D c_{pl} \frac{\partial C_l}{\partial z} \frac{\partial T_l}{\partial z}\) was neglected as it was very small compared to the other terms. When the liquid started boiling, the temperature in the liquid phase was held constant at the saturation temperature. This constraint led to the condition \(\frac{\partial T_l}{\partial z} \approx 0\).

The term \(h_{int} (T_{sv} - T_l)\) in Eq. 3.6 was based on Newton’s law of cooling and represented the heat flux to the liquid phase from the solid-vapor phase. The heat transfer coefficient \(h_{int}\) was calculated from the expression in Eq. 3.7, where \(\alpha\) is the specific surface area of the solid particles. Since the particles under consideration are assumed to be perfectly spherical, \(\alpha = \frac{6}{d_p}\), where \(d_p\) is the mean particle diameter.

Also, \(\beta\) was calculated using a function that defined the fraction of surface area of the solid phase in contact with the liquid phase (Eq. 3.8) where, \(\epsilon_{crit}\) is the volume fraction of liquid after which the liquid does not wet the surface of the solid completely. The value \(\epsilon_{crit} = 0.2672\) was obtained from the geometry of a body centered cubic (BCC) packing structure.

\[h_{int} = \alpha \epsilon_s \beta h_{sv-l}\] (3.7)
\[
\beta = \begin{cases} 
1, & \text{if } \epsilon_l \geq \epsilon_{\text{crit}} \\
-\left(\frac{\epsilon_l}{\epsilon_{\text{crit}}}ight)^2 + 2\left(\frac{\epsilon_l}{\epsilon_{\text{crit}}}ight), & \text{if } \epsilon_l < \epsilon_{\text{crit}}
\end{cases}
\] (3.8)

**Energy balance on the solid-vapor phase**

In the solid-vapor phase, heat is transferred primarily through conduction and heat is lost to the liquid phase by convective transfer as shown in Eq. 3.9. Heat transferred due to diffusion of vapor given by \(D_v c_{p_v} \frac{\partial C_v}{\partial z} \frac{\partial T_{sv}}{\partial z}\) was neglected as it was three orders of magnitude smaller than the dominant terms. Also, the term \(\dot{\Gamma} c_{p_v} (T_{sv} - T_l)\) was neglected as \(h_{\text{int}} \gg \dot{\Gamma} c_{p_v}\). These simplifications reduced model complexity and improved reduced simulation efficiency. The average conductivity of the solid-vapor phase was given by \(\bar{k}_{sv} = \bar{k}_s + \bar{k}_v\).

\[
(C_s c_{p_s} + C_v c_{p_v}) \frac{\partial T_{sv}}{\partial t} = \frac{\partial}{\partial z} \left( \bar{k}_{sv} \frac{\partial T_{sv}}{\partial z} \right) - h_{\text{int}} (T_{sv} - T_l) - \underline{\dot{\Gamma} c_{p_v} (T_{sv} - T_l)} + \underline{D_v c_{p_v} \frac{\partial C_v}{\partial z} \frac{\partial T_{sv}}{\partial z}}
\] (3.9)

**Energy balance on the base layer**

The base layer, which was defined as the bottom of the dish between the cake and the heated plate, transfer heat via convection.

\[
\rho_b c_{p_b} \frac{\partial T_b}{\partial t} = \dot{q}_{\text{in}} - \dot{q}_{\text{out}}
\] (3.10)

\[
\dot{q}_{\text{in}} = h_t (T_f - T_b)
\]

\[
\dot{q}_{\text{out}} = h_b \epsilon_t (t, z = 0) (T_b - T_l(t, z = 0)) + h_b (\epsilon_s(t, z = 0) + \epsilon_v(t, z = 0)) (T_b - T_{sv}(t, z = 0))
\]

Here \(h_t\) is the heat transfer coefficient that accounts for heat flux from the hot fluid to the base layer, and \(h_b\) represents the heat transfer coefficient between the
base layer and the first layer of particles. The first layer of particles is considered to show different properties than the other particles in the cake as discussed elsewhere [14].

**Initial conditions**

The cake was considered to be completely saturated with liquid at $t = 0$. This condition matched the initial state of the cake used in my experiments. The liquid phase temperature $T_l$ and the solid-vapor phase temperature $T_{sv}$ were both obtained from data at $t = 0$ using interpolation (Eq. 3.12). The initial condition for the temperature of the base layer $T_b$ was obtained by extrapolating from temperature data. The interpolation and extrapolation methods are discussed in Section Numerical Methods.

\[
\epsilon_l(t = 0, z) = \epsilon_{\text{void}} \quad (3.11)
\]

\[
T_l(t = 0, z) = T_{sv}(t = 0, z) = \text{Interpolate}(T_{data}) \quad (3.12)
\]

\[
T_b(t = 0) = \text{Extrapolate}(T_{data}) \quad (3.13)
\]

The solid volume fraction was obtained from experimental data using Eq. 3.14, where $m_l$ is the mass of liquid used to saturate the cake and $V_c$ is volume of the cake. The cake volume was obtained from the thickness($L$) and the cross-sectional area ($A_c$) of the cake using Eq. 3.15. The average density of the solid was obtained from Eq. 3.16.

\[
\epsilon_s = 1 - \frac{m_l}{\rho_l V_c} \quad (3.14)
\]

\[
V_c = L \cdot A_c \quad (3.15)
\]

\[
\rho_s = \frac{m_s}{\epsilon_s V_c} \quad (3.16)
\]

\[
\epsilon_{\text{void}} = 1 - \epsilon_s
\]
Boundary conditions

The flux of liquid at the cake boundaries was set equal to 0 (Eq. 3.17). For both the liquid and solid-vapor phases, heat was transferred from the base layer and lost to the oven head space via convection (Eqns. 3.18 & 3.19).

\[-D \frac{\partial C_l}{\partial z} = \begin{cases} 0, \quad z = 0 \\ 0, \quad z = L \end{cases} \tag{3.17}\]

\[-k_l \frac{\partial T_l}{\partial z} = \begin{cases} h_b \epsilon_l (T_b - T_l), \quad z = 0 \\ h_{oven} \epsilon_l (T_l - T_{oven}), \quad z = L \end{cases} \tag{3.18}\]

\[-k_{sv} \frac{\partial T_{sv}}{\partial z} = \begin{cases} h_b \epsilon_{sv} (T_b - T_{sv}), \quad z = 0 \\ h_{oven} \epsilon_{sv} (T_{sv} - T_{oven}), \quad z = L \end{cases} \tag{3.19}\]

3.2.2.3 Governing equations for the oven model

The gas flows into the oven gas phase are the nitrogen purge gas and evaporating solvent from the cake. The oven has one outlet flow to the pump (Figure 3.2). The following assumptions were invoked to derive the oven model,

1. The vapor behaved like an ideal gas so the vapor density could be calculated from the ideal gas equation.
2. The gas phase was well mixed.
3. The gas phase had no heat transferred via conduction or convection. Therefore, changes in enthalpy were only due to gas flow into and out of the control volume.
Mass balances on the oven gas phase

An overall mass balance on the gas phase in the oven yielded,

\[
\frac{dm}{dt} = \dot{m}_{\text{purge}} + \dot{m}_{\text{sol}} - \dot{m}_{\text{out}} \tag{3.20}
\]

The mass balance for component ‘i’ was solved for 4 out of the 5 components in the gas phase. The mass fraction of the 5\(^{\text{th}}\) component (CO\(_2\)) was obtained using Eq. 3.22.

\[
\frac{d(mx_i)}{dt} = \dot{m}_{i,\text{in}} - \dot{m}_{\text{out}}x_i \tag{3.21}
\]

\[
\sum x_i = 1 \tag{3.22}
\]

\[
\dot{m}_{i,\text{in}} = \begin{cases} 
\dot{m}_{\text{purge}}, & i \equiv N_2 \\
\dot{m}_{\text{sol}}, & i \equiv \text{sol} \\
0, & \text{otherwise}
\end{cases}
\]

The unknown term \(\dot{m}_{\text{out}}\) was eliminated by combining Eqns. 3.20 and 3.21,

\[
m\frac{d(x_i)}{dt} = \dot{m}_{i,\text{in}} - (\dot{m}_{\text{purge}} + \dot{m}_{\text{sol}})x_i \tag{3.23}
\]

Energy balance on oven gas phase

An energy balance on the gas phase in the oven yielded,

\[
\frac{d(mh)}{dt} = \dot{m}_{\text{purge}}h_{\text{purge}} - \dot{m}_{\text{out}}h_{\text{out}} + \dot{m}_{\text{sol}}h_{\text{sol}} \tag{3.24}
\]

By substituting Eq. 3.20 into Eq. 3.24, the following equation was obtained,

\[
m c_{p_{\text{avg}}} \frac{dT_{\text{oven}}}{dt} = \dot{m}_{\text{purge}} \left( c_{p_{\text{purge}}} T_{\text{purge}} - c_{p_{\text{avg}}} T_{\text{oven}} \right) \\
+ \dot{m}_{\text{sol}} \left( c_{p_{e}} T_{sv}(t, z = L) - c_{p_{\text{avg}}} T_{\text{oven}} \right) \tag{3.25}
\]
Here $c_{p_{avg}}$ is the average specific heat capacity of the gas phase given by $c_{p_{avg}} = \sum_i c_{p_i} x_i$, $T_{purge}$ was obtained from the flow controller data, and $\dot{m}_{sol}$ was calculated as,

$$\dot{m}_{sol} = \frac{1}{L} \int_0^L \left( \frac{\partial C_l}{\partial t} + \frac{\partial C_v}{\partial t} \right) \, dz \tag{3.26}$$

**Initial conditions**

Initial conditions for the mass fractions were interpolated using data obtained from the mass spectrometer. The mole fractions provided by the mass spectrometer were converted to mass fractions and then interpolation to obtain mass fractions at $t = 0$. The initial condition for $T_{oven}$ was interpolated using the temperature data from the flow controller.

$$x_i(t = 0) = \text{Interpolate } (x_{MS-data}) \tag{3.27}$$

$$T_{oven}(t = 0) = \text{Interpolate } (T_{FC-data}) \tag{3.28}$$

**3.2.2.4 Numerical Methods**

**Model Simulation**

The complete multiphase transport model consisted of a set of partial differential equations in time $t$ and the axial cake coordinate $z$. The model was solved by discretizing the cake spatial domain using the finite volume method with $N$ nodes, such that each node corresponded to an element of thickness $dz$. Therefore, $L = N \cdot dz$ with the cake thickness $L = 2.3 \cdot 10^{-2}$ for all cases studied. Spatial derivatives were approximated using central difference formulas with accuracy of $O(dz)^2$. I found that $N = 23$ nodes ($dz = 10^{-3}$) provided sufficient accuracy of $O(10^{-6})$ given that the error in my MS data was three orders of magnitude larger. Grid dependency tests showed that nearly converged solutions were obtained with 23 nodes, and that
the main impact of further increases in \( N \) was to increase the simulation time. The chosen grid allowed a single simulation to be completed within 30 seconds, which was important to reduce the computational effort for parameter estimation.

The ODEs obtained after spatial discretization of the cake equations were combined with the ODEs from the oven model to generate a large nonlinear ODE system which was integrated forward in time. The ratio of time scales of heat and mass transfer provided a reasonable estimate of the system stiffness. Because this ratio was approximately 10, I used the MATLAB solver \textit{ode23t} specifically designed for moderately stiff problems while avoiding numerical damping. I found that stiff MATLAB solvers were not able to efficiently solve the model because the use of pressure data to calculate the time derivative of liquid temperature introduced high frequency noise into equations.

Initial conditions for temperatures in the cake and the base layer were obtained from interpolation and extrapolation of thermocouple data, respectively. The MATLAB function \textit{interp1} with the \textit{extrap} option was used for this purpose. To avoid numerical problems, a small penalty was added to \( \epsilon_t \) such that \( \epsilon_t (t = 0, z) = \epsilon_{\text{void}} - 10^{-6} \).

**Parameter estimation**

The multiphase transport model contained a number of parameters that could not be directly obtained from the literature and/or were expected to change with particle size and dryer operating conditions. These parameters were estimated from my drying data as explained below. The estimated parameters were: (1) the liquid diffusion coefficient when the cake is saturated \( D_o \); (2) the thermal conductivity of the solid \( k_s \); (3) the heat transfer coefficient between the solid-vapor and liquid phases \( h_{se-l} \); (4) the heat transfer coefficient between the heating fluid to the base layer \( h_t \); (5) the heat transfer coefficient between the base layer and the bottom of cake \( h_b \); and (6) the heat transfer coefficient between the top of cake and the oven headspace.
I assumed that $D_o$, $k_s$, $h_t$ and $h_{oven}$ would vary only with particle size. In a previous study on vacuum drying [4], I showed that solvent profiles were much more strongly affected by particle size than operating temperature and pressure. These results suggested significant differences in the mass transfer rates due to particle size. Because the diffusion coefficient $D_o$ was the only parameter that directly affected mass transfer, $D_o$ was considered to change only with particle size. The thermal conductivity $k_s$ was not expected to vary significantly over the ranges of temperature (see [46]) and pressure (see [35, 36]) considered in this work. I considered $h_t$ to be a system property independent of the particular operating conditions. The boundary condition for heat transfer at the open end of the cake shows that $h_{oven}$ should only vary with particle size. By contrast, both $h_{sv-l}$ and $h_b$ were expected vary with temperature and pressure as well as the particle size due to their roles in capturing the very complex process of heat transfer due to boiling [5, 55].

The six adjustable parameters were estimated from composition and temperature data by minimizing least-squares objective functions penalizing the difference between the measured and predicted values. More specifically, predicted temperatures of the solid-vapor phase were compared to temperature data from the three thermocouples and predicted nitrogen and acetone mass fractions from the oven model were compared to data from the mass spectrometer using the objective functions Eq. 3.29. Here $N$ is the number of data points in time available for comparison. I performed parameter estimation using temperature data alone ($\chi_T$), composition data alone ($\chi_{MS}$) and combined temperature-composition data ($\chi_{MS} + \chi_T$). The spatially discretized model described above was posed as a set of equality constraints in the optimization problem, which was solved in MATLAB with the non-linear least squares optimizer lsqnonlin. Because the optimization problem is non-convex, I used the function Multistart in the global optimization toolbox to generate 15 locally optimal solutions for each case and selected the solution with the lowest objective function value.
\[
\chi_{MS} = \sum_{j=N_2, \text{sol}} \sum_i^N \left( x_{i,j}^{\text{model}} - x_{i,j}^{\text{data}} \right)^2 
\]

\[
\chi_T = \sum_{j=1}^3 \sum_i^N \left( \frac{T_{i,j}^{\text{model}} - T_{i,j}^{\text{data}}}{T_f - T_{sat}} \right)^2 
\]

I used root mean squared (RMS) values defined in Eq. 3.31 for the mass fractions and in Eq. 3.32 for the temperatures as measures of the parameter fitting errors. The relation between RMS and \( \chi \) values is \( \chi = N \cdot RMS^2 \). Because they are based on normalized variables, the RMS values are reasonable measures of the relative percentage errors.

\[
RMS_{MS} = \sqrt{\frac{1}{N} \sum_{j=N_2, \text{sol}} \sum_i^N \left( x_{i,j}^{\text{model}} - x_{i,j}^{\text{data}} \right)^2} 
\]

\[
RMS_T = \sqrt{\frac{1}{N} \sum_{j=1}^3 \sum_i^N \left( \frac{T_{i,j}^{\text{model}} - T_{i,j}^{\text{data}}}{T_f - T_{sat}} \right)^2} 
\]

The initial guess and allowable range of each parameter are shown in Table 3.3. The initial guesses for \( k_s, h_t \) and \( h_{oven} \) were obtained by running the optimizer to match the three temperatures after the cake was dry using data collected for 70-110 \( \mu m \) beads at 40 °C and 50 torr (6.66 kPa). Initial guesses for \( h_{sv-l} \) and \( h_b \) were obtained by fitting the same dataset by trial and error to achieve approximate agreement with the model. The initial value of \( h_b \) was set to be half that of \( h_t \).

Table 3.3: Initial guesses and allowable ranges for all the adjustable model parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial guess</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_s(\frac{W}{mK}) )</td>
<td>0.6</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>( h_t(\frac{W}{m^2K}) )</td>
<td>120</td>
<td>1</td>
<td>200</td>
</tr>
<tr>
<td>( h_{oven}(\frac{W}{m^2K}) )</td>
<td>10</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>( D_0(\frac{m^2}{s}) )</td>
<td>1e-6</td>
<td>5e-8</td>
<td>1e-5</td>
</tr>
<tr>
<td>( h_{sv-l}(\frac{W}{m^2K}) )</td>
<td>0.5</td>
<td>0.01</td>
<td>10</td>
</tr>
<tr>
<td>( h_b(\frac{W}{m^2K}) )</td>
<td>60</td>
<td>1</td>
<td>200</td>
</tr>
</tbody>
</table>
3.3 Results and Discussion

3.3.1 Experimental Results

Figure 3.5 shows temperature data collected at the three points in the cake along with the saturation temperature of acetone at the pressure in the oven. Operating conditions for the experiment were a particle size range of 70-110 µm, a temperature of 40 °C, and a pressure of 50 torr (6.66 kPa). All three temperatures increased during the initial phase, indicated as zone 1 in the figure. I believe that the cake was merely heating during this period with evaporation being negligible, as the mass spectrometer reading indicated no acetate in the vapor headspace. When the bottom temperature reached $T_{sat}$, the acetone reading from the mass spectrometer started to increase rapidly. This point marked the beginning of zone 2, where the acetone at the bottom of the cake began to boil and the bottom temperature began to approximately track $T_{sat}$. At about 750 seconds, the bottom temperature exhibited a sharp increase suggesting that all the liquid had been boiled away and the cake was being heated. This point marked the beginning of zone 3, which continued until the end of the experiment. The other two temperatures exhibited similar behavior, with the end of liquid boiling occurring later. This behavior was consistently observed for all experiments in the range of operating conditions considered.
Figure 3.5: Temperature data from the three thermocouples and $T_{sat}$ calculated from pressure data. Operating conditions were particle size: 70-110 $\mu m$, temperature: 40 °C and pressure: 50 torr (6.66 kPa).

### 3.3.2 Parameter Estimation Results

#### 3.3.2.1 Base Case Conditions

I performed parameter estimation with three different objective functions ($\chi_{MS}$, $\chi_{MS} + \chi_T$, $\chi_T$) at the base case conditions of 40 °C, 50 torr (6.66 kPa) and 70-110 $\mu m$ particle size. The six estimated parameter were $D_o$, $k_s$, $h_{sv-l}$, $h_t$, $h_b$ and $h_{oven}$. In Figure 3.6, each row corresponds to a different objective function, while the two columns show results for head space compositions and cake temperatures. The quality of prediction was accessed according to the RMS value shown for each case. As would be expected, $\chi_{MS}$ produced the most accurate composition predictions, $\chi_T$ produced the most accurate temperature predictions, and $\chi_{MS} + \chi_T$ produced a com-
promise between the compositions and temperature predictions. Considerable errors were present with all three objective functions, demonstrating the complexity of the vacuum drying process and the value of cake temperature measurements in addition to solvent composition measurements for model development and validation.

Table 3.4 contains the parameter estimates generated with the three objective functions. Very similar $D_0$ values were obtained, while $h_{sv-l}$, $h_b$ and $h_t$ agreed with a factor of three or less. Larger differences were observed for $k_s$ and $h_{oven}$, with the $h_{oven}$ value obtained with $\chi_{MS}$ much smaller than the other two values. The objective function $\chi_{MS} + \chi_T$ produced nearly equal values of $h_{oven}$ and $h_t$. This results was surprising since $h_t$, which represents the heat transfer coefficient from the hot fluid through a metal plate to the base layer of particles, would be higher in value than $h_{oven}$, which represents the heat transfer coefficient between the top of cake and the oven headspace. The $k_s$ value obtained with $\chi_{MS}$ was similar to a value (0.15 $\frac{W}{mK}$) reported in literature for glass beads [36, 12], while the $k_s$ values obtained with the other two objective functions were considerably higher. Because the primary goal of this study was to predict the solvent concentration in the cake, all the remaining results used $\chi_{MS}$ as the objective function.

Table 3.4: Estimated parameters obtained using different objective functions. These values correspond to the results shown in Figure 3.6.

<table>
<thead>
<tr>
<th>Optimization type</th>
<th>$k_s$ ($\frac{W}{mK}$)</th>
<th>$h_t$ ($\frac{W}{m^2K}$)</th>
<th>$h_{oven}$ ($\frac{W}{m^2K}$)</th>
<th>$D_0$ ($\frac{m^2}{s}$)</th>
<th>$h_{sv-l}$ ($\frac{W}{m^2K}$)</th>
<th>$h_b$ ($\frac{W}{m^2K}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>0.20</td>
<td>141.47</td>
<td>1.24</td>
<td>2.62E-06</td>
<td>3.34</td>
<td>145.77</td>
</tr>
<tr>
<td>MS &amp; T</td>
<td>0.99</td>
<td>59.47</td>
<td>57.21</td>
<td>2.21E-06</td>
<td>8.92</td>
<td>91.59</td>
</tr>
<tr>
<td>T</td>
<td>1.07</td>
<td>116.97</td>
<td>16.86</td>
<td>2.42E-06</td>
<td>4.13</td>
<td>49.99</td>
</tr>
</tbody>
</table>
Figure 3.6: Comparison of mass spectrometer data and oven headspace composition predictions on the left and temperature data with solid-vapor phase temperature predictions on the right. Objective functions involved composition data only ($\chi_{MS}$), both composition and temperature data ($\chi_{MS}+\chi_{T}$) and temperature data only ($\chi_{T}$). Operating conditions were a particle size range of 70-110 $\mu$m, temperature of 40 $^\circ$C and pressure of 50 torr (6.66 kPa).
3.3.2.2 Pressure and Temperature Variations

Next I performed parameter estimation studies over a range of pressures and temperatures with 70-110 \( \mu m \) glass beads. As explained in the Section 2.2.4, only the heat transfer coefficient between the solid-vapor and liquid phases \( h_{sv-l} \) and the heat transfer coefficient between the base layer and the bottom of cake \( h_b \) were re-estimated since these two parameters were expected to vary with pressure and temperature. The remaining four adjustable parameters were held constant at their base case values obtained with \( \chi_{MS} \) (Table 3.4). Reasonably accurate temperature (Figure 3.7) and pressure (Figure 3.8) predictions were generated despite only two parameters being estimated for each case. The reported RMS values demonstrated that the quality of the model predictions were similar to those obtained for the base case conditions. The model matched the temperature data relatively well for the top most layer \((z = 1.8 \text{ cm})\), but large deviations were observed for the bottom most layer \((z = 0 \text{ cm})\). I believe that this error was attributable to radial heat transfer from the walls of the dish towards the bottom of the dish, which would cause the material at the bottom-corner of the dish to dry before the material at the bottom-center. This behavior cannot be captured by my 1-D spatial model. Therefore, the exact time when the bottom layer completely dried was difficult to predict. Once dry, the bottom layer increased in temperature quickly causing the adjacent layers to heat more rapidly than predicted. Similar behavior was observed with the pressure variations.
Figure 3.7: Comparison of mass spectrometer data and oven headspace composition predictions on the left and temperature data with solid-vapor phase temperature predictions on the right. Operating conditions were a particle size range of 70-110 µm and pressure of 50 torr (6.66 kPa).
Figure 3.8: Comparison of mass spectrometer data and oven headspace composition predictions on the left and temperature data with solid-vapor phase temperature predictions on the right. Operating conditions were a particle size range of 70-110 µm and temperature of 40 °C.

### 3.3.2.3 Other Particle Sizes

I performed parameter estimation studies for two other bead sizes (10-25 and 150-250 µm) at the base case temperature (40 °C) and pressure (50 torr (6.66 kPa)) to further analyze the predictive capability of the drying model. Of the six parameters originally used for estimation, only the heat transfer coefficient between the heating fluid to the base layer \( h_t \) was expected to be independent of particle size. Therefore, \( h_t \)
was fixed at the base case value obtained with $\chi_{MS}$ (Table 3.4) and the remaining five parameters ($D_o$, $k_s$, $h_{av-1}$, $h_t$, $h_b$, $h_{oven}$.) were estimated. The data fits were similar to those generated for the base case condition, with slightly improved fits obtained for the 150-250 $\mu$m beads and slightly less accurate fits obtained for the 10-25 $\mu$m beads according to the computed RMS values (Figure 3.9). The same trend was observed with for the cake temperatures.

![Graph showing mass fraction vs. time for different particle size ranges.](image)

(a) Particle size range is 150-250 $\mu$m. RMS = 0.0391

(b) Particle size range is 10-25 $\mu$m. RMS = 0.0506

(c) Particle size range is 150-250 $\mu$m. RMS = 0.1717

(d) Particle size range is 10-25 $\mu$m. RMS = 0.2769

Figure 3.9: Comparison of mass spectrometer data and oven headspace composition predictions on the left and temperature data with solid-vapor phase temperature predictions on the right. Operating conditions were a temperature of 40 °C and pressure of 50 torr (6.66 kPa).
3.3.2.4 Temperature and Pressure Variations for Other Particle Sizes

Next I investigated the ability of the drying model to predict composition data for small and large bead sizes when the temperature and pressure were varied. For each bead size, the parameters $k_s$, $h_t$, $h_{oven}$ and $D_o$ were fixed at the values obtained at the base case temperature and pressure (Figure 3.9) and $h_{sv-t}$ and $h_b$ were re-estimated because only these two parameters were expected to vary for these tests. For the large beads, the model was able to generate composition predictions that were slightly improved compared to the base case conditions (Figure 3.10). With the exception of low temperature and pressure case, the model also produced slightly improved composition predictions for the small beads (Figure 3.11).
(a) Temperature is 30 °C & pressure is 50 torr (6.66 kPa). RMS = 0.0242

(b) Temperature is 50 °C & pressure is 50 torr (6.66 kPa). RMS = 0.0287

(c) Temperature is 40 °C & pressure is 40 torr (5.33 kPa). RMS = 0.0340

(d) Temperature is 40 °C & pressure is 60 torr (7.99 kPa). RMS = 0.0270

Figure 3.10: Comparison of mass spectrometer data and oven headspace composition predictions for a particle size range of 150-250 µm.
(a) Temperature is 30 °C & pressure is 50 torr (6.66 kPa). RMS = 0.0478

(b) Temperature is 50 °C & pressure is 50 torr (6.66 kPa). RMS = 0.0473

(c) Temperature is 40 °C & pressure is 50 torr (5.33 kPa). RMS = 0.0517

(d) Temperature is 40 °C & pressure is 60 torr (7.99 kPa). RMS = 0.0457

Figure 3.11: Comparison of mass spectrometer data and oven headspace composition predictions for a particle size range of 10-25 µm.

3.3.2.5 Analysis of Parameter Estimation Results

The estimated parameters obtained from all the optimization runs are shown in Table 3.5. The first three rows correspond to glass beads with the particle ranges 150-250 µm, 70-110 µm and 10-25 µm at the base case conditions of 40 °C and 50 torr (6.66 kPa). The heat transfer coefficient $h_t$ was obtained from optimization of 70-110 µm beads at base case conditions and then was held constant for all other cases. A different set of the parameters $k_s$, $h_{oven}$ and $D_o$ were obtained for each bead.
size at base case conditions and then was allowed to vary only with particle size. The thermal conductivity of the solid \( k_s \) and the diffusion coefficient \( D_o \) decreased with decreasing mean particle size. More specifically, \( \log(k_s) \) and \( \log(D_o) \) appeared to vary linearly with \( \log(d_p) \) as shown in Figure 3.12. The heat transfer coefficient between the cake and the oven \( h_{oven} \) exhibited a peak at 70-110 \( \mu m \) and was two orders of magnitude smaller for the 10-25 \( \mu m \) beads than for the other two bead sizes.

Table 3.5: Parameter estimates obtained from all optimization runs. The parameters indicated in red were adjusted for the particular run shown, while the parameters indicated in black were fixed as constants for that run.

<table>
<thead>
<tr>
<th>( d_p ) (( \mu m ))</th>
<th>T (( ^\circ C ))</th>
<th>P (mmHg)</th>
<th>( k_s ) (( W/mK ))</th>
<th>( h_t ) (( W/m^2K ))</th>
<th>( h_{oven} ) (( W/m^2K ))</th>
<th>( D_o ) (( m^2/s ))</th>
<th>( h_{sv-l} ) (( W/m^2K ))</th>
<th>( h_b ) (( W/m^2K ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>150-250</td>
<td>40</td>
<td>50</td>
<td>0.26</td>
<td>141.47</td>
<td>55.07</td>
<td>8.90E-06</td>
<td>8.95</td>
<td>159.98</td>
</tr>
<tr>
<td>70-110</td>
<td>40</td>
<td>50</td>
<td>0.25</td>
<td>141.47</td>
<td>98.34</td>
<td>6.64E-06</td>
<td>8.43</td>
<td>108.45</td>
</tr>
<tr>
<td>10-25</td>
<td>40</td>
<td>50</td>
<td>0.20</td>
<td>141.47</td>
<td>1.24</td>
<td>2.62E-06</td>
<td>3.34</td>
<td>145.77</td>
</tr>
<tr>
<td>150-250</td>
<td>30</td>
<td>50</td>
<td>0.26</td>
<td>141.47</td>
<td>55.07</td>
<td>8.90E-06</td>
<td>1.28</td>
<td>175.19</td>
</tr>
<tr>
<td>150-250</td>
<td>50</td>
<td>50</td>
<td>0.26</td>
<td>141.47</td>
<td>55.07</td>
<td>8.90E-06</td>
<td>1.72</td>
<td>182.57</td>
</tr>
<tr>
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<td>40</td>
<td>0.26</td>
<td>141.47</td>
<td>55.07</td>
<td>8.90E-06</td>
<td>8.97</td>
<td>160.74</td>
</tr>
<tr>
<td>150-250</td>
<td>40</td>
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<td>0.26</td>
<td>141.47</td>
<td>55.07</td>
<td>8.90E-06</td>
<td>4.47</td>
<td>189.63</td>
</tr>
<tr>
<td>70-110</td>
<td>30</td>
<td>50</td>
<td>0.25</td>
<td>141.47</td>
<td>98.34</td>
<td>6.64E-06</td>
<td>2.99</td>
<td>173.16</td>
</tr>
<tr>
<td>70-110</td>
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<td>0.25</td>
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<td>98.34</td>
<td>6.64E-06</td>
<td>8.86</td>
<td>185.12</td>
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<tr>
<td>70-110</td>
<td>40</td>
<td>40</td>
<td>0.25</td>
<td>141.47</td>
<td>98.34</td>
<td>6.64E-06</td>
<td>2.91</td>
<td>178.25</td>
</tr>
<tr>
<td>70-110</td>
<td>40</td>
<td>60</td>
<td>0.25</td>
<td>141.47</td>
<td>98.34</td>
<td>6.64E-06</td>
<td>2.56</td>
<td>190.44</td>
</tr>
<tr>
<td>10-25</td>
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<td>141.47</td>
<td>1.24</td>
<td>2.62E-06</td>
<td>9.76</td>
<td>198.45</td>
</tr>
<tr>
<td>10-25</td>
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<td>50</td>
<td>0.20</td>
<td>141.47</td>
<td>1.24</td>
<td>2.62E-06</td>
<td>5.91</td>
<td>193.91</td>
</tr>
<tr>
<td>10-25</td>
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<td>141.47</td>
<td>1.24</td>
<td>2.62E-06</td>
<td>8.79</td>
<td>189.72</td>
</tr>
<tr>
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<td>141.47</td>
<td>1.24</td>
<td>2.62E-06</td>
<td>0.22</td>
<td>190.69</td>
</tr>
</tbody>
</table>

The parameters \( h_{sv-l} \) and \( h_b \) were allowed to vary with particle size, temperature and pressure. Figure 3.13 shows how the estimates of \( h_{sv-l} \) varied with particle size at different temperatures and pressures. At 30 \( ^\circ C \), \( h_{sv-l} \) increased with decreasing particle size (Figure 3.13a). However, the opposite trend was observed at 40 \( ^\circ C \) and no clear trend was evident at 50 \( ^\circ C \). At 50 and 60 torr (6.66 and 7.99 kPa), \( h_{sv-l} \) decreased with decreasing particle size (Figure 3.13b). However, no trend was observed at 40 torr (5.33 kPa). To further analyze the dependence of \( h_{sv-l} \) on oper-
Figure 3.12: Variation of log($k_s$) and log($D_o$) with log($d_p$), where $d_p$ is the volume weighted mean diameter of the glass beads.

Figure 3.13: Variations in $h_{sv-l}$ ($\frac{W}{m^2K}$) estimates as a function of temperature and pressure for different particle sizes.

(a) Parameter estimates for $h_{sv-l}$ at 50 torr (6.66 kPa)

(b) Parameter estimates for $h_{sv-l}$ at 40 °C

ating conditions, I prepared plots showing constant $h_{sv-l}$ contours as a function of the temperature and pressure for each bead size (Figure 3.15a). These plots clearly illustrate that $h_{sv-l}$ exhibited very different dependencies for the three bead sizes.
A possible explanation for the complex dependence of $h_{sv-l}$ on operating conditions is that the heat flux for boiling changes with temperature difference [5, p. 767]. When plotted as a function of the temperature difference driving force, the heat flux exhibits a local maxima at the beginning of transition boiling and a local minima at the end of transition boiling (Figure 3.16).

Figure 3.14 shows how the estimate of $h_b$ varied with particle size at different temperatures and pressures. The estimate exhibited relatively small variations with respect to both temperature and pressure for 150-250 μm beads ($\approx 30 \frac{W}{m^2K}$). Larger variations were observed for the 70-110 μm ($\approx 82 \frac{W}{m^2K}$) and 10-25 μm ($\approx 53 \frac{W}{m^2K}$) beads. Contour plots of $h_b$ versus temperature and pressure showed no obvious trends with respect to temperature (Figure 3.15a). While $h_b$ increased with pressure for the 150-250 μm beads, $h_b$ exhibited a minimum for both 70-110 μm and 10-25 μm beads (Figure 3.15b). I attributed the lack of clear trends in $h_b$ to the complex phenomenon, which includes the effects of heat transfer from the base layer to the first layer of particles and liquid boiling at the interface, captured by this parameter. Further studies beyond the scope of this paper would be needed to better understand these mechanisms.
(a) Parameter contours for $h_{sv-l}$

(b) Parameter contours for $h_b$

Figure 3.15: Parameter contours for $h_{sv-l} \left( \frac{W}{m^2K} \right)$ and $h_b \left( \frac{W}{m^2K} \right)$ as a function of temperature and pressure for different particle sizes.
Figure 3.16: A typical boiling curve showing the variation of the heat flux as a function of the wall superheat (adaptation of figure from [32]).

3.4 Conclusions

I constructed a highly controllable vacuum drying system with the capability for measuring both temperatures inside the cake and gas compositions in the oven headspace for the development of multiphase transport drying models. Experiments with glass beads conducted over a range of particle sizes, temperatures and pressures suggested that boiling (as opposed to evaporation) was the dominant drying mechanism. Once the local cake temperature reached the saturation temperature $T_{sat}$, the liquid at that location began to boil and the local temperature approximately tracked $T_{sat}$. Although this phenomenon is evident in another experimental study ([20]), I believe that my study provides the first explicit characterization of this boiling behavior.

I developed a multiphase transport model which captured the physics of the drying process more faithfully than existing models under conditions where boiling was the predominant mode of solvent loss. The model was based on several sim-
plifying assumptions, including that evaporation was negligible and that the vapor and solid phases could be lumped into a single phase. To investigate the predictive capabilities of the model, parameter estimation studies were performed using a dataset consisting of headspace composition measurements collected for three bead sizes (10, 100, 200 micron volume averaged means), three temperatures (30, 40, 50 °C) and three pressures (40, 50, 60 torr or 5.33, 6.66 and 7.99 kPa). The parameters estimated consisted of the liquid diffusion coefficient, the thermal conductivity of the solid and four heat transfer coefficients. First I established a base set of parameter estimates at one operating condition. Then according to their assumed dependencies, certain parameters were re-estimated as the bead size, temperature of pressure were varied.

I found that the parameterized model was capable of producing composition time profile estimates with 2.5–4% error according to calculated RMS values. Conversely, temperature measurements within the cake could only be reproduced in a qualitative manner, suggesting that the model lacked some process physics. The thermal conductivity and the diffusion coefficient were shown to have a linear dependence on mean particle size when variable were expressed in logarithmic coordinates. Other parameter trends with particle size were difficult to discern and I contribute this to the complex nature of boiling [5, p. 767]. A natural extension of my model includes the development of a full three phase description and the incorporation of evaporative drying mechanisms.
CHAPTER 4
THE EFFECT OF CONTINUOUS AGITATION AND
SOLVENT CONCENTRATION ON API ATTRITION
DURING VACUUM AGITATED FILTER DRYING

4.1 Introduction

This chapter contains the study of breakage of active pharmaceutical ingredient (API) during agitated vacuum drying demonstrating the effects of agitation speed (RPM) and solvent concentration (dry basis). The data from the experiments indicated attrition dominated the dynamics for particle size change. A simple model that can predict the evolution of particle size and could be use for scaling up to plant scale operations was chosen. Hence, a population balance model with a power law breakage function and generalized Hill-Ng daughter distribution, was chosen. The API used in this study is currently being tested at Sunovion Pharmaceuticals Inc. I use the experiment data along with population balance models to estimate parameters which give insight into the dynamics of attrition of the API.
4.2 Materials and Methods

4.2.1 Experiments

4.2.1.1 Materials

The API used in this work is the proprietary right of Sunovion Pharmaceuticals Inc. hence, limiting the details about the material provided in this paper. The crystals have an aspect ratio (length:width) of 1:2. The particle size distribution of the API is shown in Figure 4.1. The $d_{10}$, $d_{50}$ and $d_{90}$ values are 65, 105 and 160 µm, respectively. Here, $d_{50}$ refers to the particle diameter at which the cumulative volume density function has a value of 50%. The analogous definition hold for $d_{10}$ and $d_{90}$. The solvent used in all cases for the study is HPLC Grade Isoprpanol.

![Figure 4.1: Particle size distribution and Cumulative distribution of API](image-url)
4.2.1.2 Apparatus

The drying experiments were performed in a 1L Agitated Filter Dryer (AFD) from ProCepT (Figure 1.3). The AFD is equipped with a jacketed cylindrical vessel of internal diameter 8 cm. The cylinder has a filter cloth at the bottom which is held in place by a jacketed cup with four clamps. The cup has an opening in the center for filtration. The complete setup is clamped to the upper part of the device that has 4 ports, an S-type impeller in the center and the motor to control the impeller. The impeller can rotate clockwise and anti-clockwise up to 100 RPM. In addition, it can traverse vertically with the bottom of the impeller at a distance of 5 mm to 120 mm from the filter cloth.

The temperature of the fluid in the AFD jacket was regulated using a Huber Ministat 125 (Cary, NC) with an accuracy of ± 0.1 °C. Nitrogen (purity 99.998 %) was used as the carrier gas at a volumetric flow rate of 0.5 L min⁻¹ (2.9 · 10⁻⁴ m³ s⁻¹). The nitrogen flow rate was regulated by a Cole Parmer Model 32907-69 flow controller (Vernon Hills, IL) with an accuracy of ± 0.1 %. Gas in the AFD headspace consisting of evaporated solvents, nitrogen, and residual oxygen and carbon dioxide was continuously removed to maintain the oven pressure at the setpoint value. The exit gas flow was passed through a condenser and the condensate was collected in a round bottom flask. The weight of condensate was measured using a weighing scale from which data was collected continuously. Data from the flow controller and weighing scale were logged using PuTTY (open source software under the MIT license). The oven pressure was regulated with a BUCHI Model V-850 pressure controller (New Castle, DE) that manipulated a control valve on the exit gas stream. The pressure controller operated as an on-off type controller with a specified tolerance of 1 Torr. Pressure data was logged using Distillation Record software provided by BUCHI. Gas exiting the top of the oven through a tube wrapped in heat tape to avoid condensa-
tion of solvents was passed to an Extrel CMS Model Max LG 300 mass spectrometer (MS, Pittsburgh, PA) for composition analysis. The MS was capable of achieving an accuracy of 100 ppb ($10^{-7}$ mole fraction) in the absence of interference between the components. Due to the presence of some interference, an accuracy of $10^{-5}$ was attainable after calibration. The value of accuracy was attained by measuring mole fractions of gases from a mixture of which the standard was known. Mole fraction measurements were generated every 3-4 seconds and processed using Questor5 software provided by Extrel. A schematic of the complete setup is in Figure 4.2.

![Figure 4.2: Laboratory-scale agitated vacuum filter dryer connected to a portable mass spectrometer for real-time analysis of drying performance.](image)

### 4.2.1.3 Procedure

The mass spectrometer, pump, flow controller, pressure controller (30 mmHg (3.999 kPa)), weighing scale, heater (25 °C (298.15 K)) and chiller (−5 °C (268.15 K)) were turned on and data recording was initiated. The jacketed cylinder was lowered and filled with the solid material. Measured amount of solvent was then added to the material. The cylinder was raised and clamped in place. The line to the mass
spectrometer was clamped to one of the ports on the AFD. The impeller was lowered into the material until it was 5 mm above the filter cloth and was set to rotate at 25 RPM in clock-wise direction for 2 minutes. A sample was taken using a cup sampler and sealed tight in a vial for loss on drying (LOD) and particle size measurements. The pressure reduction was commenced by opening the exit gas control valve using the pressure controller. The pressure was brought down to 30 mmHg (3.999 kPa). It must be noted that there was no mixing during this period. The purpose of this step was to bring the solvent content down to a point where the pump was capable of lowering the pressure in the vessel to 30 mmHg (3.999 kPa). When the pressure controller read 30 mmHg (3.999 kPa), drying was stopped by venting the AFD with air and a sample was taken. This material is considered as the starting material ($t = 0$) for following set of experiments.

Drying was commenced again and the pressure was brought down to 30 mmHg (3.999 kPa). At this point, mixing was started at a fixed RPM in the clock-wise direction. The material was mixed for a predetermined amount of time. Following this mixing was stopped and the AFD pressure was brought back to atmospheric. A sample was collected for measurements. All the steps from bringing the pressure down to taking the sample comprise of one cycle. It must be noted here that for each cycle, time of mixing alone is considered experiment time. The time in between steps and otherwise is not included. Samples were taken after 0, 5, 10, 15, 20, 30, 40, 50, 70 and 90 minutes of mixing. For LOD measurements, the vial was dried overnight. The weight before and after drying were used to calculate the solvent concentration on dry basis. The volume based Particle Size Distribution (PSD) of the dried samples were measured with a HORIBA LA-920 static laser scattering analyzer (Albany, NY). RPMs of 25, 55 and 85 were used for the experiments. The bounds for RPM were set by matching the Froude number (25 RPM) and tip speed (85 RPM) with the pilot plant.
4.2.2 Population Balance Model

4.2.2.1 Information Flow Diagram

Figure 4.3 shows the flow of information as the model was executed. The main components were the population balance model (PBM) and objective function blocks. Initial parameters, initial PSD, the daughter particle distribution function and breakage rate function were provided to the parameter estimator. Inputs to the PBM were passed in from the parameter estimator. The PBM evaluated the particle size distributions at time steps corresponding to available data for comparison. This output was passed to the objective function. The objective function block estimates the error by comparing the output and data. The error is calculated based on a specified least-squares objective function. Updated values of selected model parameters for future simulations were generated by minimizing the objective function.
4.2.2.2 Governing equations for PBM

The purpose of a PBM is to evaluate the volume based particle size distribution \( n \), the dependent variable, with time \( t \) and particle volume \( v \) as independent variables given the agitated drying conditions. In this analysis, the material is considered to be uniformly well-mixed drying as the agitation is continuous. Hence, space is not considered as an independent variable. I observed that the particle size change showed a strong correlation to change in solvent concentration for experiments at 25, 55 and 85 RPM. For example, at 85 RPM \( d_{50} \) reduced from approximately 105\( \mu m \) to 88\( \mu m \) as the solvent concentration on dry basis reduced from 31\% to 21\%, giving a rate of 1.7 \( \frac{\mu m}{\%} \). However, the rate was only 0.5 \( \frac{\mu m}{\%} \) in the same experiment when solvent concentration reduced from 21\% to 8\%. In addition to this, when completely dry API was agitated at 85 RPM no breakage was seen for 140 min of mixing. These results are discussed in further detail later in this work. This observation introduced the third independent variable, solvent concentration on a dry basis \( (S) \).

PBM has terms that account for attrition and agglomeration. However, the experimental work suggests that attrition dominated for the majority of time. It was observed that \( d_{50} \) dropped from approximately 105\( \mu m \) to 80\( \mu m \) in the first 30 min. Similar, behavior was seen for \( d_{10} \) and \( d_{90} \). These results are discussed further in the Section 4.3.1. Hence, I included birth and death terms for attrition alone. From Ramakrishna’s work [37] the PBM for attrition only for number based particle size distribution would be that shown in eq 4.1. Here, \( v \) is the volume of a particle, \( \tilde{n} (v, t) \) is the number density function at volume \( v \) and time \( t \), \( \beta (v, v') \) is the breakage distribution function that gives the probability of particle of size \( v \) forming on breakage of particle of size \( v' \), and \( g (v) \) is the breakage rate of particles of volume \( v \).

\[
\frac{\partial \tilde{n} (v, t)}{\partial t} = -g (v) \tilde{n} (v, t) + \int_{v}^{\infty} \beta (v, v') g (v') \tilde{n} (v', t) \, dv'
\]  

(4.1)
As mentioned above, I was interested in the volume based distribution. The relation between number based distribution $\tilde{n}$ and volume based distribution $n$ is given by eq 4.2 where $V_{tot}$ is the total volume of particles. The same approach was used in [23].

$$n = \frac{\tilde{n} v}{V_{tot}}$$ \hspace{1cm} (4.2)

Using the relation in eq 4.2 and modifying the breakage rate $g$ to account for its correlation with LOD, eq 4.1 would transform to eq 4.3

$$\frac{\partial n(v,S,t)}{\partial t} = -g(v,S)n(v,S,t) + v \int_{v}^{\infty} \beta(v,v') g(v',S) n(v',S,t) dv'$$ \hspace{1cm} (4.3)

It must be noted at this point that in reality $S$ is a function of $t$. However, in this model it is considered as an independent variable and the data used to provide $S$ as an input to the model. A more comprehensive approach would be to have a transport model for vacuum drying coupled with the PBM to solve for $S$ and $n$ simultaneously. This is not the goal of this work. The interest is more in using a simplified model to estimate parameters that relate to the dynamics of particle change. The approach of using a coupled model is planned for future work.

The distribution function $\beta(v,v')$ used in this work is the generalized Hill-Ng distribution proposed in [3]. The function is shown in eq 4.4 where $p$ is the number of daughter particles that form on breakage of a single particle, $B(q,r)$ is the beta function, and $q$ is an adjustable parameter. By changing the values of $p$ and $q$, a wide variety of distribution functions can be obtained. In this study, I assumed breakage to be uniform setting $q = 1$ and attrition of a particle leading to two particles by setting $p = 2$. For $p=2$, the distribution functions are plotted in Figure 4.4.
In this work I adopted an empirical expression of the power law form for the breakage rate as shown in eq 4.5. This form of empirical breakage rate is used in many studies with solid-liquid interactions as mentioned and used in [24, p. 3341].

\[ g(v) = Av^c \] (4.5)

As mentioned above, the dependence of breakage rate on LOD is accounted for by making the amplitude a function of \( S \). The breakage rate eq 4.5 is modified to the form in eq 4.6. \( \tilde{v} \) is the normalized volume \( \left( \frac{v}{v_{\text{max}}} \right) \), normalized using the volume corresponding to maximum diameter \( (v_{\text{max}}) \) in the grid used to solve the model numerically. This grid is discussed in detail later in this work. This modification to the breakage rate was done to simplifies the parameter estimation discussed later in this work, by allowing the magnitude of \( c \) and \( A \) to be reasonably close to each other subsequently, improving the speed of code for estimation. \( c \) is considered to be a

\[
\beta(v, v') = \frac{p}{B(q, r)} \left( \frac{v}{v'} \right)^{q-1} \left( 1 - \frac{v}{v'} \right)^{r-1}
\] (4.4)

\[ r = q(p - 1) \]
representative of a material property. Hence, it does not vary with $t$, $v$ or $S$.

$$g(v, S) = A(S) \bar{v}^c$$  \hspace{1cm} (4.6)

Here, it must be noted that, the unit of $A$ is $s^{-1}$ and $c$ is dimensionless.

### 4.2.2.3 Numerical Methods

#### Model Simulation

The population balance equation in eq 4.3 is described for a continuous particle state space $v$. However, a numerical solution for the integro-differential equation needs a discrete grid for particle size. For this, a grid for particle diameter with 75 bins logarithmically increasing from 0.022$\mu$m to 550$\mu$m was chosen. 550$\mu$m was used as the maximum value on the grid because no PSD from data had a non-zero value beyond that. As mentioned above, I was modeling attrition alone making the addition of higher particle size in the grid unnecessary. The $j^{th}$ bin corresponds to a particle with diameter $d_j$ and volume $v_j$. The model is converted to the discrete form using the method mentioned in [17]. The resulting equation is shown in eq 4.7.

$$\frac{dN_j(S,t)}{dt} = \sum_{k=j}^{75} \gamma_{j,k} g_k(S) N_k(S,t) - g_j(S) N_j(S,t)$$  \hspace{1cm} (4.7)

Here, $N_j = \int_{v_j-1/2}^{v_j+1/2} n(v, S, t) \, dv$. $\gamma_{j,k}$ is obtained by evaluating the integral part of the population balance equation using a fixed pivot method. The integrals were evaluated using a 120 point gauss-quadrature.

The simplified equations (eq 4.7) obtained after the integrals were evaluated consisted of ODEs in time, which were solved using ode15s in MATLAB. The initial condition for the volume distribution was obtained from PSD data at $t = 0$. 

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Parameter estimation

Shown in Figure 4.5 are the PSDs at $t = 0$, 5, 10, 15, 20 and 30 min for the experiment at 85 RPM. The time grid will be referred to in terms of $t_i$ going further in this work. For example, $t_0 = 0$ min and $t_2 = 10$ min. The data indicates breakage and as discussed above the breakage rate changes with time and therefore solvent concentration. More results from experiments reinforcing the statement are discussed in detail further in this work. The breakage rates $g_{i,j}$ between time steps $t_{i-1}$ and $t_i$ and at particle volume $v_j$ take the form shown in eq 4.8.

$$ g_{i,j} = A_i \tilde{v}_j^c $$

(4.8)

The value of $A$ varies for each step as it changes with the value of $S$. This is represented by $A_i$ corresponding to time $t_i$. However, the value of $c$ remains constant for all the steps $a$ it represents a material property.

![Figure 4.5: Particle size distribution evolution with time from an experiment at 85 RPM](image)

lsqnonlin along with Multistart in MATLAB was used for parameter estimation. The Multistart was set to run the estimation 50 times and the best results was picked using the value of the objective function. The choice of 50 was arbitrary.
However, of the 50 runs, 17 of them converged to the same minimum where the solver returned a flag equal to 1 indicating that the function converged to a solution. These were considered as the acceptable results which are discussed later in this work. The others were stopped because the solver exited with a flag of 2 or 3 implying that the solver stopped because the tolerance was reached. The tolerance was set very aggressively to $10^{-18}$. In each iteration of estimation, the model was simulated sequentially from $t_i$ to $t_{i+1}$ with $i$ looping from 1 to 5. For each of the 5 cases, the output PSD was compared to data using the objective function given by eq 4.9. $N_{i,j}$ is the value of the PSD corresponding to the particle volume $v_j$ at time $t_i$. The final objective value is given by

$$\Omega_i = \sum_j \left( \frac{N_{i,j}^{data} - N_{i,j}^{model}}{100 - N_{i,j}^{data}} \right)^2$$

(4.9)

The parameters to be estimated are $A_i$ and $c$. The initial guesses for all parameters were obtained by fitting the first dataset by trial and error to achieve approximate agreement with the model. The lower bound for all the parameters is set to 0. The upper bound for the parameters is set to be an order of magnitude higher than the initial guess. As discussed in the results section, the estimated values are not meeting the upper bound leading to conclude that the upper bounds are acceptable. The initial guess and allowable range of each parameter are shown in Table 4.1.

Table 4.1: Initial guesses and allowable ranges for all the adjustable model parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial guess</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_i$ ($s^{-1}$)</td>
<td>$10^{-3}$</td>
<td>0</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>$c$ ($-$)</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>
4.3 Results and Discussion

4.3.1 Experimental Results

Figure 4.6 shows the PSD of dry API at $t = 0, 20, 80$ and $140$ min in a drying experiment with continuous agitation at $85$ RPM. From this it is very evident that there is no breakage when API is dry. This observation emphasizes that the breakage rate $g \to 0$ as the solvent concentration goes to zero.

![Figure 4.6: PSD of dry API at 85 RPM measured at $t = 0, 20, 80$ and $140$ min.](image)

Figure 4.6: PSD of dry API at 85 RPM measured at $t = 0, 20, 80$ and $140$ min.

![Figure 4.7: LOD vs Time at 25, 55 and 85 RPM.](image)

Figure 4.7: LOD vs Time at 25, 55 and 85 RPM.
Figure 4.7 shows solvent concentration \((S)\) vs time at different RPM. As shown in Figure 4.7 the curve corresponding to 85 RPM has error bars. This is attributed to the fact that 3 identical experiments were conducted at 85 RPM and the curve represents the mean with twice the standard deviation as the error range. The same is true for Figures 4.8, 4.9, 4.10 and 4.11. The data in Figure 4.7 shows that drying dynamics are very similar both qualitatively and quantitatively for 25, 55 and 85 RPM. This leads us to conclude that for the range of RPM used there is no significant effect on drying performance as far as solvent concentration is concerned. It must be noted here that weak the dependence of solvent concentration on RPM does not imply no effect of mixing on drying. For example, in preliminary experiments with glass beads \((150-250 \ \mu m)\) with the identical setup, drying was 30% faster when the material was mixed at 25 RPM than when it was not mixed at all. This effect of mixing reducing drying time has also been reported in [27].

Figures 4.8, 4.9 and 4.10 show the change in \(d_{10}\), \(d_{50}\) and \(d_{90}\) for experiments with different RPM. It is clear that in all cases there is attrition until the \(S\) is between 5 and 10% followed by some agglomeration and further continued by attrition.

![Figure 4.8: d10 vs Time at 25, 55, and 85 RPM](image)

Figure 4.11 shows how \(d_{50}\) varies with LOD at different RPM. As seen from previous plots, the results at all RPM are very close to one another. \(d_{50}\) at 25 RPM changes lesser than at higher RPM. However, if multiple experiments were done at
25 RPM and the error considered, the two curves would be even less distinct and the trend even weaker. The dynamics of particle change show weak dependence on RPM and are not suitable for modeling purposes. On the contrary, the variation in $d_{50}$ with $S$ is strong as mentioned above. There is significant attrition ($\approx 35 \mu m$) as the LOD reduced from $\approx 30$ to $\approx 8 \%$. This was not the case when only dry API was used as shown in Figure 4.6. This variation in particle size with change in LOD levels is the primary reason for considering LOD ($S$) as a key parameter.

As it is observed that RPM does not have a substantial effect on particle size change, only the case of 85 RPM was used for parameter estimation. As attrition is the only aspect being modeled, the PSDs corresponding to $t = 0, 5, 10, 15, 20$ and $30$ min were used for parameter estimation. The mentioned time points are when all
Figure 4.11: d50 vs LOD at 25, 55 and 85 RPM

$d_{10}$, $d_{50}$ and $d_{90}$ reduced with time at 85 RPM indicating attrition.

4.3.2 Parameter Estimation Results

Table 4.2 shows the results from the parameter estimation. In all cases the RMS (Root Mean Square) error is < 1.5%. As seen in the table, values of $A$ vary with time. However, by design the value of $c$ remains the same for all time steps. It is interesting to note that the value of $c$ is 0.3481, which is very close to $1/3$. This shows that the breakage rate $g$ is directly proportional to the diameter of the particles.

<table>
<thead>
<tr>
<th>$t$ (min)</th>
<th>$S$ (%)</th>
<th>$A$ (s$^{-1}$)</th>
<th>RMSerror</th>
<th>$c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28.61</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>23.59</td>
<td>7.2943e-03</td>
<td>1.0283e-02</td>
<td>0.3481</td>
</tr>
<tr>
<td>10</td>
<td>21.24</td>
<td>4.6820e-03</td>
<td>3.8537e-03</td>
<td>&quot;</td>
</tr>
<tr>
<td>15</td>
<td>16.55</td>
<td>1.9430e-03</td>
<td>5.4409e-03</td>
<td>&quot;</td>
</tr>
<tr>
<td>20</td>
<td>10.95</td>
<td>3.1185e-03</td>
<td>4.6736e-03</td>
<td>&quot;</td>
</tr>
<tr>
<td>30</td>
<td>6.26</td>
<td>1.4700e-03</td>
<td>4.1575e-03</td>
<td>&quot;</td>
</tr>
</tbody>
</table>
Figures 4.12, shows the plot of $A$ vs $S$. The trend shows that the magnitude of breakage rate reduces with LOD at an average. However, $A$ increases from 15 min to 20 min and reduces from 20 to 30 min. Due a lack of fundamental breakage mechanism for the API an empirical relation between $A$ and $S$ was derived. For this, the lowest order polynomial that could capture the behavior of $A$ vs $S$, a cubic, was used. It was necessary that the fit abide by the assumption that $g \rightarrow 0$ as $S \rightarrow 0$. This was considered a valid assumption based on the fact that no breakage was observed with dry API. Hence, the fit does not have a constant term for the polynomial. This gives $A(S) = a_3S^3 + a_2S^2 + a_1S$. The cubic fit gives an r-squared value of 0.9203. The value of the coefficients are $a_3 = 2.412 \times 10^{-6}$, $a_2 = -7.463 \times 10^{-5}$ and $a_1 = 7.213 \times 10^{-4}$.
The breakage rate function at different time steps are shown in figure 4.13.

Figure 4.14 show the evolution of PSDs with time from data and model. The results were split into two plots to increase readability. A quick visual inspection of the plots indicates very good fits which is supported quantitatively by the low values of RMS error mentioned above in Table 4.2.

(a) Comparing data and model using evolution of PSD with time for $t = 5$ min, 15 min and 30 min

(b) Comparing data and model using evolution of PSD with time for $t = 10$ min and 20 min

Figure 4.14: Comparing data and model PSDs using the parameter values from the estimation.
4.4 Conclusions

I used an lab filter dryer to observe dynamics of particle size change during continuous agitated drying. The results from experiments conducted at agitation speeds of 25 RPM, 55 RPM and 85 RPM at time intervals of \( t = 0, 5, 10, 15, 20 \) and 30 min showed that the breakage had very weak dependence on RPM. On the contrary \( d_{10}, d_{50} \) and \( d_{90} \) showed strong dependence on solvent concentration, with no breakage observed for mixing of dry active pharmaceutical ingredient (API). All three particle size distribution (PSD) measures reduced with solvent concentration (dry basis) as it dropped from 30% to 5%.

I used a population balance approach to model attrition of the API. The model was based on several simplifying assumptions, including perfect mixing in the AFD leading to exclusion of space as coordinates. Time, particle volume and solvent concentration were considered independent variables. Solvent concentration was included as an independent variable in the model because the data suggested a strong correlation between solvent concentration and particle size. It was provided as an input to the model using data. An empirical power law model was used for the breakage kernel. The breakage kernel included an amplitude depending on solvent concentration and normalized volume raised to some power. A generalized Hill-Ng distribution was used for the daughter particle distribution function. The distribution was assumed to be uniform and two daughter particles were expected to be formed on breakage. To investigate the predictive capabilities of the model, parameter estimation was performed using a dataset from experiment conducted at 85 RPM.

I found that the parameterized model was capable of producing PSD profile estimates with \(< 1.5\%\) error according to calculated RMS error values for the region dominated by attrition. This region spanned the first 30 min of the experiment at 85 RPM. The estimated values showed that the breakage rate reduced with time on
average with a small increase at 20 min (10.95 %) before it dropped again at 30 min (6.26 %). An empirical approach was used to relate the amplitude of breakage rate $A$ and solvent concentration $S$. The lowest order polynomial that could capture the behavior of $S$ and tend to zero as $S$ tends to zero was a cubic polynomial. The power to which normalized volume was raised, $c$, is estimated to be equal to 0.3481. This indicated that the breakage rate was directly proportional to the particle diameter. Overall the model fit the attrition region well. However, the fundamental breakage mechanism needs to be explored. In addition, the small region of agglomeration needs further investigation.
5.1 Summary

I have presented a novel Quality-by-Design (QbD) method for determining the end point of drying for pharmaceutical dryers based on on-line mass spectroscopy. The drying end point was determined algorithmically as the time at which the gas phase solvent concentration measurement of the least volatile component converged to a predicted value computed from a solvent mass balance on the oven assuming zero flow rate from the drying cake. The proposed method offers several key advantages including the ability to detect when the cake is dry from vapor phase measurements, applicability to multiple solvents, and simple off-line and real-time implementation. On the other hand, the method only predicts when drying is complete and does not generate predictions of solvent concentrations in the cake with time. Although not observed in my experiments, it is possible that low solvent concentrations could be established in the cake for an extended period and the method would lead to excessive drying.

To demonstrate application of the QbD tool, drying experiments were performed with a custom built, laboratory-scale vacuum dryer over a range of temperatures and pressures using glass beads with three different particle sizes as the solid phase. Application of the method to an API with methanol-MTBE solvents produced a substantially reduced drying rate compared to comparably sized glass beads,
most likely due to the API bimodal particle size distribution and hydrogen bonding with the solvent. The initial studies reported here suggest that the proposed method represents a powerful QbD approach for pharmaceutical drying processes.

I constructed a highly controllable vacuum drying system with the capability for measuring both temperatures inside the cake and gas compositions in the oven headspace for the development of multiphase transport drying models. Experiments with glass beads conducted over a range of particle sizes, temperatures and pressures suggested that boiling (as opposed to evaporation) was the dominant drying mechanism. Once the local cake temperature reached the saturation temperature $T_{\text{sat}}$, the liquid at that location began to boil and the local temperature approximately tracked $T_{\text{sat}}$.

I developed a multiphase transport model which captured the physics of the drying process more faithfully than existing models under conditions where boiling was the predominant mode of solvent loss. The model was based on several simplifying assumptions, including that evaporation was negligible and that the vapor and solid phases could be lumped into a single phase. To investigate the predictive capabilities of the model, parameter estimation studies were performed. The parameters estimated consisted of the liquid diffusion coefficient, the thermal conductivity of the solid and four heat transfer coefficients. I found that the parameterized model was capable of producing composition time profile estimates with 2.5–4% error according to calculated RMS values. Conversely, temperature measurements within the cake could only be reproduced in a qualitative manner, suggesting that the model lacked some process physics.

I used an lab filter dryer to observe dynamics of particle size change during continuous agitated drying. The results from experiments showed strong dependence of attrition on solvent concentration and weak dependence on agitation speeds. I used a population balance approach to model attrition of the API. The model was
based on several simplifying assumptions, including perfect mixing in the AFD leading to exclusion of space as coordinates. An empirical power law model was used for the breakage kernel and a generalized Hill-Ng distribution was used for the daughter particle distribution function. The distribution was assumed to be uniform and two daughter particles were expected to be formed on breakage. To investigate the predictive capabilities of the model, parameter estimation was performed. I found that the parameterized model was capable of producing PSD profile estimates with < 1.5% error according to calculated RMS error values for the region dominated by attrition. The parameters suggested that the breakage rate was directly proportional to the particle diameter.

5.2 Future work

Many components of this work can be stitched together to provide better quality monitoring and predictive tools. The mass spectrometer used for QbD can be coupled with a pressure controller to get the amount of solvent left behind in the wet cake. The process involves integrating over mass spectrometer and pressure data. The noise from the data would lead to spurious results making it challenging to adopt this method. However, if accomplished the method could prove to be a very powerful tool for monitoring drying. In addition, the method can be tested on other types of dryers like the agitated filter dryer.

The multiphase transport model can be improved upon by adding the component of evaporation to the model. This would involve using three distinct phases for solid, liquid and vapor. Clearly, this would make the model complex but the effect of evaporation cannot be captured otherwise. The model can be extended to include multiple solvents in the liquid and vapor phases by using appropriate thermodynamic relations. The model in its current state can be extended to a filter dryer with some
modification. The modifications would include capturing mixing in the filter dryer and changes to the boundary condition to account for heat transfer in the radial direction from the jacket.

The population balance model (PBM) used in this thesis adopted an empirical form for the breakage rate. Although this model provided a good match with the experiments, a fundamental breakage mechanism of the API needs to be explored. This would involve performing more experiments and using different particle characterization techniques to study the surface of the particles. In addition, the small region of agglomeration needs further investigation. On the modeling front this would involve adding agglomeration terms to the population balance model. Currently, the PBM uses the solvent concentration in the form of an input. This can be improve on by coupling the PBM with the transport model for the filter dryer mentioned before to produce a powerful model to study agitated filter drying of API further. As such a model would predict the solvent concentrations and particle size, it would give a holistic view of dynamics involved in agitated filter drying.
APPENDIX

MASS BALANCES FOR DRYING END POINT

In the derivation below, I obtained an equation that describes the dynamics of the solvent mass fractions in the vapor phase once drying reaches completion. This eq 2.1 is used to determine when drying is complete as described in Section 2.2. All balances derived below are performed on the control volume marked in Figure A.1 with a dotted line.

Overall mass balance on the oven:

\[
\frac{dm}{dt} = \dot{m}_{\text{purge}} + \sum_{i=1}^{N} \dot{m}_i - \dot{m}_{\text{out}} \tag{A.1}
\]

Mass balance on component \(i\) in the oven:

\[
\frac{d}{dt}mx_i = \dot{m}_i + \dot{m}_{\text{out}}x_i - \dot{m}_{\text{purge}}\delta_{i,\text{purge}} \tag{A.2}
\]

Here

\[
\delta_{i,\text{purge}} = \begin{cases} 
1 & \text{if } i = \text{purge} \\
0 & \text{otherwise}
\end{cases}
\]

Applying the product rule to the LHS of eq A.2 and substituting eq A.1 yields:

\[
m\frac{dx_i}{dt} + x_i \left( \dot{m}_{\text{purge}} + \sum_{i=1}^{N} \dot{m}_i - \dot{m}_{\text{out}} \right) = \dot{m}_i + \dot{m}_{\text{out}}x_i - \dot{m}_{\text{purge}}\delta_{i,\text{purge}} \tag{A.3}
\]
When drying is complete, that is, when no solvent remains in the liquid phase:

\[ \dot{m}_i = 0 \] (A.4)

It follows from eq A.3

\[ m \frac{dx_i}{dt} = (\delta_{i,\text{purge}} - x_i) \dot{m}_{\text{purge}} \] (A.5)

\[ m = \rho_g V \text{ and } \dot{m}_{\text{purge}} = \rho_{\text{purge}} q_{\text{purge}} \] (A.6)

We assume that gas behavior is ideal, which is very reasonable at the low operating pressures used in vacuum dryers. Also the purge gas entering the oven and the oven gas are considered to be at the same pressure and temperature.

Therefore:

\[ \rho_g = \frac{PM_g}{RT}, \rho_{\text{purge}} = \frac{PM_{\text{purge}}}{RT} \] (A.7)

Substituting eqs A.6 and A.7 into eq A.5 and considering the case where \( i,\text{purge} \) = 0 for solvents yields:

\[ \frac{dx_i}{dt} = -\frac{q_{\text{purge}} M_{\text{purge}}}{V M_g} x_i \] (A.8)

The volumetric flow rate of the purge gas is controlled with a flow controller, and the volume of the vapor phase is also constant. Over a short period of time, Mg can be considered constant such that:

\[ x_i = x_{i,0} \exp \left( -\frac{M_{\text{purge}}}{M_g} \frac{t}{\tau} \right) \text{ where } \tau = \frac{V}{q_{\text{purge}}} \] (A.9)

Here \( x_{i,0} \) is the mass fraction of component \( i \) at \( t = 0 \). This time does not
represent the beginning of the drying process but rather the initial time over which eq A.8 was integrated to obtain eq A.9. Our analysis only strictly applies when the last solvent is completely evaporated because only then does eq A.4 hold. Nonetheless, I apply eq A.9 to each solvent to determine the time at which the last solvent is completely evaporated, which defines the drying end point.
BIBLIOGRAPHY


